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ABSTRACT SUPPLEMENT

2010 ANNUAL SCIENTIFIC MEETING

November 6–11, 2010
Atlanta, Georgia

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

WILEY-BLACKWELL

AMERICAN COLLEGE OF RHEUMATOLOGY
ABSTRACT SUPPLEMENT

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

ASSOCIATION OF RHEUMATOLOGY HEALTH PROFESSIONALS
A DIVISION OF THE AMERICAN COLLEGE OF RHEUMATOLOGY

American College of Rheumatology
74th Annual Scientific Meeting

Association of Rheumatology Health Professionals
45th Annual Scientific Meeting

November 6 -11, 2010 · Atlanta, Georgia

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ACR/ARHP 2010 Annual Scientific Meeting Overall Needs Assessment/Practice Gaps

The American College of Rheumatology and the Association of Rheumatology Health Professionals are committed to providing comprehensive education to improve the knowledge and performance of physicians, health professionals and scientists. Through evidence-based educational programs, the organization strives to enhance practice performance and improve the quality of care in those with or at risk for arthritis, rheumatic and musculoskeletal diseases. The 2010 ACR/ARHP Annual Scientific Meeting program has been developed independent of commercial influence. The following groups were involved in the planning process: the ACR Committee on Education; the ACR Annual Meeting Planning Committee; the ARHP Education Committee and the ARHP Annual Meeting Program Planning Committee.

The program is the result of a planning process that identified educational needs to change or enhance the knowledge, competence or performance of rheumatology professionals. The program's content was derived from both needs assessment and practice gap analysis based on professional activities, practice setting, ABIM recertification requirements and physician attributes.

Program Highlights

- Educational tracks to help attendees identify content targeted to them. Tracks include: business of rheumatology, clinical, clinical and research, clinical practice, educators, fellow-in-training, pediatrics, pediatrics and clinical, and research
- Latest science and best-practices presented through peer-reviewed and selected clinical and scientific abstracts, and invited speakers providing clinical, evidence-based and quality focused content
- Diverse formats of education delivery, including: didactic lectures, debates, and interactive sessions, such as poster tours, Meet the Professors and Workshop sessions
- A larger forum for discussion of practical management issues such as the Curbside Consults – Ask the Professors session and Medical Aspects lectures
- Extensive learning opportunities in the basic science of rheumatology, an area of the program developed by a subcommittee of U.S. and internationally prominent basic scientists. Offerings include: the Basic Science Symposia, State-of-the-Art Lectures, a series of Immunology Updates for the Clinicians, and a Basic Science pre-meeting course
- Clinical management sessions, including the Thieves' Market and basic management of difficult issues
- A specific pediatric rheumatology track plus content integrated throughout the program designed to provide a high-level educational program to pediatric rheumatologists; and relevant updates to adult rheumatologists
- Formal presentations of new practice guidelines provided to alert the membership and explain, in an open forum, the data supporting the guidelines and propose approaches for implementation
- Over 40 workshops designed to provide hands-on skills training

About ACR/ARHP Education

ACR/ARHP Program Objectives

The American College of Rheumatology and the Association of Rheumatology Health Professionals, a division of the ACR, are organizations of physicians, health professionals and scientists serving members through programs, including education and research. Through these programs, the ACR and the ARHP foster excellence in the care of people with rheumatic and musculoskeletal diseases.

The 2010 ACR/ARHP Annual Scientific Meeting programs have been independently planned by the ACR Committee on Education, the ACR Annual Meeting Planning Committee, the ARHP Annual Meeting Program Committee, and the ARHP Clinical Focus Course Task Force.

This program is sponsored by the American College of Rheumatology for educational purposes only. The material presented is not intended to represent the only or the best methods appropriate for the medical conditions being discussed, but rather are intended to present the opinions of the authors/presenters, which may be helpful to other healthcare professionals. Attendees participating in this medical education program do so with the full knowledge that they waive any claim they may have against the ACR for reliance on any information presented during these educational activities. The ACR does not guarantee, warrant or endorse any commercial products or services.

Program Objectives

At the conclusion of the 2010 ACR/ARHP Annual Scientific Meeting, participants should be able to:

- identify recent developments in the diagnosis and management of patients with rheumatic diseases
- outline new technologies for the treatment of rheumatologic problems
- describe potential challenges in the delivery of care to patients with rheumatic diseases and to specify possible solutions
- utilize new research data to improve the quality of care of patients with rheumatic diseases

CME Credit and Certificates of Participation

Accreditation Statement: The American College of Rheumatology is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Statement of Designation: This activity has been approved for 48.5 *AMA PRA Category 1 Credit™*.

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Computers are available on-site for you to complete your CME/ Certificate of Participation application and meeting evaluation form online during the meeting. In addition, you can complete the evaluation and print your certificate after you return home. *Paper CME application forms will not be available.*

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Your evaluation of the meeting is very important. The ACR/ARHP annual meeting planning committees use feedback from attendees to assist in the development of future educational activities; therefore, we encourage you to complete your evaluation and CME/Certificate application online.

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None: Nothing to disclose

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Abstract author disclosures are published online as well as in this supplement. Disclosures for the Late-Breaking Abstracts are published online and in the December issue of *Arthritis & Rheumatism*. Any individual who refuses to disclose relevant financial relationships will be disqualified from being a planning committee member, a presenter, an author of a CME activity, and cannot have control of, or responsibility for, the development, management, presentation or evaluation of the CME activity.

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ACR Poster Session A
Antiphospholipid Syndrome
Monday, November 8, 2010, 9:00 AM–6:00 PM

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Acquired Resistance to Activated Protein C Is a Feature of Both Systemic Lupus Erythematosus (SLE) and Antiphospholipid Syndrome (APS) and Is More Marked in Patients with SLE and APS. Denis Wahl[3], Stéphane Zuily[4], Agnès Brunette[2], Marie Prestat-Tilly[4], Véronique Regnault[2], Jean Devignes[1] and Thomas Lecompte[1]. [1]Biological Haematology Department, Nancy University Hospital, Vandoeuvre les Nancy, France, [2]INSERM U961, Nancy Université, Vandoeuvre les Nancy, France, [3]Vascular Medicine Unit, Vandoeuvre les Nancy, France, [4]Vascular Medicine Unit, Nancy University Hospital, Vandoeuvre les Nancy, France

Vascular manifestations of antiphospholipid syndrome (APS) include both venous (VTE) and arterial (ATE) thromboembolic events. However VTE are more frequent than ATE. Among the underlying mechanisms of VTE in APS, it has been suggested that acquired activated protein C (APC) resistance may be a candidate mechanism. However this is difficult to demonstrate with tests based on aPTT because of the effects of lupus anticoagulants on this parameter. In order to investigate APC resistance in APS we have conducted a study with a thrombin generation test (calibrated automated thrombography). APC resistance was determined with measurement of endogenous thrombin potential (ETP) at baseline and after addition of APC. The APC sensitivity ratio (sr) was defined as ETP with APC/baseline ETP.

We included 92 patients (37 with primary antiphospholipid syndrome, 15 with SLE without antiphospholipid antibodies PAPS, 11 with both APS and SLE and 29 with antiphospholipid antibodies (APA) but without APS) and 39 controls. APCsr was higher in all patient groups compared to controls indicating resistance to activated protein C: APCsr was 0.45 ± 0.20, $p=0.005$ in PAPS, 0.55 ± 0.16,$p<0.001$ in in SLE, 0.65 ± 0.16,$p<0.0001$ in patients with both PAPS and SLE and 0.53 ± 0.22,$p<0.0001$ in patients with APA without APS whereas controls 0.30 ± 0.11. Of note APCsr was also higher in patients with both SLE and APS than in patients with PAPS ($p=0.009$). Moreover APCsr in patients with venous thrombosis was higher than in controls: 0.47 ± 0.22 vs 0.30 ± 0.11, $p< 0.001$.

Overall these results suggest that acquired APC resistance is a potential risk factor for thrombosis in SLE and PAPS and is more marked when both conditions are present. Furthermore APC resistance seems to be more specifically associated with venous thromboembolism.

Disclosure: D. Wahl: None; **S. Zuily:** None; **A. Brunette:** None; **M. Prestat-Tilly:** None; **V. Regnault:** None; **J. Devignes:** None; **T. Lecompte:** None.

2

AGTRL1 and PRKCH Are Genetic Risk Factors for Antiphospholipid Syndrome. Hisako Nakagawa[1], Tetsuya Horita[2], Toshio Odani[2], Yuichiro Fujieda[2], Masaru Kato[2], Kotaro Otomo[2], Yasuko Nakagawa[2], Shinsuke Yasuda[2], Tatsuya Atumi[2] and Takao Koike[2]. [1]Department of Medicine II, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan, [2]Department of Medicine II, Hokkaido University Graduate School of Medicine.

Background: Single nucleotide polymorphisms (SNPs) of Angiotensin receptor-like1 (AGTRL1) and Protein kinase C eta (PRKCH) were reported to be associated with cerebral infarction in recent genomewide association study in Japanese population. AGTRL1, also named APJ, is a member of the G protein-coupled receptor gene family and has important roles for the modulation of angiogenesis and also act as a human immunodeficiency virus coreceptor. PRKCH regulates various important cellular functions including proliferation, differentiation and apoptosisis is mainly expressed in vascular endothelial cells and foamy macrophages in human atherosclerotic lesions. In this study, we investigated the possible association of the functional SNP in an Sp1-binding site of AGTRL1 gene (rs9943582, G/A) and the nonsynonymous SNP (rs223050, G/A, Val372Ile) in PRKCH gene with antiphospholipid syndrome (APS) in Japanese population.

Patients and Methods: Genomic DNA samples were obtained from 111 patients with APS (45 primary APS and 66 secondly APS), 296 patients with systemic lupus erythematosus (SLE) in the absence of APS and 428 healthy controls. Among APS group, seventy nine patients (71%) had arterial or thrombosis, 58 (52%) arterial thrombosis, 37 (33%) venous thrombosis and 52 (47%) cerebral infarction, respectively. AGTRL1 SNP (rs9943582) was genotyped using TaqMan SNP genotyping assay and PRKCH SNP (rs2230500) was genotyped using direct sequencing. Chi-square tests and Odds ratio were used for statistical analysis after evaluation for Hardy-Weinberg equilibrium. In addition, the stratification analysis by thrombotic events was performed.

Results: Both AGTRL1 rs9943582 G allele and PRKCH rs2230500 A allele frequencies were significantly increased in patients with APS (OR=1.43, 95%Cl:1.03–2.31 and OR=1.89, 95%Cl: 1.17–3.05, respectively). No association was found between these 2 SNPs and SLE in the absence of APS. In the stratification analysis by clinical manifestations of APS, both AGTRL1 and PRKCH alleles were associated with arterial or venous thrombotic events in patients with APS (OR=1.69, 95%Cl:1.15–2.49 and OR=1.58, 95%Cl: 1.04–2.38, respectively)

Conclusion: The functional SNP in an Sp1-binding site of AGTRL1 gene (rs9943582, G/A) and the nonsynonymous SNP (rs223050, G/A, Val372Ile) in PRKCH are associated with APS and thrombotic events in patients with APS. Our results suggest that these 2 SNPs are additional genetic risk factors for APS, especially thrombotic events in APS in Japanese population.

Disclosure: H. Nakagawa: None; **T. Horita:** None; **T. Odani:** None; **Y. Fujieda:** None; **M. Kato:** None; **K. Otomo:** None; **Y. Nakagawa:** None; **S. Yasuda:** None; **T. Atumi:** None; **T. Koike:** None.

3

Anti-β2 Glycoprotein I Antibodies from Leprosy Patients Do Not Show Thrombogenic Effects in an In Vivo Animal Model. Ricardo Forastiero[2], Marta Martinuzzo[2], Mariano Vega-Ostertag[2], Gabriela de Larranaga[2] and Silvia S. Pierangeli[1]. [1]Univ of TX Medical Branch, Galveston, TX, [2]Universidad Favaloro, Buenos Aires, Argentina

Background: The APS-associated aPL are autoantibodies directed against β2GPI and prothrombin. Patients with leprosy present high frequency of IgM aPL that bind β2GPI, but they do not develop thrombosis. Anti-β2GPI from APS mainly bind to domain I of β2GPI while in leprosy are directed against domain V. There is convincing evidence that aPL/anti-β2GPI from APS are pathogenic in vivo and in vitro.

Objective: to investigate the thrombogenic and pro-inflammatory effects of aPL from leprosy and to compare with aPL from APS.

Methods: Sera from 6 patients with APS and 6 with leprosy were used as the source of IgM. All APS and 5 leprosy patients had strong LA activity, and high titers of IgM aCL/anti-β2GPI. The remaining leprosy patient was aPL negative (control). We treated CD1 mice, in groups of 5, at 0 hours and 48 hours later with IgM aPL/anti-β2GPI isolated from patients with leprosy (IgM-leprosy) or APS (IgM-APS) or with IgM from 2 healthy controls (IgM-NHS) or 1 leprosy aPL negative control. Seventy-two hours after the first injection, the adhesion of leukocytes (#WBC) to endothelial cells (EC) in cremaster muscle (as an indication of EC activation in vivo), as well as the size of an induced thrombus in the femoral vein of the mice were examined.

Results: IgM-APS significantly increased the thrombus size (in mum2) when compared to IgM-NHS or IgM-leprosy treated mice ($p<0.001$). There was no difference in mice injected with IgM-leprosy, IgM-NHS or IgM-leprosy control. IgM-APS increased the #WBC adhering to EC, when compared to IgM-NHS or IgM-leprosy ($p<0.001$).

	IgM-APS	IgM-leprosy	IgM-NHS	IgM-leprosy control
Mean thrombus size	4446	1378	748	851
#WBC	5.1 ± 2.2	2.0 ± 1.0	3.5 ± 1.6	1.3 ± 0.5

Conclusions: Our data shown that aPL/anti-β2GPI from leprosy patients have not thrombogenic and pro-inflammatory effects in vivo when compared with aPL derived from APS.

Disclosure: R. Forastiero: None; **M. Martinuzzo:** None; **M. Vega-Ostertag:** None; **G. de Larranaga:** None; **S. S. Pierangeli:** None.

4

Antiphospholipid Antibodies in Children with Systemic Lupus Erythematosus – 18 Years of Clinical Experience from North India. Surjit Singh[2], Jasmina Ahluwalia[1], Shano Naseem[3], Deepti Suri[2] and Amit Rawat[2]. [1]Department of Hematology, Post Graduate Institute of Medical Education and Research, Chandigarh, India, [2]Division of Pediatric Allergy and Immunology, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India, [3]Division of Pediatric Hematology, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Background: Pediatric systemic lupus erythematosus (p-SLE) is usually more severe than its adult counterpart and frequently involves vital organs (e.g. kidneys). Anti-phospholipid antibodies (APLA) have been reported in 38–87% patients with p-SLE in and reports suggest that presence of APLA can modify disease expression. Higher incidence of neuropsychiatric, renal and hematological manifestations has been reported in APLA positive p-SLE, but influence of APLA on disease course remains unclear. While APLA have been extensively studied in adults with SLE, there is paucity of data on APLA in p-SLE.

Materials and Methods: We report a single centre study on 64 patients with p-SLE seen during the period June 1992 - May 2010 in whom APLA testing was performed. Diagnosis of SLE was based on ACR criteria. Mean age at diagnosis was 10.3 years (range 3–17) with a female:male ratio of 3:1. Of these 24 (37.5%) had renal, 17 (26.6%) hematological (7-hemolytic anemia, 6-thrombocytopenia and 4-leucopenia), 14 (21.9%) neurological, 8 (12.5%) pulmonary, 29 (45.3%) musculo-skeletal and 42 (65.6%) had mucocutaneous involvement. APLA tested included: i) lupus anticoagulant [by kaolin clotting time, diluted Russell viper venom time (LA Screen and LA Confirm, Dade Behring) and STACLOT-LA kit] ii) anticardiolipin antibodies (ACLA) – IgG, IgM and iii) anti-β2 glycoprotein I (β2 GPI) antibodies – IgG, IgM (Orgentec GmBH by ELISA). Our laboratory is registered in World Health Organization's United Kingdom National External Quality Assurance Scheme for these tests.

Summary of Results: Patients was tested for APLA on 155 occasions - minimum being once and maximum being 10 during a mean follow-up period of 59.3 months (range 1–211 months). Thirty eight (59.4%) patients were positive for one or other APLA at some point of time of their disease. Overall LA was positive in 39.1%, IgG ACA in 23.4% and IgM ACA in 18.6%. At diagnosis, 37.8% children were positive for LA, 16.3% for IgG ACA and 20.9% for IgM ACA. During follow-up LA was positive in 26.2% patients, IgG ACA in 31%, IgM ACA in 19% patients. Anti-β2GPI (IgG and IgM) could be tested in 10 patients only and was found to be positive for anti-β2GPI IgG in 1 patient.

Thrombosis was seen in 5 patients - of these, 4 (80%) were positive for APLA. Of the 24 patients with nephritis, class II nephritis was seen in 4—of these none was positive for any of the APLA; class III nephritis was seen in 1–patient tested positive for APLA; class IV nephritis was seen in 15—of these 9 (60%) were positive for 1 of the APLA; class V nephritis was seen in 3–of these 2 (66.6%) were positive for APLA. Of the 17 patients with hematological involvement, 11 (64.7%) had positive APLA; of 14 with neurological involvement, 12 (85.7%) had positive APLA. Six (9.4%) children had a fatal course—5 (83.3%) of these had positive APLA.

Conclusion: 59.4% p-SLE patients had APLA positivity during the disease course. The commonest APLA was LA (39.1%), followed by IgG ACA (23.4%) and IgM ACA (18.6%). APLA positivity is more common in p-SLE patients with advanced nephritis, neurological involvement, thrombosis and a fatal course. Presence or persistence of these antibodies, however, may not always predict thrombosis in children with p-SLE.

Disclosure: S. Singh: None; **J. Ahluwalia:** None; **S. Naseem:** None; **D. Suri:** None; **A. Rawat:** None.

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Antiphospholipid Score (aPL-S): A Comprehensive Predictive Marker of Developing Thrombosis in Autoimmune Diseases. Kotaro Otomo[1], Tatsuya Atsumi[2], Yuichiro Fujieda[3], Masaru Kato[3], Olga Amengual[3], Tetsuya Horita[3], Shinsuke Yasuda[3] and Takao Koike[3]. [1]Hokkaido Graduate School of Medicine, Department of Medicine II, Sapporo, Hokkaido, Japan, [2]Hokkaido Graduate School of Medicine, Department of Medicine II, Sapporo, Japan, [3]Hokkaido Graduate School of Medicine, Department of Medicine II

Objective: We have previously defined the Antiphospholipid Score (aPL-S) by testing multiple antiphospholipid antibodies (aPL), and evaluated its efficacy for the diagnosis of antiphospholipid syndrome (APS) as well as its predictive value for the development of thrombotic events in patients with autoimmune diseases (Presentation Number 1216 in ACR 2009). In the present study, we further analyzed the associated-risk of thrombosis for each aPL assay in autoimmune diseases. Further, we investigated the relationship between the aPL-S and each single aPL test.

Patients and Methods: This study comprised 411 patients with autoimmune diseases who visited our Rheumatic and Connective Tissue Disease Department. Between 2002 and 2003, five Lupus Anticoagulant (LAC) assays (the mixing studies: activated partial thromboplastin time (APTT), kaolin clotting time, the dilute Russel's viper venom test (dRVVT), and the confirmatory tests: APTT and dRVVT) and 6 ELISAs (IgG/M anticardiolipin (aCL) antibodies, IgG/M anti-beta2-glycoprotein I (aβ2GPI) antibodies and IgG/M phosphatidylserine dependent antiprothrombin (aPS/PT) antibodies) were performed in all subjects. Among all the patients, 296 (72.0%) were followed-up with a mean duration of 67 $\pm$15 months. The disease profile of these patients was as follows; 17(6%) primary APS, 26(9%) APS associated with other autoimmune disease, 89(29%) SLE (without APS), 50(17%) rheumatoid arthritis and 114 patients with several other autoimmune diseases. To evaluate the predictive value of thrombosis for each aPL-analyzed test, positive results in each assay were contrasted with the presence of new thrombotic events during the follow-up period.

Results: Thirty-two patients newly developed thromboses during the observation period; 22 arterial thromboses and 14 venous thromboses.

Patients with either positive LAC or IgG aPS/PT had a stronger risk of thrombosis than those without. The odds ratio (OR [95%CI]) associated to each test was 3.26 [1.55–6.90, p=0.001] and 4.80 [2.03–11.04, p=0.0001], respectively. The OR values in patients with aPL-S more than 10, 30 and 50 were 2.86 [1.33–6.16, p=0.006], 5.27 [2.32–11.95, p<0.0001] and 5.31 [1.81–15.53, p=0.0008], respectively. Thus, the positive predictive values of aPL-S more than 30 and 50 were higher than any other value of each single aPL test (see figure.). The negative predictive values of aPL-S, LAC and IgG aPS/PT were within the similar levels (90.7–92.9%).

Conclusion: The aPL-S may be a useful comprehensive quantitative marker for predicting thrombosis in autoimmune diseases.

Disclosure: K. Otomo: None; **T. Atsumi:** None; **Y. Fujieda:** None; **M. Kato:** None; **O. Amengual:** None; **T. Horita:** None; **S. Yasuda:** None; **T. Koike:** None.

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Antiphospholipid Syndrome (APS) Clinical Research Task Force (CRTF) Report. Doruk Erkan[2], Ronald Derksen[6], Roger A. Levy[3], Samuel Machin[5], Thomas Ortel[1], Silvia S. Pierangeli[4], Robert A. S. Roubey[7], Michael D. Lockshin[2] and on Behalf of APS Clinical Research Task Force. [1]Duke University Health System, Durham, NC, [2]Hospital for Special Surgery, New York, New York, NY, [3]Univ Estado Do Rio de Janeiro, Rio de Janeiro, Brazil, [4]Univ of TX Medical Branch, Galveston, TX, [5]University College London Hospitals, London, UK, [6]University Medical Centre, Utrecht, Netherlands, [7]University of North Carolina, Chapel Hill, NC

Background: The 13th International Congress on Antiphospholipid Antibodies (aPL) was held in Galveston, TX in April 2010. The APS CRTF was one of six task forces developed by the meeting organization committee with the purpose of: a) evaluating the limitations of APS clinical research and developing guidelines for researchers to help improve the quality of APS research; and b) prioritizing the ideas for a well-designed multicenter clinical trial and discussing the pragmatics of getting such a trial done (organization, ideal protocols, practical protocols, and financing).

Objective: The purpose of this abstract is to summarize the discussions and progress of APS CRTF.

Methods: The original eight members of CRTF were chosen among experienced APS researchers. The task force working algorithm was: a) a questionnaire that was sent to the members before the congress; b) a summary report that was prepared based on the responses to facilitate discussions during the pre-meeting workshop; c) a pre-meeting workshop; d) two plenary sessions based on the conclusions of the task force discussions where input from all the meeting attendees was received; and e) a final report that was circulated among all the task force chairs for final remarks.

Results: The task force identified five major issues that impede APS clinical research and the ability to develop evidence-based recommendations for the management of aPL positive patients: 1) aPL detection has been based on partially or non-standardized tests, and clinical (and basic) APS research studies have included patients with heterogeneous aPL profiles with different clinical event risks; 2) clinical (and basic) APS research studies have included a heterogeneous group of patients with different aPL-related manifestations

(some controversial); 3) thrombosis and/or pregnancy risk stratification and quantification are rarely incorporated in APS clinical research; 4) most APS clinical studies include patients with single positive aPL results and/or low-titer aPL ELISA results; furthermore, study designs are mostly retrospective and not-population based, with limited number of prospective and/or controlled population studies; and 5) lack of information on the particular mechanisms of aPL-mediated clinical events limits the optimal clinical study design.

Conclusion: The task force recommended that there is an urgent need for a true International collaborative approach to design and conduct well-designed prospective large-scale multi-center clinical trials of patients with persistent and clinically significant aPL profiles. An International collaborative meeting to formulate a good research question using "FINER" (Feasible; Interesting; Novel; Ethical; and Relevant) criteria will take place in early November and the conclusions will be presented at the ACR meeting.

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Decreased Fibrin Clot Porosity in Patients with Antifosfolipid Syndrome. Anna Vikerfors[2], Aleksandra Antovic[1], Elisabet Svenungsson[2], Katarina Bremme[3] and Margareta Holmström[4]. [1]Department of Clinical Sciences, Karolinska Institutet/Danderyd Hospital, Stockholm, Sweden, [2]Department of Medicine, Rheumatology Unit, Karolinska Institutet/Karolinska University Hospital, Stockholm, Sweden, [3]Department of Woman and Child Health, Division of Obstetrics and Gynaecology, Karolinska Institutet/Karolinska University Hospital, Stockholm, Sweden, [4]Hematology Division, Department of Medicine, Karolinska Institutet/Karolinska University Hospital, Stockholm, Sweden

Background: It has been reported that patients with type 1 diabetes and young males with myocardial infarction form a fibrin clot which is tighter and more resistant to fibrinolysis in comparison to the fibrin clot formed by healthy controls. The structure/porosity of the fibin clot in patients with the Antiphospholipid syndrome (APS) has not previously been investigated and we hypothesised that a tight fibrin clot may contribute to the procoagulant state in these patients.

Materials and Methods: We thus evaluated fibrin clot porosity in plasma-samples from 47 patients with Antifosfolipid Syndrome (APS), strictly fulfilling the Sydney criteria for APS. Previously established flow measurement technique was used to determine the fibrin clot porosity, as expressed as the Darcy constant (Ks). A low Ks level indicates a tighter fibrin clot. Ks-levels were compared to reference Ks values used in our laboratory obtained from healthy individuals. Within the APS-group, associations between Ks-levels and clinical manifestations, specificities of antiphospholipid antibodies (aPL) were explored. For a majority of the patients data regarding markers of inflammation and on-going medication was available to guide interpretation.

Results: The mean Ks-levels were significantly lower in the samples from patients with APS (6.7, +/−2.9) as compared to reference Ks values (10.7+/−1.6), indicating a tighter fibrin network, p<0,0001. Within the APS-group Ks-levels did not vary depending on different clinical APS manifestations or aPL pattern. There was however a trend towards lower Ks-levels for the 20 patients with previous obstetric morbidity (5.7, +/−2,0) as compared to the 27 patients without this clinical manifestation (7.4 +/−3.2), p=0,09.

CRP-levels were generally low in the APS-patients (median 1.06, range 0–7.4, n=28). A majority of the patients were treated with anticoagulants: either vitamin K-antagonits or dalteparin (19/34) and many with statins (7/34). Patients treated with these two groups of drugs had all experienced a previous arterial or venous tromboembolic event. Almost half of the patients (15/34) were treated with low-dose ASA, sometimes in combination with vitamin K-antagonists or dalteparin. The majority of the ASA-treated patients (12/15) had a previous tromboembolic manifestation.

Conclusion: APS-patients form a tighter and more stable fibrin clot as estimated by Ks levels, which measure in vitro fibrin clot porosity. There was a significant difference compared to reference material obtained from healthy individuals, even though a majority of the APS-patients were treated with low dose ASA, warfarin, dalteparin, statins or a combination of these drugs. To our knowledge this is a new finding.

We observed a trend towards a tighter fibrin network in APS-patients with obstetric morbidity compared to other individuals with APS. This finding could be attributed to differences in medications between the two groups.

Future studies including larger patient materials and controls may shed further light on the aetiology of APS and may thereby contribute to better risk assessment and management for APS patients.

Disclosure: A. Vikerfors: None; **A. Antovic:** None; **E. Svenungsson:** None; **K. Bremme:** None; **M. Holmström:** None.

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Global Analyses of Antiphospholipid Antibodies That Impair Antithrombin Inactivation of Procoagulant Factors. Meifang Wu[2], Jennifer M. Grossman[3], John FitzGerald[2], Bevra H. Hahn[4] and Pojen P. Chen[1]. [1]UCLA Schl of Medicine, Los Angeles, CA, [2]UCLA School of Medicine, [3]University of California Los Angeles, Sherman Oaks, CA, [4]University of California Los Angeles School of Medicine, Los Angeles, CA

Background: Previously, we reported that 6 of the 8 patient-derived IgG monoclonal anti-phospholipid antibodies (aPL) bound to thrombin, and that one such reactive aPL (CL24) significantly impaired inactivation of thrombin by antithrombin (AT). Subsequently, we found that all 6 thrombin-reactive aPL also bound to FXa; and that all 6 thrombin-reactive aPL plus two later generated IgG monoclonal aPL (i.e., B2 and P1) also interacted with FIXa. Importantly, some of these reactive aPL (such as CL24) could reduce AT inactivation of FXa and FIXa. The purpose of this study was to study the overall effects of such aPL on hindering AT from inactivating its target procoagulant factors.

Methods: First, we developed an activated-partial-thromboplastin-time (APTT)-based assay to study the overall effects of aPL on impairing AT function and shortening plasma clotting times. Second, to avoid the problem that some aPL possess lupus-anticoagulant activity (that prolongs clotting times) and could obscure shortened clotting time (from aPL-impaired AT function), we evaluated each test aPL (or purified IgG, or plasma sample) individually by determining its clotting times in plasma in the presence or absence of heparin (with optimal AT function, or little AT function, respectively), and then dividing the former clotting time by the latter clotting time, and expressing the result as a "clotting ratio". Third, as a first step to translate the above findings of AT-interfering IgG aPL into a feasible clinical assay, we adapted the above assays to study two chosen patient plasma samples. Plasma P76 contained IgG aPL that reacted with FXa and FIXa; and P80 contained IgG aPL that interacted with thrombin, FXa and FIXa.

Results: First, monoclonal antibodies B2 and CL24 at the final concentration of 27 μg/ml (representing about 0.3% of total plasma IgG) significantly shortened clotting times from 85 seconds to about 60 seconds ($p < 0.001$), most likely reflecting that B2 and CL24 impaired AT inactivation of one or more procoagulant factors in plasma. Second, using the "clotting ratio" analyses, B2 and CL24 at the physiological concentration reduced clotting ratios from 250% for normal human IgG to 144 % ($p < 0.01$) and 171% ($p < 0.05$), respectively. Moreover, purified IgG from 2 patients with antiphospholipid syndrome (APS) also reduced clotting ratio to 153% and 145%, as compared with a clotting ratio of 175% for normal human IgG. Third, when heparin was added, the clotting times of normal plasma, P76 and P80 were increased respectively to 96 seconds, 99 seconds and 166 seconds. These led to a clotting ratio of 178% for the normal plasma, while those of plasma P76 and the P80 were respectively 113% and 134% ($p < 0.001$). These data suggested that both patient plasma samples had the AT-interfering Ab. The above reduced clotting ratios apparently reflected that certain aPL reacted with the target procoagulant factors of AT and paradoxically impair AT inactivation of the involved procoagulant factors in plasma.

Conclusion: These results show the AT-interfering IgG aPL are present in some APS patients and could contribute to thrombosis in such patients.

Disclosure: M. Wu: None; **J. M. Grossman:** None; **J. FitzGerald:** None; **B. H. Hahn:** None; **P. P. Chen:** None.

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Influenza Vaccination Can Induce New Onset Anticardiolipins but Not β2-Glycoprotein-I Antibodies among Patients with Systemic Lupus Erythematosusβ. Evan Glenn Vista[3], Sherry R. Crowe[3], Amy B. Dedeke[3], Jourdan R. Anderson[2], Linda F. Thompson[3], Gillian Air[4] and Judith A. James[1]. [1]Oklahoma Med Research Foundation, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]University of Oklahoma Health Science Center, Oklahoma City, OK

Background: Antiphospholipid syndrome is characterized by pathogenic autoantibodies against anticardiolipins (aCLs), lupus anticoagulant, and Independent β2-glycoprotein (β2GPI). The factors causing production of these antiphospholipid antibodies (aPLs) remain unidentified but have been documented in a large number of infectious diseases. Controversy exists as to whether vaccination triggers the same autoimmune reactions as infections in systemic lupus erythematosus (SLE) patients. Among the aPLs, β2GPI has been described as the actual target antigen for autoimmune aPLs, but conflicting reports still exist.

Methods: A total of 102 patients fulfilling the ACR criteria for SLE and 104 age, race and gender matched healthy controls enrolled in our lupus flu cohort from 2005 to 2009 and received regular seasonal influenza vaccinations. Sera were tested by ELISA for aCL IgG at the time of vaccination and 2, 6 and 12 weeks after vaccination. The international standardized ratios for aCL reactivity were calculated for each and manufacture cut-offs were used to define low, moderate, and high levels of aCL. Logistic regression was used to account randomly for those enrolled in multiple years to select the unique 206 individuals. Vaccine responses were ranked either as high or low according to an overall anti-influenza antibody response index (which includes hemagglutination inhibition, relative avidity and maximum native antibody responses). Those who have new onset reactivity to aCL IgG were further tested for β2GPI IgG antibodies. Paired t-testing for all patients with aCL reactivity was used to determine changes after vaccination at 2, 6, and 12 weeks compared to baseline.

Results: More SLE patients compared to healthy controls developed new low aCL reactivity (14/102 cases and 4/104 controls; OR 4.1, p 0.02) and new moderate aCL reactivity (13/102 cases and 3/104 controls; OR 5.1, p 0.01) after influenza vaccination. From specific timepoints after vaccination, new low aCL reactivity were significant for SLE patients after 6 weeks (11/102 cases and 1/104 control) and 12 weeks (10/102 cases and 2/104 control) (OR 12.8, p 0.02 and OR 5.7, p 0.03 respectively) and for new moderate aCL reactivity only after 6 weeks (10/102 cases and 1/104 controls; OR 11.5, p 0.02). High aCL reactivity was only seen among 2 patients with low and moderate aCL reactivity pre-vaccination. Overall, vaccine response was significantly higher among patients with new onset aCL reactivity compared to controls (p 0.02). No new β2GPI antibodies were detected post-vaccination among patients with new aCL reactivity. The normalized optical density measurements for patients with recorded aCL reactivity at any time points were significantly higher after 2 weeks (0.43±0.24, p 0.0013), 6 weeks (0.49±0.37, p 0.004), and 12 weeks (0.47±0.44, p 0.03) after vaccination compared to the baseline (0.30±0.15).

Conclusions: This study shows transient increases in aCLs, but not anti-β2GPI responses, after influenza vaccination supporting the possibility that these changes in autoantibody levels may not be clinically important for increased thrombosis risk post-vaccination.

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Platelet Activation and Paradoxical Inhibition of ADP Induced Aggregation by Antiphospholipid Antibodies. Kenji Oku[4], Tatsuya Atsumi[2], Olga Amengual[3], Masahiro Ieko[1], Shin Furukawa[6], Hirohiko Kitakawa[6], Yuji Hori[6], Kazuyoshi Nihei[6], Yuuichiro Fujieda[3], Kotaro Otomo[5], Masaru Kato[3], Tetsuya Horita[3], Shinsuke Yasuda[3] and Takao Koike[3]. [1]Health Sciences University of Hokkaido, [2]Hokkaido University Graduate School of Medicine Internal Medicine II, Sapporo, Japan, [3]Hokkaido University Graduate School of Medicine Internal Medicine II, [4]Hokkaido University Graduate School of Medicine Internal Medicine II, Kushiro Red Cross Hospital, Japan, [5]Hokkaido UniversityGraduate School of Medicine Internal Medicine II, [6]Kushiro Red Cross Hospital

Purpose: Autoantibodies against beta2-glycoprotein I (β_2GPI) and those against prothrombin are two major populations of antibodies found in patients with antiphospholipid syndrome (APS). The platelet activation and aggregation are crucial procedures in the development of arterial thrombosis. There are some reports suggesting a link between platelet activation and anti-β_2GPI antibodies, but only little data are available regarding antiprothrombin antibodies and platelets. We previously showed that presence of IgG phosphatidylserine-dependent antiprothrombin antibodies (aPS/PT) was a strong risk of having arterial thrombosis in our cohort of 500 patients with autoimmune diseases, and that monoclonal aPS/PT affected ADP induced platelet aggregation *in vitro* (abstract 1594, ACR 2009).

In this study, we investigated further the *in vitro* behaviour of platelet exposed by aPS/PT and anti-β_2GPI antibodies. Additionally, we quantitatively-analyzed CD62P, a surface marker of activated platelets and thromboxane B2(TXB2), a member of eicosanoid family molecules produced by activated platelets.

Methods: A monoclonal aPS/PT, 231D, that shared the properties with autoimmune aPS/PT, a human monoclonal anti-β_2GPI antibody, EY2C9, and purified IgG from APS patients' sera were used for the following experiments. Normal platelets were treated with monoclonal antibodies or purified IgG. Conventional ADP or collagen induced platelet aggregation assay by turbidimetric method were performed using platelet riched plasma (PRP) spiked with monoclonal antibodies or purified IgG. To explore, in this system, the involvement of P2Y12, one of the ADP receptors on platelet controlling the secondary aggregation, we evaluated the activation of vasodilator stimulated phosphoprotein (VASP), using a standard assay. VASP represents P2Y12 inhibition as the intra-molecular signal protein. Positive ratio of CD62P was detected by two-colored flow-cytometry. TXB2 was quantitatively-analyzed by Enzyme-Linked ImmunoSorbent Assay (ELISA.).

Results: ADP induced secondary platelet aggregation was significantly inhibited in 231D, EY2C9, and purified IgG affected PRP, whereas collagen induced platelet aggregation was not affected by any of the antibodies. VASP activities were significantly increased in 231D and EY2C9 treated platelets ($p<0.01$).

Both positive rates of CD62P and TXB2 levels were significantly raised on platelets treated with 231D or EY2C9 in the presence of their antigen.

Conclusion: The effects of monoclonal aPS/PT on platelets were similar to those of monoclonal anti-β_2GPI antibodies and IgG fractions of APS patients' sera. Antiphospholipid antibodies activated platelets shown by CD62P expression and TXB2 production. Paradoxical inhibition of ADP induced platelet aggregation by antiphospholipid antibodies might be correlated with P2Y12 signal suppression. Those observations suggest that the platelet involvements with aPS/PT and anti-β_2GPI are paradoxical and complex, leading to the heterogeneous clinical features of patients with APS.

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Prevalence and Prognostic Significance of Thrombotic Microangiopathy in Rheumatologic Patients: Clinical and Immunological Associations. Spyros Aslanidis, Athina Pyrpasopoulou, Stella Douma, Areti Triantafyllou, Michail Doumas and Chrysanthos Zamboulis. 2nd Propedeutic Dept of Internal Medicine, Hippokration Hospital, Thessaloniki, Greece

Background/Aim: The aim of this study was to assess the prevalence of microangiopathy in rheumatologic patients featuring signs of vasculopathy. As the occurrence of small-vessel occlusions (thrombotic microangiopathy) in the nail fold of patients with antiphospholipid syndrome is well documented, a major target point of this study was to evaluate capillaroscopy in the diagnosis of APS. Capillaroscopic findings and matching autoantibody profiling were subsequently correlated with the incidence of arterial and venous thrombotic events.

Materials/Methods: 738 patients from a Rheumatology Outpatients cohort were consecutively screened with capillaroscopy. Criteria for selection included Raynaud's phenomenon, livedo reticularis, diagnosis of SLE, positive antiphospholipid profile and/or previous thrombotic events, and atypical musculoskeletal symptomatology. Scleroderma patients were excluded. Patients with microhemorrhages were tested for ACL and anti-b2GP1 Abs and data was analyzed with the SPSS 16.0 software.

Results: 149 of the screened patients (85.2% ♀/14.8%♂, 49.28±14.31 yrs) exhibited capillary microhemorrhages. Running diagnosis in these patients was MCTD (24.2%), SLE (18.8%), RA (16.1%), APS (12.8%), Sjogren's syndrome (4.7%), B51 (3.4%), and vasculitis (2%). Antiphospholipid profile was tested in the affected individuals, and revealed an additional 14.7% of secondary laboratory APS in 28.6% of the SLE and 22.2% of the MCTD patients. The presence of ACL and anti-b2GP1 Abs was found to both independently significantly correlate with thrombotic events ($p<0.001$). Subanalysis of the type of anti-b2GP1 Abs indicated that the correlation with thrombotic events was significant for G-type ($p<0.001$) and M-type ($p=0.012$), but not A-type Abs ($p=0.292$, NS). No significant predilection for arterial or venous thromboses was observed in patients with ACL Abs; patients with anti-b2GP1 Abs exhibited a trend for arterial thromboses, $p=0.174$, NS.

Conclusions: Capillaroscopy is a useful microangiopathy screening tool in rheumatologic patients featuring signs of clinical vasculopathy, and can aid

diagnostically to screen for, or verify, APS in patients with a history of thrombotic events. Associations of autoantibody profiling of patients with capillaroscopic microangiopathy with clinically manifested thromboses resulted in similar findings with studies involving patients with clinical APS. The observation that, although IgA-b2GP1 Abs were detected in patients with microangiopathy, they lacked any significant association with thrombotic complications, suggests, that additional factors may be needed for the development of clinical thrombotic events.

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Prevalence of Antibodies to Prothrombin (PT) and Prothrombin/Phosphatidylserine (PS) in a Cohort of Lupus Anticoagulant (LAC) Positive Samples. R. Aguilar-Valenzuela[2], J. Dlott[1], U. Khan[2], M. Belter[1], E. Doan[2], N. Gould[1], A. Schleh[2] and S. Pierangeli[2]. [1]Quest Diagnostics, Chantilly, VA, [2]Univ of TX Med Branch, Galveston, TX

Background: ELISA tests have been developed to detect anti-PT and anti-PT/PS antibodies in serum but the clinical diagnostic value and their relationship with the LAC remains elusive.

Objective: to evaluate anti-PT/PS and anti-PT antibodies in a cohort of 150 confirmed LAC and the corresponding controls.

Methods: 150 LAC positive and 150 LAC negative plasma samples were tested by ELISA for anti-PS/PT (IgG and IgM) and LAC PS/PT screening assay (kindly provided by INOVA Diagnostics) and anti-PT (IgG and IgM) in-house assay. LAC positivity was confirmed by either dRVVT Confirm (American Diagnostica) or by the STACLOT LA (Diagnostica Stago) tests (3% of samples were positive for dRVVT only and 94% were positive for STACLOT only, 3% were positive for both).

Results:

	aPS/PT IgG	aPS/PT IgM	aPS/PT Screen	aPT IgG	aPT IgM
# of positive samples (%)	43/150 (29%)	33/150 (22%)	32/150 (21%)	44/150 (29.3%)	39/150 (26%)

All negative LAC samples were negative in the anti-PS/PT and anti-PT tests. 125/150 (83%) of all LAC positive samples were positive in at least one of the PS/PT or PT ELISA. There was no correlation between any of the tests and LAC Staclot delta values or dRVVT ratios and the PT/PS or PT tests. Strong correlation was observed between anti-PS/PT IgG or IgM and LAC Anti-PS/PT screen test.

Conclusions: PS/PT and PT antibodies altogether recognize the majority of LAC positive samples and may represent an additional specific serological laboratory marker to confirm diagnosis of Antiphospholipid Syndrome.

Disclosure: R. Aguilar-Valenzuela: None; **J. Dlott:** None; **U. Khan:** None; **M. Belter:** None; **E. Doan:** None; **N. Gould:** None; **A. Schleh:** None; **S. Pierangeli:** None.

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The Influence of Thrombovascular Events on the Quality of Life in APS and SLE Patients. Amaris K. Balitsky, Valentina Peeva, Jiandong Su, Erik Yeo, Carol Landolt-Marticorena, Dafna D. Gladman, Murray B. Urowitz and Paul R. Fortin. University of Toronto Antiphospholipid Clinic, Division of Rheumatology, Toronto Western Hospital

Objective: The antiphospholipid syndrome (APS) is defined by the presence of antiphospholipid antibodies (aPLs) with clinical manifestations such as: venous or arterial thrombosis or recurrent pregnancy complications. The syndrome is either primary, or secondary due to an underlying condition, most commonly systemic lupus erythematosus (SLE). The purpose of this study was to describe and compare the characteristics and quality of life (QoL) of patients with previous thrombovascular events (TE) to those with no TE. To analyze the data, we used t-tests and one-way ANOVAs with Bonferroni post-hoc tests.

Methods: Five patient groups followed at the University of Toronto SLE and APS clinics were defined as patients with: 1) (PAPS) primary APS, 2) (SAPS) APS secondary to SLE, 3) (SLE+TE) SLE patients who had a TE, but do not have positive aPLs, (i.e., do not have APS), 4) (SLE-TE+aPL) SLE without TE, but with a persistent positive aPL defined as anticardiolipin antibody of IgG and/or IgM > 40 GPL or MPL, on two or more occasions, at least 12 weeks apart, 5) (SLE-TE) SLE without TE, and without aPL. QoL was determined using the mental component score (MCS) and the physical component score (PCS) of the Medical Outcomes Study Short Form 36 (SF-36) at the most recent visit. To analyze the data, we used t-tests and one-way ANOVAs with Bonferroni post-hoc tests.

Results: The table summarizes the data and marks significant differences with an asterisk. Mean age at the time of the questionnaire completion was similar across the five groups, except for a younger average age (42.9 years) in the SLE-TE group ($p<.05$). A high majority of patients were female across all groups, with a smaller majority (60.5%) in the PAPS group. There were more venous TEs in the PAPS group (65.8%) compared to the SAPS group (30.8%); however, the overall number of patients with arterial and venous TEs was similar. Patients with arterial events (44.7 ± 11.5) scored lower than patients with venous events (49.2 ± 11.6) in the MCS score ($t(149.5) = -2.4$, $p = .02$); however there was no difference in PCS scores between arterial and venous TE. There was a difference in PCS scores across the five groups ($F(4,897) = 3.33$, $p<.05$); however there was no difference in MCS scores. Patients in the SLE+TE group showed lower scores compared to the PAPS and SLE-TE+aPL groups (table). SLE+TE patients also scored lower on a number of QoL subscales.

Conclusions: It appears that the combination of two severe conditions, SLE and thrombotic events, has a more negative influence on reported PCS, compared to having SLE or APS alone. This influence was not seen for the MCS score.

Group	N	Age	Sex (% F)	TE type (% v)	MCS	PCS
PAPS	38	47.5 ± 15.4	60.5	65.8	48.6 ± 12.5	43.5 ± 11.1*
SAPS	39	54.8 ± 15.0	92.3	30.8	47.1 ± 10.9	38.6 ± 13.8
SLE+TE	79	51.1 ± 15.8	84.8	50.6	46.0 ± 11.7	36.5 ± 12.15*
SLE-TE+aPL	79	51.1 ± 16.8	84.8	n.a.	47.3 ± 12.2	42.5 ± 13.8*
SLE-TE	667	42.9 ± 15.2*	90.1	n.a.	46.9 ± 11.6	40.4 ± 12.2

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Utility of Anti-Phosphatidylserine/Prothrombin and IgA Antiphospholipid Assays in Antiphospholipid Syndrome. Ehtisham Akhter[3], Walter L. Binder[2], Zakera Shums[2] and Michelle A. Petri[1]. [1]Timonium, MD, [2]Inova Diagnostics Inc, San Diego, CA, [3]Johns Hopkins University, Baltimore, MD

Purpose: Currently three antiphospholipid assays are in wide use clinically (lupus anticoagulant, anticardiolipin (aCL), and anti-beta2 glcyoprotein I (anti-beta2 GPI)). The lupus anticoagulant is the most specific assay, conferring the highest risk of thrombosis and pregnancy loss, but it cannot be validly performed in an anticoagulated patient. We investigated anti-phosphatidylserine/prothrombin (anti-PS/PT), which detects most lupus anticoagulants, in terms of its association with thrombosis. We also investigated the utility of IgA assays for APS in SLE.

Methods: Stored samples from SLE patients with and without past thrombosis were assayed for anti-beta2 GPI (IgG/IgM/IgA), Domain 1 (IgG) and Domain 4/5 (IgA), aCL (IgG/IgM/IgA) and anti-PS/PT (IgG, IgM and IgG/M).

Results: For any thrombosis, the highest association was with aCL IgA, followed anti-beta2 GPI IgG and anti-beta2 GPI IgA. Anti-PS/PT IgG, IgM and IgG/M were similar (Table 1).

Table 1: Any Thrombosis

		Thrombosis (n = 160)	No thrombosis (n = 166)		
	Assay	Number (% positive)	Number (% positive)	Odds Ratio 95% CI	P-value
IgG	beta2 GPI	18 (5.5%)	6 (3.6%)	3.4 (1.3, 8.7)	.0083
	beta GPI Domain 1	11 (6.7%)	9 (5.4%)	1.3 (0.5, 3.2)	.5845
	Anticardiolipin	22 (13.8%)	16 (9.6%)	1.5 (0.8, 3.0)	.2475
	PSPT	26 (16.3%)	14 (8.4%)	2.1 (1.1, 4.2)	.0315
IgM	beta2 GPI	8 (5.0%)	9 (5.4%)	0.9 (0.3, 2.4)	.8641
	Anticardiolipin	18 (1.3%)	15 (9.0%)	1.3 (0.6, 2.6)	.5077
	PSPT	42 (26.3%)	26 (15.7%)	1.9 (1.1, 3.3)	.0187
IgA	beta2 GPI	48 (30.0%)	24 (14.5%)	2.5 (1.5, 4.4)	.0007
	Anticardiolipin	10 (6.3%)	2 (1.2%)	5.5 (1.2, 25.4)	.0156
	beta2 GPI D4/5	35 (21.9%)	28 (16.9%)	1.4 (0.8, 2.4)	.2523
IgG/M	PSPT	38 (23.8%)	24 (14.5%)	1.8 (1.0, 3.2)	.0326

For venous thrombosis, the highest association was again with aCL IgA, followed by anti-beta2 GPI IgG, and then anti-PS/PT IgG and IgG/M (Table 2).

Table 2: Venous Thrombosis

	Assay	Thrombosis (n = 102) Number (% positive)	No thrombosis (n = 224) Number (% positive)	Odds Ratio 95% CI	P-value
IgG	beta2 GPI	15 (14.7%)	9 (4.0%)	4.1 (1.7, 9.8)	.0006
	beta2 GPI Domain 1	9 (8.8%)	11 (4.9%)	1.9 (0.8, 4.7)	.1722
	Anticardiolipin	17 (16.7%)	21 (9.4%)	1.9 (1.0, 3.8)	.0571
	PSPT	21 (21.0%)	19 (8.5%)	2.8 (1.4, 5.5)	.0020
IgM	beta2 GPI	6 (5.9%)	11 (4.9%)	1.2 (0.4, 3.4)	.7145
	Anticardiolipin	13 (12.8%)	20 (8.9%)	1.5 (0.7, 3.1)	.2895
	PSPT	27 (26.5%)	41 (18.3%)	1.6 (0.9, 2.8)	.0924
IgA	beta2 GPI	31 (30.4%)	41 (18.3%)	1.9 (1.1, 3.3)	.0147
	Anticardiolipin	8 (7.8%)	4 (1.8%)	4.7 (1.4, 15.9)	.0111
	beta2GPI D4/5	20 (19.6%)	43 (19.2%)	1.0 (0.6, 1.9)	.9305
IgG/M	PSPT	29 (28.4%)	33 (14.7%)	2.3 (1.3, 4.1)	.0035

For Stroke, the only assay with a significant association was antibeta2 GPI Domain 4/5 (32.7% vs. 17%, OR 2.4, p=0.01)

Conclusion: The importance of IgA isotypes (beta2GPI, aCL) in secondary antiphospholipid syndrome has not been previously recognized. We also found that IgA antibeta2 glycoprotein domain 4/5 was associated with stroke. Domain 1 IgG is not important in secondary APS. Anti-PS/PT, either IgG or IgG/M, is a promising alternative to coagulation assays to detect the lupus anticoagulant

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ACR Poster Session A
Cytokines, Mediators, Gene Regulation I
Monday, November 8, 2010, 9:00 AM–6:00 PM

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BAFF Expression Correlates with Idiopathic Inflammatory Myopathy Disease Activity Measures, Interferon Signature and Autoantibodies. Kelly T. McNallan[1], Hatice Bilgic[3], Cynthia S. Crowson[2], Steven R. Ytterberg[2], Shreyasee Amin[2], Peterson J. Erik[3], Emily C. Baechler[3] and Ann M. Reed[2]. [1]Mayo Clinic, Rochester, MN, [2]Mayo Clinic, [3]University of Minnesota

Background: We have previously reported increased mRNA levels of B cell survival cytokines, B cell activating factor (BAFF) and its splice isoform transcript ΔBAFF, in blood cells of patients with idiopathic inflammatory myopathies (IIM.) Elevated BAFF and BAFF receptor levels influence increased survival of autoreactive B cells. We therefore investigated the relation of disease activity, autoantibody profiles and interferon pathway activation in IIM to B cell survival cytokines [BAFF, ΔBAFF and a proliferation inducing ligand (APRIL)] and their receptor expressions [BAFF receptor (BAFFR), transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI) and B cell maturation antigen (BCMA)].

Methods: RNA was extracted from whole blood in 108 IIM subjects (74 adult and juvenile dermatomyositis, 25 polymyositis and 9 inclusion body myositis). Gene expression of BAFF, ΔBAFF, APRIL, BCMA, TACI, BAFFR and three type I interferon (IFN)-regulated genes were measured by quantitative real-time RT-PCR. The whole-blood IFN gene expression signature was defined by average expression levels of 3 IFN-regulated genes (G1P2, IFIT1 and IRF7). Autoantibodies including Jo-1, Scl-70, Ribosome P, Chromatin, Sm, RNP, SSA, SSB were measured on the Luminex platform. Disease activity was assessed using visual analog scale (VAS) ratings defined by the International Myositis Assessment and Clinical Research (IMACS) group. Associations of gene expression with IFN gene score, disease activity measures and autoantibodies were assessed by Spearman correlation analysis.

Results: We find a positive correlation of BAFF and ΔBAFF expression with disease activity measures, including the global VAS score, muscle VAS score and extraskeletal muscle VAS score. Elevated BAFF and ΔBAFF expression also correlate with increased IFN gene scores. Furthermore, we find IIM subjects with autoantibodies to SSA, SSB or any RNA-binding protein (SSA, SSB, RNP and Sm) have increased expression of BAFF and ΔBAFF. APRIL, BAFFR, TACI and BCMA expression did not correlate with disease activity measures, autoantibodies or IFN score.

	BAFF	ΔBAFF
Extraskeletal muscle VAS score	r=0.32, p=0.001	r=0.47, p<0.0001
Muscle VAS score	r=0.25, p=0.01	r=0.35, p<0.001
Global VAS score	r=0.34, p<0.001	r=0.52, p<0.0001
IFN score	r=0.28, p=0.02	r=0.31, p<0.009
Autoantibodies		
SSA	r=0.23, p=0.02	r=0.30, p=0.001
SSB	r=0.30, p=0.001	r=0.28, p=0.003
Any RNA binding protein	r=0.26, p=0.007	r=0.32, p<0.001

Conclusion: Our findings suggest that in IIM, elevated BAFF and/or ΔBAFF expression may be predictive of increased disease activity, increased type 1 interferon regulated gene expression and presence of antibodies to autoantigens SSA, SSB or any RNA-binding protein. Further work is needed on the potential role of BAFF and/or ΔBAFF expression serving as markers of disease activity or treatment response in IIM.

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Blockade of TLR2 Prevents Spontaneous and Induced Cytokine Release from Rheumatoid Arthritis Ex Vivo Synovial Explant Cultures. Sinead Nic An Ultaigh[1], Tajvur Saber[1], Jerome Dellacasagrande[2], Brian Keogh[2], William McCormack[2], Mary Reilly[2], Luke O' Neill[2], Peter McGuirk[2], Ursula Fearon[1] and Douglas J. Veale[1]. [1]Dublin Academic Medical Centre, Dublin, Ireland, [2]Opsona Therapeutics Ltd, Dublin, Ireland

Objective: Toll-like receptors are involved in activation of the immune system by triggering release of inflammatory cytokines that can contribute and/or perpetuate inflammation, and have been implicated in autoimmune diseases such as Rheumatoid Arthritis (RA). The aim of this study is to examine the effect of blocking Toll-like receptor 2 (TLR2) in RA synovial cells.

Methods: RA synovial tissue (ST) biopsies, obtained under direct visualization at arthroscopy, were established as synovial explant cultures ex vivo or snap frozen for immunohistology. Mononuclear cell cultures were isolated from peripheral blood (PB) and synovial fluid (SF) of RA patients. Cultures were incubated with the TLR1/2 ligand, Pam3CSK4 (200ng, 1 and 10μg/ml), an anti-TLR2 antibody (OPN 301, 1μg/ml) or an IgG (1μg/ml) matched control. The comparative effect of OPN301 and Humira on spontaneous release of proinflammatory cytokines from RA synovial explants was determined using quantitative cytokine MSD multiplex assays or ELISA. OPN301 penetration into RA synovial tissue explants cultures was assessed by immunohistology.

Results: Pam3CSK4 significantly upregulated IL-6 and IL-8 in RA PBMCs, RA SFMCs and RA synovial explant cultures ($p<0.05$). OPN301 significantly decreased Pam3CSK4-induced cytokine production of TNF-α, IL-1, IL-6, IFN-γ and IL-8 compared to IgG control in RA PBMCs and SFMCs cultures (all $p<0.05$). OPN301 penetration of RA synovial tissue cultures was demonstrated, with expression localized to the lining layer and perivascular regions. OPN301 significantly decreased spontaneous cytokine production of TNF-α, IL-1, IFN-γ and IL-8 from RA ST explant cultures (all $p<0.05$). Importantly, the inhibitory effect of OPN on spontaneous cytokine secretion was comparable to inhibition by anti-TNF mAb Humira.

Conclusion: Our findings further support targeting TLR2 as a potential therapeutic agent for the treatment of RA.

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CCL15/Leukotactin-1: A Novel Mediator of Rheumatoid Arthritis Fibroblast-Like Synoviocyte Migration Via CCR3 and MAP Kinases. Eric K. Owens[1], Karolina Klosowska[2], Michael V. Volin[2], Brian Zanotti[2] and James M. Woods[2]. [1]Midwestern University, Downers Grove, IL, [2]Midwestern University

Background: Rheumatoid arthritis (RA) fibroblast-like synoviocytes (FLS) play a key role in mediating inflammation and joint destruction. CCL15 has previously been shown to be expressed in RA synovial tissue and synovial fluids. CCL15 has been characterized to interact with its receptors, CCR1 and CCR3, where the former serves as a weak agonist and the latter serves more potent functions. We hypothesized that CCL15 induces RA FLS migration and proliferation, acting through CCR1 and/or CCR3, and signaling through mitogen-activated protein (MAP) kinases.

Methods: FLS were derived from hip or knee synovial membrane at the time of joint replacement due to RA with IRB approval, and were subsequently analyzed using Alexa Fluor 488 Phalloidin staining of F-actin, proliferation assays, chemotaxis assays, and flow cytometry. In addition, we used MAP kinase inhibitors in combination with chemotaxis assays to determine whether MAP kinase signaling was required for CCL15-induced RA FLS migration.

Results: Evaluation of F-actin staining subsequent to CCL15 stimulation demonstrates significant reorganization of the cytoskeletal structure. When stimulated with 1 or 10 nM CCL15, maximal cytoskeletal rearrangement occurs after 2 to 3 hrs, consistent with the slow migration associated with fibroblasts. Chemotaxis assays demonstrate that CCL15 is a novel chemoattractant for RA FLS, effectively inducing migration of all 4 RA patients that we tested ($p<0.05$). Concentrations of 1 to 50 nM CCL15 induced migration that was significantly higher than background, however, similar concentrations of CCL15 had no effect on RA FLS proliferation. Flow cytometry demonstrates that a significant number of RA FLS express CCR3 but not CCR1. On average, 73% of RA FLS express CCR3. Consistent with CCR3 being a G protein coupled receptor, pertussis toxin (PTX) completely abolishes CCL15-induced migration. Finally, pre-incubation of FLS with a MEK 1/2 inhibitor (U0126), the kinase which activates ERK 1/2, significantly decreased chemotaxis induced by CCL15 in RA FLS derived from 2 of 3 patients. Similarly, pre-incubation of cells with a JNK inhibitor (SP600125) likewise decreased CCL15-induced migration in FLS from 2 of 3 patients.

Conclusions: Our results suggest the novel finding that CCL15 regulates the migration and cytoskeletal structure of RA FLS. Migration is likely induced by a G protein (Gi/Go) coupled receptor, since this event is inhibited by PTX. To our knowledge, these are the first results to suggest that RA FLS express CCR3. Finally, migration of RA FLS from some patients can be significantly decreased by inhibiting the ERK and JNK pathways.

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Chronic Exposure to IL-6 Amplifies Macrophage Response to Toll-Like Receptor (TLR) Ligands. Raffaele Strippoli[1], Francesco Carvello[2], Loredana De Pasquale[2], Luisa Bracci-Laudiero[2] and Fabrizio de Benedetti[2]. [1]IRCCS Ospedale Pediatrico Bambino Gesu, Rome, Italy, [2]IRCCS Ospedale Pediatrico Bambino Gesu, Rome, Italy

Background: High levels of IL-6 are a characteristic feature of chronic inflammatory arthritis. Little is known on the effect of IL-6 on innate immune responses in particular regarding TLR activation mediated by both endogenous and exogenous TLR ligands, the latter being important in the relation between infections and exacerbations. In this study, we analyzed whether prolonged exposure of mouse and human macrophages to IL-6 affects inflammatory cytokine and chemokine production upon stimulation with TLR ligands and the activation of signalling pathways involved in this event.

Methods: Splenocytes and peritoneal macrophages were isolated from IL-6 transgenic or wild tipe (WT) mice. These cells were stimulated with different TLR ligands, such as LPS, LTA, poly I:C or CpG. Cytokine production was measured by ELISA on cell supernatants or by RT-PCR on total RNA from cell lysates. Activation status of STAT3, ERK MAPK, NF-kappaB vas measured by western blot from cell lysates or by confocal analysis on fixed cells. Human peripheral blood derived macrophages were treated for 4 days in presence of IL-6 plus IL-6 soluble Receptor (sIL-6R) and then stimulated with LPS. Cells were then analyzed as above.

Results: Treatment of splenocytes from IL-6 transgenic mice with different TLR ligands led to increased production of inflammatory cytokines, such as IL-1 beta, TNF alpha, IL-6, with respect to cells from WT mice. This was accompanied by increased phosphorylation of STAT3, ERK and by increased NF-kappaB nuclear translocation. Human macrophages treated with IL-6 plus sIL-6R and then stimulated with LPS showed also increased expression of cytokines, such as IL-1 beta, and chemokines such as IL-8 and a similar increased activation of stimulatory pathways. IL-6 transgenic mice treated with LPS showed increased lethality and higher levels of IL-1 beta, TNF-alpha and IL-6 than WT mice.

Conclusions: Our results show that prolonged exposure to IL-6 alters the response of macrophages to TLR ligands suggesting that signals from IL-6 and from TLR cooperate in the amplification of the inflammatory response. Our data also show the presence of a positive amplification loop between IL-1 beta and IL-6. These results suggest that IL-6 may contribute, on the one hand, to the amplification of chronic inflammation and, on the other, to abnormal responses to infectious agents that may trigger clinical relapses or an acute manifestation such as macrophage activation syndrome in the course of systemic JIA.

Disclosure: R. Strippoli: None; **F. Carvello:** None; **L. De Pasquale:** None; **L. Bracci-Laudiero:** None; **F. de Benedetti:** Hoffmann-La Roche, Inc., 5.

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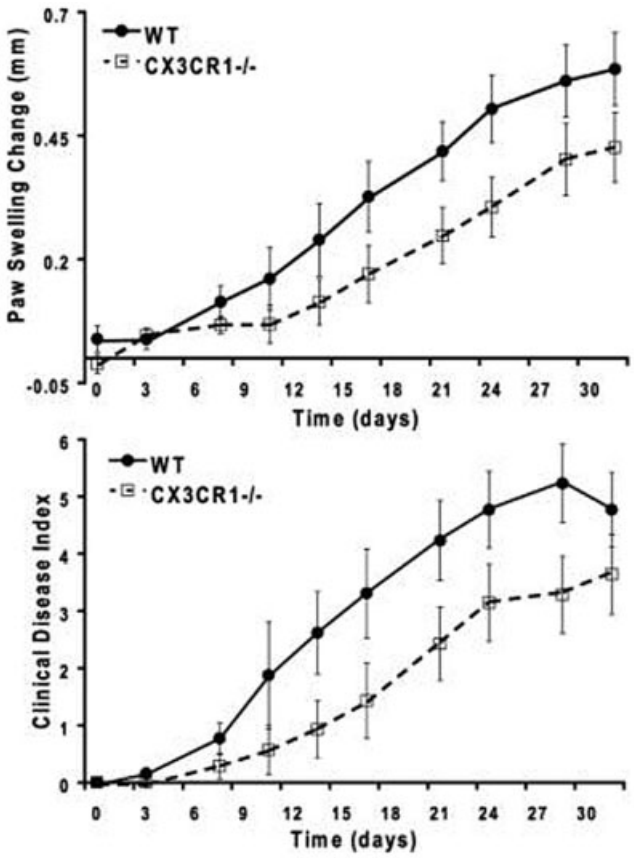
CX3CR1 Deficient Mice Have Decreased Th17 and Antigen-Specific Humoral Responses in the Collagen Induced Arthritis (CIA) Model. Teresa K. Tarrant[2], Peng Liu[3], Rishi Rampersad[3], Denise Esserman[3], Lisa Rothlein, Marcus W. McGinnis[3], David J. Fitzhugh[3], Dhavalkumar D. Patel[1] and Alan M. Fong[3]. [1]Novartis Pharma AG, Basel, Switzerland, [2]UNC School of Medicine, Chapel Hill, NC, [3]UNC School of Medicine

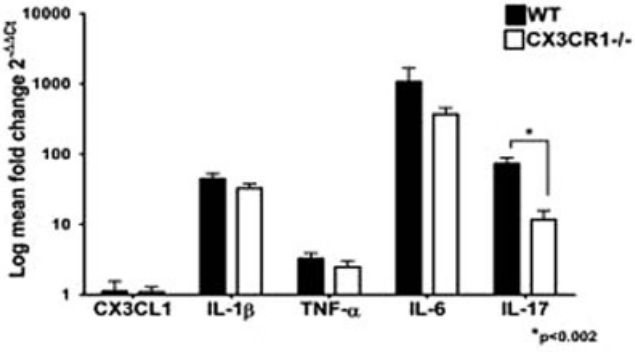
Objective: CX3CR1 is a chemokine receptor that uniquely binds to its ligand fracktalkine (FKN or CX3CL1) and has been shown to be important in inflammatory arthritis responses, largely due to effects on cellular migration. In this study, we tested the hypothesis that genetic deficiency of CX3CR1 would be protective in the chronic inflammatory arthritis model, collagen induced arthritis (CIA). Because CX3CR1 is expressed on T cells and antigen-presenting cells, we additionally examined adaptive immune functions in this model.

Methods: Autoantibody formation, clinical, histologic, T cell proliferative, and cytokine responses were evaluated in DBA-1J mice deficient in (−/−) or wildtype (+/+) for CX3CR1 after immunization with heterologous type II collagen.

Results: CX3CR1−/− mice had an approximately 30% reduction in arthritis by two independent measures of paw swelling ($p<0.01$) and clinical disease index($p<0.0001$).



CX3CR1−/− mice had an approximate 50% decrease in anti-type II collagen antibody formation ($p<0.05$). Additionally, CX3CR1−/− mice had a unique 5-fold decrease in intra-articular levels of IL-17 ($p<0.002$), as measured by RT-PCR, despite a preserved capacity to induce Th17 de novo responses *in vitro*.



Proinflammatory MMP-13 and cytokines IL-6, IL-1β, and TNF-α were reduced in CX3CR1−/− mice, but were not statistically significant.

Conclusions: Deficiency of CX3CR1 is protective in inflammatory arthritis and may have effects that extend beyond migration that involve adaptive immune responses.

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Cytokine Expression in Synovial Tissue of Psoriatic Arthritis and Its Relation to Lymphoid Neogenesis, Erosive Disease and Disease Activity: A Longitudinal Study. Raquel Celis[1], Julio Ramírez[1], Raimon Sanmarti[1], José L. Pablos[2] and Juan D. Cañete[1]. [1]Servicio Reumatología, Hospital Clinic and IDIBAPS, Barcelona, Spain, [2]Unidad de Investigación, Hospital 12 de Octubre, Madrid, Spain

Objective: To analyse the expression of a wide range of cytokines in synovial tissue (ST) of patients with psoriatic arthritis (PsA) and its relation with synovial lymphoid neogenesis (LN), erosive disease and EULAR response to therapy.

Methods: ST samples were obtained by needle arthroscopy from the inflamed knee joint of 30 patients fulfilling the CASPAR criteria for PsA. Five samples from each patient were paraffin-embedded and sections were immunostained with CD3 (T cell), CD20 (B-cell) and MECA-79 (high endothelial vessels).

Total RNA was extracted from ST samples from 30 patients and from 2 controls without synovial inflammation following the recommendations of the Rneasy FFPE Kit (Qiagen). mRNA was measured by TaqMan Gene Expression Assay (Applied Biosystem). Relative changes in gene expression were assessed by comparative analysis of quantitative PCR by the delta-delta Ct method using GAPDH as a endogenous control gene. The following genes were analysed: CCR7, Lymphotoxin (LT)-beta, IL-7, IL-10, IL-1beta, IL-6, TNF-alpha, IL-17 A, IL-21, IL-22 and IL-23. Data were collected at inclusion and at the end of follow-up.

Results: Clinical and demographic data of patients are in Table 1.

Table 1. Clinical and demographic data of PsA patients (n=30) at time of arthroscopy*

Age (years) at time of arthroscopy	47	(*37; 60*)
Disease duration before arthroscopy (months)	110	(*30; 170*)
Time of follow-up after arthroscopy (months)	35	(*22:45*)
Tender Joint Count	2	(*1; 2*)
Swollen Joint Count	2	(*1; 3*)
CRP (mg/dL)	1.77	(*0.30; 5.51*)
ESR (mm/1st hour)	18.5	(*8; 52*)
ACPA (UI/mlL) (n, positive > 25)	0	
Rheumatoid Factor (UI/ml) (n, positive >20)	2	
DAS28 3v	3.63	(*2.73; 4.59*)
Joint Pattern		
Polyarthritis; n (%)	11	*36.7*
Oligoarthritis, n (%)	19	*63.3*
Type of Psoriasis		
Type I (<40 years), n (%)	22	*70.3*
Type II (>40 years), n (%)	8	*29.7*

* Data are expressed as median and IQR. CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ACPA: anti-citrullinated peptide/protein antibodies; DAS: disease activity score.

LN. Twelve out of 30 patients (40%) had LN. These patients had significantly higher expression of CCR7 and LT-beta than patients without LN ($p<0.005$ and $p<0.04$, respectively). LN positive patients had a trend to higher IL-23 ($p=0.051$) and TNF-alfa ($p=0.075$) expression than patients LN negative. There was no association between LN and clinical or biological variables.

Erosive disease. Fifteen out of 30 (50%) of patients had erosive disease at end of follow-up. Disease duration, DAS28, PCR and SJC at inclusion were all correlated with erosive disease ($p<0.05$).

Disease activity. There was a positive correlation between IL-6 expression and SJC, CRP and DAS28 at inclusion ($p=0.02$, $p=0.001$ and $p=0.034$, respectively) and between IL-1b expression and CRP levels at inclusion ($p=0.015$). We found also a strong negative correlation between IL-10 expression at inclusion and ESR levels ($p=0.008$).

Conclusion: PsA patients with LN have a different profile of cytokine expression in ST compared with patients without LN, with significantly higher expression of CCR7, LT-beta, which are implicated in the follicular organization, and higher expression of IL-23, a relevant cytokine in joint inflammation and damage. Also IL-6 and IL-1 are positively and IL-10 negatively correlated with markers of inflammation and/or disease activity.

Disclosure: R. Celis: None; **J. Ramírez:** None; **R. Sanmarti:** None; **J. L. Pablos:** None; **J. D. Cañete:** None.

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DNA Hypomethylation Upregulates CXCL12 in Rheumatoid Arthritis Synovial Fibroblasts. Emmanuel Karouzakis[1], Yvonne Rengel[1], Astrid Jüngel[1], Christoph Kolling[3], Renate E. Gay[1], Beat A. Michel[1], Paul P. Tak[2], Steffen Gay[1], Michel Neidhart[1] and Caroline Ospelt[1]. [1]Center of Experimental Rheumatology and Zurich Center of Integrative Human Physiology (ZIHP), University Hospital Zurich, [2]Department of Clinical Immunology and Rheumatology, University of Amsterdam, [3]Schulthess Clinic, Zürich

Objective: Previously we described global genomic hypomethylation in rheumatoid arthritis synovial fibroblasts (RASF). Now, we searched for specific genes that are induced by DNA hypomethylation in RA. Since CXCL12 was reported to be upregulated in RA, we investigated its expression in SF as well as the DNA methylation status of its promoter and determined the contribution of this chemokine to the expression of matrix metalloproteinases (MMPs).

Methods: DNA was isolated from SF and methylation was analysed by bisulphite sequencing. CXCL12 protein was quantified by ELISA before and after treatment with the DNA hypomethylator 5-azacytidine. RASF were stimulated with CXCL12 recombinant protein (100 ng/ml). Expression of MMPs was analysed by Real-time PCR.

Results: Basal expression of CXCL12 was higher in RASF (85±12 pg/ml, n=9, $p<0.05$) than osteoarthritis (OA) SF (52±10 pg/ml, n=7). In normal SF (n=1), the promoter region −477 to −741 had a CpG methylation percentage of 52%. In OASF treated with different concentrations of 5-azacytidine (0, 0.5 and 1 μM), the percentage of CpG methylation in the 1μM 5-azaC treated cells was reduced (0 μM: 45.2±11.2% and 1 μM: 15.0±3.3% percentage of CpG methylation of 6 clones). CXCL12 protein expression was dose dependently upregulated (0 μM: 29.3±5.3 pg/ml, 0.5 μM: 41.6±4.9 pg/ml, 1 μM: 53.0±6.1, n=4, $p<0.05$). A lower percentage of CpG methylation was found in the CXCL12 promoter of RASF (21.0±7.2%, percentage of methylation of 9 clones per pool of 4 patients) compared to OASF (42.0±7.8%, percentage of CpG methylation of 9 clones per pool of 3 patients, $p<0.05$). Stimulation of RASF (n=6) with CXCL12 significantly increased the expression of MMP-1 (6±3 fold), MMP-3 (2±0.2 fold) and MMP-13 (4±1 fold) ($p<0.05$).

Conclusion: We show here that RASF produce more CXCL12 than OASF due to promoter hypomethylation and that stimulation with CXCL12

induces the expression of MMPs in SF. Thereby we describe an endogenously activated pathway in RASF which promotes joint destruction.

Disclosure: E. Karouzakis: None; **Y. Rengel:** None; **A. Jüngel:** None; **C. Kolling:** None; **R. E. Gay:** None; **B. A. Michel:** None; **P. P. Tak:** None; **S. Gay:** None; **M. Neidhart:** None; **C. Ospelt:** None.

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Downregulation of the Chemokine Receptor CX3CR1 in Active RA Associated with a Pro-Osteoclastognic Phenotype. Grainne Murphy[1], John Ryan[1], Harney Sinead[1], Fergus Shanahan[1], Michael Molloy[1] and Noel Caplice[2]. [1]Cork University Hospital, Cork, Ireland, [2]University College Cork, Cork, Ireland

Monocytes are the primary source of inflammatory cytokines in RA. They can be further defined by their surface expression of CD14 and CD16.CD16+cells are more inflammatory in nature and possess discordantly high surface CX3CR1, the receptor for the chemokine fractalkine (FKN). The interaction of FKN with CX3CR1 contributes to the chemotaxis and transmigration of the CD16+ monocytes and subsequent cytokine release. The FKN-CX3CR1 interaction has been implicated in the pathological T cell response in RA, however little is known about this relationship in monocytes, despite CX3CR1s ubiquitous expression.

Objective: To characterize the expression of CX3CR1 on monocyte sub-populations in early and established RA. To assess the functional consequences of FKN interactions with CX3CR1 in relation to osteoclastogenesis and cytokine release.

Methods: We recruited 83 subjects with early (21), established active (46) or inactive RA (16) and 13 healthy controls as a comparator group. Monocyte subsets (CD14+CD16- and CD14+CD16-) were defined by flow cytometry and CX3CR1 surface expression was determined by its Relative Fluorescent Intensity(RFI). Soluble FKN(sFKN) was quantified in peripheral blood (PB) and synovial fluid (SF) by ELISA. The effect of membrane-bound FKN (mbFKN) on osteoclast differentiation of monocyte subsets was assessed in vitro. Serum from subjects with the combination of elevated CD16+ monocytes and increased sFKN were analysed using a multiplex cytokine array and compared with controls.

Results: The CD16+ monocyte subset was expanded in the active RA groups [early, mean (+/−SEM) 24.22% (3.9) and active RA, 21.99% (2.61] in comparison with inactive disease 12.9% (2.2), $p=0.04$, and healthy controls 11.1% (0.89), $p=0.03$. Furthermore, individuals with elevated CD16+ monocytes and increased sFKN had significantly more circulating Il1a,-1b,-2,-10 and TNFα than controls.

CX3CR1 surface expression was down-regulated on CD16+ monocytes in established RA but not in early arthritis, $p=0.004$. Downregulation of CX3CR1 on the osteoclast progenitor CD16- sub-population was restricted to active RA, $p<0.005$. Similarly in active RA there was a significant increase in serum and SF sFKN, $p=0.02$. CX3CR1 down-regulation was replicated in vitro by co-incubation with sFKN. MbFKN significantly enhanced the osteoclastogenesis of the CD16-monocyte subset ($p<0.0001$) potentially mediated by a decrease in CX3CR1 surface expression.

Conclusion: These findings support the presence of a unique monocyte phenotype in established RA. The downregulation of CX3CR1 on osteoclast precursors is mediated by the inteaction with FKN. In addition the pro-osteoclastogenic effect of mbFKN strongly supports that this chemokine partnership is critical to the erosive process in RA.

Disclosure: G. Murphy: IRCSET, 2; **J. Ryan:** None; **H. Sinead:** None; **F. Shanahan:** None; **M. Molloy:** None; **N. Caplice:** None.

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Downstream Targets of IL-17 in Rheumatoid Arthritis. Sarah R. Pickens[4], Richard M. Pope[3], Michael V. Volin[1] and Shiva Shahrara[2]. [1]Midwestern University, [2]Northwestern Univ Feinberg, Chicago, IL, [3]Northwestern Univ Med School, Chicago, IL, [4]Northwestern University

Introduction: IL-17 plays an important role in the pathogenesis of rheumatoid arthritis (RA) since anti-IL-17 therapy ameliorates the clinical symptoms of RA. However, the downstream targets of IL-17 are undefined in RA.

Purpose: Studies were performed to identify the downstream targets of IL-17 in human microvascular endothelial cells (HMVECs), macrophages and RA synovial tissue (ST) fibroblasts, and subsequently the expression of the identified factors were confirmed in RA ST explants.

Methods: HMVECs, peripheral blood in vitro differentiated macrophages and RA ST fibroblasts were treated with IL-17 for 0–8h. Real-time RT-PCR was used to identify IL-17-induced downstream molecules in these cell types. Next, expression of IL-17-induced factors was verified by real-time RT-PCR in RA ST explants that were activated with IL-17.

Results: Genes differentially regulated by IL-17 in HMVECs were neutrophil chemokines such as CXCL1, CXCL2, CXCL3, CXCL12 and monocyte chemokines including CCL7, CCL20 and CXCL16 and adhesion molecule VCAM1. Similarly, IL-17 was able to modulate neutrophil (CXCL1, CXCL3 and CXCL5) and monocyte (CXCL16, CCL20 and CCL2) chemokines in peripheral blood in vitro differentiated macrophages. In RA ST fibroblasts, in addition to neurophil (CXCL1, CXCL2, CXCL3 and CXCL5) and monocyte (CCL2, CCL7 and CCL20) chemokines, IL-17 greatly upregulated expression of proangiogenic factors such as VEGF and FGF. Further, to determine which of these factors may play an important role in the pathogenesis of RA, IL-17-activated RA ST explants were screened for the identified molecules. Factors that were induced by IL-17 in two or more cell types were highly upregulated in RA ST explants compared to those expressed in only one cell type. Among the factors that were greatly induced by IL-17 in RA ST explants were CXCL1 (150 fold increase), CXCL3 (10 fold increase), CXCL5 (360 fold increase), CCL2 (20 fold increase), CCL7 (14 fold increase) and CCL20 (30 fold increase). Since neutrophil and monocyte chemokines are strongly induced by IL-17 in the RA synovium, cell trafficking may be an important mechanism by which IL-17 contributes to inflammation.

Conclusion: These results suggest that IL-17 may play an important role in acute and chronic inflammation seen in patients with RA in part through promoting neutrophil and monocyte migration. Therefore, the decrease in clinical symptoms seen with anti-IL-17 treatment of RA may be in part due to this decrease in leukocyte migration.

Disclosure: S. R. Pickens: None; **R. M. Pope:** None; **M. V. Volin:** None; **S. Shahrara:** None.

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Elevated BLyS Levels Are Associated with an Increase in Autoantibody Specificites and ANA Titer in Systemic Lupus Erythematosus. Lauren L. Ritterhouse[3], Amanda R. Moyer[3], Virginia C. Roberts[2], Amy B. Dedeke[2], Sherry R. Crowe[3], Gillian M. Air[4], Linda F. Thompson[3], Joel M. Guthridge[3] and Judith A. James[1]. [1]Oklahoma Med Research Foundation, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Oklahoma Medical Research Foundation, [4]University of Oklahoma Health Sciences Center

B Lymphocyte Stimulator (BLyS) is a cytokine that belongs to the TNF ligand family, and has been shown to play an important role in the proliferation and differentiation of B cells. Elevated serum levels of BLyS have been demonstrated in autoimmune disease patients, including those with SLE. BLyS is hypothesized to contribute to SLE pathogenesis by affecting survival signals and apoptosis of autoantibody-producing B cells. In this study we seek to investigate the relationship between serum BLyS levels and humoral autoimmunity, as well as the effect of serum BLyS on an antigen-specific humoral immune response.

This study enrolled 61 female SLE patients who met ACR criteria. BLyS levels were measured by a quantitative sandwich enzyme immunoassay. Lupus-associated autoantibodies (Ro, La, Sm, nRNP, ribosomal P, dsDNA, ANAs and phospholipid antibodies) and influenza vaccination humoral immune response parameters including Bmax (relative amounts of anti-influenza antibodies against native antigen), Ka (relative affinity), and hemagglutination inhibition (relative protective antibody response) were measured. SLE patients were given a cumulative index score based on these three vaccination response parameters and classified as being either a “high responder” (greater than the median cumulative index score) or a “low responder” (less than the median cumulative index score).

African Americans (AA, $n=24$) had significantly ($p=0.021$, unpaired t-test) higher serum BLyS levels than did European Americans (EA, $n=35$) (1649 ± 224 pg/mL in AA versus 1045 ± 144 pg/mL in EA). No differences were seen in BLyS levels between high responders to influenza vaccination ($n=31$) and low responders ($n=30$) ($p=0.72$, unpaired t-test). SLE patients with greater than or equal to 2 autoantibody specificities had higher BLyS levels than those patients with less than 2 specificities ($p=0.035$, unpaired t-test with Welch’s correction). Additionally, BLyS levels were increased in patients with an ANA titer of greater than 1:120 ($p=0.0012$, unpaired t-test with Welch’s correction). ACR classification criteria and disease activity measures were assessed in relation to serum BLyS levels. Increased serum

BLyS correlated with an increase in disease damage as measured by SLICC (r2=0.12, p=0.006), and an increase in disease activity as measured by PGA (r2=0.10, p=0.013), and SLAM (r2=0.07, p=0.046). Patients with the criteria discoid rash, proteinuria, and lymphopenia had higher serum BLyS levels than did those patients without these criteria (p=0.029, p=0.011, and p=0.008, respectively, unpaired t-test).

Increased serum BLyS levels were observed in African Americans, but were not associated with the ability to make a humoral response to influenza vaccination. Elevated BLyS levels were also associated with an increase in number of autoantibody specificities, as well as an increase in ANA titer. Additionally, increased disease activity measures correlated with increased serum BLyS levels. This evidence strongly supports the role for BLyS in humoral autoimmunity and SLE disease pathogenesis.

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Elevated Levels of CXCL9 or CXCL10 in Sera of Patients with Early RA Predict Greater Difficulty in Achieving Remission during the First Year of Treatment. Gregory R. Emkey[5], Klemen Strle[6], Christopher R. Antolini[3], Deborah S. Collier[5], Margaret Seton[5], Arezou Khosroshahi[5], Mark Fisher[2], Nancy D. Kim[4], John H. Stone[1], Andrew D. Luster[4] and Allen C. Steere[5]. [1]Massachusetts General Hospital, Sudbury, MA, [2]Massachusetts General Hospital, Haddon Heights, NJ, [3]Massachusetts General Hospital, Denver, CO, [4]Massachusetts General Hospital, Charlestown, MA, [5]Massachusetts General Hospital, Boston, MA, [6]Massachusetts General Hospital

Purpose: The inflammatory immune response in patients with early rheumatoid arthritis (RA) is not well characterized. Depending on the series, dominant Th1-, Th2-, or Th17-type immune responses have been reported. We hypothesized that cytokine and chemokine levels, which act as indicators of these types of responses, may serve as biomarkers to help stratify subgroups of RA patients and predict their disease course. Here we report a preliminary analysis of a prospective study evaluating immune responses in early RA patients.

Methods: Patients who met EULAR criteria for RA, had symptoms for <12 months, and had not yet received DMARD therapy, were entered into the study and followed at 3, 6, and 12 months. They were treated with DMARDs, primarily methotrexate; and with a TNF inhibitor if the response was incomplete. At each visit, clinical parameters were determined (HAQ and DAS28 [CRP]), and serum samples and synovial fluid, if available, were collected. The levels of 20 cytokines and chemokines were determined in all samples at the same time using bead-based Multiplex assays. Elevated levels of each factor were defined as >2SD above the mean value of 40 control subjects.

Results: To date, 35 patients have been enrolled in the study; 30 patients have completed 3 months follow-up, and 12 have completed 12 months follow up. Of the 20 cytokines and chemokines measured, elevated levels of CXCL9 or CXCL10 (IFN-inducible chemoattractants for Th1 effector cells) or IL-23 (a marker for Th17 responses) were most common. In the initial visit, prior to DMARD therapy, 17 patients (49%) had elevated levels of CXCL9 or CXCL10, 17 (49%) had elevated IL-23 levels, and 26 (74%) had one or both of these responses. At study entry, patients who had elevated levels of CXCL9 or 10 had similar DAS28 scores (median, 5.2) as patients who did not have elevated levels of these chemokines (4.8). However, at the 3 month follow-up, patients with elevated levels of CXCL9 or 10 had a median DAS28 score of 3.1 compared with 2.2 in patients without elevated levels (P=0.03), and by 12 months, the 2 groups had diverged more (3.1 versus 1.25, P=0.004). Similar differences between the 2 groups were observed with HAQ scores. All 5 patients in whom it was possible to obtain joint fluid had elevated levels of both CXCL9 and 10 in serum and at least 10-fold higher levels of both chemokines in joint fluid. Elevated serum levels of IL-23 alone, without CXCL9 or 10, were not a risk factor for more severe disease.

Conclusions: Patients with early RA who had elevated serum levels of CXCL9 or CXCL10 prior to DMARD therapy had greater difficulty in achieving remission during the first year of treatment. This predictive information was not apparent from standard biomarkers of disease activity. Measurement of these chemokines at disease onset may help in the management of patients with early RA.

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Elevated Serum CX3CL1 Levels in Adult-Onset Still's Disease: Potential Involvement in Hemophagocytic Syndrome. Tsuyoshi Kasama[1], Kumiko Ohtsuka[2], Michihito Sato[2], Ryo Takahashi[2], Kuninobu Wakabayashi[2] and Takeo Isozaki[2]. [1]Showa University School of Med, Shinagawa-ku Tokyo, Japan, [2]Showa University School of Med

Objective: Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disease of unknown etiology characterized by chronic and fluctuant fever with accompanying rash, polyarthritis and involvement of multiple organs, especially lymphoid tissues. To investigate the prevalence of AOSD and its clinical characteristics, serum chemokines levels and the associated systemic manifestations, especially hemophagocytic syndrome (HPS), were assessed in patients complicated with AOSD.

Methods: Seventeen patients diagnosed with AOSD and 20 healthy controls were enrolled after obtaining informed consent, and clinical and laboratory findings were analyzed. Serial serum samples were collected from patients with active and inactive AOSD and from the controls, after which levels of the chemokines including CXCL8, CXCL10, CCL2 and CX3CL1, and soluble IL-2 receptor (sIL-2R) were determined by ELISA. Multivariate analysis was used to evaluate the correlation between serum chemokine levels and disease activity and the clinical features of AOSD.

Results: Serum CXCL8, CXCL10, CCL2 and CX3CL1 levels were significantly higher in patients with active untreated AOSD than in healthy controls. The elevated CX3CL1 levels seen in AOSD patients correlated positively with either CRP, sIL-2R or ferritin levels. While, there were no significant correlations between serum levels of the other chemokines and either CRP or ferritin. Among the 17 AOSD patients, 4 were complicated with HPS, and serum levels of both CX3CL1, sIL-2R and ferritin were significantly higher in AOSD patients with HPS than in those without HPS. Notably, serum CX3CL1 levels were significantly diminished following successful treatment and clinical improvement.

Conclusion: The serum CX3CL1 level may be a useful clinical marker of disease activity in AOSD. We suggest that especially high levels of CX3CL1 as well as either ferritin or sIL-2R reflect the presence of HPS, and that the association between chemokine profiles and distinct clinical manifestations reflects the heterogeneity of the pathogenesis of AOSD.

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Gallic Acid Diminishes Cellular Proliferation and Pro-Inflammatory Gene Expressions in Fibroblast Like Synoviocytes from Patients with Rheumatoid Arthritis. Soo-Jin Chung[1], Tae-Yeon Kim[2], Yong-Jin Kwon[2], Yong-Beom Park[2], Soo-Kon Lee[2] and Min-Chan Park[3]. [1]Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea, [2]Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea, [3]Division of Rheumatology, Yonsei University College of Medicine, Seoul, Korea, Republic of

Purpose: Gallic acid is the naturally occurring substance which is found in gallnuts, grapes, tea leaves, and oak bark. Gallic acid has been known as an antioxidant and to exhibit anti-tumor activity through regulation of tumor cell differentiation and induction of apoptosis by suppression of NF-κB. NF-κB regulates the expression of several genes involved in inflammation, thus these anti-inflammatory properties of gallic acid can be used for treatment of immune-mediated diseases. A previous study showed that gallic acid treatment inhibited the production of inflammatory mediators in oral epithelial cells, indicating a certain role of gallic acid in immune response. This study was performed to investigate the efficacy of gallic acid in regulating cellular proliferation and pro-inflammatory gene expressions in fibroblast like synoviocyte (FLS) from patients with rheumatoid arthritis (RA).

Method: Synovial tissues were obtained from patients with RA during total knee replacement surgery. RA FLS were subsequently isolated and cultured. RA FLS were treated with various concentrations of gallic acid (1 μM, 10 μM, and 100 μM) with or without TNF-α (10 ng/mL) stimulation. The mRNA expression of pro-inflammatory cytokines (IL-1β, IL-6), chemokines (CCL-2, CCL-7), cyclo-oxygenase2 (COX-2), and matrix metalloproteinase-9 (MMP-9) were determined using quantitative real-time PCR. The proliferation of RA FLS in response to gallic acid treatment was measured by the MTT assay.

Results: Gallic acid treatment induced dose-dependent reduction in constitutional mRNA expression of IL-6 in RA FLS. Constitutional mRNA expressions of CCL-2, CCL-7, IL-1β, COX-2, and MMP-9 were increased by treatment with lowest dose (1 μM) of gallic acid, but these expressions were decreased as the doses of gallic acid were escalated. After stimulating with TNF-α, gallic acid treatment inhibited the mRNA expression of all pro-inflammatory genes tested in dose- and time-dependent manner in RA FLS. Gallic acid treatment also suppressed the cellular proliferation of RA FLS (10% by 1 μM, 18% by 10 μM, 39% by 100 μM, at 72 hr).

Conclusion: In this study, we found that gallic acid treatment suppressed cellular proliferation and mRNA expressions of pro-inflammatory mediators in RA FLS. These findings suggest that gallic acid may play a role in regulation inflammation and synovial hyperplasia in RA patient and can be considered as a potential candidate for RA treatment.

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28 WITHDRAWN

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Interleukine 34 Is Expressed in the Synovial Tissue from OA and RA Patients. Celine Cozic[1], Benoit Le Goff[1], Anne Riet[1], Marie-Francoise Heymann[1], Celine Charrier[1], Regis Brion[1], Sophie Touchais[3], Marguerite Chemel[4], Dominique Heymann[1] and Jean-Marie Berthelot[2]. [1]INSERM UMR S 957, [2]INSERM UMR S 957 and Rheumatology Unit, CHU Nantes, Nantes, France, [3]Orthopedic Surgery Unit, CHU Nantes, [4]Rheumatology Unit, CHU Nantes

Background: Interleukin 34 (IL-34) is a recently discovered cytokine involved in monocyte differentiation and survival. This cytokine can bind to M-CSF receptor and induce colony-forming-unit macrophages (CFU-M) formation from human bone marrow cells. Interestingly, IL-34 also promotes osteoclastogenesis and can be substituted for M-CSF in RANKL induced osteoclastogenesis. It is expressed in spleen, skin, brain, and other tissues. The aim of this study was to assess the expression of IL-34 in the synovial tissue of rheumatoid arthritis (RA) and osteoarthritis (OA) patients by immunohistochemistry.

Methods: Synovial biopsy specimens were obtained surgically at the time of an arthroplasty in 17 RA patients, 4 patients with other inflammatory athritis and 3 patients with OA. The mean duration of the RA was 11+/−5 years, with 15 patients treated with Methotrexate and 3 with anti-TNF alpha therapy. All the samples were embedded in paraffin and immunohistochemistry for IL34 expression was performed using an automated staining system. The histopathological severity of synovitis was graded using the synovitis score described by Krenn et al, which quantitatively evaluates on a scale from 0 to 3 the hyperplasia of the synovial lining layer, activation of synovial stroma, and inflammatory infiltrates, giving a total score ranging from 0 to 9. Clinical and biological characteristics of the patients were also recorded. Statistical analysis was performed using a Mann-Whitney non parametric test. $P<0.05$ was considered as statistically significant.

Results: Overall, 27 biopsies were available for the histological analysis. The mean synovitis score was 4.7+/− 1.9 (range 2–8). The mean score of synovial hyperplasia, stroma activation and inflammatory infiltrates was 1.42+/−1.2, 1.58+/−0.6 and 1.7+/−0.5 respectively. According to the grading system, of all the biopsies, 9 had slight synovitis, 8 had moderate synovitis, and 7 had strong synovitis. IL-34 was detected in 24 of the 27 biopsies with 3 samples from RA patients being negative. In the synovial tissue, IL-34 was expressed by the synovial fibroblasts (SFs), endothelial cells and the smooth muscular cells. A significant correlation was found between IL-34 expression by the SFs and the proliferation and infiltration of the synovial lining layer: the mean score of synovial hyperplasia was 2.15+/−0.8 and 0.54+/−0.3 in the biopsies with and without IL34 positive SFs respectively ($p=0.0013$). We found also an association between IL34 expression and the histological severity of the synovitis with a mean score of 5.5+/−1.9 and 3.7+/−1.5 in the IL34 SFs positive and negative biopsies respectively ($p=0.026$). No significant association was found between IL34 expression and any of the clinical or biological parameters.

Conclusion: IL-34 is expressed in the synovial tissue from RA and OA patients. Interestingly, we found a significant correlation between IL-34 expression by the synovial fibroblasts and the histological severity score of the synovitis. Considering the importance of IL-34 in monocyte maturation and osteoclastogenesis, the role of this cytokine in the pathogenesis of OA and RA should be further explored.

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Oncostatin M, Acting through Oncostatin M Receptor, Is a Potent Regulator of IL-6 and RANKL Expression in Mouse Synovial Fibroblasts. Benoit Le Goff[3], Narelle M. McGregor[1], T. John Martin[2], Evange Romas[1], Natalie A. Sims[1] and Nicole C. Walsh[1]. [1]St Vincent's Institute, Fitzroy, VIC, Australia, [2]St Vincent's Institute, Fitzroy, Australia, [3]St Vincent's Institute and INSERM, UMR-S 957, Fitzroy, VIC, Australia

Background: In rheumatoid arthritis, synovial fibroblasts (SF) mediate many effects of inflammatory cytokines that contribute to focal bone loss within the arthritic joint. The IL-6 family cytokine oncostatin M (OSM) is produced at high levels by macrophages and T cells in RA synovial fluid and synovial tissues, and is known to induce osteoclast formation via its action on osteoblasts. OSM acts by binding to the signal transducer gp130 and recruiting its ligand specific receptor α-chain, OSM Receptor (OSMR) or the leukemia inhibitory factor receptor (LIFR). It is not known which receptor complex mediates OSM effects on gene expression in SFs. In this study we sought to identify the effects of murine (m) OSM signalling via OSMR on SF expression of modulators of inflammation and osteoclast function, in comparison with the prototypical inflammatory cytokine, TNF.

Methods: Immunohistochemical staining (IHC) for OSMR was performed in tissues from mice induced with mono-articular antigen induced arthritis (AIA). Synovial fibroblasts (SFs) were isolated from hind paws of mice deficient in OSMR (OSMR KO) and strain-matched wildtype control mice (WT). Isolated SFs were passaged at least 4 times prior to stimulation with mOSM (2 ng/mL and 50 ng/mL) or TNF (7.5 ng/mL, maximal, non-apoptotic dose). Cells were harvested at 1, 6 and 24 hours following stimulation, and RNA was isolated for subsequent quantitative RT-PCR analyses.

Results: OSMR protein expression detected by IHC staining was observed in SFs within normal knee joints and its expression was increased with the induction and progression of AIA, indicating a possible role in mediating AIA. OSMR mRNA expression was observed in WT SFs but as expected, was absent in OSMR KO SFs. mOSM treatment increased OSMR mRNA levels in WT SFs at 6 and 24 hrs. In contrast, gp130 and LIFR mRNA levels were similar in OSMR KO and WT SFs and were not modified by mOSM treatment. TNF did not modify OSMR, gp130 or LIFR mRNA expression but did increase LIF mRNA expression at 1, 6 and 24 hrs in both OSMR KO and WT SFs. mOSM treatment increased IL-6 mRNA expression 50–100 fold in WT SFs at 1, 6 and 24 hrs. This effect was absent in OSMR KO SFs. In contrast, TNF transiently induced IL-6 expression by both WT and OSMR KO SFs at 1 and 6 hrs (10–15 fold), with no effect at 24hrs. In WT SFs, mOSM significantly increased expression of the osteoclast differentiation factor RANKL at 1, 6 and 24hrs, with only a maximum of 2 fold increase in expression of the RANKL inhibitor, OPG. This effect was not observed in SFs derived from OSMR KO mice. In contrast, TNF treatment resulted in increased RANKL mRNA expression at 1 and 6 hrs with expression returning to baseline by 24 hrs in both OSMR KO and WT SFs.

Conclusion: Our results demonstrate that OSM acts on SFs, through the OSMR, to stimulate sustained IL-6 and RANKL expression in SFs. Induction of OSMR mRNA expression in SFs by OSM suggests that this may contribute to the sustained effect on RANKL and IL-6 expression. Increased expression of OSMR protein in SFs in arthritic tissues and OSM's dependence on OSMR for its effects on IL-6 and RANKL expression identifies OSMR as a potential therapeutic target in the treatment of RA, which could reduce both inflammation and bone erosion.

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Oral Bisphosphonates and Risk of Atypical Femur Fractures in a Population-Based Cohort: A Propensity Score-Matched Analysis. Seo Young Kim[2], Sebastian Schneeweiss[3], Jeffrey N. Katz[1], Raisa Levin[4] and Daniel H. Solomon[2]. [1]Brigham and Women's Hosp, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA, [3]Brigham and Women's Hospital, Boston, [4]Brigham and Women's Hospital

Background: Bisphosphonates are the primary therapy for postmenopausal and glucocorticoid-induced osteoporosis. While case series suggest a potential link between prolonged use of bisphosphonates and low-energy atypical fracture of the femur, a recent study based on three randomized clinical trials found no significant risk of atypical femur fracture in patients taking bisphosphonates. We assessed this potential association using a large population-based observational cohort.

Methods: Using health care utilization data, we conducted a cohort study to examine the risk of atypical (subtrochanteric or diaphyseal) femur fractures in new users of oral bisphosphonates compared with those of raloxifene or calcitonin nasal spray. Oral bisphosphonates included in the study were alendronate, risedronate, and etidronate. Subjects were followed until they experienced either subtrochanteric or diaphyseal femur fracture based on the primary hospital discharge diagnosis code. The incidence rates (IRs) and hazard ratios (HRs) of atypical femur fractures with the 95% confidence interval (CI) were calculated in the propensity score-matched cohorts. A Cox proportional hazards model evaluated the risk of atypical femur fractures associated with duration of osteoporosis treatment.

Results: Among 33,815 patients (17,028 in the bisphosphonates and 16,787 in the raloxifene/calcitonin group), a total of 104 atypical femur fractures occurred during a mean 2.13-year follow-up. The estimated IR of atypical femur fractures was 1.46 per 1,000 person-years among the bisphosphonate users and 1.43 per 1,000 person-years among the raloxifene/calcitonin users. Overall, no significant association between bisphosphonate use and atypical femur fractures was found (HR 1.03, 95% CI 0.70–1.52), compared with raloxifene/calcitonin. We had little precision in the subgroup analysis estimating the risk of atypical femur fractures in patients treated with bisphosphonates for longer than four years (HR 1.46, 95% CI 0.59–3.62, Figure 1).

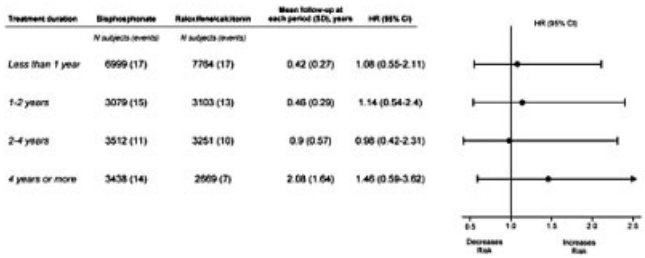

Figure 1. Hazard ratios for atypical (subtrochanteric or diaphyseal) femur fractures, according to osteoporosis treatment duration.

Conclusions: The occurrence of atypical femur fracture was rare. No evidence of an increased risk of atypical femur fractures was found in bisphosphonate users, compared to raloxifene/calcitonin users. We, however, cannot fully rule out an increased risk for these fractures associated with long-term bisphosphonate use even with this large-scale cohort.

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Selective Involvement of ERK and JNK MAP Kinases in the Synovial Tissue of Patients with Early Arthritis. Daphne de Launay, Marleen van de Sande, Gijs van de Sande, Carla Wijbrandts, Danielle Gerlag, Paul Peter Tak and Kris Reedquist. Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Little is known about mitogen-activated protein kinase (MAPK) contribution to disease in rheumatoid arthritis (RA), although inhibitors targeting one of these enzymes, p38, have already entered the clinic. Here we investigated synovial MAPK activation status in disease-modifying antirheumatic drug (DMARD) -naïve early arthritis patients.

Methods: 50 DMARD -naïve early arthritis patients (disease duration $<$ one year) were prospectively followed and diagnosed at baseline and after 2 years according to criteria for undifferentiated arthritis (UA), rheumatoid arthritis (RA), or spondyloarthritis (SpA). Synovial biopsies from actively inflamed joints were obtained at baseline by needle arthroscopy and examined by immunohistochemistry for expression and phosphorylation of p38, ERK 1/2 and JNK MAPKs, using computer-assisted image analysis. Results were compared between patients with different diagnoses and disease outcomes.

Results: Activation of ERK was enhanced at inclusion in patients meeting RA criteria after two years (n = 27) compared to SpA (n = 7) ($P < 0.05$) and UA (n = 16) ($P < 0.005$). JNK activation was significantly higher in RA than in SpA ($P < 0.005$) and UA $P< 0.01$). p38 activation was similar between diagnostic groups. Logistic regression analysis demonstrated that synovial JNK activation, but not p38 or ERK activation, predicts fulfillment of RA classification criteria after two years (R^2 = 0.59, P = 0.02). Comparing patients diagnosed with UA at baseline who fulfilled RA classification criteria after two years (n = 8) with those who remained UA (n = 16), activation of JNK ($P < 0.005$), but not p38 or ERK was significantly enhanced. Activation of ERK ($P < 0.01$) and JNK ($P < 0.01$) at baseline was also enhanced in RA patients with progressive joint destruction as assessed by comparison of X-rays at baseline and after two years. Comparing all early arthritis patients, activation of p38 ($P < 0.05$), ERK ($P < 0.005$) and JNK ($P < 0.001$) was elevated in patients with erosive disease.

Conclusions: In patients with early arthritis, elevated ERK and JNK activity distinguish RA from other forms of arthritis, and JNK activation is already elevated in patients with RA even before classification criteria of RA are met. Activation of MAPKs is also associated with development of erosive disease, and JNK activation predicts the development of erosive disease in early arthritis patients. Together, our data suggest that strategies targeting ERK and JNK, rather than p38, may be beneficial in treating RA and preventing joint destruction early in the disease process.

Disclosure: D. de Launay: None; **M. van de Sande:** None; **G. van de Sande:** None; **C. Wijbrandts:** None; **D. Gerlag:** None; **P. P. P. Tak:** None; **K. Reedquist:** None.

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Serum Concentrations of Cytokines in the IL-23/IL-17A Pathway May Be Modulated by Polymorphisms in *IL-23R*. Lisa K. Stamp[1], Jody Hazlett[2], Tony Merriman[2], John Highton[2] and Paul Hessian[2]. [1]University of Otago, Christchurch, New Zealand, [2]University of Otago

Purpose: The IL-17/IL23 pathway has been recognised as an important pro-inflammatory system in RA. IL-23 is required for maintenance of Th17 cells whereas IL-12 inhibits IL-17A production from Th17 cells. Polymorphisms of the IL-23 receptor (IL-23R) and IL-21 have been associated with RA. The aims of this study were to determine the effect of polymorphisms in interleukin (IL)-23R, IL-12 and IL-21 on serum cytokine concentrations in patients with RA and to assess the relationship between serum cytokines in the IL-17/IL-23 pathway and these genes.

Methods: Serum and DNA were collected from 81 patients with RA. Concentrations of IL-1β, IL-12, IL-17A, IL-21, IL-22, IL-23, and TNF–α were measured using a bead-based multiplex assay. Genotyping of individual SNPs was determined by Taqman assays and PCR-RFLP. Data were analyzed using Prism software. For statistical analysis the genotypes were grouped as positive or negative for the minor allele.

Results: The mean age was 57.7 years (22–80), 74% female, 70% RF +ve and 58% CCP +ve. In 18 patients none of the cytokines were detectable.

There was no significant difference in serum concentrations of any of the cytokines examined in patients with the major vs minor alleles of IL-23R rs11209026, IL-12B rs3213337, IL-12bpro rs17860508 and IL-21 rs6822844.

In the subgroup of 48 patients who had detectable IL-17A, patients homozygous for the *IL-23R rs11209026* major allele had significantly higher

IL-17A concentrations as compared to patients with the IL-23 minor allele (394.51 ± 529.72pg/ml vs 176.11 ± 277.32pg/ml; p= 0.017). Similar differences were not observed in IL-21 or Il-22 concentrations. There was a strong positive correlation between serum IL-17A concentrations and IL-23 in patients with the IL-23R major allele (p=0.0003), which was not present with the IL-23R minor allele. Similarly, while there was a significant positive correlation between serum IL-12 and IL-23 in patients with the IL-23R major allele (p=0.036), this was not evident in patients with the IL-23R minor allele (p=0.24).

Conclusions: These data suggest that the *IL-23R rs11209026* polymorphism may have an impact on IL-23R function. However, this SNP as not been associated with RA. In patients with the variant higher concentrations of IL-23 may be needed to produce similar IL-17A concentrations as seen in patient with the major allele IL-23R, indicating reduced IL-23R function in those patients with the minor allele.

Disclosure: L. K. Stamp: None; **J. Hazlett:** None; **T. Merriman:** None; **J. Highton:** None; **P. Hessian:** None.

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Synovitis in Rheumatoid Arthritis: Paradoxical Inverse Relationship between Kinase Phosphorylation Status and CXCL13, a Biomarker of Inflammation. Sanna Rosengren and David L. Boyle. UCSD School of Medicine, La Jolla, CA

Purpose: Serum levels of the B-cell attracting chemokine, CXCL13 has been proposed as a marker of synovitis in rheumatoid arthritis (RA). In previous studies, we observed a strong correlation between serum CXCL13 protein and synovial CXCL13 mRNA. Hence, we sought to examine the relationship of synovial CXCL13 expression to putative markers of synovitis: 1) expression of inflammatory markers, and 2) the synovial phosphorylation state of several inflammation-associated signaling kinases.

Methods: RA synovial tissues were obtained during arthroplasty. Message RNA expression levels were determined by qPCR and were normalized to GAPDH yielding relative expression units (REU). Synovial kinase phosphorylation status was determined by Western blot. Phospho-Stat3 and MMP3 protein levels were measured by ELISA on synovial extracts. All statistical analysis was performed on log-transformed data.

Results: A screen of 58 individual RA synovial tissues revealed that CXCL13 REU ranged over 2600 fold, and when log-transformed, exhibited a bimodal distribution with two distinct maxima. From these, twelve each were selected from the upper and lower tertiles of the CXCL13 expression to yield High and Low CXCL13 sets. When compared to the Low CXCL13 tissues, significantly higher expression of TNF and MMP3, as well as the B- and T-cell markers CD19 and CD3E, respectively, were observed in High CXCL13 expression synovia ($p < 0.0028$ for all). In parallel, MMP3 protein levels also differed significantly between the two sets. Interestingly, no difference in expression of IL6 or MCP1 was observed between High and Low CXCL13 synovia. Surprisingly, p38, Erk, Stat3, and Akt were significantly less phosphorylated in High CXCL13 synovia. For example, when normalized to the Low CXCL13 within-gel mean, the phospho/total p38 ratios were 0.55±0.086 and 1.00±0.077, respectively, for High and Low CXCL13 tissues ($p < 0.001$). For Stat3, the corresponding numbers were 0.46±0.077 and 1.00±0.11, respectively ($p = 0.001$). No difference was observed in total p38/GAPDH or total Stat3/GAPDH protein ratios between the two synovial sets. The phospho-Stat3 results were confirmed using phospho-ELISA. Interestingly, expression of the anti-inflammatory factors SOCS1, SOCS3, and IL10 was significantly higher in High CXCL13 synovia. For example, the geometric mean (95% confidence interval) for SOCS1 REU was 0.074 (0.048–0.11) and 0.015 (0.010–0.025) for High and Low CXCL13 tissues, respectively ($p < 0.0001$).

Conclusions: Rheumatoid synovial tissues with elevated CXCL13 express higher levels of inflammatory mediators and contain more infiltrating cells. Unexpectedly, the same tissues display reduced phosphorylation of several kinases crucial to pro-inflammatory signaling, such as p38, Erk, Stat3, and Akt, when compared to synovia with low CXCL13 levels. These data might be explained by signaling kinetics or the fact that High CXCL13 tissues also contain elevated levels of anti-inflammatory factors, such as SOCS and IL10. These findings might be relevant to the therapeutic application of kinase inhibitors in RA synovitis, suggesting that stratification of patients might lead to improved clinical response.

Disclosure: S. Rosengren: None; **D. L. Boyle:** None.

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The microRNA 18a Enhances IL-6 Signaling through Inhibition of PIAS3. Matthias Brock[2], Michelle Trenkmann[1], Renate E. Gay[3], Beat A. Michel[4], Steffen Gay[5], Rudolf Speich[6] and Lars C. Huber[6]. [1]Center for Experimental Rheumatology and Zurich Center for Integrative Human Physiology (ZIHP), University Zurich, Zurich, Switzerland, [2]Center for Experimental Rheumatology and Zurich Center for Integrative Human Physiology (ZIHP), University Zurich, Zürich, Switzerland, [3]Rheum Clinic, Univ Hospital, Zurich, Switzerland, [4]University Hospital, Zurich, Switzerland, [5]University Hospital Zurich, Zurich, Switzerland, [6]Working Group for Pulmonary Hypertension, Department for Internal Medicine, University Hospital Zurich, Zurich, Switzerland

Introduction: Interleukin-6 (IL-6), a key proinflammatory cytokine in the pathogenesis of certain diseases, mediates the hepatic production of cytokines and acute phase reactants such as fibrinogen gamma chain (FGG) and haptoglobin (Hp). We have shown that signal transducer and activator of transcription 3 (STAT3), which is the major intracellular mediator of IL-6 signaling, regulates the expression of the microRNA (miRNA) cluster miR-17/92. Here we addressed whether miRNAs derived from this cluster might modulate IL-6 signaling and acute phase response in human hepatoma (HepG2) cells.

Methods: Overexpression of miRNA precursor molecules (pre-miR-17-5p, −18a, −19a, −20a and −92a) in HepG2 cells (n=6) was achieved by nucleofection (AMAXA). Following an incubation period of 72h, cells were stimulated with IL-6 for 4h. Gene expression of FGG, Hp, suppressor of cytokine signalling 3 (SOCS3), and protein inhibitor of activated STAT 3 (PIAS3) were measured by SYBR Green real-time PCR. HepG2 cells (n=5) were further transfected with reporter gene constructs of FGG or Hp promoters. 4h after stimulation with IL-6, cells were lysed and promoter activities were measured using the Dual-Luciferase Reporter Assay System (Promega).

Novel miRNA targets were identified by a computational algorithm (TargetScan) and validated by constructing a luciferase-based reporter gene system which contained the 3'UTR of the predicted target gene. Luciferase expression was assessed after co-transfection of HEK293 cells (n=7) with precursors of miR-18a and the respective reporter gene constructs.

Results: Stimulation of HepG2 cells with IL-6 for 4h resulted in overexpression of mRNA levels of SOCS3 (48.11 ± 15.3), FGG (2.86 ± 0.93) and Hp (4.43 ± 1.0) as compared to unstimulated control cells. Additional transfection with miR-18a further increased these expression levels (SOCS3: 81.49 ± 20.84, $p < 0.05$; FGG: 3.89 ± 1.35, $p = 0.08$; and Hp: 6.31 ± 0.75, $p < 0.05$). These data could be confirmed by performing reporter gene assays revealing 15.96 ± 4.62 fold change in the promoter activity of FGG for mock transfected cells upon stimulation with IL-6 and 26.67 ± 4.15 fold change in pre-miR-18a transfected cells ($p < 0.05$). For Hp, similar results were achieved showing 15.48 ± 4.51 in mock and 26.4 ± 4.47 fold change in pre-miR-18a transfected cells ($p < 0.05$). Next, we identified PIAS3 as a novel target of miR-18a. Transfection of miR-18a resulted in reduced mRNA expression levels of PIAS3 (0.86 ± 0.09, $p < 0.05$). Similarly, the activity of Luciferase containing the 3'UTR of PIAS3 was reduced in pre-miR-18a transfected cells (0.127 ± 0.038) when compared to mock transfected cells (0.21 ± 0.044, $p < 0.05$). Conversely, this effect could be abrogated by mutation of the miR-18a seed match (0.247 ± 0.049 for mock and 0.265 ± 0.063 fold change for pre-miR-18a transfected cells).

Conclusion: We show here that miR-18a enhances IL-6 signaling in HepG2 cells thereby increasing the production of acute phase proteins. We further identified PIAS3, an endogenous inhibitor of STAT3, as a direct target of miR-18a. Our data emphasize an important link between miR-18a and STAT3 activity in the regulation of inflammation and acute phase response.

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TL1A Expressed on the Rheumatoid Fibroblast-Like Synoviosytes Mediates Signalling Induced by DcR3. Masayasu Takahashi. Dept. of Orthopaedic Surgery, Kobe Univ. Graduate School of Medicine, Kobe, Japan

Background: TNF-like ligand 1A (TL1A)/ vascular endothelial growth inhibitor (VEGI)-251, is a member of the TNF superfamily(TNFSF-15) and exerts its effects by binding to its specific receptor, death receptor 3 (DR3). TL1A activates multiple signalling pathways including NFkB, p38MAPK,

ERK, and FADD for mitosis, inflammation, and apoptosis. Recently, it is reported that TL1A is expressed in rheumatoid fibroblast-like synoviosytes(RA-FLS) and synovial fluids of rheumatoid factor (RF) seropositive patients. TL1A aggravate collagen-induced arthritis in mice. Meanwhile, decoy receptor 3 (DcR3)/TNFRSF6b, a soluble receptor binding to TL1A, LIGHT, and FasL, does not only inhibit the signals by competitively binding to these ligands, but also directly induces the differentiation of macrophage to osteoclasts as a ligand. In this study, we tested the interaction of DcR3 and TL1A in RA-FLS for cell proliferation and activation of MAPKs.

Methods: The relative expression levels of DcR3-specific ligands (TL1A, LIGHT and FasL) in RA-FLS were quantified by real-time PCR. RA-FLS were starved for 24h in OPTI-MEM media and incubated with various concentrations of recombinant DcR3-Fc protein, TNFα, IL-1β, anti-TL1A Ab, and control Ig for 24h, and the proliferation rate was analysed by WST assay. RA-FLS pretreated with anti-TL1A Ab or control Ig for 24h was stimulated with DcR3-Fc for 30sec, 2 and 5min, and the phosphorylation of p38MAPK and ERK was detected by Western blotting.

Results: Real-time PCR showed that mRNA of TL1A s expressed in RA-FLS 140 times of FasL and 14 times of LIGHT. DcR3-Fc significantly inhibited the proliferation of RA-FLS induced by 0.1ng/ml TNFα (7.8% with 100ng/ml and 25.4% with 1000ng/ml) or 0.05ng/ml IL-1β (33.6% with 100ng/ml and 40.7% with 1000ng/ml) in a dose dependent manner. DcR3-Fc did not inhibit the proliferation of RA-FLS induced by TNFα or IL-1β when the cells were pre-treated with anti-TL1A Ab. p38 MAPK and ERK signalling was activated 3.32 times and 5.20 times of control at 2min by 1000ng/ml of DcR3-Fc, and the activation was suppressed by the pre-treatment with anti-TL1A Ab.

Conclusion: DcR3 activates p38MAPK and ERK in RA-FLS and inhibits the proliferation of RA-FLS induced by the inflammatory cytokines. TL1A expressed on RA-FLS is essential for the effect. Hence, DcR3 may directly bind to TL1A on RA-FLS and activate p38MAPK and ERK resulting negative regulation of cell proliferation induced by the inflammatory cytokines. DcR3 overexpressed in RA-FLS stimulated by TNFa protects the cells from Fas-induced apoptosis. Further, TL1A binds to DR3 and act mainly pro-inflammatory, but also induce apoptosis. Both DcR3 and TL1A have reciprocal functions in RA-FLS and DcR3/DR3-TL1A axis may play a critical role for the regulation of RA-FLS proliferation.

Disclosure: M. Takahashi: None.

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Visfatin/NAMPT-Mediated NGF Stimulation in Articular Chondrocytes: A Potential Link between Pain and Obesity-Induced Osteoarthritis. Sabrina Priam[2], Emilie Pecchi[3], Marjolaine Gosset[3], Xavier Houard[2] and Francis Berenbaum[1]. [1]Faculty of Medicine P&M Curie, Paris, France, [2]UPMC, Paris, France, Metropolitan, [3]UPMC

Background and Aim: Obesity is the main risk factor for knee OA. The two main features of the pathophysiology of obesity-induced OA are based on a local component (mechanical stress) and a systemic component (pro-inflammatory adipokines). Nerve growth factor (NGF) is present within OA synovial fluid and may be involved in pain associated with OA. We previously showed that visfatin/NAMPT, an adipokine, has pro-degradative effects (Gosset et al. Arthritis Rheum. 2008). However, its role in OA pain has not been evaluated yet.

Methods: Primary cultures of newborn mouse articular chondrocytes or cartilage explants were stimulated by increasing amounts of visfatin/NAMPT, IL-1 beta, prostaglandin E_2 (PGE_2) or by cyclic mechanical compression (0.5 Hz, 1 MPa). mRNA NGF levels were assessed by real-time quantitative PCR and NGF released into media was determined by ELISA.

Results: Unstimulated articular chondrocytes expressed low levels of NGF. Mechanical stress induced NGF mRNA expression and release in conditioned media. Visfatin/NAMPT, a pro-inflammatory adipokine produced by chondocytes in response to IL-1 beta, stimulated NGF expression (2 fold) and release (3.7 fold). When stimulated by IL-1 beta, a dose-dependent increase in NGF mRNA expression (5.7 fold increase with 10 ng/ml IL-1) and NGF release (19 fold increase with 10 ng/ml) in chondrocyte conditioned media was observed. Neither siRNA visfatin/NAMPT nor APO 866, an inhibitor of NAMPT enzymatic activity, prevented the production of NGF induced by IL-1 beta. Interestingly, PGE_2, which is produced by chondrocytes in response to IL-1 beta and visfatin/NAMPT, did not stimulate NGF production. Consistently, indomethacin, a cyclooxygenase inhibitor, did not counteract IL-1-induced NGF production.

Conclusion: These results suggest that obesity-induced OA pain may involve NGF mediated by the overexpression of visfatin/NAMPT and mechanical stress. These effects seem to be independent of the well-known pro-inflammatory mediators involved in OA pain, IL-1b and PGE_2. Thus, along with reduction of weight, visfatin/NAMPT could be an interesting target for pain in OA.

Disclosure: S. Priam: None; **E. Pecchi:** None; **M. Gosset:** None; **X. Houard:** None; **F. Berenbaum:** None.

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Vitamin D Suppresses Th17 Cytokines Via Down Regulation of ROR-gammat and NFATC2 and by Differential Regulation of GATA3. Anne-Marie Mus[2], Jan Piet van Hamburg[2], Patrick Asmawidjaja[2], Johanna M. W. Hazes[2], Hans van Leeuwen[2], Louis Boon[1], Edgar Colin[2] and Erik Lubberts[2]. [1]Bioceros, [2]Erasmus MC, University Medical Center

Introduction: Recently, we showed that vitamin D modulated Th17 polarization and IL-22 expression by memory T cells from patients with early rheumatoid arthritis and stimulates IL-4 production by PBMC from early RA patients. Furthermore, it has been shown that vitamin D inhibited collagen-induced arthritis and diminished the severity of existing CIA, although the mechanism is unknown.

Objective: To identify the molecular mechanism of vitamin D on suppression of Th17 cytokines and Th17 differentiation in an ex vivo model using CD4+ T cells from the prone autoimmune DBA-1 mice with and without collagen-induced arthritis or naïve CD4+ cells from DBA-1 mice.

Methods: Splenic CD4+ T cells of non-immunized DBA-1 and type II collagen immunized DBA-1 mice were isolated using the MACS system. In addition, naïve splenic CD4+CD62L+ T cells were FACS sorted from DBA-1 mice. These cells were stimulated *in vitro* under either Th0, Th1 (IL-12/anti-IL-4) or Th17 (IL-23, TGF-β, IL-6, anti-IL-4 and anti-IFN-γ) conditions with or without the presence vitamin D. Intracellular flowcytometric stainings for the detection of cytokine and transcription factor expression were performed. In addition, cytokine expression in supernatant was detected by specific ELISA. Moreover, mRNA expression of factors involved in Th differentiation and function was analyzed by Q-PCR.

Results: Higher percentages of IL-17+IFN-g- (Th17) cells were obtained after Th17 polarizing cultures of splenic CD4+ T cells of CII-immunized mice, compared to non-immunized mice DBA-1. In cultures of both non-immunized mice and CII-immunized DBA-1 mice, Vitamin D significantly inhibited Th17 polarization, as indicated by reduced IL-17A and IL-17F cytokine expression. Moreover, reduced RORgt expression and enhanced GATA3 expression was noted. Interestingly, vitamin D showed an increase in IL-4 and IL-10 positive cells under Th17 polarizing conditions of both non-immunized and CII-immunized DBA-1 mice. However, using FACS sorted naïve CD4+ T cells, vitamin D enhanced IL-4 and GATA3 under Th0 conditions, but not under Th17 polarizing conditions. Interestingly, in this latter condition, RORgt and NFATC2 were markedly suppressed. No effect of vitamin D on T bet and RUNX1 expression was noted.

Conclusion: These data show that vitamin D is a strong inhibitor of Th17 polarization and Th17 cytokine expression of splenic CD4+ T cells from non-immunized and CII-immunized DBA-1 mice. Furthermore, Th17 differentiation from naïve T cells was affected by Vitamin D. These data implicate a regulatory mechanism on Th17 cells by Vitamin D, through the reduction of RORgt expression. This regulatory function of Vitamin D in memory Th17 cells, may in part be dependent on the induction of GATA3 expression leading to a induced Th2 cytokine expression profile.

Disclosure: A.-M. Mus: None; **J. P. van Hamburg:** None; **P. Asmawidjaja:** None; **J. M. W. Hazes:** None; **H. van Leeuwen:** None; **L. Boon:** None; **E. Colin:** None; **E. Lubberts:** None.

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XCL1/Lymphotactin Induces Rheumatoid Arthritis Fibroblast-Like Synoviocytes Migration through MAP Kinases. Karolina Klosowska and James M. Woods. Midwestern University, Downers Grove, IL

Purpose: Chemokines are small secreted molecules that function in leukocyte recruiting and trafficking during an immune response. They play a key role in rheumatoid arthritis (RA), a chronic disorder that results in joint destruction. Fibroblast-like synoviocytes (FLS) are key contributors to the pathogenesis of RA, and they accumulate in the synovial lining, where they are positioned to aid in driving perpetual inflammation. XCL1 (Lymphotactin) is a chemokine known to be prominently present in the synovial tissue and

fluid of RA patients. In this study, we investigated the effect of XCL1 on FLS migration, proliferation, F-actin localization, and the role of MAP kinases in RA FLS stimulation.

Methods: RA FLS were obtained with IRB approval from knee or hip synovial membrane at the time of joint replacement and were employed in chemotaxis assays, proliferation assays, and Alexa Fluor 488 Phalloidin staining of F-actin. Further, MAP kinase inhibitors were utilized in conjunction with chemotaxis assays to evaluate whether MAP kinases played a role in signaling that contributed to RA FLS migration.

Results: Chemotaxis assays revealed that XCL1 is a novel chemoattractant for RA FLS, effectively inducing significant migration for RA FLS derived from 4 different patients. Moreover, concentrations of 1 nM to 50 nM all induced significant migration above background chemotaxis ($p<0.05$). Consistent with this finding, exposure of RA FLS to XCL1 results in a significant restructuring of F-actin, most noticeable after 2 hours. Specifically, cytoskeletal staining appeared as diffuse actin cables that were barely noted in non-stimulated cells, but upon stimulation with 10 nM XCL1 intense concentrations of F-actin could be seen in most cells along with a complete change in cell morphology. While we did not detect a proliferative effect of XCL1 on RA FLS, we did note that pertussis toxin (PTX) could completely abolish XCL1-induced migration, suggesting that migration is induced through a G protein (Gi/Go) coupled receptor. Additionally, pre-incubation of cells with U0126, an inhibitor of MEK 1/2 (the kinase known to activate ERK 1/2), significantly reduced XCL-1-induced migration of FLS from 2 of 3 RA patients tested. Similarly, pre-incubation of cells with the JNK inhibitor (SP600125) significantly repressed chemotaxis induced by XCL-1 in 2 of 3 RA FLS.

Conclusions: We have identified a novel role for XCL1 in regulating RA FLS migration, which is consistent with changes in cytoskeletal structure. XCL1 induces RA FLS migration in a dose dependent manner, where application of PTX, a MEK1/2-, or a JNK-specific inhibitor significantly reduces cell migration. This suggests involvement of ERK and JNK pathways in XCL1-induced RA FLS migration, presumably through its receptor, XCR1. A better understanding of XCL1 and FLS is warranted, since FLS are recognized to be directly responsible for cartilage destruction and driving inflammation and autoimmunity in RA, where XCL1 is present.

Disclosure: K. Klosowska: None; **J. M. Woods:** None.

ACR Poster Session A
Education
Monday, November 8, 2010, 9:00 AM–6:00 PM

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An Audit on Patients' Knowledge of Methotrexate. Evin Sowden, Wajeed Hassan, Ann Gooden, Bridget Jepson, Tamsheela Kausor, Ifraz Shafait, John Brockbank, Robert Ley and Lee-Suan Teh. Royal Blackburn Hospital, Blackburn, United Kingdom

Background: Methotrexate is a first line disease modifying agent and anchor drug for biologics therapy used in rheumatoid arthritis and other inflammatory rheumatic disorders. Adverse effects may occur in patients and are a common cause of drug discontinuation. Analysis of serious and fatal toxicity incidents led the National Patient Safety Agency (NPSA) to issue an alert identifying patient education and drug monitoring as an important part of a harm reduction strategy. In view of this, we audited patients prescribed methotrexate to assess adherence to patient education and patient knowledge in the rheumatology clinic setting of a district general hospital in the north of England.

Methods: All patients prescribed methotrexate for inflammatory rheumatic disease were eligible to take part. A proforma to record clinical and demographic characteristics, provision of patient education and monitoring, knowledge of drug administration, potential side effects and drug interactions was completed by case record review and patient self-administration. Questionnaire answers were discussed and an information leaflet on methotrexate given to the patient at the end of their audit participation.

Results: 51 patients were audited. The mean age was 58.6 ±13.1 years and median duration of disease 3.7 (IQR 1.7–7.6) years. Counselling by specialist nurses prior to starting methotrexate was documented in 94.1%, written information was provided in 94%, methotrexate dose and frequency were known to the patient in 84% and 100%, folic acid was co-prescribed in 90% and awareness of pregnancy and breastfeeding risks was 87.5% in females of reproductive age (<45 years). There was limited awareness of methotrexate's mode of action (60%), true side effects (21.6%-62.7%), false side effects (5.9%-37.3%), risks related to alcohol (68.4% in drinkers), risks related to male conception (47.1%), true drug interactions (7.8–11.8%) and false drug interactions (11.8–19.6%). The mean patient global knowledge score was 6.3 ±1.2 on a scale of 0–10 points. Univariate and multivariate analyses identified male gender, non-speakers of english as a first language and a trend toward longer duration of therapy as significant predictors of lower levels of patient knowledge.

Conclusion: Our audit shows that despite systematic patient education interventions as part of routine care, knowledge of important aspects of methotrexate therapy is limited. A number of recommendations are suggested: 1. Use of clearer safety-driven booklets such as that produced by the National Patient Safety Agency (NPSA); 2. Provision of information in languages other than English and in audio or audiovisual formats; 3. Regular knowledge assessments using validated tools; and 4. Targeted education to ensure consistent levels of knowledge to prevent unnecessary methotrexate-related harm.

Disclosure: E. Sowden: None; **W. Hassan:** None; **A. Gooden:** None; **B. Jepson:** None; **T. Kausor:** None; **I. Shafait:** None; **J. Brockbank:** None; **R. Ley:** None; **L.-S. Teh:** None.

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Educating Primary Care Providers on Rheumatoid Arthritis Translates to Changes in Practice and Referrals: Results from the RAPID Continuing Medical Education Program. Clifton Bingham[3], Karen Costenbader[1], Steven Bender[2], Daniel Duch[2] and Michael Weinblatt[1]. [1]Brigham and Women's, [2]Curatio CME Institute, [3]Johns Hopkins, Baltimore, MD

Background: To determine whether a continuing medical education (CME) program focused on rheumatoid arthritis (RA) changed primary care provider (PCP) new patient (pt) referrals to rheumatologists.

Background: The impact of rheumatology CME on physician behavior is not well known. The Rheumatoid Arthritis Primary Care Initiative for Improved Diagnosis and Outcomes (RAPID) is a multi-supported CME initiative developed in 2007 to educate PCPs on the benefits of screening/diagnosing pts with suspected RA and co-managing those pts with a specialist for optimal evidence-based care. More than 49,274 physicians, nurse practitioners (NPs), and physician assistants (PAs) have completed RAPID activities. These were live CME activities with a multi-disciplinary faculty (rheumatologists and generalists),mobile Epocrates CME activities, and journal supplements.

Methods: Short-term learning for knowledge, confidence, and competence used audience response questions before and after live presentations. The same measures were used for online and printed materials. To evaluate impact, we matched 6,000 learners from the 2007 program with medical claims data from a data aggregator (multiple source clearinghouse representing claims for approximately 300,000 clinicians) to determine if there was a change rheumatologist office visit rates for pts with an RA diagnosis ("referral rate"). We compared before and after the CME activity by tracking ICD9 codes to compare rheumatology referral rates to those of (n=15,930) nonparticipants. To create a control group of nonparticipants, for every PCP in the test group, we identified 30 similar providers based on specialty, state, urban/rural, claim volume, who did not complete RAPID and averaged figures to create 1 control group subject.

Results: There was a significant increase in short-term learning at the time of participation through pre/post test results. We identified 531 participants with sufficient claims data covering a period of 4 months (mo) pre-participation and 4 mo post-participation. Of 531 CME participants identified in the claims database, pre-educational measurement showed that of the 1183 patients that were diagnosed with RA, 443 had an office visit with a rheumatologist within the next 4 mo, a referral rate of 37.4%. In the 4 mo post-educational intervention, the same providers' "referral rates" increased to 41.8%. There were no changes in the RA pt referral rates in the control group 18.1% to 18.0%.

Conclusions: This is the first study to examine the impact of an educational program on referral of RA pts by PCPs to rheumatologists.

Administrative claims data can be employed successfully to measure the impact of a CME program on changes in clinical practice. A program focused on PCP education concerning RA resulted in increased referrals to rheumatologists to provide optimal pt care. This emphasizes the continuing importance of PCP education to improve outcomes for RA pts.

Disclosure: C. Bingham: Chatham Institute CME, 5; **K. Costenbader:** Chatham Institute CME, 5; **S. Bender:** Curatio CME, 3; **D. Duch:** Curatio CME Institute, 3; **M. Weinblatt:** Chatham Institute CME, 5.

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Information Sources for Rheumatoid Arthritis: More Than Just the Rheumatologist. Katie Garneau[1], Maura Iversen[4], Saira Jan[3], Hsun Tsao[1], Daniel Hal Solomon[2] and Kavita Parmar[3]. [1]Brigham and Women's Hospital, [2]Brigham and Womens Hospital, Boston, MA, [3]Horizon Blue Cross Blue Shield, [4]Northeastern University, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Background: Studies show that patients who make high quality medical decisions are more likely to have better health outcomes. One defining characteristic of what constitutes a high quality decision is a well-informed patient. However, there has been little research studying patient behaviors regarding how they seek information about treatments for RA.

Methods: We surveyed beneficiaries of Horizon Blue Cross Blue Shield of New Jersey from 2009–2010, who were over age 18 and had 2 or more visits coded with RA (ICD 9 714.x). 101 (13%) of 799 invited subjects agreed to and completed interviews. Subjects answered a questionnaire consisting of items regarding sources of RA treatment information (provider and non-provider) and their usefulness, sociodemographic items, as well as 10 validated scales shown in table 1. Provider sources of information included primary care physician, rheumatologist, nurse practitioner or physician's assistant, and occupational or physical therapist. Non-provider sources included the Arthritis Foundation, books or magazines, friends or family, advertisements, health insurance, and the World Wide Web. Outcomes of interest include the average number of sources described (range 0 – 10) and the rating of usefulness for each source (1 = not useful and 4 = extremely useful).

Results: Most subjects (95%) reported at least 2 years of disease and had a mean age of 59 years. 76% of respondents were female, 71% had completed at least some college, and 43% reported earning over $100,000 in the past year. Methotrexate was the most widely used medication reported (85%). The average number of sources utilized was 5.0 (SD 2.1). Participants rated the information they utilized with an average score of 2.5 (SD 0.8). We found no strong patient correlates of these outcomes when comparing with the aforementioned domains, however positive correlations were noted between number of sources and social supports as well as usefulness of sources and trust in physician (see Table). 87% of the 98% of the total sample that used a Rheumatologist for information gave that source a 4 out of 4. The internet was the most frequently used non-provider source, with 63% of subjects reporting use, and an average usefulness rating of 3.0 (SD 1.03).

Conclusion: Participants, on average, use 5 sources of information regarding treatment decisions for RA. Participants rated these sources as useful, with Rheumatologists rated extremely useful. Strategies to enhance care and appropriate use of DMARDs should take this information into consideration.

Table 1. Correlations between patient characteristics and information sources for RA treatment decision making

	# of sources		Usefulness of sources	
	Correlation coefficient (r)	p-value	Correlation coefficient (r)	p-value
Trust in Physician	0.12	0.23	0.21	0.03
Self-Efficacy	0.43	0.67	0.16	0.11
Beliefs In Medicines	0.22	0.03	−0.11	0.26
Social Support	0.20	0.04	0.06	0.57
Brief Illness Perception*	0.12	0.24	−0.02	0.87
Social Norms	0.00	1.00	0.46	0.65

* Higher scores indicate a higher perception of illness, all other high scores denote more of the measured attribute.

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Knee and Shoulder Cadaver Teaching Improves Internal Medicine Residents' Self-Reported Anatomy, Exam and Injection Skills. Jessica Berman[2], Michael H. Pillinger[3], Bradley Jensen[2], Jennifer Hammann[2] and Stephen A. Paget[1]. [1]Hospital for Special Surgery, New York, NY, [2]Hospital for Special Surgery, New York, NY, [3]NYU-Manhattan VA Med Hospital, New York, NY

Purpose: Medicine residents need to gain confidence and ability in basic musculoskeletal skills such as the joint exam, anatomy knowledge and joint injections. However, opportunities to develop these skills are frequently limited. Possible impediments include inadequate hands-on experience and the ineffectiveness of lectures and simulation models. To address these limitations, we have developed a series of innovative modules that focus on instruction in knee and shoulder anatomy, examination and injection teaching in the cadaver lab.

Methods: Rheumatology knee and shoulder teaching modules were designed for 3–4 second-year medicine residents each month, with over forty completing the program in the past year. Residents were surveyed (9-point Likert scale) before and after the rotation for their self-assessed ability to perform joint examination and aspiration. Modules were taught by an experienced rheumatologist and consisted of twice-monthly participation in interactive lectures with demonstrations of the relevant anatomy and injection classes employing cadaveric models. Examination skills relevant to the area discussed were also emphasized. Ample opportunity was given to practice injections using different approaches on the cadaver knee and shoulder joints.

Results: Before and after completing the above curriculum, second-year residents surveyed rated their abilities (1=poor to 9=very good) in specific musculoskeletal tasks as follows:

	Pre-lab (N=43)*	Post-lab (N=24)*
Injection knee	2.42	6.12
Injection shoulder	1.56	5.54
Examination of knee	4.23	6.76
Examination of shoulder	3.93	6.40
Anatomy of knee	4.09	6.44
Anatomy of shoulder	4.05	6.28

*$p<0.001$ for all comparisons

The average number of joints injected by each resident prior to the rotation was 0.88. By the end of the rotation this had risen only to 2.08.

Conclusion: Even in the setting of only limited opportunity to perform actual joint procedures, a rheumatology curriculum that includes an integrated, intense, hands-on exposure to musculoskeletal anatomy and injection teaching in the cadaver lab can improve residents' perceptions of their abilities and confidence in the anatomy, examination and injection of the knee and shoulder. This teaching approach may be a valuable alternative for programs wishing to improve musculoskeletal procedure skills, particularly in settings where actual experience may be limited.

Disclosure: J. Berman: None; **M. H. Pillinger:** None; **B. Jensen:** None; **J. Hammann:** None; **S. A. Paget:** None.

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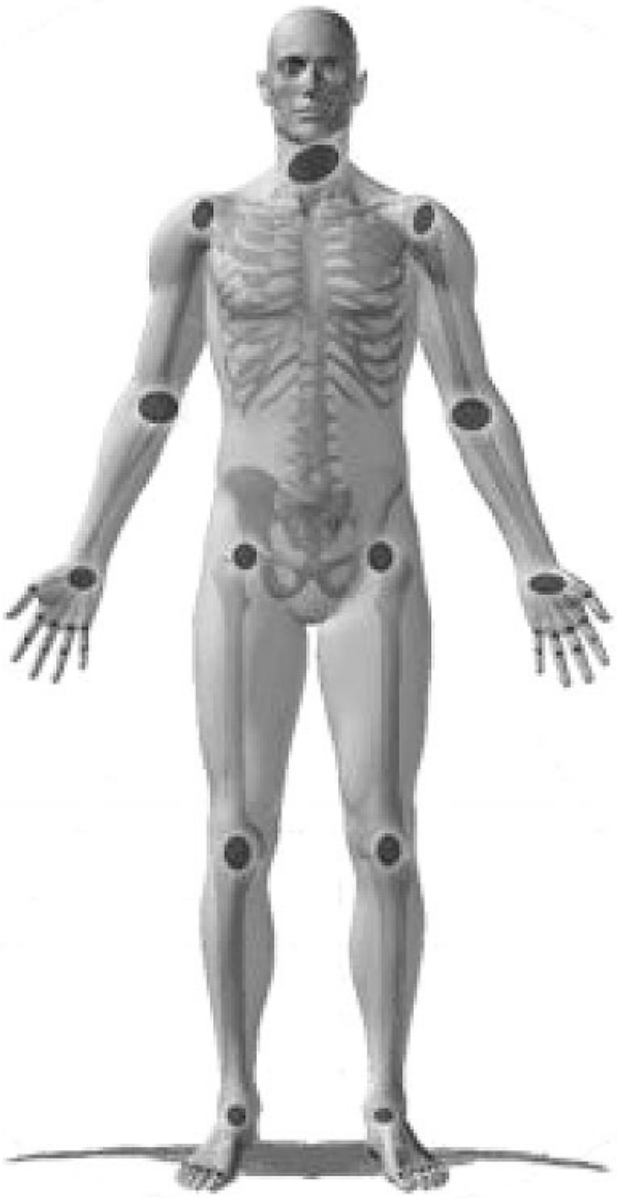
Medical Student Education in the Electronic Age: A Web-Based Virtual Teaching Tool. Ernesto J. Rodriguez[1], Abie Alias[1], Aasim Rehman[1], Vanessa Osting[1], Tanisha Battle[2], Lara Westphal[2], Ashley G. Sterrett[3], Helen Bateman[3], John D. Carter[1] and Joanne Valeriano-Marcet[3]. [1]University of South Florida, Tampa, FL, [2]University of South Florida, [3]USF/JAHVA, Tampa, FL

Objective: Musculoskeletal (MSK) complaints have a high prevalence in primary care practice, yet many physicians continue to identify themselves as deficient in MSK medicine. Recognizing joint pattern involvement in rheumatic diseases is integral to establishing a differential diagnosis. Therefore there is an impetus to improve the quality and consistency of MSK teaching

in medical schools. This qualitative study was conducted to assess the effectiveness and satisfaction of 4th year medical students with "Arthur" (shown below).



Methods: "Arthur" is a web-based virtual education program that teaches joint pattern recognition of MSK disorders. Thirty cases highlight different joint pattern presentations (ie. Symmetric polyarthritis illustrated in above case). "Arthur" was developed by the University of South Florida Rheumatology and Education Departments. All fourth year medical students had access to "Arthur" and the accompanying survey. This survey contained open-ended questions designed to gather feedback on the students' experience, as well as the program's utility and possible areas of improvement.

Results: A total of 64 out of 107 (59.8%) fourth year medical students completed "Arthur" and the follow up survey. In response to the question regarding the strengths of "Arthur": 35 % of the respondents identified the program to be a useful tool for learning joint pattern recognition, 42.4% stated it was helpful in learning differential diagnoses of rheumatic diseases, and 20.3 % reported "Arthur" to be useful as a visual aid. In response to the question regarding areas for improvement: 48.4% identified the need for addition of explanations for each differential diagnosis, 10.9% reported the need for additional history, and 9.3% felt that "Arthur" did not need any improvement.

Conclusions: The "Arthur" virtual interactive teaching program was found to be most helpful in determining differential diagnoses, joint pattern recognition, and as a visual aid for learning. Based on this data, the most recent version of "Arthur" includes detailed explanations of the differential diagnoses for each case.

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Rheumatology Fellowship Curricular Rotation in Musculoskeletal Ultrasound. Dimitrios A. Pappas[2], Marzouq A. Qubti[2], Clifton O. Bingham III[2] and Allan C. Gelber[1]. [1]Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD

Background: Within the American rheumatology community, musculoskeletal ultrasound (MSK-US) has over the last decade gained substantial support as a valuable diagnostic tool to evaluate swollen joints, bursae and tendons. Notwithstanding ongoing efforts to integrate MSK-US training into fellowship training, there remains a paucity of information detailing the experience of individual rheumatology programs at furnishing MSK-US training in their respective curricula.

Methods: We describe our new curricular rotation with MSK-US at a single academic medical center in the United States. In the 2009–2010 academic year, a new clinic was implemented wherein patients referred in consultation for acute sites of musculoskeletal swelling could be scheduled and evaluated within 72 hours of referral receipt. The attending rheumatologist was previously trained in musculoskeletal ultrasound. At this clinic, faculty-mentored, ultrasound-focused rheumatologic evaluations were conducted one afternoon each week over the course of 11 consecutive months.

Results: Between July, 2009 and May, 2010, there were 100 consecutive patients evaluated in tandem by a rheumatology fellow and faculty preceptor at this acute musculoskeletal clinic. These ultrasound-focused evaluations were conducted across a broad spectrum of patients with arthritis and rheumatic disorders, including osteoarthritis (n=20), rheumatoid arthritis (n=14), trochanteric bursitis (n=10), unspecified arthritis (n=9), gout (n=9), spondyloarthropathy (n=8), shoulder tendinitis/bursitis (n=7), pseudogout (n=5), tendinopathies (n=5), and other miscellaneous diagnoses (n=13). Ultrasound guidance was used to evaluate a knee (n=27), shoulder/rotator cuff (n=13), wrist (n=11), hip (n=10), elbow (n=5), ankle (n=5), interphalangeal joint (n=10), and other miscellaneous sites (n=19). Among these patients, a subset of 75 underwent an ultrasound-guided procedure, consisting of 52 patients who underwent ultrasound-guided joint, bursal or tendinous injections; 15 additional patients who underwent aspiration & injection, and 8 who underwent an aspiration procedure alone.

Conclusions: In the context of this new fellowship curricular offering, a single rheumatology trainee, working in unison with a single faculty preceptor, was able to achieve considerable exposure across a broad range of rheumatic disorders. Substantial proficiency was attained at use of ultrasonography, to identify and localize sites of joint, tendinous and bursal swelling, and to guide aspiration and/or injection procedures. Moreover, completion of 100 ultrasound-guided evaluations is a recognized target for an intermediate level of knowledge and skills for performing MSK-US [*J Clin Rheum* 2010;16:113).

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Team-Based Learning in Rheumatology Resident Education: Two-Year Results on Receptiveness and Attitudes of Residents towards Collaborative Learning and Teamwork. Karina Marianne D. Torralba[2], Beatrice A. Boateng[1], Ron Ben-Ari[4] and Francisco P. Quismorio[3]. [1]Arkansas Children's Hospital-University of Arkansas for Medical Sciences, [2]University of Southern California-Los Angeles County Medical Center, Pasadena, CA, [3]University of Southern California-Los Angeles County Medical Center, Los Angeles, CA, [4]University of Southern California-Los Angeles County Medical Center

Objective: Team-based learning (TBL) is a structured small group learning approach that is well-recognized in medical education. It encourages accountability, teamwork and has been demonstrated to improve board scores and patient care. Since 2008, TBL has been utilized for Internal Medicine core curriculum learning sessions (CCLSs) in Rheumatology. Two of the aims of this study are to determine the level of satisfaction or receptiveness by residents of the strategy in improving their overall learning experience, and to determine their attitudes towards teamwork in learning and professional success.

Methods: Seven TBL modules had been developed on various topics including Rheumatoid arthritis, Osteoarthritis. Over 2 years, 13 modified-TBL sessions have been conducted. Learning materials provided a week before are reviewed briefly at start of class. Residents undergo individual readiness assessment test (IRAT), followed by group-RAT (GRAT) and case application done in teams of 3–4 members. Class discussion is supervised by the instructor. To assess receptiveness, a 5-point Likert scale evaluationa survey with two open-ended questions was anonymously filled out by residents at end of each session. To evaluate perception of collaborative learning, Value of Teams Survey (VOTS) was filled out yearly at the end of the CCLS series. In-training and board exam scores were tracked to determine effectiveness of TBL (results in separate abstract). Descriptive statistics and t-tests were used.

Results: Of 240 residents over a two year period (60 per year, including graduated residents and new PGY1s), 220 have gone through TBL-CCLSs. Over two years a sustained majority (80–100%) agreed-strongly agreed that TBL was conducive for CCLSs due to organization of activities, quality of learning and teammate and instructor interactions. Most commonly cited themes: 1) as to what was they liked best was that it was a fun and interactive format, it allowed them to learn from co-residents, it allowed them to review materials they already knew and to also advance their knowledge by using critical thinking; 2) as to what they liked least was the time constraint. For VOTS, a sustained majority (85–100%) agreed that utilizing teamwork is an effective way of learning, and is a necessary and valuable skill to learn, and is needed for better decision-making. At least 80% felt teamwork is necessary for professional success in their careers.

Conclusion: There is sustained acceptance and satisfaction by medical residents of TBL as a teaching strategy for CCLSs from year 1 to year 2 of implementation. Collaborative learning through teamwork is a recognized effective way of learning and a valuable skill to acquire.

Disclosure: K. M. D. Torralba: None; **B. A. Boateng:** None; **R. Ben-Ari:** None; **F. P. Quismorio:** None.

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The First Pediatric Rheumatology Objective Structured Clinical Examination: Providing Clinical Skills Feedback for Fellows and Program Directors. Megan L. Curran[1] and David D. Sherry[2]. [1]Children's Memorial Hospital, Northwestern University's Feinberg School of Medicine, Chicago, IL, [2]The Children's Hospital of Philadelphia, Philadelphia, PA

Background: Since objective data is often lacking, it is difficult for fellowship program directors (PDs) to provide meaningful feedback regarding fellows' communication and professionalism skills. To reliably assess these non-knowledge based competencies we conducted an OSCE for pediatric rheumatology fellows to measure pre-test expectations and actual scores in communication and professionalism skills and overall performance rank.

Methods: 22 fellows from 13 training programs were tested in 7 unique scenarios. The 21 evaluators were pediatric rheumatologists mostly from participating programs. Before the OSCE, fellows and PDs used 100 mm visual analog scales (VAS) to indicate expected performance in communication and professionalism. Evaluators scored fellows using identical VAS during scenarios. Scenario scores were averaged to give final scores in these areas. Before the OSCE, fellows and PDs estimated overall performance (upper, middle or lower third) compared to others. After all 7 fellows finished an evaluator's station, their performances were ranked from 1 (best) to 7 (worst). Rankings were averaged to determine each fellow's overall performance score. Scores were ordered numerically and divided into upper, middle and lower thirds.

Results: The 22 fellows' pre-test communication VAS estimates ranged 22–80 (56, 57, and 49 were the mean, median and mode). Post-test communication VAS scores ranged 26–89 (78, 80, 86). Fellows' pre-test professionalism VAS estimates ranged 39–98 (60, 60, 50). Post-test professionalism VAS scores ranged 26–90 (84, 88, 88). Upper, middle and lower third overall performance rank averages ranged respectively from 1.25 to 3.33 (n=8), 3.43 to 4.29 (n=7) and 4.43 to 5.83 (n=7). The following statistics show the number of fellows who estimated their performance ranking to fall into the specified third with the number actually achieving upper, middle, and lower third rankings listed in parentheses. 2 fellows estimated their performance as upper third (1, 0, 1), 12 as middle third (6, 4, 2) and 8 as lower third (1, 3, 4). 1st year fellows estimated their performance ranking to be lower than 2nd year fellows, whose estimates were lower than estimates of 3rd year fellows. PDs estimated 10 of their fellows' performances as upper third (4, 3, 3) and 4 as middle third (1, 2 and 1). No program director thought that their fellow would rank in the lower third. With few exceptions, attendings expected 1st year fellows to rank in the middle third and 2nd & 3rd year fellows to rank in the top third.

Conclusions: Our pediatric rheumatology OSCE was the first of its kind. Fellows tended to underestimate their communication skills, professionalism skills and overall performance ranking. PDs overestimated performances. Limitations of our study include inter-rater reliability of evaluators and comparison of fellows from different training levels. However, the pediatric rheumatology OSCE provided innovative feedback for program directors about their fellows' communication and professionalism skills. This OSCE provides the first opportunity to compare the clinical skills of pediatric rheumatology fellows from programs nationwide.

Disclosure: M. L. Curran: None; **D. D. Sherry:** None.

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Utilization of Ambulatory Medical Clinic for Rheumatology Education. James M. Ross Lehigh Valley Health Network, Macungie, PA

Purpose: Development and assessment of a model of rheumatology education using medical residents own clinic patients with direct supervision of rheumatic cases by an academic rheumatologist.

Methods: An education model was developed utilizing an academic rheumatologist for direct supervision and education concerning rheumatic cases seen during internal medicine resident's clinic. The rheumatologist attended each resident's clinic monthly and saw scheduled patients specifically for rheumatology and non-scheduled rheumatic cases. The diagnoses, residents involved and any procedure performed were recorded. Assessment of this educational experience included testing of general rheumatology knowledge with multiple-choice questions, an annual assessment of overall resident impression and assessment of utility of the experience using a 5 point scale. This assessment was performed at baseline and yearly.

Results: Patient visits: There were 90 sessions attended by the rheumatologist over 24 months. 253 patients including 193 scheduled patients with rheumatology issues were seen. Due to initiation of EMR there was a transient decline in patients seen in the past year. 35% of the cases were followed over time giving residents experience of continuity of care of rheumatic disorders. Cases encompassed all aspects of rheumatology with the most common diagnoses being rheumatoid arthritis, osteoarthritis and soft tissue rheumatism with need for injections. Waiting time for patient seen with this program was 0– 40 days. Sixty different residents were supervised in this model including 40 without previous rheumatology rotation experience.

Educational assessment: At baseline the majorities of the first and second year groups of residents were not comfortable with rheumatic patients and scored poorly on basic rheumatology questions. As a group the third year residents were less than moderately comfortable in seeing rheumatology patients. On repeat assessment each of the resident groups demonstrated improvement in basic knowledge including those residents without a previous rheumatology rotation experience. They also reported an improvement in their level of comfort in dealing with rheumatic patients and performing arthrocentesis. The overall resident impression was that this model provided a useful clinical and educational experience.

Conclusions: This medical clinic educational model provides several additional benefits in addition to or combined with a standard rheumatology rotation. Benefits include residents having more responsibility for the care of these cases plus an increase in comfort level. This model provides an increased and earlier exposure to rheumatology that may interest residents into considering this field, in addition to improved medical clinic patient access to care and quality of care.

Disclosure: J. M. Ross: REF-Clinical Scholar Educator award, 2.

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A Novel Baseline Biomarker of Acute-Phase Serum Amyloid A (A-SAA) and Serum Interleukin–2 Receptor alpha (sIL-2Rα) Predicted Long-Term (18 to 35 Yrs) Mortality of Incident Rheumatoid Arthritis (RA) and Matched Non-RA Cohort Controls (CN). Alfonse T. Masi[2], Jean C. Aldag[2] and Jean D. Sipe[1]. [1]Center for Scientific Review, NIH, Bethesda, MD, [2]University of Illinois College of Medicine at Peoria, Peoria, IL

Purpose: Research on biomarkers of mortality has high priority, especially for cardiovascular causes. Serum markers have predicted such mortality but not over decades-long intervals. This prospective study aimed to identify baseline, long-term biomarker predictors of mortality outcomes of incident RA and matched non-RA cohort CN.

Design: In 1974, 54 subjects had enrolled into a community-based cohort (n = 21,061 adults) who later had onset of ACR-positive RA, after 3 to 20 (mean 12) years (1977 – 1994). Each RA case was matched by age, gender, and race (all Caucasian) at baseline with 4 cohort non-RA CN. Baseline stored (-70°C) sera were assayed (ELISA) blindly for biomarkers. High sensitivity CRP (hsCRP) and A-SAA were assayed (Hemagen kits) at Boston University (sensitivity 0.1 μg/ml for hsCRP and 1 μg/ml for A-SAA). Three cytokines (IL-1β, IL-6, and TNF-α) and 3 cytokine receptors/antagonists (sIL-2Rα, sTNF-R1, and IL-1ra) were assayed (R & D Systems, high sensitivity kits) at Specialty Laboratories, Santa Monica, CA. Two baseline (1974) biomarkers correlated with mortality of all subjects from 1992–2009, i.e., A-SAA, p = 0.001 and sIL-2Rα (CD25), p = 0.036 (but not CRP, p = 0.125). Sex- and age-specific upper quartile values of A-SAA and sIL-2Rα were determined and a gradient score of their combined results was formulated: 1 = all negative tests (single only or both assayed); 2 = one test negative and other positive (or neither test assayed), and 3 = all positive tests (single only or both assayed). All cause, primary cardiovascular (ICD-9, 390–459 & ICD-10, 00–99), and all other combined mortality was monitored from 1992 thru 2009, excluding 12 pre-1992 deaths. Percentages of deaths by the biomarker gradient were determined. Hazard ratios (HR) of the biomarker gradient for mortality were estimated by Cox regression models.

Results: Deaths from all causes occurred in 27 (50%) of 54 RA vs 63 (31%) of 204 non-RA, OR = 2.24, 95% CI 1.22 – 4.12, p = 0.010. For all causes, HRs of the biomarker gradient were significant for deaths in RA (p = 0.026), non-RA (p = 0.002), and total (p < 0.001) subjects. For circulatory mortality, HRs of the biomarker gradient were significant for deaths in total (p < 0.001) and non-RA (p = 0.001) subjects, and nearly in RA (p = 0.072). For non-circulatory deaths, the biomarker only weakly predicted deaths in total subjects, p = 0.049 (Table):

Causes of Deaths and the Biomarker Gradient	Rheumatoid Arthritis (N=54) N (%) of Deaths	Non-Rheumatoid Arthritis (N=204) N (%) of Deaths	Total Cohort Subjects (N=258) N (%) of Deaths
All Causes of Deaths:			
Negative Only	8 (34.8%) of 23	22 (22.2%) of 99	30 (24.6%) of 122
No Assays or Neg & Pos	13 (56.5%) of 23	31 (36.0%) of 86	44 (40.4%) of 109
Positive Only	6 (75.0%) of 8	10 (52.6%) of 19	16 (59.3%) of 27
Total Mortality	27 (50.0%) of 54	63 (30.9%) of 204	90 (34.9%) of 258
Cox Regression Model: HR (95% CI) of Biomarker Gradient for Mortality (p Values)	1.80 (1.07–3.03) (p = 0.026)	1.78 (1.24–2.55) (p = 0.002)	1.83 (1.36–2.46) (p < 0.001)
Circulatory Deaths:			
Negative Only	1 (4.3%) of 23	6 (6.1%) of 99	7 (5.7%) of 122
No Assays or Neg & Pos	4 (17.4%) of 23	14 (16.3%) of 86	18 (16.5%) of 109
Positive Only	2 (25.0%) of 8	6 (31.6%) of 19	8 (29.6%) of 27
Total Mortality	7 (13.0%) of 54	26 (12.7%) of 204	33 (12.8%) of 258
Cox Regression Model: HR (95% CI) of Biomarker Gradient for Mortality (p Values)	2.57 (0.92–7.19) (p = 0.072)	2.62 (1.51–4.54) (p = 0.001)	2.62 (1.61–4.25) (p < 0.001)
Non-Circulatory Deaths:			
Negative Only	7 (30.4%) of 23	16 (16.2%) of 99	23 (19.9%) of 122
No Assays or Neg & Pos	9 (39.1%) of 23	17 (19.8%) of 86	26 (23.9%) of 109
Positive Only	4 (50.0%) of 8	4 (21.1%) of 19	8 (29.6%) of 27
Total Mortality	20 (37.0%) of 54	37 (18.1%) of 204	57 (22.1%) of 258
Cox Regression Model: HR (95% CI) of Biomarker Gradient for Mortality (p Values)	1.59 (0.87–2.92) (p = 0.134)	1.33 (0.82–2.17) (p = 0.253)	1.47 (1.00–2.16) (p = 0.049)

Conclusions: Baseline (1974) upper quartile values of serum A-SAA and sIL-2Rα predicted long-term (18 to 35 yrs) mortality (p < 0.001), mainly attributable to circulatory (p < 0.001), than other (p = 0.049), causes of death. This novel biomarker deserves further testing as a long-term predictor of cardiovascular mortality.

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A Prediction Score To Differentiate Rheumatoid Arthritis from Undifferentiated Arthritis in an Early Arthritis Cohort. Christian Waimann[2], Fernando DalPra[2], Jimena Hogrefe[2], Josefina Marcos[2], Soledad Retamozo[2], Francisco Caeiro[2], Luciana Casalla[2], Mariana Benegas[2], Oscar Rillo[2], Horacio Berman[2], Alberto Berman[2], Rodrigo García Salinas[2], Antonio Catalán Pellet[2], Federico Ceccato[2], Sergio Paira[2], Juan Carlos Marcos[2], José Maldonado Cocco[2], Luis Cattogio[2], Enrique Soriano[2] and Gustavo Citera[1]. [1]CONAART, Buenos Aires, Argentina, [2]CONAART, Argentina

Objective: to identify predictor factors for progression into rheumatoid arthritis (RA) in patients with undifferentiated arthritis (UA).

Methods: A prediction score was developed using data from CONAART (Argentine Consortium for Early Arthritis), the first early arthritis cohort in Argentina (n=714). Patients with at least one swollen joint and less than 2 years of symptoms duration were followed for 6 months. The clinical characteristics associated with RA in univariate analysis were later selected using a logistic regression model. A weighted score was set according to strength of association (odds ratio: OR) of main variables as follows (OR 1 to 2=1 point, OR 2.1 to 4=2 points, OR 4.1 to 8=3 points and OR > 8=4 points), given a total score from 0 to 20. A prediction score of 7 variables (tender and swollen joint count, symmetric involvement, acute phase reactants, rheumatoid factor (RF) positivity and anti-CCP positivity) was obtained. Categorical variables were compared using chi square and Fisher exact test and continue variables using student T test and ANOVA. The discriminative ability of the score to differentiate RA from UA was evaluated using the area under the curve (AUC). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for different cut-off points of the score were calculated.

Results: 619 patients were included (UA=312, RA=307), 515 (83.2%) were women, median age 47 years, median disease duration 6 months. Patients with RA had significantly higher disease activity (DAS28), and worse functional capacity and quality of life compared to UA patients. In the logistic regression analysis, the independent predictive variables for development of RA and their corresponding score were: more than 5 tender joints = 3 points, more than 4 swollen joints = 3 points, symmetric involvement = 2 points, ESR > 22.5 mm/h = 1 point, C-Reactive protein > 8.5 mg/L = 3 points, RF positive = 4 points, Anti CCP positive = 4 points. The AUC value of the score was 0.84 (95% CI: 0.80–0.87). A cut-off value of 9 had sensitivity of 80% and specificity of 81.4%, PPV of 82% and NPV of 81.4% to differentiate RA from UA. The validation of the van der Helm van Mil (A&R 2007;52:433–440) prediction rule in our population showed an AUC of 0.80 (95%CI 0.76–0.83).

Conclusion: The present score had an excellent ability to discriminate between RA and UA using simple variables obtained from daily practice.

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Association of Patient Cost-Cutting Behaviors with Clinical Outcomes, Health Status, and Lost Work Productivity in Individuals with Rheumatoid Arthritis. Susan C. Bolge[1], Ahmad B. Naim[2], Chureen Carter[2], Marco DiBonaventura[3] and Mike Ingham[2]. [1]Centocor Ortho Biotech Services, LLC, Horsham, PA, [2]Centocor Ortho Biotech Services, LLC, [3]KantarHealth

Background: In an effort to reduce rising healthcare costs, there has been a trend in managed care toward greater patient cost sharing. However, in this time of economic recession, high costs may necessitate cost-cutting decisions by patients, especially those with multiple, costly, chronic conditions. This study seeks to quantify cost-cutting behaviors in patients with rheumatoid

arthritis (RA) and assess the association of these behaviors with patient-reported clinical outcomes, health status, and work productivity loss.

Methods: In August 2009, individuals aged ≥18 and reporting an RA diagnosis completed a cross-sectional, self-administered, Internet-based questionnaire. Cost-cutting behaviors were assessed for the prior six months. Differences in outcomes were compared between patients with identified cost-cutting behaviors and those without. Patient-reported clinical outcomes included the Health Assessment Questionnaire (HAQ) and severity of morning stiffness, fatigue, and pain, measured as 1=none experienced to 10=severe. Health status was assessed using the SF-36, and work productivity loss was assessed using the Work Productivity and Activity Impairment questionnaire. Patient demographics and comorbidities were adjusted using linear regression for clinical outcomes and health status and negative binomial regression for lost work productivity.

Results: Of 1580 patients, 41.6% (n=658) reported at least one cost-cutting behavior. The most frequently reported behaviors were delaying RA related physician visits (59.0%), taking RA prescription medication less often (25.7%), and reducing number of RA prescriptions filled (22.9%). After adjustment, cost-cutting behavior was associated with greater functional disability (HAQ: regression coefficient b=0.19, $P<0.001$); severity of morning stiffness (b=0.76, $P<0.001$), fatigue (b=0.80, $P<0.001$), and pain (b=0.84, $P<0.001$); and poorer health status (SF-36 physical component summary: b=-1.75, $P<0.001$ and mental component summary: b=-3.33, $P<0.001$). Among the employed, patient cost-cutting behaviors were associated with 1.39 times ($P<0.001$) the amount of overall work impairment compared to those without.

Conclusion: A substantial proportion of RA patients engage in cost-cutting behaviors which are associated with worsening patient-reported clinical outcomes, poorer health status, and decreased work productivity; however, due to the cross-sectional nature of the study, the direction of these associations cannot be determined. Further research is needed to investigate the potential impact of patient cost sharing on clinical effectiveness and disease progression markers.

Disclosure: S. C. Bolge: Centocor Ortho Biotech Services, LLC, 3; **A. B. Naim:** Centocor Ortho Biotech Services, LLC, 3; **C. Carter:** Centocor Ortho Biotech Services, LLC, 3; **M. DiBonaventura:** Centocor Ortho Biotech Services, LLC, 5; **M. Ingham:** Centocor Ortho Biotech Services, LLC, 3.

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Baseline Factors Related to Response to Conventional DMARD Treatments. Kimberly L. Sterling[1], Gebra Cuyun Carter[1], Susan Messing[6], George Reed[5], Rui Chen[6], Kimberly Kaukeinen[6], Xin Tu[6], David R. Nelson[2], Khaled Sarsour[3], Ronald A. Cantrell[3], Carlos I. Alatorre[3] and Jeffrey Greenberg[4]. [1]Eli Lilly and Co, Indianapolis, IN, [2]Eli Lilly and Co, [3]Eli Lilly and Co, Indianapolis, IN, [4]New York University School of Medicine, New York, NY, [5]University of Massachusetts, Amherst, MA, [6]University of Rochester, Rochester, NY

Background: Heterogeneity of treatment response exists in rheumatoid arthritis (RA), while there is a lack of understanding of genetic and non-genetic factors that predict treatment response. Identifying baseline factors associated with patient response to RA treatment will assist tailoring therapies for patients. This study aimed to determine non-genetic baseline factors associated with treatment response at one year among RA patients initiating conventional disease-modifying antirheumatic drugs (DMARD) therapy with no previous biologic use.

Methods: The study included RA patients previously naïve to biologic therapy who initiated a conventional DMARD and had at least one year of follow-up in the Consortium of Rheumatology Researchers of North America (CORRONA) registry. Treatment response was assessed using the Clinical Disease Activity Index (CDAI) at one year (±3 months), evaluated in both a continuous (change from baseline to endpoint) and categorical (endpoint score ≤19.6 and improvement from baseline > 4.3) manner. The registry allowed for exploration of a broad set of baseline factors including socio-demographics, clinical factors, patient reported measures (i.e. behaviors, comorbidities, function), and prior healthcare use. Multivariate stepwise regression using backward elimination was conducted to determine variables significantly associated ($p<0.05$) with improvement.

Summary of the Results: A total of 1,350 patients met the entry criteria, and 893 (66%) of those had complete data and were included in the multivariate analyses. Of those with complete data, the mean age was 59.7 years, 662 (74%) were female, 750 (84%) were white, and the mean initial CDAI score was 14.5. The following baseline factors were associated with greater CDAI improvement (continuous) ($R^2=0.39$): higher initial CDAI score (β=-0.598, $p<0.0001$), lower BMI (β=0.086, p=0.05), lower modified Health Assessment Questionnaire (mHAQ) score (β=3.738, $p<0.0001$), no history of infection (β=-1.336, p=0.03), no use of analgesics (β=1.303, p=0.04), and not being disabled (β=-3.839, p=0.0002). For the categorical CDAI improvement outcome, the odds of improvement in disease activity is greater for those at baseline with a higher initial CDAI score (odds ratio [OR]=1.101, $p<0.0001$), younger in age (OR=0.986, p=0.03), light to no alcohol consumption history (moderate/heavy vs none/light, OR=0.302, p=0.01), and are not disabled (yes vs no, OR=0.413, p=0.002) ($R^2=0.22$).

Conclusions: This study identified that higher baseline disease activity and not being disabled were consistently associated with treatment response (continuous and categorical CDAI). Additional exploration is needed to understand the predictive role of variables such as BMI, physical function, history of infections, and analgesic use, which were inconsistently associated with response; and differences in sets of risk factors between medication classes (e.g. conventional vs biologic DMARDs). With a broad set of predictors, clinicians will be able to tailor treatment based on baseline characteristics to improve patient outcomes.

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Cerebrovascular and Venous Thromboembolic Events Predict Mortality in Rheumatoid Arthritis. A. Kirstin Bacani[2], Sherine E. Gabriel[2], Cynthia S. Crowson[1] and Eric L. Matteson[2]. [1]Rochester, MN, [2]Mayo Clinic, Rochester, MN

Purpose: While survival in patients with rheumatoid arthritis (RA) appears to have improved in recent years, RA patients still experience excess mortality compared to patients without RA. The purpose of our study was to examine the potential of cerebrovascular events, venous thromboembolic events, and peripheral arterial events as predictors of mortality in RA patients.

Methods: A population-based inception cohort of RA patients who fulfilled 1987 ACR criteria for RA between 1/1/1980 and 12/31/2007 was assembled and followed until death, migration, or the present. The occurrence of cerebrovascular events (hemorrhagic stroke, nonhemorrhagic stroke, transient ischemic attack or amaurosis fugax), venous thromboembolic events (deep venous thrombosis or pulmonary embolism), and peripheral arterial events (abdominal aortic aneurysm, renal artery stenosis, peripheral vascular disease, or arterial thromboembolism), was ascertained by review of the medical record. Cox proportional hazard models were used to examine these noncardiac vascular disease events as predictors of mortality after adjusting for risk factors.

Results: The study population included 814 RA patients (mean age [SD] 55.9 [15.7] years; 68% women). The average length of followup was 9.6 [6.9] years. In this cohort, 204 have died. After adjusting for age, sex, calendar year of RA incidence, smoking status, rheumatoid factor positivity, history of alcoholism, obesity, cardiovascular disease (including hospitalized or silent myocardial infarction, heart failure, revascularization, angina, or physician diagnosis of coronary artery disease), renal disease, liver disease, cancer, metastases, dementia, severe extra-articular manifestations (i.e. pleuritis, pericarditis, Felty's syndrome, RA vasculitis, scleritis, neuropathy or glomerulonephritis), and steroid use, we found cerebrovascular events (hazard ratio [HR]: 1.60, 95% confidence interval [CI]: 1.06, 2.43; p=0.026) and venous thromboembolic events (HR: 2.52; 95% CI: 1.61, 3.95; $p<0.001$) were independent predictors of mortality. Additional adjustment for RA therapies (methotrexate, hydroxychloroquine, other disease modifying antirheumatic drugs, and biologics) did not change these results.

Conclusion: Our findings suggest that cerebrovascular events and venous thromboembolic events are associated with increased mortality in RA patients. Further study is needed to understand the contribution of these events to the excess mortality in RA patients.

Disclosure: A. K. Bacani: None; **S. E. Gabriel:** None; **C. S. Crowson:** None; **E. L. Matteson:** None.

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Changes in Corticosteroid Use after DMARD Initiation in Patients with Rheumatoid Arthritis. Vivian K. Kawai[5], Carlos Grijalva[6], Patrick Arbogast[6], Jeffrey R. Curtis[4], Daniel Hal Solomon[1], Elizabeth Delzell[3], Rita Ouellet-Hellstrom[2], Ed Mitchel[6], C. Michael Stein[5] and Marie R. Griffin[6]. [1]Brigham and Womens Hospital, Boston, MA, [2]FDA, [3]University of Alabama, [4]University of Alabama–Brimingham, Birmingham, AL, [5]Vanderbilt University, Nashville, TN, [6]Vanderbilt University

Background: Disease modifying anti-rheumatic drugs (DMARDs) and corticosteroids are both used to treat rheumatoid arthritis (RA). Corticosteroids have dose-related side effects, and therefore, clinicians strive to minimize their use. Biologic and non-biologic DMARD use reduces RA disease activity and thus would be expected to result in decreased use of corticosteroids. There is, however, little information about the effect of DMARD therapies on corticosteroid use. Thus, we examined the hypothesis that initiation of DMARD therapies decrease corticosteroid use.

Methods: We assembled 4 retrospective cohorts of patients with RA from 1998 to 2005 enrolled in Tennessee's Medicaid Program (TennCare), Kaiser Permanente Northern California (KPNC), Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE), and multi-State Medicaid programs (MAX) and identified 5 mutually exclusive patient groups initiating DMARD regimens: new methotrexate (MTX) without (new MTX) or with (MTX) use of other non-biologic DMARDs in the previous year; new hydroxychloroquine and/or sulfasalazine with use of MTX in the previous year (HCQ/SSZ); new leflunomide with use of MTX in the previous year (LEF); and new TNF-α antagonists. We used McNemar's test to assess within-person differences in any use of oral corticosteroids (>= 1 prescription) during the 6 months before versus 6–12 months after starting one of the study DMARD regimens.

Results: We identified 32476 initiators of study DMARD regimens who had a full year of baseline and one follow-up year of data available: 13% from TennCare, 18% from KPNC, 7% from PACE and 62% from MAX. In all groups, the percentage of users of corticosteroids increased in the 0–6 months before new DMARD initiation compared to the previous 6 months, likely representing worsening of the disease that led to the new DMARD regimen. In most groups, the percentage of users of corticosteroid then decreased significantly by 6 to 12 months after DMARD initiation (Figure 1). Across the 4 datasets, the absolute decrease in % of RA patients using corticosteroids ranged from 8.0% to 10.9% in new MTX users and 9.3% to 12.1% in MTX users (all P<0.05). Absolute changes ranged from 7.1% to 11.5% in group HCQ/SSZ users, 4.0% to 6.9% in group LEF users, and 3.6% to 11.5% in TNF-α antagonists (all changes <0.05 except for PACE participants who had both the lowest % corticosteroid use at DMARD initiation and the lowest absolute change).

Conclusions: The percentage of patients with RA receiving corticosteroids increased in the 6 months prior to the initiation of a new DMARD regimen and then decreased 6–12 months after initiation. Decreased corticosteroid use may be due to DMARD effectiveness or other reasons for disease improvement.

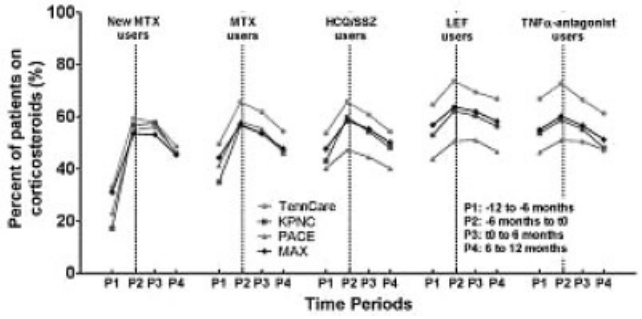

Figure 1. Changes in percent of users of corticosteroid after initiation of RA therapies.

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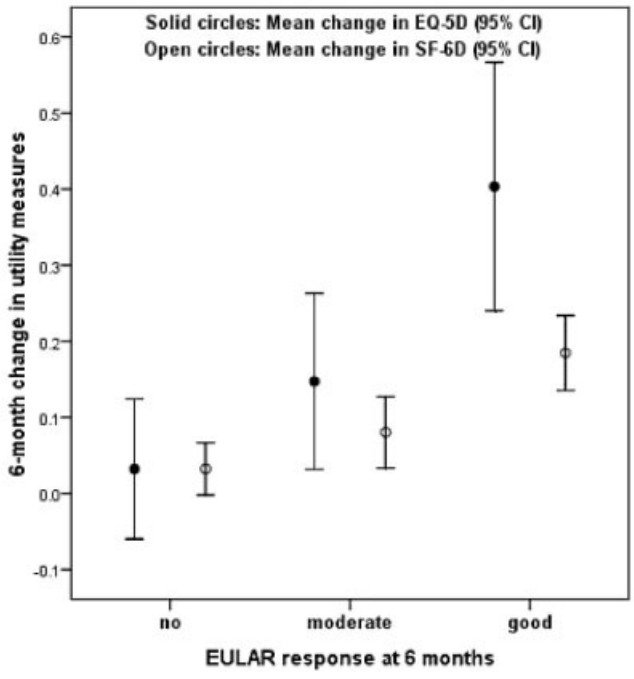
Changes in EQ-5D and SF-6D during Rituximab Treatment—Results from the CERERRA Collaboration. Elisabeth Lie[4], Katerina Chatzidionysiou[7], Evgeny Nasonov[9], Galina Lukina[9], Cem Gebay[12], Karel Pavelka[2], Dan Nordström[6], Matija Tomsic[13], Merete L. Hetland[3], Ulrik Tarp[1], Piet L. C. M. van Riel[10], Juan J. Gomez-Reino[11], Ronald Van Vollenhoven[8] and Tore K. Kvien[5]. [1]Aarhus University Hospital, Aarhus, Denmark, [2]Charles University, Prague, Czech Republic, [3]Copenhagen University Hospital at Glostrup/DANBIO Registry, Copenhagen, Denmark, [4]Diakonhjemmet Hospital, Oslo, Norway, [5]Diakonhjemmet Hospital, Oslo, Norway, [6]Helsinki University Central Hospital, Helsinki, Finland, [7]Karolinska University Hospital, Stockholm, Sweden, [8]Karolinska University Hospital, Stockholm, Sweden, [9]Moscow Institute of Rheumatology, Moscow, Russian Federation, [10]Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, [11]University Hospital of Santiago, Santiago, Spain, [12]University Hospitals of Geneva/SCQM Registry, Geneva, Switzerland, [13]University Medical Center of Ljubljana, Ljubljana, Slovenia

Background: Rituximab (RTX) has been shown to be efficacious in rheumatoid arthritis (RA) pts failing DMARDs or anti-TNF. However, biologic therapies are costly, raising an interest in the economics of treatment. Utility instruments (e.g EQ-5D, SF-6D) yield health state utility values for cost-utility analyses. The purpose of this study was to assess the 6-month utility gain across disease characteristics and levels of clinical response in pts treated with RTX, and to compare the performance of EQ-5D and SF-6D in patients in whom both measures had been recorded.

Methods: In a data set of patients treated with RTX (n=2265, from 10 European registries), EQ-5D and/or SF-36 had been recorded in a subset of Russian, Swiss and Norwegian pts. Mean ΔEQ-5D was compared across baseline characteristics and EULAR response categories by two samples t test and ANOVA. ΔEQ-5D and ΔSF-6D within patients were compared by paired samples t test & Wilcoxon's test.

Results: 192 pts (111 Russian, 75 Norwegian, 6 Swiss) had EQ-5D recorded at baseline and 6 months: These pts were younger than the other pts (51 vs 54 yrs, p=0.002) and more often treated with concomitant DMARDs (82% vs 74%, p=0.008). Other baseline characteristics were similar. 83% were female, 73% RF pos, 76% aCCP pos. Median(IQR) # of previous biologics/synthetic DMARDs was 1(0–2)/3(2–4); 41% were given RTX as the first biologic. Mean(SD) disease duration was 11.2(7.8) yrs, DAS28 5.9(1.3) and EQ-5D 0.29(0.34) [median(IQR) 0.52(-0.02–0.59)]. 21%/44%/35% achieved good/moderate/no EULAR response at 6 months, mean(SD) ΔDAS28 was −1.8(1.4) (both N.S. vs remaining pts) and ΔEQ-5D was 0.22(0.32) [median(IQR) 0.07(0.00–0.53)]. EQ-5D changes were not significantly different when comparing groups based on RF, gender, DMARD co-therapy, or # of previous biologics. There was a trend towards larger utility gain in aCCP pos vs neg pts (mean(SD) 0.21(0.32) vs 0.08(0.22), p=0.06), and mean ΔEQ-5D was larger in pts achieving EULAR response (mean(SD) 0.37(0.30)/0.24(0.32)/0.13(0.31) for good/moderate/no response, p=0.001; good vs no response post-hoc Bonferroni p=0.001). 68 pts had 6-month changes in both EQ-5D and SF-6D available. The two instruments yielded different results for change in utility values, figure shows change across clinical response. For patients achieving EULAR good response utility gain was significantly larger measured by EQ-5D vs SF-6D (mean/median 0.40/0.41 vs 0.18/0.22, paired t test p=0.002/Wilcoxon p=0.007). For individual pts the difference btw EQ-5D/SF-6D was 0.50–0.75 units.



Conclusion: This group of RA pts treated with RTX in a real life setting gained a mean of 0.22 units in EQ-5D during the first 6 months. Improvement in EQ-5D was associated with clinical response. The data also demonstrated that changes in EQ-5D and SF-6D can differ considerably, and thus the choice of instrument may substantially influence the cost-utility results.

Disclosure: E. Lie: Abbott Immunology Pharmaceuticals, 5, Bristol-Myers Squibb, 8, Roche, 5; **K. Chatzidionysiou:** Roche, 5; **E. Nasonov:** Roche, 5; **G. Lukina:** Roche, 5; **C. Gebay:** Roche, 5; **K. Pavelka:** Roche, 5; **D. Nordström:** Roche, 5; **M. Tomsic:** Roche, 5; **M. L. Hetland:** Roche, 5; **U. Tarp:** Roche, 5; **P. L. C. M. van Riel:** Roche, 5; **J. J. Gomez-Reino:** Roche, 5; **R. Van Vollenhoven:** Roche, 5; **T. K. Kvien:** Abbott Immunology Pharmaceuticals, 5, Bristol-Myers Squibb, 5, Merck Pharmaceuticals, 5, Pfizer Inc, 5, Roche, 5, UCB, Inc., 5, Wyeth Pharmaceuticals, 5.

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Comparison of the Efficacy of Tocilizumab and TNFα-Inhibitors on the DAS28 in "Real Life" Conditions in Rheumatoid Arthritis (RA) Patients after DMARD Failure. Jörg Kaufmann[2], Eugen Feist[1], Hagen Schmidt[3], Anne-Eve Roske[4] and Adrian Kielhorn[4]. [1]Campus Charité Mitte, Med. Klinik Abt. Rheumatologie u. Klin. Immunologie, Berlin, Germany, [2]Praxis für Innere Medizin und Rheumatologie, Ludwigsfelde, Germany, [3]Praxis für Innere Medizin und Rheumatologie, Berlin, Germany, [4]Roche Pharma AG, Grenzach-Whylen, Germany

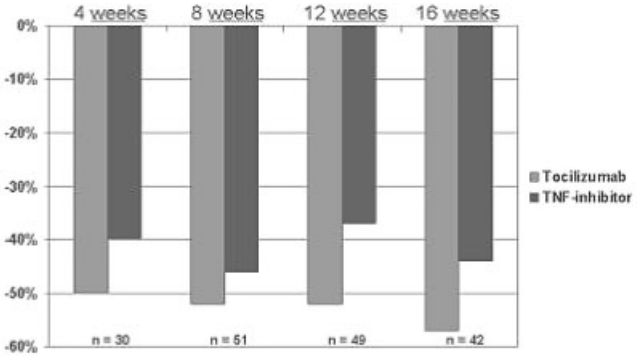
Clinical trials for a direct comparison of efficiency data between TNFα-inhibitors and tocilizumab are not available yet. Meta analysis could demonstrate no differences at least for various TNFα-inhibitors.

Objectives: The aim of this study was to compare the efficacy of TNFα-inhibitors and tocilizumab on the Disease Activity Score (DAS28) in patients with an inadequate response to DMARDs.

Methods: Retrospective, pseudonymous data from RA patients who received their first biologic, were documented. Two cohorts were formed: patients who received a first biologic TNFα-inhibitor (TNF cohort) or tocilizumab (TCZ cohort). Each center documented pseudonymous data of at least 3, maximum of 5 patients per cohort. From each of these groups each center selected the two best patients with justification. DAS28 data at baseline and either 4, 8, 12 or 16 weeks were documented.

Results: Data of 298 patients from 47 centres have been documented. The patients in both cohorts have similar clinical characteristics and can be considered to be representative of RA patients in accordance with the German Registry RABBIT

After 12 weeks the DAS28 in the TCZ cohort had fallen by 52%, which corresponds to a reduction of 2.6 points. In the cohort of TNF, DAS28 decreased by 38% and an absolute value of 1.8 points. For each of the observation dates was a greater reduction in DAS28 of TCZ cohort compared with the TNF cohort found (see figure).



Summary: In RA patients after failure or inadequate response to a DMARD therapy was a greater improvement in DAS28 with a tocilizumab therapy in comparison with a TNFα-inhibitor therapy during the observation period of 16 weeks.

Disclosure: J. Kaufmann: Roche, 5; **E. Feist:** Roche, 2, 5, 6; **H. Schmidt:** Roche, 5; **A.-E. Roske:** Roche, 3; **A. Kielhorn:** Roche, 3.

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Demyelinating Events in Seniors with Rheumatoid Arthritis (RA): A Population-Based Study. Jessica Widdifield[7], Sasha R. Bernatsky[2], J. Michael Paterson[1], Nadia Gunraj[1], Janet E. Pope[5], J. Carter Thorne[4], Alfred A. Cividino[3] and Claire Bombardier[6]. [1]Institute for Clinical Evaluative Science, [2]McGill UHC/RVH, Montreal, QC, Canada, [3]McMaster University, Hamilton, ON, Canada, [4]Southlake Regional Health Care, Newmarket, ON, Canada, [5]St Joseph Health Care London, London, ON, Canada, [6]University of Toronto, Toronto, ON, Canada, [7]University of Toronto

Background: Up until recently, multiple sclerosis and other demyelinating syndromes were reported only rarely in rheumatoid arthritis (RA). However, since the introduction of RA therapies targeting tumour necrosis factor (TNF), numerous case reports have arisen in the literature. Currently there are very few cohort-based assessments of the incidence of demyelinating events in RA, and/or the possible influence of drug exposures. The Ontario Biologics Research Initiative (OBRI) is an innovative undertaking to promote real-world rheumatic drug surveillance. Some of the OBRI analyses make use of Ontario's administrative healthcare databases. Since universal drug coverage occurs comprehensively for Ontario residents aged $\geq$ 65 years, we were able to assess the risk for developing demyelinating events in seniors with RA, and explore for potential drug effects in this sample.

Methods: An RA cohort was assembled from Ontario billing and hospitalization data, 1992–2009. Analyses were limited to subjects aged $>$ 65 with a diagnosis of RA, who filled at least 1 prescription for an oral glucocorticoid, disease-modifying agent (DMARD) or biologic. We excluded any individuals with a diagnosis of a demyelinating event, prior to their entry into the RA cohort. Then, over 1998–2009, we identified all new cases of demyelinating events occurring within this cohort. Our case definition of a demyelinating event was based on one or more hospitalization diagnoses, or at least 2 billing claims diagnoses (at least 8 weeks apart, but within 2 years). Identified cases were matched (on age, sex, and date of cohort entry) to up to 5 controls from the same RA cohort. We calculated the incidence rate of demyelinating events in the cohort of seniors with RA, and described medication use in relationship to these events.

Results: In 85,458 seniors with RA (over 614,915.5 person-years), 51 demyelinating events occurred. This provides an event rate of 8.3 events/100,000 person-years, which is comparable to recent figures for demyelinating events for seniors in the Canadian general population. Biologic exposures were rare in our cohort, and none of the cases of demyelinating events in our RA cohort had been exposed to an anti-TNF agent at the time of the event, or within the 12 months preceding the event. In both cases and controls, the most common medication exposures were NSAIDs/COXIBs, glucocorticosteroids, hydroxychloroquine, and methotrexate.

Conclusions: We provide novel data on the incidence of demyelinating events in a cohort of seniors with RA. The incidence rate of 8.3 new demyelinating events/100,000 patient-years is comparable to recent rates for Canadian seniors. None of these events appeared to have been triggered by anti-TNF drug exposures. Estimating the risk for demyelinating events due to these agents was problematic in our sample, given relatively low drug exposure rates.

Disclosure: J. Widdifield: None; **S. R. Bernatsky:** None; **J. M. Paterson:** None; **N. Gunraj:** None; **J. E. Pope:** None; **J. C. Thorne:** None; **A. A. Cividino:** None; **C. Bombardier:** None.

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Descriptive Epidemiology of Adult Rheumatoid Arthritis in an Insurance Claims Database. Martin M. Crane[1], Maneesh Juneja[3], Fayaz A. Aziz[3], Regina H. Kurrasch[2], Myron E. Chu[2], Emilia Quattrocchi[3], Stephanie Manson[4] and David J. Chang[2]. [1]GlaxoSmithKline R&D, Research Triangle, NC, [2]GlaxoSmithKline R&D, King of Prussia, PA, [3]GlaxoSmithKline R&D, [4]United Biosource

Background: Our goal was to estimate the incidence and prevalence of rheumatoid arthritis (RA) in a US administrative medical claims database. Databases such as this one contain the majority of encounters and prescriptions for any disease that can be defined using an ICD9 code in an insured US population ("real-world" practice); however, the major disadvantages are lack of any clinical information, left-censoring (incom-

plete medical history)and right-censoring (truncated follow-up) of data, and under-representation of the elderly due to Medicare coverage at age 65 years.

Methods: The study population was defined as all patients ≥ 18 years having medical information for the entire 4.75-year period of 1-Jan-2004 to 30 Sept-2008 (N=4.65 million) in a health claims database (IMS LifeLink: Health Plan Claims Database, PharMetrics, Inc, Watertown, WA.) Prevalent RA was defined as having at least one occurrence of a code (ICD9 7140–7142) prior to 2006, and one occurrence during 2006, with the two occurrences at least 30 days apart. Incident RA was defined as no RA codes prior to 2006, and two codes at least 30 days apart during the interval 1-Jan-2006 to 31-March 2007. Polyarthritis or undifferentiated arthritis (7149) was not part of the algorithm; however, an "aggressive" incident subset was defined based on having >8 RA physician visits in the 12 months post diagnosis and no prior 7149 code.

Summary: Prevalence was 0.65% overall (0.92% in females and 0.36% in males) and incidence was 0.07% (0.10% female; 0.04% male). Median age at the occurrence of the first RA code was 57.0 in the incident and 55.0 years in the prevalent patients and, prior to 2006, 47.8% of the latter had received at least one prescription for methotrexate. Other connective tissue diagnoses (based on two occurrences 30 days apart) were present in 7.9% and 9.7% of the incident and prevalent patients respectively. In the 12 months after the first RA visit, 64.0% of incident and 55.1% of prevalent patients were prescribed a non-biologic DMARD and 20.4% and 22.1% were prescribed an anti-TNF. The "aggressive" subset was approximately 11% of all incident patients.

Conclusions: Prevalence rate (0.65%) was lower than in other cohorts (Mayo Clinic – 0.72%; UK Norfolk– ~0.80%) that used ACR diagnostic criteria and fully captured RA in the aged. Incidence (0.07%) was greater than reported in either prior cohort (0.04% and ~0.025% respectively for Mayo Clinic, US and Norfolk, UK). Claims databases probably underestimate the true prevalence of RA but may better reflect the proportion of patients actively seeking care; incidence is likely to be overestimated due to left-censoring.

Disclosure: M. M. Crane: None; **M. Juneja:** None; **F. A. Aziz:** None; **R. H. Kurrasch:** None; **M. E. Chu:** None; **E. Quattrocchi:** None; **S. Manson:** None; **D. J. Chang:** None.

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Different Factors Are Important for RA Patients and Rheumatologists Regarding DMARD Escalation. Laura van Hulst[2], Wietske Kievit[1], Piet van Riel[2] and Liana Fraenkel[3]. [1]Radboud University Nijmegen Medical Centre, Department of Rheumatology, Nijmegen, The Netherlands, [2]Radboud University Nijmegen Medical Centre, Department of Rheumatology, [3]Yale University School of Medicine, Department of Medicine, VA Connecticut Healthcare System, Section of Rheumatology

Background: Studies showed that treatment is not always escalated in RA patients with active disease which might by explained by differences in how rheumatologists and patients prioritize the factors relevant to the decision to escalate DMARDs.We determined which factors are most important to patients and rheumatologists in deciding whether or not to escalate DMARDs and if the importance that patients and rheumatologists assign to these factors differs.

Methods: We administered a Maximum Difference Scaling survey to 106 Dutch rheumatologists and 93 RA patients. The survey was composed out of 58 factors related to DMARD escalation. Respondents were presented with 24 choice tasks. For each choice, composed out of 5 items, respondents were asked to indicate the factor that was most important to them in their decision whether or not to escalate DMARDs. The design of the survey was determined by the Sawtooth Software ®. Data were analyzed using Hierarchical Bayes modelling resulting into individual item importance scores (IS) ranging from 0 to 100. Independent sample t-tests were performed to compare the importance scores of the top 5 reasons amongst rheumatologists and patients.

Results: Patients' mean age was 60.2 (sd: 12.6) years, mean disease duration was 12.3 (sd: 12.6) years, and 66% were female. Rheumatologists' mean age was 47.2 (sd: 9.3) years, 51% were male, The 5 most important reasons to escalate DMARDs for rheumatologists were: number of swollen joints (mean IS: 5.2; sd: 0.4), DAS28 (mean IS: 5.2; sd: 0.5), their global assessment of RA disease activity (mean IS: 5.2; sd: 0.6), worsening of patient's erosions (mean IS: 5.2; sd: 0.6) and RA disease activity now compared to 3 months ago (mean IS: 5.1; sd: 0.6). For patients, the top 5 was: current level of physical functioning (mean IS: 4.2; sd: 1.2), trust in their rheumatologist (mean IS: 4.0; sd: 1.2), number of painful joints (mean IS: 3.5; sd: 1.2), satisfaction with current DMARDs (mean IS: 3.4; sd: 1.4) and overall general health (mean IS: 3.3; sd: 1.5). Figure 1 shows that these 5 items are approximately twice as important for rheumatologists compared to patients (all statistically significant; p<0.001).

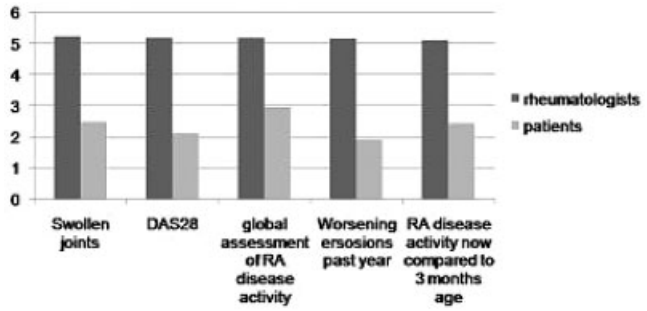

Figure 1. Most important factors that are considered by rheumatologists regarding DMARD escalation. A comparison with patients' importance scores.

A comparison of the 5 most important factors for patients vs rheumatologist showed that patient's trust in the rheumatologist (4.0 vs 0.4), number of painful joints (3.5 vs 3.0) and satisfaction with current DMARDs (3.4 vs 2.3) were statistically more important for patients than for rheumatologists, respectively (p<0.001). Physical functioning (4.2 vs 4.4) and current general health (3.3 vs 3.1) were equally important.

Conclusions: Different factors are important for patients and rheumatologists regarding DMARD escalation. Improved communication between physicians and patients regarding the factors influencing decision making might increase the number of RA patients receiving treatment concordant with published guidelines.

Disclosure: L. van Hulst: None; **W. Kievit:** None; **P. van Riel:** None; **L. Fraenkel:** None.

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DMARD Use for Rheumatoid Arthritis as Reported in the National Ambulatory Medical Care Survey, 1996–2007. Daniel Hal Solomon[4], John Ayanian[3], M. Alan Brookhart[6], Sebastian Schneeweiss[2], Tamara Shaykevich[2], Edward H. Yelin[5] and Jeffrey N. Katz[1]. [1]Brigham & Womens Hosp, Boston, MA, [2]Brigham and Women's Hospital, [3]Brigham and Women's Hospital, Harvard Medical School, [4]Brigham and Womens Hospital, Boston, MA, [5]University of California, San Francisco, CA, [6]University of North Caroline

Background: There is broad agreement on the value of disease modifying anti-rheumatic drug (DMARD) treatment for rheumatoid arthritis (RA). In fact, a DMARD prescription for patients with RA has become a quality measure for various US-based health insurance programs. There are few population-based estimates of the rates of DMARD use for RA. We studied correlates of DMARD use in a large nationally representative US sample.

Methods: The study database consisted of visits in the US National Ambulatory Medical Care Survey (NAMCS), 1996–2007. Visits for RA were defined based on diagnosis codes reported by the providers.

Providers list all medications, up to 8, used by the patient. Medication lists were checked for DMARDs, synthetic or biologic. Unadjusted and adjusted risk ratios were calculated to assess associations between patient and provider characteristics and receipt of any DMARD, as well as a biologic DMARD. All models accounted for the sampling design of NAMCS, using Rlogist in SUDAAN.

Results: From the 317,416 visits recorded in NAMCS over the study period, we identified 859 (0.3%) visits associated with an RA diagnosis. 404 (47%) of these visits had a DMARD noted in the medication list—273 of 377 (72%) visits to rheumatologists and 131 of 482 (27%) to non-rheumatologists. Nine percent of RA visits had a biologic DMARD noted. There was no significant trend towards improved DMARD use rates over the 12 year study period. In adjusted models, black race was associated with reduced DMARD use and use of more medications was associated with increased DMARD use (see Table). Visits to non-rheumatologists were associated with a 60% reduction in DMARD use and a 50% reduction for biologic DMARDs.

Table: Risk Ratios for DMARD use in the National Ambulatory Medical Care Survey, 1996–2007

	Any DMARD* use, risk ratio (95% CI)			Biologic DMARD use, risk ratio (95% CI)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Age						
65+		1.0	1.0		1.00	1.0
45–64y		1.3 (1.1–1.5)	1.1 (0.9–1.4)		1.4 (1.1–1.7)	1.2 (1.0–1.4)
0–44y		1.3 (1.0–1.6)	1.1 (1.0–1.3)		1.5 (1.1–1.8)	1.3 (1.0–1.6)
Gender						
Male		1.0	1.0		1.0	1.0
Female		0.9 (0.8–1.1)	0.9 (0.8–1.1)		0.9 (0.8–1.2)	1.0 (0.8–1.2)
Race/ethnicity						
White non-hispanic	1.00	1.00	1.00	1.0	1.00	1.00
Hispanic	1.1 (0.9–1.4)	1.1 (0.8–1.4)	1.1 (0.9–1.4)	1.1 (0.9–1.4)	1.0 (0.8–1.4)	1.1 (0.9–1.3)
Black	0.7 (0.4–1.1)	0.6 (0.4–1.0)	0.7 (0.5–1.0)	0.7 (0.4–1.2)	0.6 (0.4–1.1)	0.7 (0.5–1.1)
Other race non-hispanic	0.9 (0.5–1.5)	0.8 (0.5–1.4)	1.2 (0.9–1.6)	1.1 (0.9–1.6)	0.8 (0.4–1.4)	1.1 (0.8–1.6)
# of non-DMARD drugs						
Zero		1.00	1.00		1.00	1.00
1-2		1.6 (1.2–2.3)	1.4 (1.1–1.9)		1.5 (1.0–2.1)	1.3 (1.0–1.8)
3+		1.9 (1.4–2.7)	1.8 (1.4–2.4)		1.8 (1.2–2.5)	1.7 (1.3–2.3)
Rheumatologist						
Yes			1.00			1.00
No			0.4 (0.3–0.5)			0.5 (0.4–0.6)

*Any DMARD includes methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, cyclosporine, gold preparations, D-penicillamine, azathioprine, etanercept, adalienumab, infliximab, rituximab, abatacept, anakinra. Model 1 only includes race/ethnicity and calendar year of NAMCS visit. Model 2 also includes age, gender, and number of drugs. Model 3 includes all of Model 2 variables and rheumatologist.

Conclusions: While there is likely misclassification of some visits, the use rate for DMARDs for RA was sub-optimal as reported in NAMCS over the 12-year study period. A visit to a rheumatologist was the most important correlate of DMARD use. Race/ethnicity remained associated with DMARD use after full adjustment. Interventions to improve DMARD use should target improving access to rheumatic disease specialists and identifying and overcoming barriers to DMARD use faced by Black patients.

Disclosure: D. H. Solomon: Abbott Immunology Pharmaceuticals, 2, Amgen Inc., 2, Bristol-Myers Squibb, 9; **J. Ayanian:** None; **M. A. Brookhart:** Amgen Inc., 2, Rockwell Medical, 2; **S. Schneeweiss:** None; **T. Shaykevich:** None; **E. H. Yelin:** None; **J. N. Katz:** None.

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Early Life Socioeconomic Factors and Rheumatoid Arthritis (RA) in Adulthood. Christine G. Parks[2], Aimee A. D'Aloisio[1], Lisa A. DeRoo[1], Huiber Kirstin[3] and Dale P. Sandler. [1]National Institute of Environmental Health Science, Research Triangle Park, NC, [2]National Institute of Environmental Health Science, Research Triangle Park, NC, [3]UNC, School of Public Health, Chapel Hil NC

Objective: To determine whether early life socioeconomic environment is related to prevalence of rheumatoid arthritis (RA) in adult women.

Methods: The study sample included the first 32,017 women (ages 35 to 74; median age 55 years;91% non-Hispanic white, 4% black, 5% other) participating in the Sister Study, a national cohort study of environmental factors and health. Data were obtained from baseline questionnaires. Cases were defined as women reporting doctor-diagnosed RA, with current or past use of disease modifying anti-rheumatic drugs (DMARDs) or steroids for RA, and history of bilateral joint swelling lasting 6 weeks or longer. Early life factors included childhood food insecurity, relative household income, highest household education, and parental ages at participants' birth. Odds Ratios (OR) and 95% Confidence Intervals (CI) were estimated by logistic regression, adjusting for age. Fully-adjusted models also included multiple early life factors and race/ethnicity.

Results: We identified 233 (0.7%) women reporting RA diagnosed after age 16 (median age 46 years at diagnosis) who also reported DMARD use or steroids for RA and bilateral joint swelling. Compared to 30,951 women without reported RA, cases were more likely to report childhood food insecurity (13% vs. 8%), younger maternal age (under age 21; 13% vs. 7%), and lower household income and education (chi-squared p-values <0.01). After adjusting for age, significant associations were seen for food insecurity (OR=1.8; 95%CI 1.2, 2.7), low household education (OR=1.7; 95%CI 1.0, 2.9; less than high school versus college degree) and young maternal age (OR=1.8; 95%CI 1.2, 2.9; ages <21 vs. ≥ 32 years at birth). Non-significantly elevated ORs were also seen for low household income and younger paternal age. In mutually-adjusted models, significant associations persisted for food insecurity (OR=1.7) and young maternal age (OR=1.8), and were not confounded by race/ethnicity.

Conclusions: These results suggest lower socioeconomic status in childhood may be related to DMARD-treated RA in women. Few studies have addressed early life factors in RA, but research across a broad spectrum of other diseases supports an important role of early life influences on the immune system in both humans and experimental models. The etiologic pathway linking childhood socioeconomic factors and RA may include maternal and childhood characteristics and environmental exposures, as well as adult socioeconomic status and exposures. Disease severity, reporting, and survival may impact case identification, so these preliminary findings need to be confirmed in incident cases.

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Effect of Disease-Modifying Anti-Rheumatic Drug (DMARD) Exposure on Head and Neck Cancer in a National Cohort of Veterans with Rheumatoid Arthritis. Christopher R. Phillips[2], Angelique L. Zeringue[3], Jay R. McDonald[1], Seth A. Eisen[3], Liron Caplan[4] and Prabha Ranganathan[5]. [1]Division of Infectious Disease, St. Louis Veterans Affairs Medical Center, [2]Division of Rheumatology, Washington University School of Medicine, Paducah, KY, [3]St. Louis Veterans Affairs Medical Center, [4]Univ of CO–Denver Med Sc, Aurora, CO, [5]Washington University School of Medicine, St. Louis, MO

Purpose: A role for virus-induced malignant transformation has been postulated for primary squamous cell carcinoma of the head and neck (HNC). Previous studies have examined the effect of disease-modifying ant-rheumatic drug (DMARD) exposure on the risk of overall malignancy in patients with rheumatoid arthritis (RA). The effect of tumor necrosis factor (TNF) antagonists on the natural history of HNC in RA, which may be detrimental, given the possible viral etiology of these cancers, has not been explored. Our aim was to determine the effect of exposure to TNF antagonists on HNC in terms of incidence, recurrence, and death from HNC in a national cohort of veterans with RA.

Methods: We examined a retrospective cohort of 49,539 patients with an International Classification of Disease, Version 9, (ICD-9) diagnosis of RA and at least one DMARD prescription from the Department of Veterans' Affairs (VA) national administrative data-

bases enrolled between October 1, 1998 and September 30, 2008. Pharmacy data was obtained from national VA databases. Subjects with an ICD-9 code for HNC after entry into the cohort underwent medical record review to confirm the diagnosis of HNC and RA. Details on HNC diagnosis, recurrence, treatment, HNC-related death, and comorbidities were abstracted.

Results: Of 807 patients with an ICD-9 diagnosis of RA and HNC, 255 patients had both RA and HNC after validation by medical record review. Demographic and clinical characteristics of these patients are presented in Table 1. Of these, 65 patients received a TNF antagonist, and 190 received only non-biologic DMARDs. Of the 65 patients exposed to TNF antagonists, 43 were exposed prior to diagnosis of HNC, 20 had continued exposure after diagnosis, and 20 received TNF antagonists only after HNC diagnosis. Of the 255 patients, 201 had HNC remission, 42 had a recurrence or developed a second HNC (at a different site), and 60 had HNC-related death. Of the 40 patients exposed to a TNF antagonist post-HNC diagnosis for whom information was available, 7 developed a recurrence, and 5 had a HNC-related death. The incidence of HNC recurrence and HNC-related death was 27.3 and 18.8 per 1000 patient-years in patients exposed to TNF antagonists after HNC diagnosis compared to 29.3 and 30.3 per 1000 patient-years in patients exposed only to non-biologic DMARDs.

Conclusion: Exposure to TNF antagonists does not appear to increase the risk of HNC recurrence or HNC-related death in patients with RA compared to exposure to non-biologic DMARDs. The use of TNF antagonists may be safe in patients with RA and head and neck cancer with careful monitoring.

	Exposed only to non-biologic DMARDs	Exposed to TNF antagonists
Number	190	65
Age (std dev)	62.9 (9.1)	64.7 (9.2)
Male gender (%)	188 (99.0%)	64 (98.5%)
White race (%)	57 (87.7%)	171 (90.0%)
Smoker (%)	180 (94.7%)	59 (90.8%)
Alcohol Abuse (%)	132 (69.5%)	51 (78.5%)
Other Cancers (%)	13 (6.8%)	2 (3.1%)

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Elaboration and Validation of a Questionnaire To Assess the Impact of Rheumatoid Arthritis (RA) on Sexuality, with Patient Involvement: QUALISEX. Laure Gossec[2], Catherine Solano[4], Simon Paternotte[2], Catherine Beauvais[3], Christelle Sordet[6], Philippe Gaudin[1] and Aleth Perdriger[5]. [1]Grenoble University Hospital, France, [2]Paris Cochin University Hospital, France, [3]Paris Saint Antoine University Hospital, France, [4]Paris, France, [5]Rennes University Hospital, France, [6]Strasbourg University Hospital, France

Background: RA may have consequences on sexual life either through physical or psychological aspects. These consequences are not evaluated, because current questionnaires do not assess the impact of RA on sexuality. A new questionnaire is needed with a particular attention to face validity and phrasing to avoid missing data in this sensitive field of research.

Objective: To develop a questionnaire assessing the impact of RA on sexuality (QUALISEX) then to assess the psychometric properties of this questionnaire.

Methods: Four-step process. (1) A steering group of 6 patients (5 women, 1 man) with RA, 2 rheumatologists and 1 sexologist elaborated during a one-day focus-group type meeting, an exhaustive list of issues relating to impact of RA on sexuality. Relative weights by importance were obtained for each item. (2) A preliminary questionnaire was developed with input from these patients, with particular attention for phrasing so as to avoid missing data. (3) The questionnaire was assessed by 5 external reviewers (2 physicians, 1sexologist, 2 allied health professionals), then pre-tested in fact-to-face meetings with 10 patients. (4) The questionnaire was tested for psychometric properties in a longitudinal multi center study (missing data, correlations with other disease aspects, reliability).

Results: The list of aspects related to impact on sexuality included 32 aspects, categorised into general aspects (5), psychological issues/ self-esteem (9), couple/relationship issues (7), partner/spouse issues (4) and physical issues (7). The list was brought down to 10 items according to the relative weights of the items. A 10-question questionnaire was constructed, with assessment by numeric rating scales (NRS) from 0 (no impact of RA) to 10 (full impact of RA). Preliminary validation was obtained on 53 patients (44 women, mean age 50.7 years; mean disease duration 15.5 years, mean DAS: 3.5). The Qualisex mean score was 3.3 ± 2.5, missing data was acceptable (7 patients, 13%, had more than one missing question). Qualisex results were correlated with RAID ($R=0.65$), DAS28 ($R=0.55$), fatigue ($R=0.55$), pain (0.54) and mHAQ ($R=0.50$), ($p < 0.001$); but not with demographics, depression or coping. Qualisex was reliable in 40 patients: the intra-class correlation coefficient was 0.83 (95% CI: 0.70–0.91).

Conclusion: A simple (10 NRS) and valid tool investigating impact of RA on sexuality has been developed with the involvement of patients. This tool could be useful to assess the efficacy of oriented interventions or of biologics.

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Geographical Variation of Rheumatoid Arthritis in Stockholm County, Sweden. Henrik Källberg[4], Veronica M. Vieira[2], Jamie E. Hart[1], Karen H. Costenbader[3], Marie Holmqvist[5], Lars Klareskog[6], Lars Alfredsson[5] and Elizabeth W. Karlson[3]. [1]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston Massachusetts, Department of Epidemiology, Harvard School of Public Health, Boston Massachusetts, [2]Department of Environmental Health, Boston University School of Public Health, Boston, MA, [3]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital and Harvard Medical School, Boston Massachusetts, [4]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, [5]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, [6]Rheumatology Unit, Department of Medicine, Karolinska Institutet/Karolinska Hospital, Stockholm, Sweden

Background: Past studies have displayed geographical variation in RA incidence, suggesting the influence of environmental factors on RA etiology. We aimed to investigate geographical distribution of risk of developing RA within Stockholm County, Sweden.

Methods: We studied spatial variation in incident RA among 1095 incident cases and 1251 controls participating in a Swedish case-control study. The Swedish RA study is a population-based case-control study that has collected information from almost all newly diagnosed RA cases in Stockholm County. Analyses were limited to those subjects living in Stockholm County prior to RA diagnosis for cases and prior to matched date for controls and having geocoded addresses. We used Generalized Additive Models (GAM) to create a risk surface, calculate odds ratios and adjust for potential confounding by smoking and socioeconomic status defined through occupation held at the time of diagnosis. We performed a stratified analysis based on presence/absence of antibodies to citrullinated peptides (ACPA).

Results: We found significant spatial variation regarding risk of developing RA in adjusted models ($p < 0.05$, Figure 1.). The spatial variation decreased for some areas but remained significant after adjusting for potential confounding from smoking and socioeconomic status. The stratified analysis for ACPA positive RA cases ($n = 700$) showed similar results as for the non-stratified analysis. We did not manage to estimate valid odds ratios for the RA subgroup without ACPA because of few cases ($n = 395$) in that subgroup.

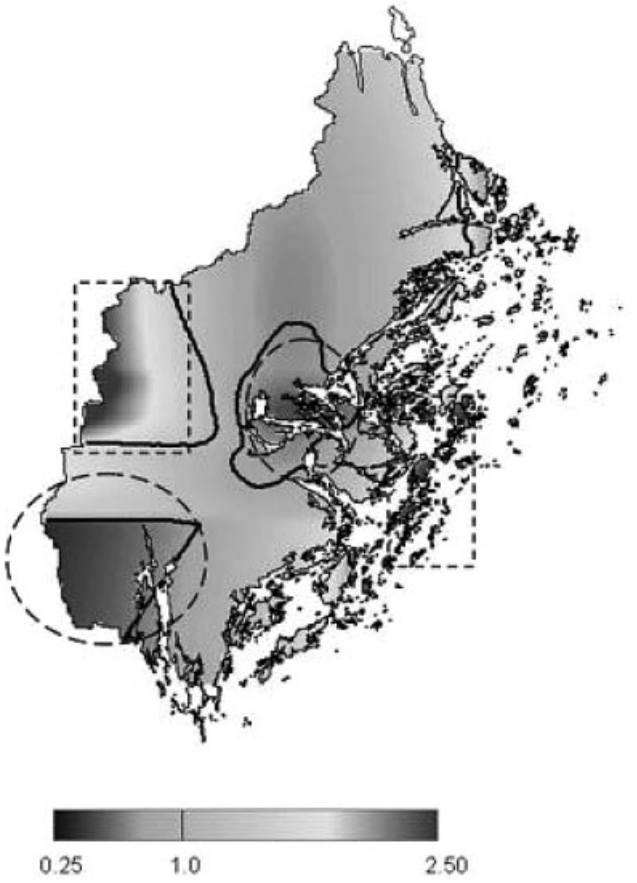

Figure 1. Spatial variation regarding odds ratios of developing RA in Stockholm County. Yellow-Red indicate areas (Dotted squares) associated with increased odds ratios for RA and Blue indicate areas (Dotted circles) with associated with decreased risks of developing RA.

Conclusions: Our analysis indicates that there is geographical variation within Stockholm County regarding risk of developing RA. This variation is not explained by smoking or current socioeconomic status according to occupational status. Therefore we suggest further studies in order to investigate potential sociodemographic or environmental factors to explain this variation.

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H2607—Country of Residence Affects the Ability of Patients with Rheumatoid Arthritis (RA) To Achieve a Favorable Employment Status. Ronald van Vollenhoven[2], Mary Cifaldi[1], Annelies Boonen[4], Sanjoy Roy[1], Naijun Chen[1] and Vibeke Strand[3]. [1]Abbott Laboratories, Abbott Park, IL, [2]Karolinska University Hospital and Karolinska Institute, Stockholm, Sweden, [3]Stanford University, Palo Alto, CA, [4]University Hospital Maastricht, Maastricht, The Netherlands

Background: Clinical trials are conducted in many countries with varying social systems; country of residence may influence access to employment, disability benefits, and attitudes toward missing work for patients (pts) enrolling in RA trials. We examined differences in pts' probabilities of achieving favorable employment status (FES) in the PREMIER Health Economic Companion Study (DE032), based on country of residence.

Methods: PREMIER was a 2-year, randomized controlled trial of adalimumab (ADA), methotrexate (MTX), and ADA+MTX in pts with early RA (<3 years). DE032 was conducted in parallel with PREMIER and collected work productivity data for a large subset of pts. Countries were included if they had >25 employed pts at baseline. FES was defined as retaining baseline employment or gaining employment during the trial. Multivariate logistic regression models were used to evaluate association between FES at the end of the study for pts in each country vs. the other countries as a group. Adjustments were made for age, sex, Health Assessment Questionnaire Disability Index (HAQ DI), total Sharp score (TSS), treatment, and time on treatment. Baseline work-related outcomes were compared by country, including self-reported employed/homemaker status, missed work, % unfit for work at home, hours of missed work, and work productivity measured on a visual analog scale.

Results: Four countries enrolled >25 working pts at baseline: Germany, Australia, the United States (US), and Canada. Approximately half of the pts were employed at baseline in Germany and Canada vs. about two-thirds in Australia and the US. Pts in Germany tended to miss work more often and for more days than pts in other countries. Germany had fewer homemakers vs. other countries. Impacts of RA on performance at work and at home were similar across countries. Multivariate regressions comparing the odds ratios (ORs) for FES by country relative to all other countries showed that residing in the US (OR=2.3, $p<0.0001$) had an independent effect on FES. Age, male sex, HAQ DI, and TSS were predictors for FES. ADA+MTX vs. MTX alone was a predictor of FES in every country studied, whereas ADA monotherapy was not.

Independent Effect of Country of Residence on Favorable Employment Status

	Employed Workers			Homemakers		Favorable Employment Status		
	N	% at Baseline	% Missed Work	% at Baseline	% Unfit for Work	OR	95% CI	P-value
Australia	28	70	46	42	53	1.5	0.7–3.2	NS
Canada	37	49	38	37	43	0.9	0.5–16	NS
Germany	42	52	50	15	50	0.7	0.4–1.2	NS
United States	130	68	33	40	55	2.3	1.5–3.4	<0.0001

Conclusions: Employment status and % missing work, which are driven by health and social policies, differed more than performance at work or at home. Residents of the US were more likely to achieve favorable employment status, perhaps because of greater access to employment, a tendency for employees to miss less work, and greater financial pressure to return to remunerative employment. These results are important in consideration of transferability of data between countries. Patients who received ADA+MTX (vs. MTX) were more likely to achieve favorable employment status in all countries, regardless of health care and social system differences.

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HLA Class II Associations Differ in Indian (Asian) Patients Suffering from RA: Regional Population (Urban and Rural) Surveys Using COPCORD Bhigwan Model. Anuradha Venugopalan[2], Arvind Chopra[3] and Renu Bharadwaj[1]. [1]BJ Medical College, Pune, India, [2]Center for Rheumatic Diseases, Pune, India, [3]Center for Rheumatic Diseases

The prevalence of RA and its association with HLA Class II alleles has varied considerably in different ethnic groups and populations. The data from Indian (Asian) studies, largely hospital based, is limited and supports association with HLA DRB1*04. We reported a striking prevalence (0.55%) of RA (ACR) in Bhigwan rural community but association with HLA DRB1*04 alleles was negligible (Chopra. Arthritis Rheum 2000: 7(Suppl)S71). Later, we completed 8150 population survey (house-house) in neighboring urban Pune using a similar COPCORD (Community oriented program for control of Rheumatic Diseases) Bhigwan model and found an unusually low prevalence (0.3%) of RA (Chopra. J Rheumatol 2009; 36:614). Seropositive RF (nephlometry, cut off 40 IU/ml) and anti-CCP (second generation ELISA, cut off 5 RU/ml) was 45% and 59% in Bhigwan: corresponding 57% and 89% in Pune. There were several other differences found in the results from the surveys. We decided to determine HLA associations of RA in Pune and Bhigwan population based cohorts which included post survey incident cases. After ethic committee approval, consent-

ing patients were bled. 101 rural and 54 urban subjects, ethnically matched and unrelated, were selected as healthy controls. HLA Class II typing for DRB1 (34), DQ (A1=10, B1=21) and DP (A1=5, B1=21) region alleles was performed by Polymerase Chain Reaction using sequence specific primers: number of alleles tested shown in parenthesis.

Results: Table 1 shows significant OR of alleles and shared epitope (SE) genotype; 95% confidence interval (CI) is shown in parenthesis.

	RURAL Bhigwan (n=55)	URBAN Pune (n=37)
Allele		
DRB1*1001	3.92 (1.57, 9.78)*	1.19 (0.41, 3.47)
DQA1*0103	3.72 (2.09, 6.62)*	3.07 (1.33, 7.07)*
DQB1*0303	4.15 (1.89, 9.10)*	1.04 (0.27, 3.95)
DPB1*0201	2.29 (1.03, 5.07)*	0.80 (0.24, 2.61)
DPB1*0401	0.68 (0.34, 1.33)	3.55 (1.56, 8.08)*
SE Genotype		
SE+/x	1.96 (0.86, 4.44)	1.10 (0.87, 5.25)
QKRAA/x	5.91 (0.24, 147.71)	4.74 (0.25, 115.14)
QRRAA/x	0.10 (0.01, 1.85)	1.58 (0.51, 14.94)
RRRAA/x	3.20 (1.14, 8.97)*	0.74 (0.49, 3.79)
SE+/SE+	1.96 (0.12, 32.0)	8.13 (0.39, 152.97)

*P<0.05

DRB1*04 and *01 were conspicuous by their absence/low frequency. Though not significant, HLA-DQA1*0101 and HLA-DQB1*0601 was more frequent in seropositive (RF) RA patients. None of the alleles tested showed significant association with anti-CCP antibody or articular deformities. None of the haplotype chosen showed significant association with RA or its selected features.

Conclusions: This COPCORD study demonstrated HLA Class II including SE associations of RA in an ethnically distinct Indian (Asian) community. To an extent, our small RA sample size is offset by the community study design and population sampling frame.Our results differ from several Caucasian and other ethnic studies and support the complex gene-environment interactions in the etiology of RA.

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Hospitalizations Following Heart Failure Diagnosis in Rheumatoid Arthritis Patients. Cynthia S. Crowson, John M. Davis III, Veronique L. Roger, Eric L. Matteson, Terry M. Therneau and Sherine E. Gabriel. Mayo Clinic, Rochester, MN

Purpose: Patients with rheumatoid arthritis (RA) suffer from an excess burden of cardiovascular disease, especially heart failure (HF). In addition, RA patients have a higher mortality rate following HF diagnosis compared to patients without RA. Hospitalizations in patients with HF are a major public health problem. The purpose of our study was to compare the rate of hospitalizations and length of stay after HF diagnosis in patients with and without RA.

Methods: A population-based inception cohort of RA subjects who fulfilled 1987 ACR criteria for RA and subsequently developed HF (Framingham diagnostic criteria) between 1-1-1987 and 7-1-2008 was assembled and compared to an age, sex and calendar year matched (3:1) sample of HF patients without RA from the same population. Patients in both groups were followed until death, migration, or 1-1-2010 and all hospital admission and discharge dates were obtained. Person-year methods were used to estimate hospitalization rates. Andersen-Gill models, a modification of Cox models accounting for multiple hospitalizations per patient, were used to compare hospital admission rates between the groups.

Results: The study included 548 HF patients (137 with RA and 411 non-RA). Both groups had mean age of 77 (s.d. 10) years with 64% women. The RA patients were followed up for a mean of 3.9 years (528 person-years) after which the majority (83%) were deceased; similarly for the non-RA patients the mean follow-up was 4.8 years (1991 person-years)and 72% died. During this time RA patients experienced a higher rate of hospitalization (1.09 hospitalizations per year compared to 0.88 per year for non-RA; p<0.001). Thus, RA patients experienced 20% more hospitalizations (hazard ratio: 1.2; 95% confidence interval: 1.01, 1.5; p=0.038) compared to non-RA patients In addition the length of stay per hospitalization was on average 0.66 days longer for the RA patients compared to the non-RA patients (p=0.025). Significant independent predictors of hospitalization among patients with RA and HF include male gender, duration of RA, ischemic heart disease, diabetes, comorbidities (cerebrovascular disease, ulcers, renal disease, and cancer). In addition, steroid users were more likely to be hospitalized, even after adjusting for all other significant predictors (hazard ratio: 1.4; 95% CI: 1.03, 1.8; p=0.03).

Conclusion: Patients with RA and HF have a higher rate of hospitalization than HF patients without RA and they experience longer hospital stays. A complex constellation of comorbidities and other factors, including steroid use, are associated with the risk of hospitalization for RA patients with HF. More research is needed to improve the outcomes for RA patients with HF.

Disclosure: C. S. Crowson: None; **J. M. Davis III:** None; **V. L. Roger:** None; **E. L. Matteson:** None; **T. M. Therneau:** None; **S. E. Gabriel:** None.

68 WITHDRAWN

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Importance of Changes in People/Patient Reported Outcomes in Rheumatoid Arthritis Patients Treated with Anti-TNF Therapies. The Example of the RAID (Rheumatoid Arthritis Impact Disease) Score after Etanercept Therapy. Maxime Dougados[2], Mahaut Ripert[4], Pascal Hilliquin[1], Patrice Fardellone[5], Olivier Brocq[3] and Isabelle Logeart[4]. [1]CH sud Francilien, Corbeil-Essonnes, France, [2]Hôpital Cochin and University of Paris, Paris, France, [3]Hopital Princesse Grace de Monaco, Monaco, [4]Pfizer France, la Défense, France, [5]University Hospital Amiens, Amiens, France

Purpose: OMERACT has emphasized the role of People/Patient Reported Outcomes (PROs) in the evaluation of rheumatic disorders. Under the umbrella of EULAR, a preliminary new score, a patient-derived composite response index, has been elaborated to assess the impact of rheumatoid arthritis (RA), the Rheumatoid Arthritis Impact Disease (RAID) score. The objective was to evaluate the importance of changes in the RAID score in RA patients treated with etanercept.

Methods: *Study design*: Open-label, 12-week duration. *Study treatment*: etanercept 50 mg once a week. *Patients*: adult (>18 years old) with active rheumatoid arthritis (DAS >3.2 and 4 clinical synovitis or CRP >10 mg/l or ESR >28 mm/h). *Outcome measures*: Apart from the RAID score composite index including the 7 following domains: pain, functional disability, fatigue, sleep disturbances, coping and overall assessment of physical and psychological well being, and the DAS, at week 12, the patients were asked whether their condition was acceptable using the PASS (Patient Acceptable Symptom State) question. *Statistical analysis*: Standardized Response Mean (mean change/SD of change) and its 95% confidence interval (Bootstrap method) were calculated to evaluate the magnitude of changes (a SRM over 0.60 is usually considered as clinically relevant). Moreover, the changes in RAID were compared in the groups of patients who achieved or not a PASS at week 12.

Results: Of the 87 screened patients, 81 (female: 72%, age: 54±13 years old, disease duration: 8.4±7.1 years) were enrolled. At baseline, patients had active disease (DAS: 5.5±0.8, CRP: 18.9±33.5 mg/l, painful joints: 10.5±5.6 and swollen joints: 8.5±4.1). During the 12 weeks of the study, 9 patients discontinued the treatment. At week 12, 49% the patients had a DAS below or equal to 3.2 (LDA), and 67% considered their condition as acceptable (PASS).

After etanercept therapy, both the RAID score and its different components improved significantly (table). Moreover, the changes in RAID were of much higher magnitude in the group of patients who achieved (*versus* those who did not) a PASS condition at week 12 (-3.6±1.8 *versus* −0.9±1.8, $p<0.001$).

	Improvement from baseline	
Outcomes	**Mean**	**SD**
DAS 28	−2.1	1.0
	SRM	95% CI
EULAR RAID	1.44	[1.13–1.88]
Pain*	1.49	[1.15–1.97]
Function*	1.25	[0.96–1.68]
Fatigue*	1.16	[0.92–1.47]
Sleep*	0.96	[0.73–1.26]
Physical well being*	1.39	[1.11–1.76]
Emotional well being*	1.16	[0.90–1.51]
Coping*	0.95	[0.65–1.36]

* These domains have been evaluated using a single question and a 0–10 Numerical Rating Scale for the answer.

Conclusion: This study 1) confirms the symptomatic efficacy of etanercept in rheumatoid arthritis; 2) demonstrates the clinically relevant sensitivity of change of both the different domains and the composite index (*e.g.* RAID score) of the PROs' perceived as important for the patients.

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Inadequate Treatment of Rheumatoid Arthritis (RA). K. Andrew Crighton[3], Elliot D. Rosenstein[4], Jared S. Young[5], Yukiko Kimura[2] and Victor S. Sloan[1]. [1]Celgene Corporation, Summit, NJ, [2]Hackensack Univ Medical Ctr, Hackensack, NJ, [3]Prudential Financial, Newark, NJ, [4]Saint Barnabas Medical Center, Livingston, Far Hills, NJ, [5]Thomson Reuters, Ann Arbor, MI

Objective: Assess the adequacy of pharmacologic treatment of patients with RA.

Background: Treatment guidelines recommend DMARDs for all RA patients unless contraindicated. We recently assessed DMARD utilization in a large database and determined that RA patients were receiving suboptimal treatment.

Methods: The initial study used a database of Medical and Pharmacy claims for Prudential's employee and dependent population (PD) (~87,000 lives). Additional data were obtained from Thomson Reuters MarketScan Commercial Database (TRD), which assesses ~ 18 million lives. Not only is TRD substantially larger than PD, but it has a geographic breakdown reflecting a broader experience outside the northeastern US.

There were 849 (PD) and 99,687 (TRD) RA pts defined as:

- ≥18 yrs old as of 2007
- Treated for RA in 2007-8, with claims having these ICD9 codes: 714.0, 714.1, 714.2, 714.3, 714.31, 714.32, 714.33, 714.4, 714.81
- Continuously enrolled in a medical and pharmacy plan in 2007-8

DMARDs included small-molecule and biologic, identified by National Drug Code (Pharmacy Claims) and by Health Care Common Procedure Coding System (Medical Claims).

Subgroups were defined as:

- Non-compliant (NC): 0 days DMARD supply and 0 office procedures for DMARD administration (infusion) in 1 yr.
- Partially compliant (PC): 1 – 269 days DMARD supply or 1 – 11 office DMARD administration in 1 yr.
- Fully compliant (FC): ≥ 270 days DMARD supply or ≥ 12 office DMARD administration in 1 yr.

Subgroups were analyzed by demographic factors (age group, geography, job grade and whether subject was seen by a rheumatologist).

Results: <40% of patients received adequate DMARD therapy, as defined by being FC, and >40% were not on any DMARD (NC). There was no clear relation between adequacy of treatment and age (PD & TRD). Slight geographic differences were observed, with better results in the South and Midwest (TRD). Based on earning level, cost did not appear to be a factor in adequacy of treatment. (PD)

57% were seen by a rheumatologist and were more likely to receive adequate treatment, but 25% were still not on a DMARD. (PD) The most commonly prescribed traditional, self-administered biologic and IV biologic (adjusted to reflect standard dosing intervals) DMARDs were methotrexate, etanercept, and infliximab respectively. (PD)

Limitations: This is a retrospective, observational study based on administrative data. The diagnosis of RA was not independently adjudicated, but the prevalence is consistent with that observed in the US population (~1%). The consistency of the findings in the 2 databases support our initial findings.

Conclusions: Despite the proven benefits of DMARD therapy and recommended guidelines, most RA patients receive inadequate treatment. Adequacy of treatment does not appear to be influenced by age, income, or geography. As in other studies, RA patients in this population are more likely to receive adequate treatment from a rheumatologist, yet even specialist care remains deficient. Our findings warrant further investigation to determine those factors which impede effective treatment of RA patients.

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Increased Risk of Total Mortality with Anti-Cyclic Citrullinated Peptide (Anti-CCP) Positivity among Postmenopausal Women Reporting RA. Rachel H. Mackey[5], Lewis H. Kuller[5], Michael Holers[4], Kevin Deane[4], Brian Walitt[2], Bill Robinson[3], Yuefang Chang[5], Charles Eaton[1], Iulia Grillo[1], Monica Bertoia[1] and Larry W. Moreland[5]. [1]Brown University, [2]Georgetown University, [3]Stanford University, [4]University of Colorado, [5]University of Pittsburgh

Background: The objective of this report is to evaluate the relationship between rheumatoid arthritis (RA) and total mortality among postmenopausal women from the Women's Health Initiative (WHI). Among the 161,808 postmenopausal women aged 50–79 years who enrolled in the Women's Health Initiative (WHI) at baseline and who have been followed up for ~ ten years, we evaluated total mortality risk for women who reported rheumatoid arthritis (RA) at baseline or followup (n= 16,461 (10.2%) compared with women with no reported RA (n=125,372). A study in 2 WHI centers documented that ~15% of self-reported RA was probable clinical RA, and that self-reported use of disease-modifying anti-rheumatic drugs (DMARDS) improved the positive predictive value of the self-report RA to 62%. To further improved classification we measured anti-cyclic citrullinated peptide (anti-CCP), a sensitive and specific marker of RA.

Methods: We sampled n=9,988 (66%) of the white, black, or Hispanic WHI participants who reported RA at baseline or followup and who had adequate stored serum specimens, and measured anti-CCP via 2nd generation ELISA. Cox proportional hazards regression was used to model the relationships of self-reported RA, DMARD use and anti-CCP positivity to total mortality using followup data through April 2009.

Results: At baseline, mean(SD) age was 64(7) years, 24.5% were African-American and 10% were Hispanic. The overall prevalence of anti-CCP positivity was 8.13% (n=812), but was much higher (~51%) among women reporting both RA at baseline and DMARD use (Table.)

Table: Anti-CCP positivity and age-adjusted mortality rates by self-reported RA and DMARD use

Reported RA	DMARD*	Anti-CCP	N	%	Total Mortality rate/1000 Person Years
At BL (or BL & followup					
	No	−	4650	95.8%	14.16 (12.50, 16.06)
	n=4855	+	205	4.2%	22.38 (15.12, 33.34)
	Yes	−	395	49.3%	18.35 (10.84, 32.34)
	n=802	+	407	50.7%	25.74 (17.01, 39.23)
At followup only					
	No	−	3852	96.5%	10.45 (8.91, 12.26)
	n=3992	+	140	3.5%	18.70 (10.65, 33.49)
	Yes	−	279	82.3%	23.14 (10.40, 51.50)
	n=339	+	60	17.7%	32.05 (8.02, 128.14)
Never	n/a	n/a	128,758	-	8.39 (8.15, 8.64)

Age-adjusted all-cause mortality rates were strikingly higher among anti-CCP positive women, regardless of reported DMARD use. Compared with women in WHI who never reported RA, total mortality was also substantially elevated among women who reported RA but did not report DMARD use and who were negative for anti-CCP.(Table) Among those who reported RA at baseline (excluding women with CVD or cancer at baseline), the hazard ratio (HR)(95% CI) for total mortality was 1.74 (1.33, 2.27) for anti-CCP positivity and 1.90 (1.42, 2.53) for reported DMARD use, in Cox models adjusted for age, white blood cell count (WBC), ethnicity, smoking, waist circumference, hypertension, diabetes, education and hormone therapy. Age, smoking, diabetes and WBC were also significant predictors.

Conclusions: Among postmenopausal women in WHI, anti-CCP positivity was associated with a substantial excess in total mortality compared with women who reported RA but were anti-CCP negative (regardless of self-reported DMARD use), or with women who did not report RA. Evaluation of additional risk markers is in progress to understand the reasons for this anti-CCP -associated excess mortality in older women.

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Independent Impact of Statin Discontinuation on Mortality in Patients with Rheumatoid Arthritis: A Population-Based Study. Mary A. De Vera[1], Hyon K. Choi[3], Michal Abrahamowicz[2], Jacek Kopec[1] and Diane V. Lacaille[1]. [1]Arthritis Research Centre of Canada, Vancouver, BC, Canada, [2]McGill University, Montreal, QC, Canada, [3]Univ of British Columbia, Vancouver, BC, Canada

Purpose: Discontinuation of statin therapy is common and associated with increased risk of mortality in the general population, but no corresponding data are available among individuals with rheumatoid arthritis (RA). Since cardiovascular diseases (CVD) are the primary cause of excess mortality in RA, RA-specific data are highly relevant to clinical care of RA. Our objective was to evaluate the impact of statin discontinuation on risk of mortality in individuals with RA.

Methods: We conducted a population-based cohort study of RA patients with incident statin use followed from May 1996 to March 2006 with administrative health data. Exposure was statin discontinuation for ≥3 months at any time during follow-up, measured both as a categorical (y/n) and continuous (time since discontinuation) variable. Primary outcome was death due to all CVD and secondary outcome was death due to all causes. We used Cox's proportional hazards analyses, modeling statin discontinuation as a time-dependent dichotomous variable updated every month and in separate analyses, as a continuous time-dependent variable that increased with every month since discontinuation. Factors known to influence statin discontinuation, CVD, or mortality were considered as covariates, including age, gender, comorbidities (acute myocardial infarction, cerebrovascular accidents, malignancy, infections, chronic obstructive pulmonary disease, gastrointestinal diseases, renal failure, angina, use of diabetes, hypertension, and congestive heart failure medications), and use of medications known to influence cardiac risk (hormone replacement therapy, anticoagulants), all measured at baseline. As well, markers of RA severity (RA medication use [DMARDs, glucocorticosteroids, NSAIDs, methotrexate] and rate of RA-related medical visits) were included as time-dependent covariates. Established risk factors for mortality in RA (e.g., AMI, malignancy) were forced into multivariable models and for putative risk factors, a forward selection procedure with $p \leq 0.20$ criterion for entry, was used.

Results: The cohort of RA patients with incident statin use included 4,102 individuals with 16,144 person-years of follow-up (60% females; mean age 66 years). We documented 467 deaths overall with 198 due to CVD. Statin discontinuation was associated with a 60% increased risk of CVD mortality (adjusted hazard ratio [HR]=1.60 [95%CI=1.15–2.23]). When we modeled statin discontinuation as a continuous time-dependent variable, we found that with each additional month of discontinuation, the risk of CVD mortality was increased by 0.4% (adjusted HR=1.004 [95%CI=1.001–1.016]). We found similar increased risks associated with statin discontinuation in analyses of all cause mortality outcomes (adjusted HR [statin discontinuation as a dichotomous variable]: 1.79 [95%CI=1.46–2.20]; adjusted HR [statin discontinuation as continuous variable]: 1.010; 95%CI=1.002–1.015]).

Conclusion: These population-based data indicate that RA patients who discontinue statins have a higher risk of death from cardiovascular diseases and from all causes. Findings emphasize the importance of compliance with statin therapy in RA.

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Joint Damage Progresses in DAS28 Remission and Is Driven by Residual Joint Swelling. Daniel Aletaha and Josef S. Smolen. Medical University of Vienna, Austria

Background: Remission is usually defined as a state of no (or minimal) residual clinical disease activity and ideally should go along with maximal reduction of physical disability and halt of progression of joint damage. The Disease Activity Score employing 28 joint counts (DAS28) is frequently used to assess remission (DAS28<2.6), however, there is often residual disease activity in this state[1]. It is currently not known to which extent joint damage is retarded in DAS28 remission.

Methods: We evaluated data from methotrexate (MTX) monotherapy arms of recent trials (ASPIRE, ERA, Leflunomide, PREMIER, TEMPO). We pooled patients with complete clinical data at baseline, 6, 9 and 12 months and X-ray data at baseline and 12 months (n=865). We identified patients who attained persistent DAS28 remission, defined as an average DAS28 from 6 to 12 months ($DAS28_{6-12}$) <2.6. For each of these patients, we calculated mean SJC for the 6–12 month period and then divided the patients into those without ($SJC_{6-12}<2$) and with ($SJC_{6-12}\geq 2$) joint swelling. We assessed the radiographic progression of TSS between these two groups. We compared the proportion of patients progressing radiographically (increase of TSS score of $>0.5^2$) by Chi^2 statistics.

Results: 115 patients (13.3%) achieved DAS28<2.6; 22 of them (19%) had a mean $SJC_{6-12}\geq 2$. DAS28 remitters without residual joint swelling showed a 1 year radiographic progression of 0.56±4.17, while those with residual swelling progressed by 2.16±4.22 TTS points. The proportion of patients with a TSS progression >0.5 was significantly higher in patients with residual joint swelling (50.0%) compared to those without (23.9%; p=0.015). Residual SJC were decisive for damage progression in DAS28 remission, since neither DAS28 levels nor tender joint count or ESR influenced it in DAS28 remission (not shown). We then compared DAS28 remission data with those in remission by the simplified and clinical disease activity indices: in SDAI (≤3.3) and CDAI (≤2.8) remission no patient had SJC>2 and damage progressed only by 0.5±5.9 and 0.6±5.3, almost identical as in DAS28 remitters who had no residual SJC. Interestingly, there were also significant differences in physical function: while HAQ was low in DAS28 remission (0.21±0.35), it was even lower in SDAI (0.09±0.18; p=0.0023) and CDAI remission (0.12±0.26; p=0.057).

Conclusions: A large proportion of patients in DAS28 remission not only have significant residual swollen joint count but also significant progression of damage, indicating that more stringent criteria for remission are needed. SDAI and CDAI criteria were more stringent regarding progression of joint damage and residual disability.

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Large Discrepancy between Expected and Observed Ratios of Biologic Treated Rheumatoid Arthritis Patients Also Compliant on DMARDs. Denis Choquette[2], Mark Arundine[1] and Oliver Thomas[1]. [1]Mississauga, ON, Canada, [2]Institut de Rhumatologie de Montréal, Montreal, QC, Canada

Objective: It is common for most Canadian Rheumatologists to prescribe a biologic in combination with one or more DMARDS to 80–90% of their RA patients. Despite this practise, databases linked to drug plans indicate that RA patients receiving biologics do not fulfill DMARD scripts, and especially methotrexate at the same level as is prescribed by physicians. This study, examines this discrepancy more closely and suggests potential causal etiologies.

Methods: Biologic and DMARD concomitant therapy based on actual patient purchases was examined by tracking 6,744 anonymous patient records from public and private drug plans in Quebec and Ontario through a licensed 3rd party. A treatment algorithm criterion was applied to isolate RA patients. All patients who purchased a biologic for the treatment of RA over a 1 month period were monitored to determine if they filled prescriptions for DMARDS within a period of 90 days before and 90 days after they purchased their biologic. The month of September 2009 was randomly selected and deemed as a typical representative month. Each patient was linked in the public or private system with a unique identifier so that their acquisition of all drugs through their drug plan could be monitored over time to determine the relative prevalence of biologic monotherapy vs. combination therapy with a DMARD based on drug purchases.

Results: Among patients on their first biologic for more than 6 months, 45% did not purchase a DMARD. Likewise, 41% of patients who were on biologic therapy for more than 24 months did not purchase a DMARD. For patients on their 2nd biologic, rates of patients who did not purchase a DMARD ranged from 36% to 38% over the same time period. Furthermore, the proportion of patients on their first biologic who did not purchase methotrexate ranged from 58% for those on biologic therapy for more than 6 months to 54% for those on therapy for more than 24 months.

Conclusion: Despite what is prescribed by physicians, the data suggests that many RA biologic patients do not comply with taking DMARDs as

directed. This is especially evident for those patients prescribed methotrexate. These findings also suggest that approximately half of RA biologic patient's studied in this cohort failed to adhere to expected treatment regimes. This rate is inconsistent with the majority of physician's intended treatment regimens. Reasons for this discrepancy include efficacy and safety elements. Closer examination of actual combination therapy, compliance rates and therapy discontinuation at the patient level warrants further investigation.

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Leflunomide and the Risk of Hepatotoxicity: A Review of Post-Marketing Data. Jane L. Gilbert[1], Kate Gelperin[2], Joann Lee[2], Poonam Mishra[2], Lauren Choi[2], Allen Brinker[2], David Graham[2], Robert Boucher[2], Mark Avigan[2] and John Senior[2]. [1]FDA, Washington, DC, [2]FDA

Background: This abstract summarizes a review undertaken by FDA to evaluate the risk of hepatotoxicity in patients receiving leflunomide (LEF). LEF is an oral, disease-modifying, antirheumatic drug (DMARD), approved in the US for the treatment of rheumatoid arthritis (RA) in 1998. ACR guidelines (2008) recommend "leflunomide monotherapy for [RA] patients with all disease durations and for all degrees of disease activity. . . ." Combination therapy with methotrexate (MTX) is "recommended for patients with intermediate or longer disease duration. . . as long as disease activity [is] high." The potential for LEF hepatotoxicity was noted at the time of product approval and a bolded warning describing severe liver injury with LEF as well as a recommendation to monitor serum transaminase levels every 6–8 weeks was added to the U.S. label in 2003.

Methods: Using pre-specified criteria, a comprehensive search of FDA's Adverse Event Reporting System (AERS) database was undertaken to identify post-marketing cases (US and foreign) of serious liver injury and acute liver failure (ALF) from 8/25/2002 through 5/1/2009. Additional cases reported to the Drug-Induced Liver Injury Network (DILIN), a multicentre network established to assess liver injury due to medications, were also retrieved. A multidisciplinary group of experts from the FDA, including hepatologists, adjudicated these cases based on DILIN criteria. Cases involving death and ALF were further analyzed for common features.

Results: A total of 111 reports were identified (106 from AERS and 5 from DILIN). Many of these reports (62) were either duplicates, had insufficient information or were clearly unrelated to LEF. The remaining 49 reports (including 27 describing ALF) met criteria for the DILIN definition of severe liver injury, formed the case series, and were adjudicated. Based upon DILIN causality criteria, adjudicators classified all 27 cases of ALF (including 12 deaths and 5 liver transplants) as at least possibly associated with leflunomide. Case series analysis revealed that LEF hepatotoxicity may be rapid in onset and progress to ALF. This contrasts with MTX hepatotoxicity which usually involves chronic fibrosis or cirrhosis. Among the cases resulting in death or transplant, 88% (15 of 17) of patients were using concomitant hepatotoxic medications such as MTX, TNF inhibitors or statins. In the same group, 24% (4 of 17) had evidence of hepatitis B (active or chronic) or previous hepatitis A.

Conclusion: Leflunomide is approved in the US (for RA) and Europe (RA and psoriatic arthritis). It is recommended by the ACR for mono- or combination therapy. Our review shows a LEF risk for hepatoxicity which may present with rapid onset. The review further points to specific risk factors: concomitant hepatotoxic medication and pre-existing liver disease. Appropriate patient selection and careful monitoring may mitigate this risk.

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Meta-Analysis and Biologics—Comparing Apples to Apples: An Example Using Radiographic Outcomes in Rheumatoid Arthritis. Mike Ingham[1] and Chureen Carter[2]. [1]Centocor Ortho Biotech Services, LLC, Horsham, PA, [2]Centocor Ortho Biotech Services, LLC

Background: Many meta-analyses exist for biologics in rheumatoid arthritis (RA). Most have focused on signs and symptoms. Few have attempted to look at radiographic outcomes of disease progression.

Methods: This study used meta-analytic techniques to compare adalimumab (ADA), certolizumab (CER), etanercept (ETA) and infliximab (IFX). Randomized controlled trials (RCTs) of biologics in active RA, added to methotrexate, reporting 1 year radiographic outcomes, Erosion scores (ES), Joint Space Narrowing scores (JSNS) and modifications of Total Sharp scores (mTSS) were included. Sources for trials were drawn from recent Cochrane and Agency for Health Care Research and Quality publications. Moderator variables related to outcome were created from trial baseline patient population results, with dichotomization of continuous variables to allow for simplified stratification of trials. Trial data were split into higher or lower dose intensity, based on trial arms. Primary outcomes included differences in mean change scores from baseline of mTSS between active and control groups (MD). Due to varying versions of mTSS used in trials, standardized mean differences (SMD) were also analyzed (standardized by change scores' standard deviation). Negative results favor the biologic.

Results: Four trials met inclusion criteria (one for each product). For higher dose intensity, mTSS MD [95% confidence limits] were ADA: −2.60 [−3.82 to −1.38]; CER: −2.60 [−2.74 to −2.46]; ETA: −3.34 [−3.46 to −3.22]; IFX: −6.80 [−9.26 to −4.34]. SMD were: −0.44; −3.10; −5.24; −0.92 respectively. Simultaneous inclusion of all four trials however was complicated by observed differences in baseline moderator variables, confirmed by an I^2 heterogeneity score of 99.5 out of 100. Stratifying the ADA/IFX separately from the ETA/CER trials optimized reduction in the I^2 statistic vs. all four trials together. Within these strata, for SMD comparisons, IFX demonstrated twice the effect size of ADA, while ETA was 1.7 times that of CER.

Conclusion: Meta-analytic comparisons that do not consider more in depth RCT inclusion criteria risk ignoring important baseline population differences that might mask clinically meaningful results or lead to inaccurate conclusions. In the absence of access to patient level data, this type of stratification may prove useful for reducing heterogeneity. Confirmation using other outcomes and larger numbers of trials, while keeping treatment constant, is warranted.

Baseline moderator variable dichotomization of RCTs in active RA for radiographic outcomes (DMARD=Disease Modifying Anti-Rheumatic Drug, MTX=Methotrexate, CRP=c-Reactive protein, EU=European union, NA=North America)

High dose cohorts	ADA	CTZ	ETA	IFX
Site locations	NA	Global	EU	Global
Mean disease duration <10 yrs=0	1	0	0	1
Inclusion min tender/swollen joint count<9=0	0	1	1	0
Mean age<54 yrs=0	1	0	0	1
Rheumatoid Factor Positive <80%=0	1	1	0	1
# of prior failed DMARDs <2=0	1	0	1	1
MTX dose <15mg/wk=0	1	0	0	1
Mean CRP<3mg/dl=0	0	0	0	1

Disclosure: M. Ingham: Centocor Ortho Biotech Services, LLC, 3; **C. Carter:** Centocor Ortho Biotech Services, LLC, 3.

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Multiple Serum Cytokines/Chemokines Are Associated with RA-Related Autoantibodies in First-Degree Relatives without Rheumatoid Arthritis (RA): Studies of the Etiology of Rheumatoid Arthritis (SERA). Jan M. Hughes-Austin[8], Kevin D. Deane[9], Lezlie Derber[8], Jason R. Kolfenbach[10], Michael Weisman[2], Jane Buckner[12], James R. O'Dell[6], Ted R. Mikuls[11], Peter K. Gregersen[3], Richard M. Keating[1], William Robinson[4], V. Michael Holers[5] and Jill Norris[7]. [1]Oak Park, IL, [2]Cedars Sinai Medical Center, [3]N Shore Univ Hosp Rsch Ctr, Manhasset, NY, [4]Stanford Univ School of Med, Stanford, CA, [5]Univ of Colorado School of Med, Aurora, CO, [6]University of Nebraska Medical Center, Omaha, NE, [7]University of Colorado Denver, Aurora, CO, [8]University of Colorado Denver, [9]University of Colorado School of Med, Aurora, CO, [10]University of Colorado School of Medicine, Aurora, CO, [11]University of Nebraska Medical Center, Omaha, NE, [12]Virginia Mason Research Center

Background: Studies have shown that serum cytokine levels are higher in people with RA prior to the onset of their disease. We explored the relationship between RA-related autoantibodies and serum cytokine/chemokine levels in a population without RA but at an elevated risk for future development of RA due to family history of disease.

Methods: A cohort of RA-free first-degree relatives (FDRs) is being prospectively followed with serial epidemiologic questionnaires, joint exam-

inations and blood testing to investigate the relationships of genetic and environmental factors to RA-related autoimmunity. From this cohort, we selected 113 FDRs who had been positive for any of 5 RA-associated autoantibodies (Ab): rheumatoid factor (RF), RF isotypes—IgM, IgG, or IgA, or anti-cyclic citrullinated peptide (anti-CCP) on at least one of their visits. Additionally, we selected 100 FDRs (frequency-matched on age, sex, and ethnicity) who had never been autoantibody positive. The study population had a mean age of 50 years, was 75% female, and 83% non-Hispanic white. A panel of 27 cytokines/chemokines was measured using a bead-based assay in serum obtained from 397 visits of these FDRs. HeteroBlock™ was used to minimize effects of RF in these samples. For analyses, cytokine/chemokine levels were log transformed, and the relationship between cytokine/chemokine levels (as continuous variables) and autoantibody positivity (dichotomous, either RF alone or combination of RF isotypes with or without anti-CCP positivity) was calculated using a non-linear mixed model [SAS PROC NLMIXED]. Results are reported as odds ratios (OR), which were calculated to indicate change in risk of RA-related autoimmunity for every 1 standard deviation increase in cytokine/chemokine levels.

Results: Of 397 visits, 73 were positive for RF, and 50 were positive for the high-risk autoantibody profile. Eleven cytokines/chemokines were significantly associated with either RF or the high-risk autoantibody profile or both in RA-free FDRs, as summarized in Table 1. For example, for each standard deviation increase in IL-6 levels, there is an ~3-fold increased risk of RF and a 67% increased risk of the high-risk autoantibody profile. Cytokines/chemokines that were not associated with autoantibody positivity in this dataset include: PDGF, IL -1β, -1rα, -7, -8, -13, -15, -17, FGF-basic, G-CSF, MCP-1-MCAF, MIP-1α, -1β, RANTES, TNF-α, and VEGF.

Table 1. Summary of Significant Odds Ratios (OR) for Positivity for Either Rheumatoid Factor or the High-risk Autoantibody Profile (Bold ORs indicate $p<0.05$)

	Rheumatoid Factor			*High-risk Autoantibody Profile* (2 or more RF isotypes and/or Anti-CCP)*		
	OR	***95% CI***		***OR***	***95% CI***	
IL-2	1.20	0.67	2.16	**1.62**	**1.06**	**2.49**
IL-4	**2.44**	**1.09**	**5.44**	1.37	0.86	2.18
IL-5	**2.92**	**1.19**	**7.18**	1.39	0.89	2.17
IL-6	**2.89**	**1.34**	**6.22**	**1.67**	**1.08**	**2.58**
IL-9	**2.51**	**1.17**	**5.41**	**2.56**	**1.47**	**4.44**
IL-10	**2.46**	**1.10**	**5.52**	**1.64**	**1.05**	**2.58**
IL-12	**2.68**	**1.21**	**5.93**	**1.71**	**1.08**	**2.71**
Eotaxin	**3.35**	**1.31**	**8.54**	1.28	0.78	2.13
GM-CSF	**3.36**	**1.48**	**7.65**	**1.68**	**1.03**	**2.74**
IFN-γ	**3.12**	**1.30**	**7.50**	1.39	0.88	2.18
IP-10	**2.07**	**1.01**	**4.24**	1.42	0.87	2.32

* This autoantibody profile has been shown in prior work using pre-clinical RA samples to be >96% specific for future RA

Conclusion: Increases in multiple cytokines are associated with RA-related autoantibody positivity in FDRs, suggesting that autoantibodies are associated with evidence for circulating inflammation in subjects without clinically apparent RA. Further longitudinal study is needed to determine the significance of these findings in relationship to the natural history of RA-related autoimmunity and RA.

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Noncardiac Vascular Disease in Rheumatoid Arthritis (RA): Increase in Venous Thromboembolic Events? A. Kirstin Bacani, Sherine E. Gabriel, Cynthia S. Crowson and Eric L. Matteson. Mayo Clinic, Rochester, MN

Purpose: Patients with rheumatoid arthritis (RA) suffer from an excess burden of cardiovascular disease, but little is known about the incidence of noncardiac vascular disease in RA patients. The purpose of our study was to examine whether the incidence of venous thromboembolic events and other noncardiac vascular disease events has changed in recent years among RA patients and to compare the incidence to that in a non-RA cohort.

Methods: A population-based inception cohort of RA patients who fulfilled 1987 ACR criteria for RA between 1/1/1980 and 12/31/2007 and a cohort of non-RA subjects from the same underlying population were assembled and followed until death, migration, or the present. The occurrence of venous thromboembolic events (deep venous thrombosis or pulmonary embolism), cerebrovascular events (hemorrhagic stroke, nonhemorrhagic stroke, transient ischemic attack or amaurosis fugax), and peripheral arterial events (abdominal aortic aneurysm, renal artery stenosis, peripheral vascular disease, or arterial thromboembolism), was ascertained by review of the medical record. Cox proportional hazard models were used to compare development of noncardiac vascular disease in RA subjects diagnosed in 1980–1994 to those diagnosed in 1995–2007 and to compare RA patients diagnosed in 1995–2007 to the non-RA comparison cohort.

Results: The study included 814 RA patients (mean age [SD] 55.9 [15.7] years; 68% women). The average length of follow-up was 9.6 years [SD 6.9] and 66% were rheumatoid factor positive. Among RA patients, the incidence of venous thromboembolic events was more than 3-fold higher in the 1995–2007 time period compared to the 1980–1994 time period (cumulative incidence [$\pm$SE] 7.6 $\pm$ 1.9 vs 2.4 $\pm$ 0.9, respectively; $p=0.004$). The incidence of cerebrovascular events was similar in the 1995–2007 time period compared to the 1980–1994 time period (cumulative incidence [$\pm$SE] 4.4 $\pm$ 1.3 vs 3.3 $\pm$1.0, respectively; $p=0.52$), as was the incidence of peripheral arterial events (cumulative incidence [$\pm$SE] 3.5 $\pm$ 1.1 vs 3.7 $\pm$ 1.1, respectively; $p=0.81$).

Patients diagnosed with RA in 1995–2007 were compared to non-RA subjects of similar age and sex (mean age [SD] 55.6 [15.5] years; 69% women). RA patients had a higher incidence of venous thromboembolic events compared to non-RA subjects (cumulative incidence [$\pm$SE] 7.6 $\pm$ 1.9 vs 3.1 $\pm$ 1.2, respectively; $p=0.003$). The incidence of cerebrovascular events was similar between RA patients and non-RA subjects (cumulative incidence [$\pm$SE] 4.4 $\pm$ 1.3 vs 4.6 $\pm$ 1.6, respectively; $p=0.38$), as was the incidence of peripheral arterial events (cumulative incidence [$\pm$SE] 3.5 $\pm$ 1.1 vs 4.1 $\pm$ 1.6, respectively; $p=0.54$).

Conclusion: The incidence of venous thromboembolic events appears to have increased over time among RA patients and is increased in RA patients compared to non-RA subjects. The incidence of cerebrovascular events and peripheral disease events was similar over time among RA patients and was similar in RA patients compared to non-RA subjects. Further investigation is needed to explore the reasons for the increased incidence of venous thromboembolic events among RA patients.

Disclosure: A. K. Bacani: None; **S. E. Gabriel:** None; **C. S. Crowson:** None; **E. L. Matteson:** None.

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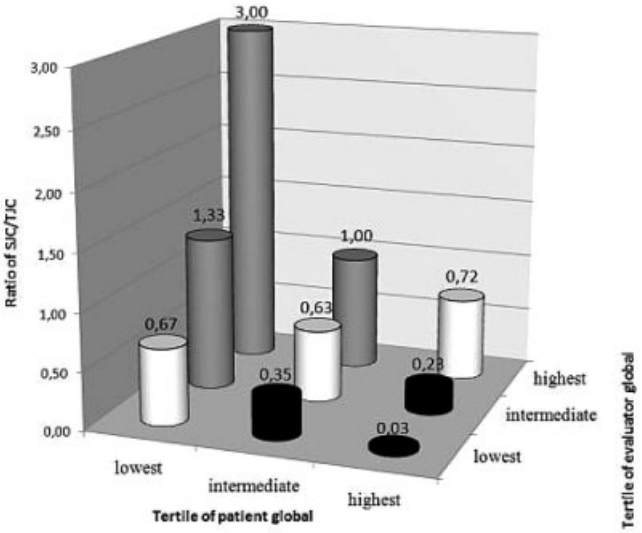
Perception of RA Disease Activity by Patients and Physicians: Reasons for and Estimators of Discrepancies. Paul Studenic, Josef S. Smolen and Daniel Aletaha. Medical University of Vienna, Austria

Background: In clinical practice, the perception of disease activity in rheumatoid arthritis (RA) often differs between physicians and patients. These discrepancies may impact the patient-physician relationship. It is not completely clear in what proportion of patients the perception is different, and why. We aimed to investigate this discordant perception in more detail.

Methods: We identified RA patients from an observational, prospective RA outpatient database, and obtained visual analogue scores (VAS) for global disease activity perception by the patients (PGA) and evaluators (EGA). Patients were divided into tertiles by PGA and by EGA, and the groups were then cross-tabulated. We explored the other RA core set variables in patient groups, formed according to concordant (tertile of PGA equivalent to tertile of EGA) or discordant tertiles (differing tertiles: PGA>EGA or EGA>PGA). For statistical comparisons, Mann-Whitney-U-Test was performed.

Results: Of the 302 RA patients (81% women, 61% rheumatoid factor positive, mean disease duration: 10.1 years), 49.3% fell into concordant PGA and EGA tertiles; 25.5% were discordant with higher tertile by PGA, and 25.2% were discordant with higher tertile by EGA. Those falling into higher EGA than PGA tertiles, had significantly higher swollen joint counts (SJC), but lower pain scores, and lower HAQ-scores, suggesting that EGA is primarily influenced by SJC and PGA by pain.

Given the impact of swelling for EGA and pain for PGA, we calculated the SJC/TJC ratio as an estimate for this discrepancy, finding good correlation with the additional variable "EGA minus PGA" ($r=0.399$, $p=0.0001$, Spearman-rho) and association with the respective tertiles (Figure). A SJC/TJC ratio of 0.6–0.7 appears associated with a balanced perception by patients and evaluators, irrespective of disease activity (Figure).



White: concordant groups; black: group PGA>EGA; gray: group PGA<EGA

Figure 1. SJC/TJC ratio of PGA/EGA tertiled groups.

Conclusion: The evaluator's perception of disease activity is strongly driven by the SJC, while the patient's perception is driven by pain and functional disability. A SJC/TJC ratio of ~0.65 seems associated with a balanced perception. For the rheumatologist, a ratio of >1.0 may serve as an indicator for the need of more detailed explanation of treatment changes, while a ratio of <0.4 may indicate a need for more intensified pain management to better comply with the patient's perception.

Disclosure: P. Studenic: None; **J. S. Smolen:** None; **D. Aletaha:** None.

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Permanent Working Disability Caused by Rheumatoid Arthritis Is Declining, Partly Due to Use of TNF-Inhibitors—Results from a Nationwide Finnish Register in 2000–2007. Vappu Rantalaiho[6], Hannu Kautiainen[1], Salme Järvenpää[3], Lauri Virta[5], Timo Pohjolainen[4], Markku Korpela[6], Timo Möttönen[7] and Kari Puolakka[2]. [1]Jyväskylä Central Hospital, Finland, [2]Lappeenranta Central Hospital, Finland, [3]Medcare Foundation, Finland, [4]Orton Rehabilitation Unit, Finland, [5]Social Incurance Institution, Finland, [6]Tampere University Hospital, Finland, [7]Turku University Hospital, Finland

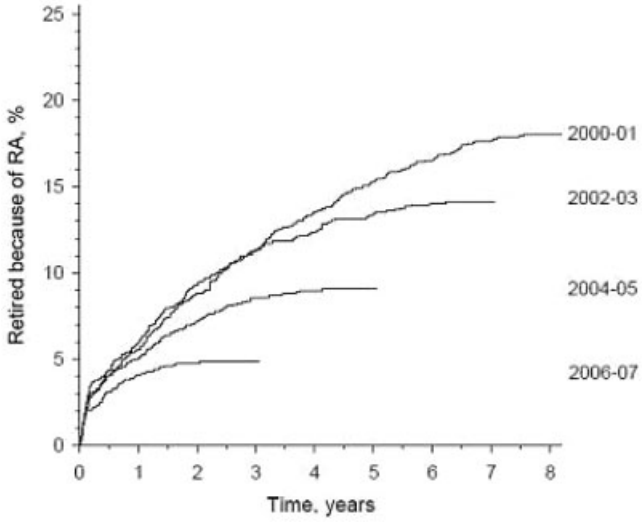
Background: Rheumatoid arthritis (RA) often leads to premature retirement. Globally, the treatment of RA has intensified, but whether this active strategy helps preserving the patients' working ability, is unclear.

Methods: From a nationwide register maintained by The Finnish Social Insurance Institution (SII) we collected information on sex, age, and date of medicine reimbursement decisions indicating the date of diagnosis (index date), of all new, not-retired, RA patients during the time period from 1 Jan 2000 to 31 Dec 2007. Patient cohorts were analyzed in 2-year time periods (2000-01, 2002-03, 2004-05, 2006-07) and work disability pensions due to RA up to 31 Dec 2008 were identified. Initial disease modifying antirheumatic drugs (DMARDs) during the first 3 months after the index day, as well as the initiation of etanercept or adalimumab at any time point were elucidated.

Results: A total of 7 909 (73% female, 61% RF-positive) patients were identified. During the first 2 years after the index day, the incidence of RA related work disability pensions were 8.8 %, 9.3 %, 7.2 %, and 4.7 % in the year cohorts 2000-01, 2002-03, 2004-05, and 2006-07, respectively (age, sex, and RF adjusted $p<0.001$ for linearity) (Figure). In a Cox multivariate analysis for the 8-year follow up, the year cohort (HR 0.67, 95 % CI 0.64 to 0.72), higher age (HR 1.06, 95 % CI 1.05 to 1.07), male gender (HR 1.53, 95 % CI 1.33 to 1.75), and the presence of RF (HR 1.17, 95 % CI 1.01 to 1.34) were related to premature retirements.

Throughout the follow-up, the use of single-DMARD treatment during the first 3 months decreased from 57 to 35 %, and that of combination-DMARDs increased from 36 to 61 %. The use of methotrexate, either alone or in combinations, increased from 31 to 67 %. However, presumably due to the confounding effect of indication, in seronegative patients, the ones with more active initial treatments (methotrexate, combination-DMARDs) had a higher risk of disability pensions than the ones with less active treatments (non-methotrexate single DMARD, no DMARDs); in seropositive patients the initial treatment had no effect on consequent pensions (data not shown).

During the follow-up, etanercept or adalimumab were prescribed to 278 patients while still available to workforce. Of these patients, 11.0 % (95 % CI: 6.9 to 17.3) became prematurely retired, whilst altogether 14.4 % (95 % CI: 13.4 to 15.5) of the patients without TNF-inhibitors did so during the 8-year follow-up ($p = 0.024$, adjusted for age, sex, RF presence, initial treatment strategy, and diagnosis cohort).



Conclusions: During the present millennium, parallel to increasingly active treatment strategies, the frequency of disability pensions in early RA has declined. Even though we failed to confirm any protective effect of aggressive initial DMARD treatment, the commencement of adalimumab or etanercept seemed to help preserve the patients' working capacity.

Disclosure: V. Rantalaiho: Abbott Immunology Pharmaceuticals, 5, Bristol-Myers Squibb, 5, Pfizer Inc, 5, UCB, Inc., 5; **H. Kautiainen:** Abbott Immunology Pharmaceuticals, 5; **S. Järvenpää:** None; **L. Virta:** None; **T. Pohjolainen:** Abbott Immunology Pharmaceuticals, 5, Novartis Pharmaceuticals Corporation, 5; **M. Korpela:** Abbott Immunology Pharmaceuticals, 5, Bristol-Myers Squibb, 5, Pfizer Inc, 5, Roche, 5, UCB, Inc., 5; **T. Möttönen:** Abbott Immunology Pharmaceuticals, 5, Amgen Inc., 5, AstraZeneca, 5, Bristol-Myers Squibb, 5, Eli Lilly and Company, 5, Merck Pharmaceuticals, 5, Novartis Pharmaceuticals Corporation, 5, Pfizer Inc, 5, Roche, 5, UCB, I; **K. Puolakka:** Abbott Immunology Pharmaceuticals, 5, Bristol-Myers Squibb, 5, Merck Pharmaceuticals, 5, Pfizer Inc, 5, Roche, 5, UCB, Inc., 5.

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Prescription Patterns in Pregnant Women with Rheumatoid Arthritis. Bindee Kuriya[3], Sonia Hernandez-Diaz[4], Jun Liu[2], Gregory Daniel[5] and Daniel Hal Solomon[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital, [3]Harvard School of Public Health, Brookline, MA, [4]Harvard School of Public Health, [5]HealthCore Inc., Wilmington, DE

Background: Little is known about how pregnant women with RA are treated in routine clinical practice. Our aim was to characterize the frequency and type of therapy prescribed during pregnancy to women with RA.

Methods: We conducted a cohort study using data from a U.S. commercial insurance plan from 2002–2008. We included women aged 18–45 years with RA (≥ 2 ICD-9 diagnoses) who had pregnancies ending in delivery (1° analysis) or abortion, identified by diagnostic/procedural codes. The estimated date of conception (EDC) was calculated as date of delivery - 270 days. We examined the use of therapeutic drug classes, including NSAID/coxibs, glucocorticoids (GCs), non-biologic DMARD and biologic DMARD during 90-day pregnancy trimesters and two 90-day periods prior to pregnancy. Drugs were categorized by the U.S. FDA pregnancy risk system. We defined exposure as the first filling of a drug from each class during each of the 90-day periods. We analyzed the distribution of drugs used for RA in the peri-partum period. Differences in the distribution between periods, and between women with deliveries compared to abortions, were determined by chi-square tests. Annual exposure, by year of EDC, for deliveries, to each therapeutic class was also calculated. Drug use was evaluated in the 180 days prior to abortion date due to risk of misclassification.

Results: 393 pregnancies were identified among 34,169 women. The mean age for women with deliveries was 32.8 ± 4.8 years and for abortions was 33.7 ± 5.3 years. More than 1/3 of women used ≥ 1 DMARD in the pre-conception period (Table). During pregnancy, 64 women were dispensed ≥ 1 DMARD and the proportion of use significantly declined from the first to third trimester (p=0.03). More women were prescribed GCs during pregnancy than before pregnancy. In contrast, use of NSAID/coxibs, any DMARD, combined use of DMARD or exposure to category D/X medications was significantly lower compared to pre-pregnancy use (p<0.05). Use of biologics occurred in ~ 13% of women during pregnancy. GCs were the most prescribed therapy in each of the study years, and the pattern of exposure to other classes remained relatively constant over time. Women who experienced abortions were more frequently exposed to each therapeutic class in the 180 days before abortion, compared to deliveries, except for GCs or biologics (p<0.05). Dispensing of category D/X medications was also higher in women with abortions compared to deliveries, and primarily involved methotrexate (p<0.01).

Table. Therapeutic class and drug-specific exposure (N and %) among women with deliveries (N=281).

	91-180 Days Prior to EDC	0-90 Days Prior to EDC	During Pregnancy
NSAID/coxibs	54 (19.2)	37 (13.2)	31 (11.0)[1]
Glucorticoids (GCs)	88* (31.3)	92* (32.7)	156* (55.5)[2]
Combination of NSAID/Coxibs and GCs	24 (8.5)	21 (7.5)	23 (8.2)
Any DMARD (≥1)	97 (34.5)	90 (32.0)	64 (22.8)[2]
Combination of ≥ 2 DMARD	32 (11.4)	24 (8.5)	16 (5.7)[1]
Non-Biologic DMARD (Category A, B or C)	47* (16.7)	40* (14.2)	32* (11.4)
Chloroquine	---	1 (0.4)	---
Cyclosporine	1 (0.4)	1 (0.4)	---
Gold	1 (0.4)	---	1 (0.4)
Hydroxychloroquine	34 (12.1)	30 (10.7)	25 (8.9)
Sulfasalazine	17 (6.1)	15 (5.3)	11 (3.9)
Non-Biologic DMARD (Category D or X)	36* (12.8)	23* (8.2)	11* (3.9)[2]
Azathioprine	1 (0.4)	1 (0.4)	1 (0.4)
Leflunomide	5 (1.8)	4 (1.4)	3 (1.1)
Methotrexate	32 (11.4)	19 (6.8)	8 (2.9)
Biologic DMARD (Category A, B or C)	42* (14.9)	47* (16.7)	35* (12.5)
Adalimumab	9 (3.2)	10 (3.6)	7 (2.5)
Anakinra	---	---	1 (0.4)
Etanercept	25 (8.9)	28 (9.9)	23 (8.2)
Infliximab	9 (3.2)	9 (3.2)	6 (2.1)
Rituximab	1 (0.4)	1 (0.4)	---

[1] χ^2 test p-value <0.05 comparing overall pregnancy to 91-180 days prior to EDC
[2] χ^2 test p-value <0.05 comparing overall pregnancy to 0-90 days prior to EDC
*Category totals may be smaller than sum of individual drugs due to use of combination therapy

Conclusion: Approximately 1/3 of women used a DMARD in the 180 days before conception. This proportion dropped during pregnancy. Exposure to category D/X drugs during pregnancy was 3.9%; the use of GCs was 55.5% Our results suggest that continued efforts directed at counseling women and their physicians about the potential risks/benefits of GCs and DMARD use during pregnancy are warranted.

Disclosure: B. Kuriya: None; **S. Hernandez-Diaz:** Novartis Pharmaceuticals Corporation, 2, Pfizer Inc, 2; **J. Liu:** None; **G. Daniel:** None; **D. H. Solomon:** Abbott Laboratories, 2, Amgen Inc., 2, Bristol-Myers Squibb, 2.

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Relative Importance of Patient's Opinion and Physician's Criteria of Disease Activity Versus Information of Disease Duration and Rheumatologist Type of Exercise for Treatment Decision in Rheumatoid Arthritis: DUO Study. Maxime Dougados[2], Henri Nataf[1], Ghislaine Steinberg[4], Géraldine Martineau[4], Stéphanie Rouanet[4] and Bruno Falissard[3]. [1]Centre Hospitalier François Quesnay, Mantes-La-Jolie, France, [2]Hospital Cochin, Paris, France, [3]INSERM U669, PSIGIAM, Paris, France, [4]Roche, Neuilly-sur-Seine, France

Background: The decision to initiative/intensify a DMARD therapy in rheumatoid arthritis (RA) is based on the evaluation of the activity of the disease. Such evaluation is performed using both subjective (patient's opinion) and objective (e.g. physical exam.) information. The composite index DAS (Disease Activity Score) elaborated in the 90's based on such treatment decision is emphasizing the role of the patient's perspective.

Objectives: To assess the respective weight of subjective and objective information in DMARDs changes in RA patients in 2009 as well as the information related to both the other disease and rheumatologist characteristics.

Methods: *Study design*: Prospective, non interventional, cross-sectional epidemiological study. *Patients*: Consecutive RA adult patients. *Rheumatologists*: Randomly selected to be representative of the French rheumatologist population. *Outcome measures*: Dependent variable: changes (initiation/intensification) of DMARD at the end of the outpatient visit. Independent variables: physicians characteristics (age, gender, type of practice, region), disease duration (DD), information provided by both the patient (RAID, HAQ, visual analogue scale [VAS] patient global assessment [PGA], Patient Acceptable/Non Acceptable Symptom State [PASS]) and the physician (swollen joint count [SJC], tender joint count [TJC], ESR/CRP). *Analysis*: Uni and multivariate analysis, adjusted attributable risk fraction [1].

Results: The 200 participating rheumatologists were practicing either in a full time community office (37%), hospital (28%) or mixed (35%).

The 1107 evaluable (1115 enrolled) patients (female: 76%, age: 58±13 years) were suffering from RA with the following characteristics: median (range) DD: 6.2 (0–60) years, SJC 1 (0–24), TJC 2 (0–28), ESR 15 (1–126) mm, mean DAS 28-ESR 3.5±1.4 and HAQ 1.1±0.6.

Factors (OR[95%CI]) influencing such DMARD changes were hospital based rheumatologist (versus community office and mixed) (2.5[1.4; 4.3]), physicians age<40 years (2.5[1.2; 5.1], DD <5 years (2.4[1.5; 3.7]), SJC >3 (2.1[1.3; 3.4]), TJC >3 (1.9[1.1; 3.2]), VAS PGA >40 mm (3.0[1.7; 5.2]) and non acceptable PASS (2.1[1.2; 3.6]). Using the adjusted attributable risk fraction, physicians characteristics weight (type of practice and age) was 47%, DD weight was 38%, physician global disease activity weight (SJC and TJC) was 42%, and patient global disease activity weight was 61% (VAS PGA and PASS) for treatment intensification decision.

According to DAS 28 and PASS questionnaire, the intensification was proposed to 24% of the patients with DAS 28 > 3.2 and to 39% of the patients with a non acceptable PASS and DAS 28 > 3.2.

Conclusion: This study showed that: 1/ despite the current EULAR recommendations, the majority of patients with DAS 28 > 3.2 had no treatment intensification of their RA treatment 2/ treatment intensification decision was mainly based on the patient's disease activity evaluation compared to the physician's one 3/ a part from disease activity, treatment intensification decision was also based on other dimensions such as DD and mode of practice of rheumatologists

[1] = Kenneth J. Rothman – Modern Epidemiology: third edition

Disclosure: M. Dougados: Abbott Laboratories, 2, 5, Bristol-Myers Squibb, 2, 5, Pfizer Inc, 2, 5, Roche, 2, 5, UCB, Inc., 2, 5; **H. Nataf:** None; **G. Steinberg:** Roche, 3; **G. Martineau:** Roche, 3; **S. Rouanet:** Roche, 3; **B. Falissard:** None.

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Respiratory Cause Mortality Was Greater in 54 Incident Rheumatoid Arthritis (RA) Patients Than 204 Community-Based, Non-RA Matched Cohort Controls (CN). Alfonse T. Masi and Jean C. Aldag. University of Illinois College of Medicine at Peoria, Peoria, IL

Purpose: Mortality from interstitial lung disease (ILD) is known to be increased in RA (Bongartz T et al. A&R 2010; 62: 1583-91). This study aimed to analyze non-malignant respiratory cause mortality in incident RA cases from a prospective, community-based cohort, and as compared to matched non-RA CN.

Design: The 54 cases studied had onset of ACR-positive RA, 3 to 20 (mean 12) years, after entry into the cohort (n = 21,061 adults) in 1974. RAs were matched by age, gender, and race (all Caucasian) at baseline with 204 cohort non-RA CN. All study subjects (n=258) had baseline (1974) data on: demographic variables; cigarette smoking, and immunological testing on stored (−70°C) sera. A novel baseline biomarker predicted cohort mortality (data separately submitted), consisting of upper quartile values of acute-phase serum amyloid A (A-SAA) or serum interleukin-2 receptor alpha (sIL-2Rα). Each RA was also grouped in 1995 by the sole community rheumatologist into 3 course-wide *therapy responses*: 1 = *full*; 2 = *moderate*, and 3 = *limited*, (data separately submitted). Deaths from primary non-malignant respiratory causes (ICD-9, 460–519 & ICD-10, J00-J99) were analyzed, over 1992–2009. Hazard ratio (HR) for respiratory cause mortality was estimated using Cox regression models, adjusting for covariates.

Results: Deaths from non-malignant respiratory causes occurred in 8 (15%) of 54 RA vs 10 (5%) of 204 non-RA, OR = 3.37 (95% CI 1.30 – 8.79), p = 0.017. None of the 8 RA had deceased from chronic airway disease (ICD-9 496 or ICD-10 J44.9) or pulmonary edema (ICD-9 518.4 or ICD-10 J81), unlike 5 of the 10 respiratory deaths in non-RA CN (p = 0.036). Respiratory deaths occurred in 4 (22%) of 18 male RA, and 4 (11%) of 36 female RA. Three of the 4 males who had respiratory deaths were treated in 1995 with oral methotrexate (MTX) doses of 20+ mg weekly and with predisone (Pred) doses of 10+ mg daily vs only 1 of the remaining 14 male RA (p = 0.019). Only 2 of 4 female RA respiratory deaths had received low-dose MTX (7.5 mg/wk) and prednisone (5 mg/d) therapy, similar to the other 32 female RA. Respiratory cause mortality was greater in RA than non-RA (HR=2.88, 95% CI 1.06–7.82), after adjusting for cohort entry age (p = 0.027), baseline heavy cigarette (30+ daily) smoking (p = 0.018), limited therapy responses (p = 0.033), and the biomarker (p = 0.056). Mean (± 1 SE) features of the 8 RA deceased from respiratory causes vs the other 46 RA are shown (Table):

8 Respiratory Deaths vs 46 Other RA Cases	Age at RA Onset (X ± SE)	Age in 1995 (X ± SE)	Last Age At Follow (X ± SE)	Baseline Cigs/Day (X ± SE)	1995 Pred mg/d (X ± SE)	1995 MTX mg/wk (X ± SE)
18 Male RA						
4 Respiratory	52.0 ± 4.9	57.8 ± 5.2	70.0 ± 5.3	18.8 ± 7.2	13.1 ± 2.8	18.1 ± 3.7
14 Other RA	55.1 ± 2.7	64.0 ± 2.2	74.5 ± 2.0	20.3 ± 6.0	3.0 ± 1.7	8.0 ± 3.5
36 Female RA						
4 Respiratory	51.8 ± 2.4	64.5 ± 3.3	71.6 ± 1.9	11.3 ± 7.2	2.5 ± 1.4	3.8 ± 2.2
32 Other RA	56.1 ± 2.4	64.8 ± 2.3	74.7 ± 1.9	10.4 ± 2.3	3.8 ± 0.7	5.5 ± 1.1

Conclusions: Respiratory deaths were greater ($p = 0.036$) in incident RA (15%) than non-RA (5%), especially after excluding chronic airway disease and pulmonary edema ($p = 0.001$). Respiratory mortality was increased in RA after adjusting for multiple relevant covariates. Respiratory cause mortality of RA patients deserves further prospective study.

Disclosure: A. T. Masi: None; **J. C. Aldag:** None.

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Rheumatoid Arthritis (RA) Is the Only One of 8 Diseases for Which a Patient History and Physical Examination (Versus Laboratory Tests and Ancillary Studies) Were Rated as Most Important for Clinical Decisions by >50% in a Physician Survey. Lauren McCollum[4], Sangmo Park[4], Tuulikki Sokka[2], Hasan Yazici[1] and Theodore Pincus[3]. [1]Cerrahpasa Medical Faculty, Istanbul, Turkey, [2]Jyvaskyla Central Hospital, Jyvaskyla, Finland, [3]New York University Hospital for Joint Disease, Hastings-on-Hudson, NY, [4]NYU Hospital for Joint Diseases

Purpose: To survey physicians concerning the relative importance of 5 sources of information in the clinical encounter—vital signs, patient history, physical examination, laboratory tests, and ancillary studies—in diagnosis and management of 8 chronic diseases: congestive heart failure (CHF), diabetes mellitus, hypercholesterolemia (HC), hypertension (HTN), lymphoma, pulmonary fibrosis (PF), rheumatoid arthritis (RA), and ulcerative colitis (UC).

Methods: An Internet survey using Survey Monkey™ was sent to about 6,636 rheumatologists and 6,964 non-rheumatologists, with the following query: "Please indicate the relative importance of 5 sources of information in diagnosis of CHF, diabetes, HC, lymphoma, HTN, PF, RA, and UC." A second query with identical language addressed management decisions in the 8 diseases. Response options were 0–20%, 21–40%, 41–60%, 61–80%, and 81–100%. The proportions of physicians who estimated each element as most important (or tied for most important) in diagnosis or management of each disease was computed.

Results: The survey was completed by 588 physicians (5% response rate), including 329 rheumatologists and 254 non-rheumatologists (5 unknown specialty), and 313 U.S. and 187 non-U.S. physicians (88 unknown country). Substantial differences were seen in the physicians' estimates of the most important element in diagnosis and management of the 8 diseases (Table 1): vital signs for HTN (82–83%), physical examination for RA (70–72%), laboratory tests for diabetes (96–96%) and HC (97–99%), and ancillary studies for lymphoma (75–77%), PF (75–93%) and UC (67–92%). One-third or more of respondents rated patient history as most prominent (or tied) in CHF (39–49%), RA (57–59%) and management of PF (40%) and UC (55%). RA was the only disease for which history and physical examination were rated as most important by >50%, including rheumatologists and non-rheumatologists.

Table 1. Highest ranked source of information in clinical encounter estimated in survey by 329 rheumatologists (Rh) and 254 non-rheumatologists; sources selected by >50% are shaded.

		Vital signs		Patient history		Physical examination		Laboratory tests		Ancillary studies	
		Rh	Non-Rh	Rh	Non-Rh	Rh	Non-Rh	Rh	Non-Rh	Rh	Non-Rh
Congestive heart failure	Diagnosis	21%	22%	35%	45%	61%	64%	8%	14%	69%	56%
	Management	38%	39%	44%	55%	63%	61%	10%	15%	54%	39%
Diabetes mellitus	Diagnosis	2%	4%	10%	15%	3%	6%	97%	95%	3%	4%
	Management	2%	9%	8%	24%	6%	12%	97%	94%	6%	7%
Hyperchol-esterolemia	Diagnosis	2%	2%	3%	4%	2%	2%	99%	98%	2%	5%
	Management	3%	4%	6%	11%	4%	6%	97%	97%	7%	7%
Hypertension	Diagnosis	84%	84%	8%	9%	24%	24%	3%	5%	4%	4%
	Management	82%	82%	6%	19%	22%	23%	6%	13%	8%	9%
Lymphoma	Diagnosis	2%	4%	10%	16%	23%	26%	33%	50%	85%	67%
	Management	4%	11%	12%	30%	20%	24%	40%	51%	78%	69%
Pulmonary fibrosis	Diagnosis	5%	8%	14%	19%	15%	23%	8%	9%	95%	91%
	Management	15%	26%	32%	50%	23%	35%	10%	16%	82%	65%
Rheumatoid arthritis	Diagnosis	2%	5%	54%	63%	85%	57%	17%	43%	10%	18%
	Management	3%	7%	52%	69%	83%	53%	16%	35%	21%	20%
Ulcerative colitis	Diagnosis	2%	4%	19%	32%	2%	6%	3%	8%	95%	89%
	Management	3%	11%	50%	63%	11%	16%	13%	16%	69%	62%

Conclusion: A patient history and physical examination are estimate by physicians to provide a larger proportion of the information for clinical decisions in diagnosis and management of RA than for 7 other chronic diseases. The patient history and physical examination may be regarded as "clinician-intensive," compared to vital signs, laboratory tests, and ancillary studies. This greater physician effort might be recognized in policies for scheduling, reimbursement, and allocation of physician resources by planners, regulators, and payers.

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Similar Performance of New and Old Criteria for Rheumatoid Arthritis in an Early Arthritis Cohort in Amsterdam. Karin Britsemmer, Jennie Ursum and Dirkjan van Schaardenburg. Jan van Breemen Institute Amsterdam

Background: The 1987 RA classification criteria of the American College of Rheumatology (ACR) were developed using patients with established RA. At least partly for this reason, the usefulness of these criteria in early RA, when criteria are most needed, is low. Recently an ACR/EULAR taskforce presented a revised set of criteria for RA. The aim of the present study was to validate the diagnostic capacity of the ACR/EULAR RA classification criteria for the diagnosis of early RA compared to the 1987 ACR criteria in an independent EAC, and to evaluate the capacity of the new criteria to identify erosive disease.

Methods: Data were used of those patients from the EAC at the Jan van Breemen Institute in Amsterdam who were included from 2000 onwards. The inclusion criteria of this EAC are age >=18 years, symptom duration <= 2 years, at least 2 swollen joints, no prior DMARD treatment. Exclusion criteria are osteoarthritis, crystal arthropathy, connective tissue diseases and infectious arthritis. Thus the study population consists of patients with oligo- or polyarthritis, who would formerly be classified as having RA or undifferentiated arthritis. The gold standard for the diagnosis of RA was methotrexate (MTX) treatment at 6 and/or 12 months. The classification criteria were applied as proposed by the ACR/EULAR task force. 3-year radiographic progression was assessed with the Sharp/Van der Heijde Score (SHS) in patients with available scores at the time of data collection.

Results: 383 patients were included (mean age 52 [SD13] years, 69% female, median symptom duration 4 months, median swollen and tender joint count 5 [IQR 2–9] and 4 [IQR 2–8], respectively, mean DAS28 4.63 ±1.34, anti-CCP 55%, RF 41%). 305 patients had RA according to the gold standard. Sensitivity and specificity of the new criteria for RA were 77% and 69%, respectively, the positive and negative predictive values were 91% and 44%, respectively. The corresponding values of the 1987 ACR criteria for RA were 75%, 64%, 89% and 40%, respectively. The Area Under the Curve of the Receiver Operating Characteristics curve shows good discrimination between patients who did and did not use MTX at 6 or 12 months (0.79, $p<0.0001$)

Radiographic scores were available of 156 patients, of whom 121 fulfilled the new criteria at baseline. The median SHS progression was 0 (IQR 0-0) and 0 (IQR 0–4) in patients with and without RA according to the new classification, respectively (P 0.008). 71% of "non-RA" patients according to the new criteria used MTX in the first year. A similar difference in radiographic progression was observed between the groups of patients with and without RA according to the 1987 ACR criteria (data not shown).

Conclusion: The performance of the new ACR/EULAR RA classification criteria in this EAC was similar compared to the ACR 1987 RA criteria. Patients with RA according to the ACR/EULAR criteria had significantly higher median radiographic progression rates versus those without RA, which supports the aim of the new criteria to identify patients who are at high risk of joint damage. However, the low radiographic progression in the group of "non-RA" patients may be more a consequence of a high rate of MTX use than of a good prognosis per se.

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86 WITHDRAWN

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The Impact of Health Beliefs on Therapeutic Adherence in Patients with Rheumatoid Arthritis (RA). Tara J. Rizvi[1], John Gomez[1], Sofia de Achaval[2], Michael A. Kallen[2], Vanessa L. Cox[2], Marsha N. Richardson[2], Bernard Ng[1], John D. Reveille[3] and Maria E. Suarez-Almazor[4]. [1]Baylor College of Medicine, Houston, TX, [2]The University of Texas M. D. Anderson Cancer Center, Houston, TX, [3]Univ Texas Health Sci Ctr, Houston, TX, [4]University of Texas, MD Anderson Cancer Center, Houston, TX

Objective: To determine whether the health beliefs of persons with RA influence their adherence to planned treatment.

Methods: We ascertained a cohort of patients with RA followed at publicly funded hospitals in Houston, TX. Eighteen specific components of the health belief model (HBM), including perceived severity and susceptibility, perception of self efficacy, benefits and risks of treatment, and barriers to treatment were measured using a self-report questionnaire. Treatment adherence was assessed with a previously validated questionnaire used in patients with rheumatic disease: de Klerk's Compliance Questionnaire Rheumatology (CQR). Pearson correlations between HBM components at baseline and CQR at baseline and 24 months were calculated. Stepwise linear regression modeling to predict adherence was then conducted, using HBM components that were statistically significantly ($p<.05$) correlated with adherence; select demographic and clinical patient characteristics such as age, gender, education level, and disease duration, were included in the modeling.

Results: 201 patients with RA were included: 75% were female; mean age was 51 years; 172 patients completed the 24 month follow-up. Ten of 18 HBM components ascertained were significantly related to treatment adherence at baseline and/or 24 months (Table 1). HBM components with a negative impact on treatment adherence were: belief in natural remedies, barriers in access to care, barriers due to beliefs about medication side effects, and beliefs about therapeutic lack of efficacy of RA therapies. Positive correlations with treatment adherence were observed with the following HBM components: belief in treatment benefits, belief in traditional medical treatment benefits, and positive attitudes towards risks of treatment. In the multi-variable regression analysis, belief in benefits of traditional treatment, willingness to take more risk, and longer disease duration were independent predictors of increased baseline treatment adherence, while higher levels of forgetting, financial barriers, and side effects were independent predictors of decreased adherence.

Table 1. Pearson Correlations of HBM Components with de Klerk Adherence (CQR)

HBM Component	CQR Baseline	CQR 24 Months
Perceived Severity/Susceptibility	.20*	0.14
Perceived Threat	0.11	.21*
Self Efficacy-Pain	−.15*	−0.09
Self Efficacy-Function	0.01	0.04
Self Efficacy-Symptoms	−0.03	0.03
Self Efficacy-Optimism	.20*	.17*
Health Beliefs & Attitudes	0.1	.18*
Risk Items	.34*	.24*
Benefits Traditional Remedies	.35*	.21*
Benefits of Treatment	.26*	.26*
Natural Remedies	−.19*	−.18*
Barriers Scheduling	−.22*	−0.13
Barriers Transportation	−.21*	−0.13
Barriers Clinic	−0.13	−.19*
Barriers Financial	−.29*	−.20*
Barriers Forget	−.46*	−.37*
Barriers Side Effects	−.33*	−.41*
Barriers Inefficacy	−.30*	−.30*

* $p < .05$.

Conclusion: A number of patient perceptions and beliefs impact therapeutic adherence in patients with RA. Based on our findings, strategies to improve adherence may include interventions to positively modify patients' beliefs regarding treatment benefits and side effects, and to limit modifiable barriers leading to non-adherence.

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TNF and Natural Atheroprotective Antibodies Against Phosphorylcholine: Implications for Biologics in RA. Sofia Ajeganova, Roland Fiskesund, Ingiäld Hafström and Johan Frostegård. Karolinska Institutet, Sweden

Background: We have recently determined that natural antibodies against phosphorylcholine (anti-PC) are protection factors for cardiovasculardisease (CVD), where low levels of anti-PC independent of other risk factors increase the risk of CVD. Further, anti-PC is anti-inflammatory, inhibiting proinflammatory effects of inflammatory phospholipids. Levels of IgM anti-PC are low in individuals living a traditional life-style in New Guinea (where CVD and rheumatic diseases are very uncommon) as compared to a western population. We have hypothesized that an immune deficient state – low levels of anti-PC –predispose to chronic inflammatory diseases. TNF is of major importance not only in rheumatic disease but also in CVD, atherosclerosis and metabolic syndrome. We here determine the role of TNF and TNF-inhibition on anti-PC levels and anti-PC production. We compared effects by TNF-inhibitors with rituximab.

Methods: In vitro anti-PC production by B-cells isolated from peripheral blood was determined by ELISA after 6 days of cell culture. Two hundred fifteen RA patients, aged 57.9 ± 12.4 years with a mean disease duration of 8.5 (5–15) years were investigated with a one year follow up. Of these patients, 60 were treated with etanercept, 60 with infliximab and 42 with adalimumab as the first biologic, furthermore, 53 patients were treated with rituximab. The patients were followed and blood sampled at 0, 3, 6 and 12 months.

Results: TNF at 1 ng/ml was shown to drastically (more than tenfold) decrease anti-PC production in vitro ($p<0.0001$) without inducing apoptosis. Anti-TNF treatment induced a 26% increase in anti-PC after 12 months of treatment (28%, 27.8% and 22% on etanercept, infliximab and adalimumab respectively), $p<0.0001$, while rituximab decreased anti-PC levels by 14%, $p=0.023$. Non-responders had lower anti-PC levels at baseline than responders in both anti-TNF, $p=0.007$, and Rituximab-treated subjects, $p=0.041$.

Conclusion: TNF was demonstrated to inhibit anti-PC production, a finding which suggest a novel mechanism by which anti-PC IgM could be decreased. Anti-TNF treatment may decrease risk of CVD by raising anti-PC levels. The adverse effect of rituximab on anti-PC levels may influence CVD-risk negatively. If treatment with anti-PC could have a role in some patients with RA including non-responders to biologics deserves further investigations.

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TNF Therapy Reduces the Odds of Worsening Disability Trajectories in Rheumatoid Arthritis over at Least 2 Years—Data from the NDB-Portugal Cohort. Sofia Pedro[1], Elizabeth Benito-Garcia[1], Joana Vasconcelos[1], Irina Chaves[1], Rita Marques[1], Andreia Rodrigues[1], Kaleb Michaud[3] and Fred Wolfe[2]. [1]Bioepi Clinical and Translational Research Center, Oeiras, Portugal, [2]National Databank for Rheumatic Diseases, Kansas, [3]University of Nebraska Medical Center, NE

Background: The trajectories of the health assessment questionnaire (HAQ) disability scores among rheumatoid arthritis (RA) patients are known to have different courses. Wolfe et al. (2000) characterized them as being non linear, chaotic and non-time determined. It is suggested that HAQ be measured between clinic visits to monitor disability and the effect of therapy. Many studies have defined the predictors of HAQ, but few have evaluated the predictors of HAQ trends among RA patients.

Objective: To investigate the predictors of worsening disability trends compared to improving, no change or other patterns of disability trajectories among RA patients over at least 2 years.

Methods: 646 RA patients from the ongoing biannual NDB-Portugal cohort (started in 2003) with at least four consecutive HAQ scores per patient during their follow-up were used in this analysis. Questionnaires included socio-demographics, disease characteristics, function, etc.

The proportion defined by the number of 6-month positive increments in HAQ scores (worsening function) divided by the total number of differences was computed per patient and used to define patients' trajectories. The outcome was then defined as the presence of a trend of worsening disability (when the proportion was > 0.5). Univariate (UV) and multivariate (MV) generalized estimating equations (GEE) were used to study the predictors of a worsening disability trend. Age, educational level, disease duration, paid form of work, retirement, number of total major comorbidities, SF-36 mental component (MCS) (0–100, 0 is worse), RADAI (0–10, 10 is worse), the VAS scales of sleep, fatigue and pain (VAS 0–10, 10 is worse), the use of current TNF (with or without concomitant DMARDs) vs. traditional DMARD therapy and corticosteroids, were used as possible predictors.

Results: 168 patients of 646 (26%) had worsening disability trends. The UV analyses showed that all of the following factors were statistically relevant: age, educational level, number of major comorbidities, sleep disturbances and fatigue, RADAI and the use of TNF therapy. The final MV model included pain (OR: 1.003 (95%CI: (1.000; 1.005))), age (OR: 1.02 (1.01; 1.02)) and the use of TNF (OR: 0.94 (0.91; 0.97)).

Conclusions: In our study, we showed that older age and more pain predicted worsening HAQ disability trends. The use of TNF therapy (with or without concomitant DMARDs) when compared with traditional DMARD was the only factor that decreased the odds of having a worsening HAQ trajectory.

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TNF-alpha Blocking Therapy Lowers Cardiovascular Risk in Rheumatoid Arthritis. Ingrid M. Visman[1], Alper M. van Sijl[3], Mike J. L. Peters[5], Carlo J. J. van Dongen[1], Ben A. C. Dijkmans[4] and Michael T. Nurmohamed[2]. [1]Jan van Breemen Institute, [2]Jan van Breemen Institute and VU Medical Centre, Amsterdam, The Netherlands, [3]Jan van Breemen Institute and VU Medical Centre, [4]VU Medical Centre, Amsterdam, The Netherlands, [5]VU Medical Centre

Background: Patients with rheumatoid arthritis (RA) have an increased risk of developing cardiovascular (CV) disease and the underlying chronic inflammatory process appears to play a pivotal role. As tumor-necrosis factor (TNF)-alpha blocking agents have powerful anti-inflammatory effects it is conceivable that these agents will lower CV risk in RA. The objective of this study was to compare the CV disease incidence rate in RA patients receiving TNF-alpha blocking therapy with RA patients not receiving these drugs.

Methods: Two prospective cohort studies of individuals with RA (the CARRÉ study and the Biologicals-cohort of the Jan van Breemen institute in Amsterdam, the Netherlands) were followed for several years. The CARRÉ study is a prospective cohort of individuals with RA, most of whom did not use biologic agents at inclusion. Patients who did use biologicals were excluded from further analysis. The Biologicals-cohort is a prospective cohort of adult RA patients starting therapy with TNF-alpha blocking agents. Data was collected regarding traditional cardiovascular risk factors, RA related factors, cardiovascular morbidity and mortality. Cardiovascular events were defined as objectified myocardial infarction, cerebrovascular accident, transient ischaemic attack, peripheral arterial reconstruction, or coronary stent- or by-pass procedure. Cox proportional hazard model was used to evaluate the difference in cardiovascular incidence between both groups and models were adjusted for age, sex and previous cardiovascular disease.

Results: 377 and 322 individuals, with and without TNF-alpha blocking therapy, respectively, were followed for a mean duration of 2.1 and 2.7 years, resulting in 793 and 888 patient years, respectively. Cardiovascular incidence was 10.1/1000 patient years and 24.8/1000 patient years, respectively. Cox proportional hazard model showed a statistically significantly decreased cardiovascular incidence in individuals using TNF-alpha blocking therapy, hazard ratio (95%-confidence interval): 0.42 (0.18–0.97). After adjustment for age, gender and previous CVD there was still a 30% lower cardiovascular risk in RA patients treated with TNF-blockers, but this was not longer statistically significant (hazard ratio (95%-confidence interval): 0.71 (0.29–1.72).)

Table 1. Incidence of cardiovascular risk factors and cardiovascular events

	Carre cohort (n=322)		Biologicals cohort (n=377)	
	Cases	Incidence rate per 1000 patient years	Cases	Incidence rate per 1000 patient years
All cause mortality	10	11.3	3	4.1
All CV-events	22	24.8	8	10.1
IHD	13	14.6	2	2.7
CVA/TIA	5	5.6	4	5.5
PAD	3	3.4	2	2.7

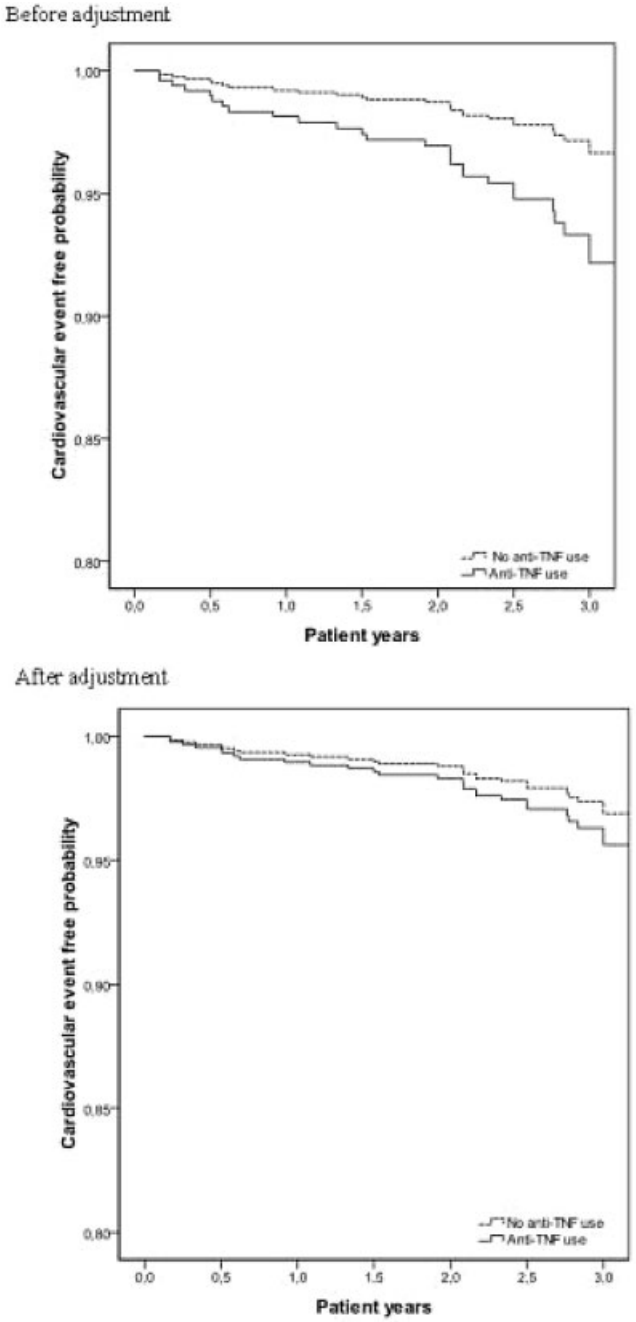

Figure 1. Cox-regression analyis of cardiovascular event free probability for patients with and without TNF-blocking therapy, corrected for age, gender and previous CVD.

Conclusions: This investigation strongly suggests that TNF-blocking agents indeed lowers the cardiovascular risk in RA. However, confirmatory investigations are still required.

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Validation of the Work Performance Visual Analog Scale: Measuring Work and Household Productivity of Patients with Early, Aggressive Rheumatoid Arthritis. Dennis Revicki[2], Sanjoy Roy[1], Miriam Kimel[2], Chris Thompson[2] and Mary Cifaldi[1]. [1]Abbott Laboratories, Abbott Park, IL, [2]United Biosource Corporation, Bethesda, MD

Background and Purpose: Visual analog scales (VASs) have been used in clinical and observational studies to assess the impact of rheumatoid arthritis (RA) on work performance for employed patients and homemakers. To date, however, the psychometric properties of these scales have not been described. To assess the appropriateness for use in clinical trials, we evaluated the psychometric properties of a work performance VAS in both employed workers and homemakers with RA.

Methods: Data from PREMIER and DE032 (health economic companion study of PREMIER), clinical trials of adalimumab (ADA) with or without methotrexate (MTX) in patients with early RA, were analyzed. The VAS measured the impact of RA on work performance on a scale of 0 to 100, in which 0=not affected at all and 100=completely affected. Data were pooled across treatment groups (ADA alone, MTX alone, and ADA+MTX) and analyzed separately for employed patients and homemakers. Psychometric assessments of the VAS included test-retest reliability, convergent validity, known-groups validity, and responsiveness based on minimum clinically important difference (MCID) criteria.

Results: This analysis included 664 patients from PREMIER who participated in the health economic companion study. Test-retest reliability for performance in employment-related and household work was evaluated for patients with no change in clinical status based on Health Assessment Questionnaire (HAQ) and Patient Global Assessment of Disease Activity (PaGA) scores from Weeks 4 to 8 and Weeks 8 to 12 (intraclass correlation coefficients of 0.78–0.85). Convergent validity for employed work performance was demonstrated through moderate to large correlations (0.40–0.72, absolute values; all $p<0.0001$) with the HAQ, 28-joint Disease Activity Score (DAS28), Functional Assessment of Chronic Illness Therapy-Fatigue scale, PaGA, Health Utilities Index Mark 3, Short Form 36 Health Survey, and tender joint counts. Similar findings were observed for household work performance (correlation coefficients ranged from 0.47 to 0.84, absolute values; all $p<0.0001$). Mean VAS scores for both employment-related and household work performance varied significantly across different levels of physical function and disease severity based on HAQ and DAS28 scores; patients with better clinical status had better work performance scores, demonstrating good known-groups validity. From anchor-based methods using American College of Rheumatology response criteria, MCID estimates for VAS scores ranged from 8.6 to 13.2 points for employment-related work performance, and the MCID estimate for household work performance was 13.1 points for all. Based on DAS28 remission status, MCID estimates for VAS scores ranged from 10.7 to 17.0 points for employment-related work performance and from 19.8 to 23.4 points for household work performance.

Conclusions: Results suggest that the work performance VAS scores for employment-related and household work possess acceptable reliability and validity, making them appropriate for use in clinical research to evaluate the impact of RA and treatment on work performance.

Disclosure: D. Revicki: Abbott Laboratories, 5, United Biosource Corporation (contractor for Abbott)., 3; **S. Roy:** Abbott Laboratories, 1, 3; **M. Kimel:** Abbott Laboratories, 5, United Biosource Corporation (contractor for Abbott)., 3; **C. Thompson:** Abbott Laboratories, 5, United Biosource Corporation (contractor for Abbott)., 3; **M. Cifaldi:** Abbott Laboratories, 1, 3.

ACR Poster Session A
Fibromyalgia and Soft Tissue Disorders Poster I
Monday, November 8, 2010, 9:00 AM–6:00 PM

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Candidate Gene Studies of Fibromyalgia: A Systematic Review and Meta-Analysis. Young Ho Lee, Sung Jae Choi, Jong Dae Ji and Gwan Gyu Song. KUMC, Seoul, Korea, Republic of

Objectives: The aim of this study was to explore whether the candidate gene polymorphisms contribute to fibromyalgia susceptibility.

Methods: The authors conducted a meta-analysis on associations between serotonin transporter (5-HTT) gene-linked polymorphic region (5-HTTLPR) S/L allele, Catechol-O-methltransferase (COMT) Val158Met, and serotonin 2A (5-HT2A) receptor 102T/C polymorphisms and fibromyalgia susceptibility as determined using 1) allele contrast, 2) recessive, 3) dominant models, and 4) contrast of homozygotes. We also performed a systematic review with available data of the candidate genes.

Results: A total of 21 separate comparisons were considered in this systematic review and meta-analysis. Seventeen candidate genes and over 35 different polymorphisms were identified in studies on fibromyalgia susceptibility. Meta-analysis of the 5-HTTLPR S/L allele and COMT val158Met failed to reveal any association with fibromyalgia. However, meta-analysis of the C allele, CC+CT genotype, and CC vs. TT genotype of the 5-HT2A receptor 102T/C polymorphism showed significant association with fibromyalgia. The overall OR of the association between the C allele and fibromyalgia was 1.333 (95% CI = 1.053 – 1.688, p = 0.017). The ORs for the CC+CT genotype, and CC vs. TT genotype showed the same pattern as that observed for the C allele (OR = 1.541, 95% CI = 1.032 – 2.303, p = 0.035; OR = 1.838, 95% CI = 1.151 – 2.936, p = 0.011).

Conclusions: This meta-analysis demonstrates that the 5-HT2A receptor 102T/C polymorphism confers susceptibility to fibromyalgia. In contrast, no association was found between the 5-HTTLPR S/L allele, COMT val158Met and susceptibility to fibromyalgia.

Disclosure: Y. H. Lee: None; **S. J. Choi:** None; **J. D. Ji:** None; **G. G. Song:** None.

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Clinical Determinants of Physical Activity in Fibromyalgia Patients. Dennis Ang[1], Anthony Kaleth[3], Silvia Bigatti[2], Steven Mazzuca[2], Chandan Saha[2] and Robert Bandy[2]. [1]Indiana University, Indianapolis, IN, [2]Indiana University, [3]Indiana University-Purdue University Indianapolis

Background: The standard of care for fibromyalgia (FM) includes recommendations for increased physical activity (PA) and exercise. Unfortunately, while most FM patients have no medical contraindications to begin a physically active lifestyle, many remain sedentary. In this report, we sought to determine modifiable clinical correlates of physical activity (PA).

Methods: This was an analysis of cross-sectional data from a randomized clinical trial of motivational interviewing (MI) to improve exercise adherence for patients with FM. Subjects (n=216) completed web-based assessments and wore an ActiGraph monitor around the waist for ≥10 waking hours/day for 4–7 days. Logistic regression was used to identify clinical factors associated with exhibiting median or greater PA in two respects: ≥3,722 steps/day and ≥77 minutes/week in moderately intense PA.

Results: Most of the FM patients were female (95.8%), white (88.4%), married (61.1%) and employed (53.7%). Baseline means for demographic and clinical variables and bivariate associations with PA indicators ($P \leq 0.15$) are tabled below.

Dependent Variable	Predictor	Mean ± SD	Odds Ratio*	95% CI
≥3,722 steps/day	Employed vs. unemployed		2.28	1.29–4.02
	# of co-morbidities	1.0 ± 1.0	0.62	0.45–0.84
	BMI, kg/m^2	31.4 ± 7.2	0.63	0.47–0.85
	Total FIQ	67.0 ± 12.7	0.65	0.47–0.89
	PHQ-8 depression severity	12.5 ± 4.9	0.71	0.54–0.94
	Age, years	45.8 ± 11.3	0.71	0.54–0.94
	FM duration, years	9.0 ± 7.0	0.74	0.56–0.98
	# of medications	3.0 ± 1.6	0.78	0.59–1.03
BPI pain intensity		6.0 ± 1.3	0.80	0.61–1.06
Moderate PA ≥77 minutes/week				
	BMI, kg/m^2	31.4 ± 7.2	0.63	0.47–0.85
	PHQ-8 depression severity	12.5 ± 4.9	0.64	0.48–0.85
	# of co-morbidities	1.0 ± 1.0	0.76	0.57–1.02
	Total FIQ	67.0 ± 12.7	0.76	0.56–1.03
	# of medications	3.0 ± 1.6	0.80	0.61–1.05

* Change in odds of being above median, relative to below, associated with a 1-SD increment in the predictor variable except for total FIQ where a 14% change is considered clinically meaningful.

In the multivariate analysis, being relatively active (≥3,722 steps/day) was associated with lower BMI (OR: 0.62, 0.45–0.86), fewer co-morbidities (OR: 0.71, 0.51–0.99), shorter disease duration (OR: 0.72, 0.52–1.0) and lower Total FIQ (OR: 0.61, 0.43–0.88). Alternatively, time spend in PA of moderate or greater intensity (≥77 min/wk) was limited by greater BMI (OR: 0.64, 0.48–0.86) and increased depressive symptomatology (OR: 0.74, 0.56–0.99).

Conclusions/Implications: Active lifestyles were rare in this sample of FM patients. Employed patients were more active than unemployed ones. While several associations with clinical variables may be bidirectional, sedentary patients tended to be more obese and have greater duration and severity of FM and more numerous co-morbidities. Clinicians may take these associations as evidence supporting the encouragement of PA early in the disease process. However, attainment of appreciable levels of moderate intensity of PA may be difficult without attention to weight loss and mood, when indicated.

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Development of Responder Definitions for Fibromyalgia Clinical Trials. Lesley M. Arnold[8], Philip J. Mease[6], David A. Williams[7], Susan A. Martin[5], Fujun Wang[2], Birol Emir[4], Chinglin Lai[3] and Rong Zablocki[1]. [1]Cypress Bioscience, Inc., [2]Eli Lilly and Company, [3]Jazz Pharmaceuticals, [4]Pfizer, Inc., [5]RTI-Health Solutions, [6]Seattle Rheumatology Associate, Seattle, WA, [7]Univ of MI Hlth System-Lobby M, Ann Arbor, MI, [8]University of Cincinnati College of Medicine, Cincinnati, OH

Background: Previous analyses of fibromyalgia (FM) clinical trial databases found patient perceptions of global improvement relied not only on improvements in pain but also on improvements in accompanying symptoms such as fatigue, sleep problems, physical functioning, and mood. These symptom and functional domains may form the components of a responder definition for FM clinical trials. The objective of this study was to develop and test responder definitions for FM clinical trials using key symptom and functional domains.

Methods: Informed by existing responder definitions for other rheumatologic disorders, 8 candidate responder definitions were developed by expert consensus. These 8 definitions were evaluated in the context of randomized placebo-controlled clinical trials of 4 medications for FM between baseline and 3 months. For each of the proposed definitions, treatment effects of the medication compared with placebo were analyzed using the Cochran-Mantel-Haenszel test. A meta-analysis of the pooled results for the 4 medications established risk ratios so as to determine the definitions that best favored medication over placebo.

Results: Two definitions performed best in the analyses and shared common features. Both definitions included ≥ 30% reduction in pain and both included ≥ 10% improvement in physical function. They differed in that one (FM 30 short version) included ≥ 30% improvement in sleep or fatigue, and the other (FM 30 long version) required ≥ 30% improvement in 2 of the following symptoms: sleep, fatigue, depression, anxiety, or cognition. In the analysis of both versions, the response rate was about 20% or greater for each medication and was significantly greater than placebo. The risk ratio (95% CI) in the pooled analysis of the FM 30 short version was 1.69 (1.04, 2.72), $P=0.03$; the risk ratio (95% CI) for the FM 30 long version was 1.60 (1.31, 1.96), $P=<0.00001$.

Conclusion: Among the 8 responder definitions tested, 2 were identified as most sensitive in identifying response to treatment. The identification of responder definitions for FM clinical trials that include assessments of key symptom and function domains will hopefully improve the sensitivity of clinical trials to identify meaningful improvements, leading ultimately to improved management of FM.

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Does Obesity in Patients with Fibromyalgia Modify Response to Tai Chi Therapy: Analysis of a Randomized Controlled Trial. Chenchen Wang[1], Christopher H. Schmid[2], Yoojin Lee[2] and Timothy McAlindon[1]. [1]Tufts Medical Center, Boston, MA, [2]Tufts Medical Center

Purpose: Fibromyalgia (FM) is a chronic pain disorder of complex etiology. Recent evidence about the association between obesity and FM suggests that this might obfuscate therapy. We evaluated the association of obesity and changes in FM severity, sleep quality and health related quality of life in a randomized controlled trial of FM patients.

Methods: We studied a sample of 66 eligible individuals (age 21 or older and fulfilled the American College of Rheumatology 1990 diagnostic criteria for FM) who participated in a single-blind, randomized controlled trial. Using computer-generated numbers, we randomly assigned participants to Tai Chi mind-body exercise (Classical Yang style, n=33) or attention control (stretching and wellness education n=33) in three cycles of 22 patients each. The 60-minute group sessions occurred twice-weekly for 12 weeks. We defined obesity as body mass index (BMI) ≥30.00 kg/m2. Study endpoints included changes from baseline to 12 weeks in FM Impact Questionnaire (FIQ) score (range, 0 to 100; higher scores indicate more severe symptoms), Pittsburgh Sleep Quality Index (range, 0–21, higher scores indicate worse sleep quality), and Physical Component Summary and Mental Component Summary of the Short Form-36 (SF-36) to assess quality of life (range 0–100; lower scores indicate worse health status). We estimated the relationship between obesity and the treatment effect by the interaction of treatment and obesity in linear regression using each of the three study endpoints.

Results: The 66 participants had mean age 50y (SD 11.1), mean disease duration 11 y (SD 7.1), mean BMI 33 kg/m^2 (SD 8.2), and were mainly female (86%) and white (56%). Thirty-six patients were obese (BMI≥30) and 29 patients were not obese (< 30.00) and 1 had missing BMI. The proportion of obese BMI remained stable in both Tai Chi and control groups. Obese patients assigned to Tai Chi group exhibited significantly greater improvement in FIQ total score (between-group difference −17.5, 95% CI, [−34.1 to −1.0]; P=0.04)

than the non-obese group. The SF-36 Physical Component Summary and Mental Component Summary tests also favored obese group but did not reach statistical significance. Both groups improved their sleep quality (Pittsburgh Sleep Quality Index) equally **(Table)**.

Table. Changes in FM severity, sleep quality and health status by BMI group at Week 12*

Variables/ BMI level	Groups	Baseline Mean (SD)	At 12 week Mean Change (95% CI)	Mean change between Tai Chi vs. control (95% CI) and P-value	Mean change between obese vs. non-obese (95% CI) and P-value
BMI ≥30 (n=36)	Tai Chi	38.7 ± (6.9)	−0.1 (−0.5, 0.4)	0.1 (−0.6, 0.8)	−0.3 (−1.3, 0.8),
	Control	38.2 (5.4)	−0.2 (−0.7, 0.4)	P=0.79	P=0.62
BMI <30 (n=29)	Tai Chi	24.7 (3.5)	0.2 (−0.4, 0.8)	0.4 (−0.4, 1.1)	
	Control	25.9 (2.5)	−0.2 (−0.6, 0.3)	P=0.37	
FIQ (0-100)	Tai Chi	66.8 (14.4)	−32.9 (−40.0, −25.8)	−26.3 (−37.2, −15.4)	−17.5 (−34.1, −1.0),
BMI ≥30 (n=36)	Control	71.5 (10.3)	−6.6 (−14.9, 1.8)	**P<0.0001**	P=0.04
FIQ (0-100)	Tai Chi	56.6 (16.2)	−20.6 (−30.2, −10.8)	−8.8 (−21.2, 3.6)	
BMI <30 (n=29)	Control	65.1 (11.0)	−11.8 (−19.4, −4.2)	P=0.17	
SF-36:PCS (0-100)	Tai Chi	26.4 (7.2)	10.1 (6.7, 13.5)	9.0 (3.7, 14.3)	4.5 (−3.5, 12.5),
BMI ≥30 (n=36)	Control	26.0 (7.4)	1.1 (−2.9, 5.2)	P=0.001	P=0.27
SF-36:PCS (0-100)	Tai Chi	31.8 (9.7)	6.1 (1.4, 10.8)	4.5 (−1.5, 10.5)	
BMI < 30 (n=29)	Control	29.6 (8.0)	1.6 (−2.1, 5.2)	P=0.14	
SF-36:MCS (0-100)	Tai Chi	42.0 (13.3)	9.0 (4.3, 13.7)	8.7 (1.4, 16.0)	5.4 (−5.6, 16.4),
BMI ≥30 (n=36)	Control	35.6 (7.3)	0.3 (−5.3, 5.9)	P=0.02	P=0.34
SF-36:MCS (0-100)	Tai Chi	43.5 (11.1)	6.0 (−0.5, 12.5)	3.3 (−4.9, 11.6)	
BMI < 30 (n=29)	Control	39.1 (12.5)	2.7 (−2.4, 7.8)	P=0.43	
PSQI (0-21)	Tai Chi	14.0 (3.0)	−3.5 (−5.0, −2.1)	−3.3 (−5.5, −1.0)	−0.2 (−3.6, 3.2),
BMI ≥ 30 (n=36)	Control	14.7 (3.7)	−0.3 (−2.0, 1.5)	**P=0.005**	P=0.91
PSQI (0-21)	Tai Chi	13.9 (3.7)	−4.2 (−6.2, −2.2)	−3.1 (−5.6, −0.5)	
BMI < 30 (n=29)	Control	12.4 (3.4)	−1.1 (−2.7, 0.5)	**P=0.02**	

* N=33 for Tai Chi and Control each group. FIQ = Fibromyalgia Impact Questionnaire. PSQI=Pittsburgh Sleep Quality Index. SF-36: PCS and MCS = Short Form-36 Physical Component Score and Mental Health Summary

Conclusion: Despite no weight loss in either group, obese patients with FM improved more in their symptoms and quality of life with Tai Chi than with attention control. Tai Chi mind-body exercise may be a particularly beneficial treatment for obese patients with FM. BMI should be considered in future behavioral intervention design.

Disclosure: C. Wang: None; **C. H. Schmid:** None; **Y. Lee:** None; **T. McAlindon:** None.

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Dorsal Root Ganglia/Sympathetic Ganglia Sodium Channels Gene Polymorphisms in Fibromyalgia. Gilberto Vargas-Alarcon, Edith Alvarez-Leon, Jose-Manuel Fragoso, Angelica Vargas, Aline Martinez, Maite Vallejo and Manuel Martinez-Lavin. National Institute of Cardiology, Mexico

Background: A consistent line of investigation suggests that autonomic dysfunction may explain the multi-system features of fibromyalgia (FM), and that FM is a sympathetically maintained neuropathic pain syndrome. Dorsal root ganglia (DRG) are potential sympathetic-nociceptive short-circuit sites. Sodium channels located in DRG (particularly Nav1.7) act as molecular gatekeepers for pain detection. Nav1.7 is encoded in gene SCN9A of chromosome 2q24.3 and is predominantly expressed in the DRG pain-sensing neurons and sympathetic ganglia neurons. Several SCN9A sodium channelopathies have been recently recognized as the cause of rare painful-dysautonomic syndromes such as paroxysmal extreme pain disorder and primary erythermalgia (Ann N Y Acad Sci. 2010;1184:196, Med Hypotheses. 2009;72:64). SCN9A polymorphisms (particularly rs6746030) have been linked to altered pain perception (Proc Natl Acad Sci USA 2010;107:5148).

Objective: To identify associations between fibromyalgia and several Nav1:7 polymorphisms encoded in gene SCN9A.

Methods: We studied 73 Mexican women with FM according to the 1990 ACR criteria and 48 Mexican women who considered themselves healthy. All participants filled out the Fibromyalgia Impact Questionnaire (FIQ). Genomic DNA from whole blood containing EDTA was extracted by standard techniques. The following SCN9A single-nucleotide polymorphisms (SNPs) were studied: rs4371369, rs4387806, rs4453709, rs4597545, rs6746030, rs6754031, rs7607967, rs12620053, rs12994338, and rs13017637. SNPs were analyzed by 5-exonuclease TaqMan assays on a 7900HT fast real-time PCR system.

Results: Are summarized in table 1. Rs6754031 nucleotide distribution was significantly different in both groups (p = 0.036) mostly due to an absence of GG genotype in controls. Interestingly, patients with this rs6754031 GG genotype had higher total FIQ scores, than patients with the other two rs6754031 genotypes (p = 0.039). Table 2.

Table 1. Nucleotide distribution.

Rs-6754031	Patients	Controls	P value
n	73	48	
Age (mean ± SD)	44.7 ± 12.8	42.8 ± 12.3	ns
Genotype	n (%)	n (%)	
GG	8 (11)	0 (0)	
GT	24 (33)	15 (31)	0.036
TT	41 (56)	33 (69)	

Table 2. Total FIQ score in patients with Rs-6754031

	FIQ score			
Rs-6754031 Genotype	Percentile 25	Median	Percentile 75	P value
GG	69.74	80.38	88.74	0.039
GT	58.55	63.29	77.53	
TT	64.23	71.25	77	

Conclusions: In this ethnic group, a disabling form of FM was associated to a particular SCN9A gene variant. These preliminary results raise the possibility that patients with severe FM may have a sodium channelopathy.

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Durability of Response in a 38-Week Open-Label Study of Sodium Oxybate in Patients with Fibromyalgia. Michael Spaeth[5], I. Jon Russell[7], Serge Perrot[6], Sarah Alvarez-Horine[3], Diane R. Guinta[1], Y. Grace Wang[2] and Robert M. Bennett[4]. [1]Jazz Pharmaceuticals Inc., Palo Alto, CA, [2]Jazz Pharmaceuticals Inc., [3]Jazz Pharmaceuticals, Inc., [4]Oregon Health and Science Univ, Portland, OR, [5]Rheumatologische Schwerpunktpraxis, [6]Service de Medecine Interne et Centre de la Douleur, Hôtel-Dieu, [7]University of Texas Health Science Center, San Antonio, TX

Background: Two pivotal phase 3 clinical trials demonstrated the efficacy and tolerability of sodium oxybate (SXB) for the treatment of fibromyalgia (FM). Fibromyalgia is a chronic disorder characterized by widespread musculoskeletal pain, fatigue, sleep disturbances, and functional impairment. The current report describes the durability of response of SXB in a FM population.

Methods: Patients with FM who completed a 14-week, placebo-controlled, phase 3 study of SXB were eligible to enroll in this international, open-label extension within 7 days after completing the previous study. Eligible subjects received open-label treatment for up to an additional 38 weeks. SXB was initiated at 4.5 g/night (administered in equally divided doses 2.5 to 4 hours apart), and increases were permitted in increments of 1.5 g/night, at intervals of at least 1 week, up to 9 g/night. Dose reductions were permitted in increments of 1.5 g/night to a minimum of 4.5 g/night; subjects unable to tolerate this dose were discontinued. Efficacy was evaluated based on reductions in pain and fatigue, recorded daily on a 100 mm Visual Analogue Scale (VAS), and improvement in function assessed using the Fibromyalgia Impact Questionnaire (FIQ) at each study visit. Study endpoint was defined as the last available data, whether obtained at study completion or early discontinuation.

Results: Of 560 subjects who were treated (mean age, 46.9 years; 91.1% female), 366 subjects (65.4%) received study drug for at least 24 weeks and 269 subjects (48.0%) received study drug at least 38 weeks. Mean dose was 6.28 g/night at last dose for all subjects. Improvements seen on multiple measures in the previous trials were maintained. At study endpoint, the mean change from prior study baseline in pain VAS for all treated patients was –35.84 mm, with 68.8% and 53.0% achieving a ≥30% and ≥50% pain reduction, respectively. At study endpoint, the mean change from baseline in fatigue VAS was –37.15 mm. At endpoint, 69.7% of patients had achieved ≥30% reduction from baseline in total FIQ score. The incidence of AEs was 88.9% overall. AEs were generally mild or moderate in severity. Twenty-three percent of subjects discontinued due to AEs. The most common AEs (≥5% in any treatment group) were nausea, headache, dizziness, nasopharyngitis, vomiting, sinusitis, diarrhea, anxiety, insomnia, influenza, somnolence, upper respiratory tract infection, muscle spasms, urinary tract infection, and viral gastroenteritis.

Conclusions: This open-label study demonstrated the long-term durability of effect of SXB for the treatment of FM over a dose range of 4.5 to 9 g/night for 38 weeks. Treatment effects were substantial across multiple fibromyalgia symptoms, including pain, fatigue, and impairments in daily living and physical functioning. SXB was generally well-tolerated over the 38 weeks of treatment.

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Effects of Milnacipran Added to Pregabalin on Cognition and Mental Clarity in Fibromyalgia Patients. Robert S. Katz[4], Robert H. Palmer[2], Yong Wang[3] and R. Michael Gendreau[1]. [1]Cypress Bioscience, Inc, San Diego, CA, [2]Forest Research Institute, Jersey City, NJ, [3]Forest Research Institute, [4]Rush University Medical Center, Chicago, IL

Purpose: Fibromyalgia (FM) is characterized by chronic widespread pain accompanied by a host of symptoms that include perceived cognitive dysfunction, which is also known as fibrofog. Cognitive impairments associated with fibrofog include problems with attention, mental confusion, and short-term memory loss. A recent clinical trial evaluating the efficacy of milnacipran when added to pregabalin utilized the Mental Clutter Scale, a new 16-item measure of fibrofog, to assess improvements in cognitive disability in FM patients.

Methods: The Mental Clutter Scale is composed of 2 subscales that measure cognition and mental clarity; each subscale consists of 8 items. This randomized, open-label, controlled study evaluated the efficacy and tolerability of milnacipran 50 mg BID when added to pregabalin 150 mg BID or 225 mg BID in FM patients who had an incomplete response to pregabalin during a 4- to 12-week open-label run-in phase. Pregabalin incomplete responders (defined as patients with weekly recall VAS pain score ≥40 and ≤90 [0 to 100 scale], Patient Global Impression of Severity score ≥4 [moderately ill to extremely ill], and Patient Global Impression of Change [PGIC] score ≥3 [minimally improved to very much worse]) were randomized to either pregabalin alone (n=180) or milnacipran added to pregabalin (n=184) for 11 weeks. Least squares mean changes from baseline in Mental Clutter Scale subscale and item scores were analyzed at endpoint using an LOCF approach.

Results: Patients treated with milnacipran added to pregabalin demonstrated significant improvements compared to pregabalin alone in the Mental Clutter Scale full scale score ($P<.001$) as well as the Cognition and Mental Clarity subscale scores ($P\leq.001$). All item scores of the Cognition subscale were significantly improved in the milnacipran added to pregabalin group compared with pregabalin alone except for memory assessment ($P=.052$). Scores for concentration ($P=.043$), staying focused ($P=.008$), multitasking ($P=.009$), expressing self ($P=.004$), thinking clearly ($P<.001$), perceptual clarity ($P=.002$), and mental speed ($P=.001$) were all significantly improved in the milnacipran added to pregabalin group compared with pregabalin alone. In addition, significant improvements were demonstrated on all items of the Mental Clarity subscale: spaciness ($P<.001$), haziness ($P<.001$), confusion ($P<.001$), cluttered thinking ($P=.005$), fogginess ($P=.009$), rushing thoughts ($P=.002$), fuzzy headedness ($P=.007$), and information overload ($P=.002$).

Conclusions: When added to pregabalin, milnacipran resulted in significant improvements in the cognitive impairments perceived by FM patients, as measured by a new self-report tool intended to measure cognition and mental clarity.

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Fatigue in Fibromyalgia Patients: A Qualitative Study Exploring a Conceptual Framework. Philip J. Mease[4], Lisa D'Ambrosio[3], Asha Hareendran[6], Maureen Mohyde[2], Robin Pokrzywinski[6], Kristin Seymour[5] and Steven Blum[1]. [1]Forest Research Institute, [2]Outcome Sciences, [3]Outcome Sciences and MIT AgeLab, [4]Seattle Rheumatology Associate, Seattle, WA, [5]Seattle Rheumatology Associates, [6]United BioSource Corporation

Purpose: In addition to pain, fatigue is a common and important symptom of fibromyalgia (FM) and has been included in the OMERACT (Outcome Measures in Rheumatology Clinical Trials) core domain set1 and the 2010 ACR Preliminary Diagnostic Criteria for FM.2 The FDA Guidance on Patient-Reported Outcome (PRO) Measures recommends input from patients in development or modification of PRO instruments. This study was conducted to further explore FM patients' experience of fatigue and to provide insight into how it can be measured in a way that captures concepts that are most relevant to patients with FM.

Methods: Two focus group discussions among clinically diagnosed FM patients were conducted (n=18). All patients were female and were recruited from a single clinical practice site. The focus groups were conducted using a semi-structured interview guide. Initial discussions began with open-ended questions about challenges of living with FM, effects of FM on daily life, interactions with others and experience with fatigue. Patients were then further probed about their experience with fatigue due to FM. Audio recordings were transcribed and analyzed using a researcher developed coding book and atlas.ti software.

Results: The data support existing frameworks for FM but offers additional insights in the experience of fatigue among patients with FM. The data suggest that fatigue in FM varies within a week and even within a single day. FM patients perceive the severity of their fatigue in terms of its implications for daily function, impacts on sleep, cognition, motivation and emotions. When discussing the impact of fatigue on functioning, patients described activities they are no longer able to participate in, such as personal care, housework, work productivity, cooking, making or keeping plans, and losing spontaneity. Although sleep disturbances were reported by patients, many perceived being fatigued and tired as separate concepts. Fatigue was not necessarily improved by sleep. Fatigue and cognitive dysfunction were closely intertwined, such as being in a 'fibro fog', not being able to concentrate, forgetting things, difficulty making decisions, and feeling like there is a mental curtain or veil. Lack of motivation as a result of fatigue was exemplified by having to push to start or complete activities, lacking initiative, and feeling depleted. The emotional impact of fatigue stemmed from feeling frustrated with not being able to do things they wanted and not being able to remember things. Patients also expressed feeling embarrassment or guilt for not being able to do things, especially with family and friends. Patients perceived physical experiences of fatigue as if being weighted down, such as wearing heavy clothing made of cement.

Conclusion: This qualitative work has provided additional insights for a framework for evaluating fatigue in FM. It is important to evaluate more than the frequency and severity of being tired. The variability of patients' experience of fatigue in FM suggests the need for more frequent assessment as well as a broader set of concepts to be evaluated when measuring fatigue in FM.

1: Mease P, et al. J Rheum 2009;36:2318–2329
2: Wolfe F, et al. Arth Care Res 2010;62:600–610

Disclosure: P. J. Mease: Forest Laboratories, 3; **L. D'Ambrosio:** Outcome Sciences and MIT AgeLab, 3; **A. Hareendran:** United BioSource Corporation, 3; **M. Mohyde:** Outcome Sciences, 3; **R. Pokrzywinski:** United BioSource Corporation, 3; **K. Seymour:** None; **S. Blum:** Forest Laboratories, 1, 3.]]

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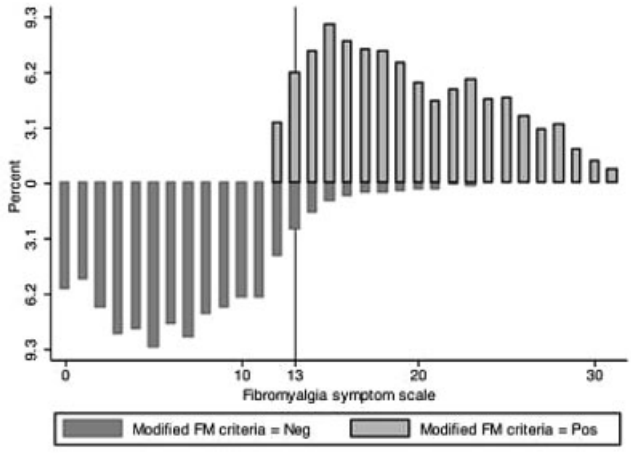
Fibromyalgia Criteria and Severity Scales for Clinical and Epidemiological Studies: A Modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. Frederick Wolfe[2], Daniel J. Clauw[7], Mary Ann Fitzcharles[1], Don L. Goldenberg[3], Winfried Häuser[6], Robert S. Katz[4], Philip J. Mease[5], Anthony S. Russell[8], I. Jon Russell[10] and John B. Winfield[9]. [1]Montreal West, QC, Canada, [2]National Data Bank for Rheumatic Diseases, Wichita, KS, [3]Newton-Wellesley Hosp, Newton, MA, [4]Rheumatology Associates, Chicago, IL, [5]Seattle Rheumatology Associate, Seattle, WA, [6]Technische Universität München, Munich, Germany, [7]UM/Chronic Pain & Fatigue Res, Ann Arbor, MI, [8]University of Alberta, Edmonton, AB, Canada, [9]University of North Carolina, Chapel Hill, NC, [10]University of Texas HSC, San Antonio, TX

Purpose: To develop a FM survey questionnaire for epidemiologic and clinical studies using a modification of the 2010 ACR Preliminary Diagnostic Criteria for Fibromyalgia (ACR2010). We also created a new FM symptom scale to further characterize fibromyalgia [FM] severity.

Methods: The ACR2010 consists of two scales, the Widespread Pain Index (WPI) and the Symptom Severity (SS) scale. We modified these ACR2010 criteria by eliminating the physician's estimate of the extent of somatic symptoms and substituting the sum of 3 specific self-reported symptoms. The 3 specific symptoms score was sum of the number of the following symptoms occurring during the previous 6 months: headaches, abdominal pain, and depression. We made this change because the physician's estimate of the extent of somatic symptoms was an evaluative measure that could be not performed in a survey. The 3 new symptoms tapped into the same domain of symptom reporting. We also created a 0–31 FM Symptom scale (FS), also known as the Fibromyalgianess scale, by summing the WPI and the modified SS scale. We administered the questionnaire to 729 patients previously diagnosed with fibromyalgia, 845 with osteoarthritis or with other non-inflammatory rheumatic conditions (OA), 439 with lupus, and 5,210 with RA.

Results: The modified ACR2010 criteria were satisfied by 60% with a prior diagnosis of fibromyalgia, 21.1% with RA, 16.8% with OA, and 36.7% with SLE. The criteria properly identified diagnostic groups according to FM severity variables. An FS score ≥13 best separated criteria (+) and criteria (-) patients, classifying 93.0% correctly, with a sensitivity of 96.6% and a specificity of 91.8% in the study population, as shown in Figure 1.



Characteristics of patients according to entry and criteria status demonstrated appropriate classification.

Fibromyalgia-related Characteristics According Entry and Diagnostic Criteria

Variable	*FM (+) Criteria +*	*FM (+) Criteria −*	*FM (−) Criteria +*	*FM (+) Criteria −*
	Mean or %	Mean or %	Mean or %	Mean or %
Widespread pain index (0–19)	12.9	5.6	11.7	3.6
4-item Modified SS score (0–12)	8.0	4.0	7.4	2.8
Fibromyalgia symptom scale (0–31)	20.9	9.6	19.0	6.5
Fatigue (0–10)	7.2	4.2	7.1	3.1
Sleep disturbance (0–10)	6.5	3.8	6.1	3.0
VAS Pain (0–10)	6.3	3.8	5.9	2.7
Mood (0–10)	4.0	2.6	3.8	2.0
Muscle tenderness (%)	89.7	63.0	65.7	18.6
Symptom count (0–37)	16.1	8.8	14.5	5.7

FM (+) and FM (−) refer to clinical diagnosis at time of data bank entry. Criteria + and Criteria − refer to results of the modified ACR 2010 diagnostic criteria.

Conclusions: A slight modification to the ACR2010 will allow their use in epidemiologic and clinical studies without the requirement for an examiner. The modified criteria can also be used to determine widespread pain according to the 1990 ACR classification criteria. The modified criteria are simple to use and administer, but they are not to be used for self-diagnosis. The FS may have wide utility beyond the bounds of FM, including substitution for widespread pain in epidemiological studies and measurement of FM severity.

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Fibromyalgia Is Associated with a Disruption of Emotional Modulation of Pain, but Not Emotional Modulation of Spinal Nociception. Jennifer L. DelVentura[1], Ellen L. Terry[2], Emily J. Bartley[2], Ashley Vincent[2], Ewa Olech[3] and Jamie L. Rhudy[2]. [1]The University of Tulsa, Tulsa, OK, [2]The University of Tulsa, [3]University of Oklahoma, Health Sciences Center

Background: Fibromyalgia syndrome (FM) is a disorder of unknown etiology that is characterized by chronic, widespread musculoskeletal pain and hyperalgesia. Recent functional imaging research has shown that FM patients exhibit differing patterns of brain activation during anticipation of and experience of experimental pain, as compared with rheumatoid arthritis (RA) patients and healthy controls (HC). Therefore, FM-related hyperalgesia may be due to an amplification of the nociceptive signal via cognitive-emotional mechanisms at the supraspinal level. Indeed, individuals with FM tend to report increased negative affect and reduced positive affect; a finding consistent with their higher rates of anxiety and depressive disorders. Given that emotion modulates pain and nociception, such that negative emotions augment pain and positive emotions inhibit it, and that FM patients exhibit hyperalgesia and greater negative affect, the present study examined whether FM patients would show disrupted emotional modulation of pain and nociception relative to RA and HC.

Methods: Patients with physician-verified diagnoses of FM or RA, and HCs with no chronic pain were recruited (N=33; FM=11, RA=8, HC=14). Participants were shown pictures that varied in emotional content (mutilation, neutral, erotica). To elicit pain and the nociceptive flexion reflex (NFR, a physiological correlate of spinal nociception), suprathreshold electrocutaneous stimuli were delivered to the left ankle over the sural nerve pseudorandomly, during and in between pictures.

Results: Pain and NFR during different picture contents were analyzed using a linear mixed model analysis. Results suggested that all groups exhibited emotional modulation of the NFR—unpleasant pictures augmented NFR and pleasant pictures inhibited NFR. Conversely, emotional modulation of pain ratings was exhibited in the RA and HC groups, but not in the FM group. Average pain ratings were not significantly different between groups (p=.28).

Conclusions: Thus, only FM patients exhibited abnormal emotional modulation of pain, while cerebrospinal modulation of the NFR was similar across groups. These data support prior research indicating disrupted supraspinal processing of the pain signal in FM. This study was funded by NIAMS (grant number: 5R03AR054571).

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Fibromyalgia with and without Comorbid Positional Cervical Cord Compression (PC3): An Iron-Clad Difference. Patrick B. Wood[2], Tobias Schmidt-Wilcke[3] and Andrew J. Holman[1]. [1]Pacific Rheumatology Assoc, Renton, WA, [2]Pacific Rheumatology Associates, Renton, WA, [3]University of Michigan

Fibromyalgia (FM) is associated with abnormalities of dopaminergic neurotransmission. Because iron is an important cofactor for dopamine

metabolism, we investigated whether FM symptom severity might correlate with iron stores as indicated by serum ferritin level (FE). Positional cervical cord compression (PC3) has also been recently identified as a common abnormality among FM patients (*J Pain 2008;9:613-22*). We therefore investigated whether FM patients with (FM/PC3+) or without (FM/PC3-) this cervical abnormality might differ with regard to symptom severity or their potential relationship to FE.

Methods: A convenience sample of 150 patients referred to a community-based FM specialty clinic was analyzed. All subjects met ACR 1990 diagnostic criteria for FM. Among these, 50% (n=75) were randomly selected from a pool of patients with: (1) a clinical history of cervical trauma and/or exacerbation of symptoms on cervical extension; and (2) PC3 on dynamic magnetic resonance imaging (dMRI). The other 50% (n=75) were randomly selected from among patients who either (1) denied a history of cervical trauma and had no exacerbation of symptoms on cervical extension, or (2) had undergone cervical dMRI and had no evidence of cord compromise. FE was drawn on all patients at intake and processed at the same clinical reference laboratory. All patients completed a comprehensive series of medical questionnaires, including a scaled review of systems and Adult ADHD Self-Report Scale (ASRS). Categorical indices of symptom severity were derived by summation of scaled symptoms from the intake review of systems (0–5 scale: 0 = none; 1 = minimal; 2 = mild; 3 = moderate; 4 = severe; 5 = extreme). Student's t-test for non-paired samples was used to compare FE and symptom severity between groups. Pearson's correlation was used to evaluate potential correlations between FE and symptom severity within each group.

Results: There were no significant differences between groups concerning FE (FM/PC3- vs. FM/PC3+, mean ± SD: 49.4 ± 33.8 ng/ml vs. 56.4 ± 35.9 ng/ml, p =.22) or the severity of any clinical index. However, among FM/PC3- significant negative correlations were found between FE and the severity of several measures, including ASRS score (rho = −.377, p =.001), dyscognition (rho = −.488, p <.001), dys-coordination (rho = −.392, p =.001), affective disturbance (rho = −.384, p =.001), and clinical pain (rho = −.231, p =.047). Conversely, among FM/PC3+, no significant correlations were found between FE and the severity of any symptoms.

Discussion: Among FM patients without comorbid PC3, negative correlations exist between FE and the severity of symptoms ostensibly linked to dopaminergic neurotransmission, including dyscognition, dys-coordination, affective disturbance, and clinical pain. These remarkable differences among FM patients suggest distinct pathophysiological subtypes within the greater 'FM construct'. Further research is needed to determine whether FM might be associated with abnormal iron metabolism and to evaluate for potential correlations between FE and objective measures of dopaminergic neurotransmission.

Disclosure: P. B. Wood: None; **T. Schmidt-Wilcke:** None; **A. J. Holman:** None.

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Flt3-L Is a Novel Biomarker Increased in Cerebrospinal Fluid of Patients with Primary Fibromyalgia and Sjogren Syndrome. Jan L. Bjersing, Mats Dehlin, Henrik Zetterberg, Anette Larsson, Malin Erlandsson, Kaisa Mannerkorpi and Maria Bokarewa. Dept Rheumatology, Gothenburg University, Sweden

Primary fibromyalgia syndrome (FM) is a non-inflammatory condition, characterised by chronic generalized pain with allodynia. Primary Sjogren syndrome (pSS) is an autoimmune inflammation of exocrine glands. Fms-like tyrosine kinase 3 (Flt3-L) is a growth factor expressed in brain microglia and regulating differentiation and recruitment of monocytes into dendritic and glial cells. Both FM and pSS are commonly associated with fatigue and non-restorative sleep, and occasionally with depression and cognitive dysfunction. The aim of the study was to compare inflammatory and axonal biomarkers in cerebrospinal fluid (CSF) of pSS and FM patients.

Paired samples of CSF and serum from female patients with pSS (age 48±12 years, disease duration 10±8 years) and FM (age 49±8 years, symptom duration 12±5 years) were evaluated for the levels of Flt3-L and related to inflammatory (IL-6, IL-8) and axonal (NFL, Tau, phosphorylated Tau, GFAP) biomarkers.

Flt3-L in CSF was significantly higher in FM patients compared to pSS patients (table 1). The proportion of phosphorylated Tau (pTau) to total Tau (tTau) was significantly higher in FM compared to SS. However, total levels of tTau and pTau were not different between the groups. Flt3-L in CSF correlated with levels of tTau and pTau, in both pSS (r=0.68, r=0.65) and FM (r=0.38, r=0.45). In FM, Flt3-L was also associated with neurofilament light chain (NFL, r=0.41) and astrocyte marker glial fibrillary acidic protein (GFAP, r=0.58). Flt3-L in CSF correlated with Flt3-L in serum of patients with pSS (r=0.53) but not in FM. IL-6 in CSF was significantly higher in pSS patients compared to FM (table 1). No correlation was found between Flt3-L and IL-6. Serum levels of IL-6, IL-8 or Flt3-L were not significantly different between pSS and FM patients.

Table 1. Levels of biomarkers in cerebrospinal fluid in primary fibromyalgia (FM) and primary Sjögren syndrome (pSS)

	Flt3-L pg/ml	IL6 pg/ml	IL8 pg/ml	tTau/pTau	NFL ng/L	GFAP ng/L
pSS	53	2.3	41	4.7	500	420
n = 15	[28; 76]	[0.7; 4.5]	[54; 25]	[3.8; 5.3]	[240; 1780]	[170; 860]
FM	$64.5^{p<0.003}$	$1.5^{p<0.003}$	$33^{p<0.02}$	$4.1^{p<0.02}$	500	510
n = 34	[46; 95]	[0; 3.3]	[20; 51]	[0; 5.2]	[250; 1550]	[230; 2320]

Values are presented as median [min, max]. Mann-Whitney U-test was used.

Flt3-L is a novel biomarker in CSF, distinguishing patients with FM and pSS. Levels of Flt3-L are positively related with axonal products, suggesting potential clinical impact of Flt3-L in fatigue and pain of patients with FM and pSS.

Disclosure: J. L. Bjersing: None; **M. Dehlin:** None; **H. Zetterberg:** None; **A. Larsson:** None; **M. Erlandsson:** None; **K. Mannerkorpi:** None; **M. Bokarewa:** None.

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Hysterectomy Status and Fibromyalgia Symptom Severity. Mary O. Whipple, Ann Vincent, Terry H. Oh, Connie A. Luedtke and Tanya L. Hoskin. Mayo Clinic, Rochester, MN

Background: Clinical observation and preliminary studies suggest that gynecological surgeries impact symptom severity in fibromyalgia. However, the literature is deficient in published studies assessing this relationship. Our objective was to compare differences in Fibromyalgia Impact Questionnaire (FIQ) scores in women with fibromyalgia who had a hysterectomy and/or oophorectomy and those who did not.

Methods: We conducted a retrospective chart review of 889 women with fibromyalgia, seen in the Fibromyalgia Treatment Program at a tertiary medical center between 2001 and 2004. Patients completed the FIQ at the time of their initial evaluation and data on age, race, duration of fibromyalgia symptoms, hysterectomy status, oophorectomy status and use of hormone therapy was abstracted from the clinical record. Linear regression analysis was used to compare FIQ scores between women who had a hysterectomy and those who did not.

Results: Of the women included in our review, 43.4% had a hysterectomy, 29.7% had a bilateral oophorectomy and 4.3% had a unilateral oophorectomy. After adjusting for age, duration of fibromyalgia symptoms and use of hormone therapy, total FIQ scores of women who had a hysterectomy were significantly higher than those who did not (p=.0013). Similarly, FIQ subscales of physical impairment (p=.0405), pain (p=.0001), stiffness (p=.0397) and depression (p=.0079) were also higher in women who had a hysterectomy than in those who did not. Though not statistically significant, trends were also observed in subscales of fatigue (p=.0979) and anxiety (p=.0517). These associations were independent of oophorectomy status and the timing of the hysterectomy.

Conclusions: Our results indicate that presence of hysterectomy influences symptom severity in women with fibromyalgia. The prevalence of hysterectomy is also higher than the rate of approximately 33% by age 60 reported in general population. To our knowledge, this is the first retrospective review assessing this relationship. Since, our retrospective review was limited by incomplete information on duration of hormone therapy use in relationship to timing of hysterectomy, we are unable to speculate on the influence of surgical menopause on FIQ scores. A prospective study with longitudinal follow-up will better characterize this influence.

Disclosure: M. O. Whipple: None; **A. Vincent:** None; **T. H. Oh:** None; **C. A. Luedtke:** None; **T. L. Hoskin:** None.

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Improvement in Multiple Dimensions of Fatigue in Fibromyalgia Patients Treated with Duloxetine. Lesley M. Arnold[2], Fujun Wang[1], Jonna Ahl[1], Paula Gaynor[1] and Madelaine Wohlreich[1]. [1]Lilly USA LLC, Indianapolis, IN, [2]Women's Health Research Program, Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati, OH

Background: In addition to widespread pain, fatigue is one of the most common and disabling symptoms of fibromyalgia. Fatigue was assessed as a secondary objective in this 2-phase 24-week trial of duloxetine in patients with ACR-defined fibromyalgia.

Methods: Outpatients 18–65 years of age, with Brief Pain Inventory average pain ≥4 were randomized to duloxetine 60–120 mg/d (N=263) or placebo (N=267) for the 12-week acute phase. At Week 12, all patients in the placebo group were switched to double-blind treatment with duloxetine for the 12-week extension phase. Fatigue was assessed at baseline and every 4 weeks by the Multidimensional Fatigue Inventory (MFI), which is comprised of the following subscales: General Fatigue (GF), Physical Fatigue (PF), Mental Fatigue (MF), Reduced Activity (RA), and Reduced Motivation (RM). The frequency of treatment-emergent adverse events (TEAE) that might be associated with fatigue, such as fatigue, insomnia and somnolence, was also assessed. Changes from baseline in MFI subscale scores during the acute phase, and from Week 12 during the extension phase were analyzed by mixed-effects model repeated measures analysis. For the acute phase, the model included baseline value, acute phase treatment, investigator, visit, treatment-by-visit, and baseline-by-visit interactions; for the extension phase, the model included: investigator, visit, Week 12 baseline score and baseline-by-visit interaction (the model was fitted separately for patients randomized to duloxetine and patients randomized to placebo then switched to duloxetine in the extension phase).

Results: At the end of the acute phase, patients who received duloxetine versus placebo had significantly reduced scores on each MFI subscale (all $p<.05$) indicating improvement (Arnold et al). In the extension phase, mean MFI subscale scores indicated that improvement was maintained for patients who received duloxetine for up to 24 weeks (n=176). For placebo-treated patients who were switched to duloxetine (n=187), significant within-group improvement in MFI subscale scores was observed at Weeks 16, 20 and 24 for PF, Weeks 20 and24 for GF, Week 20 for MF, and Weeks 20 and 24 for RA. Individual subscale scores after switching to duloxetine were similar to those for patients who received duloxetine for 24 weeks. This suggests that patients treated with duloxetine for 6 months maintained improvement in several dimensions of fatigue assessed by the MFI, and that placebo patients switched to duloxetine quickly reached the level of improvement in fatigue observed in the active treatment group. In the acute phase, TEAE rates of fatigue, somnolence and insomnia were: 9.5%, 5.7% and 9.1% for duloxetine; 7.1%, 3.4%, and 7.1% for placebo. In the extension phase, overall rates for these TEAEs were: fatigue 4.1%; somnolence, 2.5%; and insomnia, 3.6%.

Conclusion: Treatment with duloxetine significantly improved multiple dimensions of fatigue in patients with fibromyalgia, and improvement was maintained with duloxetine treatment up to 24 weeks.

Disclosure: L. M. Arnold: Allergan, 2, 5, AstraZeneca, 5, Boehringer Ingelheim, 2, 5, Cypress Biosciences, Inc., 2, 5, Eli Lilly and Company, 2, 5, Forest Laboratories, 2, 5, 8, Pfizer Inc, 2, 5, sanofi-aventis, 5, Takeda Pharmaceuticals North America; **F. Wang:** Eli Lilly and Company, 1, 3; **J. Ahl:** Eli Lilly and Company, 1, 3; **P. Gaynor:** Eli Lilly and Company, 1, 3; **M. Wohlreich:** Eli Lilly and Company, 1, 3.

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Novel Treatment of Tendinopathies with a Sulfated Disaccharide of Hyaluronic Acid-Promising *In Vitro* Results. Anna Torrent[1], Ramon Ruhí[1], Carlos Aláez[1], Constanze Buhrmann[2] and Mehdi Shakibaei[3]. [1]BIO-IBERICA S.A., Palafolls, Barcelona, Spain, [2]Ludwig-Maximilians-University, Munich, Germany, [3]Ludwig-Maximilians-University Munich, Munich, Germany

Purpose: As tendons regenerate slowly and inefficiently after trauma, tendinopathies pose a serious musculoskeletal problem. Recent studies indicate that initiators of tendinopathy include a number of pro-inflammatory cytokines such as Interleukin-1β (IL-1β), which are known to enhance and support inflammation and promote apoptosis through the production of cyclooxygenase-2 (Cox-2), metalloproteinases (MMPs) and activation of caspase-3. The aim of this study was to evaluate the potential prophylactic and/or regenerative effects of a sulphated disaccharide of hyaluronic acid (methyl 2-acetamido-2-deoxi-3-O-(β-D-glucopyranosyluronic acid)-4,6-di-sulfo-α-D-glucopyranoside, trisodium salt), BIS014, on suppression of catabolic, inflammatory and apoptotic pathways in IL-1β stimulated human tenocytes *in vitro*.

Method: Monolayer cultures of primary human tenocyes were pre-stimulated with BIS014 followed by co-treatment with IL-1β and BIS014 and evaluated with electron microscopy and western blotting. Control cultures were left untreated or treated with IL-1β or BIS014. Cell viability, adhesion, proliferation and production of extracellular matrix (ECM) were analysed with light microscopy and transmission electron microscopy. Immunofluorescence was used to evaluate production of type I collagen, the main extracellular matrix protein synthesized by tenocytes. Immunoblotting was performed to determine expression of type I collagen, β-1 integrins, caspase-3, Cox-2 and MMP-1, -9 and -13.

Results: Ultrastructural evaluation with electron microscopy demonstrated that BIS014 exerts a potent stimulatory effect on human tenocyte proliferation and was able to suppress catabolic, apoptotic and inflammatory effects induced by IL-1β. Suppression of IL-1β-induced up-regulation of activated caspase-3, Cox-2 and MMP-1, -9 and -13 by western blotting further confirmed these results.

Conclusion: These results demonstrate that the synthetic disaccharide of hyaluronic acid BIS014 may have therapeutic utility for the healing, regeneration and repair of tendons.

Disclosure: A. Torrent: Bioberica S.A., 3; **R. Ruhí:** Bioberica S.A., 3; **C. Aláez:** Bioberica S.A., 3; **C. Buhrmann:** Bioberica S.A., 9; **M. Shakibaei:** Bioberica S.A., 9.

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Outcome for a Prospective Cohort of Fibromyalgia Patients Receiving Tailored Treatments in a Multidisciplinary Pain Center. Mary-Ann Fitzcharles, Pantelis Panopalis, Ann Gamsa, Mark Ware and Yoram Shir. McGill University

Background: The ideal management of fibromyalgia (FM) is still under debate. There is increasing appreciation of the importance of the various core component symptoms in FM patients, contributing to the complexity of management. Expert opinion suggests that multimodal treatment including non pharmacologic and pharmacologic interventions are desirable. In view of the complexity of combining various treatment strategies, observational studies in real life clinical settings should provide helpful information regarding outcome. We have examined the outcome in FM patients being followed in a multidisciplinary setting with treatments tailored to individual patient needs.

Methods: Patients newly referred to a multidisciplinary pain clinic with a primary diagnosis of FM were entered into a prospective cohort study. All patients were evaluated by a physician and a psychologist, a treatment plan was developed and patients had access to nursing or physiotherapy consultation when deemed necessary. Treatments were individually based taking into consideration previous treatments and severity of core symptoms. Demographic, disease and psychosocial variables included the following: Fibromyalgia Impact Questionnaire (FIQ), visual analogue scale (VAS) for patient global status and pain scores, McGill Pain Questionnaire (MPQ), Arthritis Impact Measurement Scale, anxiety and depression (AIMS), pain catastrophizing scale (PCS), and pain disability index (PDI). All patients were advised to participate in a regular physical activity program of their choice, and were asked to identify outcome and functional goals. At follow-up, patients were queried about overall change in symptoms, and were categorized into one of two groups: improved or same/worse. Univariate comparisons were made between the two groups using Student's t-tests for continuous variables and chi-squared tests for categorical variables. Logistic regression was used to model the association between selected variables.

Results: Of the 184 patients entered in the cohort, 114 had at least one follow-up assessment at least one year after entry and were included in the analysis. The average age of the study sample was 49.0 (SD 10.0) and 92.1% were female. Improvement was reported in 80 patients (70%) whereas 34 patients (30%) reported symptoms as same or worse. Improvement was associated with improvement in measurements of the following disease parameters: FIQ ($p= 0.001$), global VAS score (0.02), pain VAS score ($p=0.004$), PDI ($p<0.001$), AIMS (depression) ($p<0.001$) and PCS ($p=0.002$). MPQ scores and AIMS (anxiety) were not associated with improved global outcome. A logistic regression model including all significant univariate associations found that only reduced AIMS (depression) was associated with improved global outcome (OR 1.4, 95% CI 1.1–2.0).

Conclusion: More than two thirds of FM patients, receiving tailored multidisciplinary treatment, had a favourable outcome. This was observed even in the setting of longstanding symptoms, and for patients seen in a tertiary care centre, likely representative of those with disease at the severe end of the spectrum. Targeting depression may improve outcome for FM patients.

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Predictors of Clinical Outcome in Fibromyalgia: Single Center Experience of a Brief Interdisciplinary Fibromyalgia Treatment Program. Terry H. Oh[1], Tanya L. Hoskin[1], Connie L. Luedtke[2], Toby N. Weingarten[2], Ann Vincent[2] and Jeffrey M. Thompson[2]. [1]Mayo Clinic, Rochester, MN, [2]Mayo Clinic

Purpose: To determine which patient characteristics are associated with a positive response to a brief interdisciplinary fibromyalgia treatment program.

Methods: Prospectively designed follow-up questionnaire study among patients who underwent the Fibromyalgia treatment program at a tertiary medical center. Patients with confirmed fibromyalgia, underwent a one and half day interdisciplinary fibromyalgia treatment program, and completed the Fibromyalgia Impact Questionnaire (FIQ) at baseline and again 6–12 months after treatment were studied (n=536). Minimally clinically important difference (MCID) in fibromyalgia derived from FIQ changes was reported to be 14%. Therefore, we defined responders as participants who reported an improvement of ≥14% in the FIQ total score from baseline to 6–12 months after treatment, and non responders as participants who either worsened or improved < 14 % in the FIQ total score 6–12 months after treatment.

Predictor variables included demographic variables, baseline FIQ depression score, psychosocial variables, numeric rating scale (NRS) pain scores and number of fibromyalgia tender points. Univariate associations with responder status were assessed using two-sample t-tests and chi-square tests. Multivariate analysis used logistic regression; these results are reported with odds ratios (OR) and 95% confidence intervals (CI)

Results: Mean (SD) age of participants was 50.3 (13.0) years; 515 (96%) women and 23 (4%) men. Two hundred forty-eight patients (46%) were responders. In univariate analysis, responders were younger (p=0.008), achieved a higher level of education (p=0.02), had fewer tender points (p=0.048) and higher FIQ depression subscores (p=0.02) when compared to non responders. Positive abuse history did not reach statistical significance but showed a trend (p=0.05).

In multivariate analysis, these factors remained statistically significant. In addition, positive abuse history became significant (p=0.03). Younger age (OR:1.03, 95% CI: 1.01 to 1.05 per 1 year decrease), having a college or graduate degree (OR: 1.59, 95% CI: 1.07 to 2.36) and higher baseline FIQ depression score (OR:1.11, 95% CI: 1.05 to 1.20 per 1 unit increase) were associated with increased odds of being a responder, while increasing number of tender points (OR:0.91, 95% CI: 0.83 to 1.0 per 1 point increase), and abuse history (OR:0.62, 95% CI: 0.40 to 0.96) were associated with decreasing odds of being a responder. Gender, duration of symptoms, marital, employment, or smoking status, geographical location and 3 NRS scores were not statistically different between the responders and non responders.

Conclusions: Younger age, college or graduate degree, higher baseline FIQ depression score, lower tender point count and absent history of abuse were all associated with increased odds of treatment response.

Disclosure: T. H. Oh: None; **T. L. Hoskin:** None; **C. L. Luedtke:** None; **T. N. Weingarten:** None; **A. Vincent:** None; **J. M. Thompson:** None.

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Should Rheumatologists Retain Ownership of Fibromyalgia? A Survey of Ontario Rheumatologists. Sassan Ghazan-Shahi, Tanveer E. Towheed and Wilma Hopman. Queen's University, Kingston, ON, Canada

Background: Fibromyalgia is a controversial widespread chronic pain disorder that includes a wide constellation of somatic and emotional symptoms. This study surveyed the opinion of Ontario Rheumatologists with respect to their beliefs about the nature and management of fibromyalgia. A key objective was to ascertain if Rheumatologists should continue to be the main care providers for these patients.

Methods: A survey questionnaire comprising 13 questions was sent electronically to all 150 Ontario Rheumatologists. The questionnaire was designed to obtain demographic data as well as opinions regarding different aspects of fibromyalgia. Data were analyzed descriptively and comparisons were made using chi-square tests.

Results: A total of 80 respondents (58% male) completed our survey for a completion rate of 53%. The majority had completed their training in Canada (85%) and had been practising for more than 15 years (50%). 55% worked in University hospitals and 45% worked in the Community. Key findings were: (1) 71% believe that Rheumatologists should not retain ownership of fibromyalgia, (2) 55% believe that fibromyalgia is primarily a psychosomatic illness as opposed to a physical illness, (3) 60% are accepting new referrals for fibromyalgia, (4) 60% are managing patients with fibromyalgia, (5) 89% believe that the family physician should be the main care provider for these patients, (6) 31% usually consider psychiatric referral for these patients, (7) 79% recommend behavioural treatment methods, (8) 58% consider severe fibromyalgia to be a potentially disabling condition that warrants financial compensation through disability, (9) Rheumatologists who consider fibromyalgia to be a physical illness were also significantly more likely to believe that Rheumatologists should retain ownership of this disease (p=0.023). They were also more likely to accept new referrals for this disease (p=0.044), and also more likely to continue managing these patients in their practice (p=0.011).

Conclusions: The majority of Ontario Rheumatologists do not wish to retain ownership of fibromyalgia. However, most of them continue to accept new referrals and continue to manage these patients, even though they believe that the family physicians should be the main care provider for patients with fibromyalgia. Rheumatologists may be providing care to these patients primarily because this care is not available to them from their primary care physicians.

Disclosure: S. Ghazan-Shahi: None; **T. E. Towheed:** None; **W. Hopman:** None.

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The Course of Fibromyalgia—A Long-Term Longitudinal Cohort Study. Brian Walitt[5], Winfried Häuser[3], Afton Hassett[4], Robert S. Katz[2] and Frederick Wolfe[1]. [1]National Databank for Rheumatic Diseases, [2]Rush University, [3]Technische Universität München, [4]University of Michigan Medical School, [5]Washington Hospital Center, Washington, DC

Purpose: Fibromyalgia (FM) is a chronic condition in which treatment is of limited effectiveness. However, the ACR 2010 criteria study reported that 25% of FM patients improved sufficiently so that they did not meet classification criteria at follow-up. Other studies have also reported various degrees of improvement. Much of the uncertainty about the course of FM can be attributed to selection bias and non-standardized measures of improvement. In this report, we followed 1,555 criteria positive FM patients for a mean of 4.0 years (range 1.0 to 11.5 years) to determine the symptomatic course.

Methods: Patients were participants in a longitudinal study of FM outcomes. They were assessed semi-annually in 11,006 observations (6,251 pt-years). Assessments included the Widespread Pain Index, fatigue, sleep disturbance, functional status and a general measure of FM severity (the Fibromyalgianess Scale). Criteria status was assessed with a survey modification of the ACR 2010 diagnostic criteria. We used generalized estimating equations (GEE) to assess the rate of change of study variables over time and Cox regression to assess incidence of loss and regain of FM diagnostic status.

Results: Patients switched between criteria positive and negative states. 716 patients became criteria negative during the study (44.0%), for an incident rate of 16.9 (15.7, 18.2) per 100 pt-years; and 378 patients (24.3%) who satisfied FM criteria at entry no longer satisfied criteria at the study close, an incident rate 6.0 (5.5, 6.6) per 100 pt-years. All FM related variables predicted the transition between positive and negative states. The strongest predictor was the 0–31 fibromyalgianess scale, which decreased by −.36 (0.32, 0.40) units annually. Other study variables also decreased during the study. Figure 1 shows fibromyalgianess in patients remaining criteria positive (23.8 ±4.5) and those who became criteria negative (12.9 ±4.2).

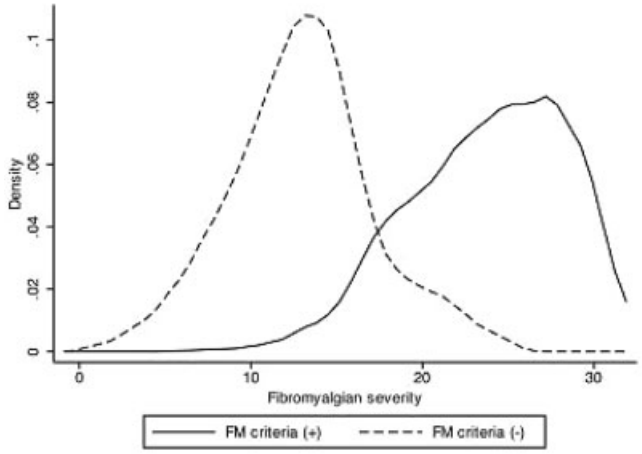
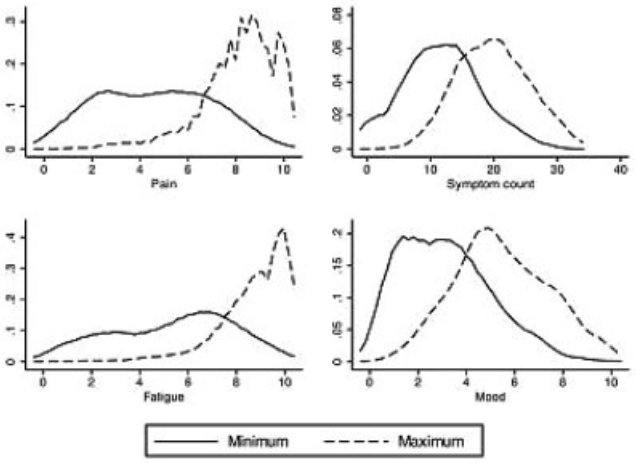


Figure 2 demonstrates minimum and maximum pain, symptom count, fatigue, and mood scores during follow-up.



Conclusions: FM patients often switch between criteria positive and negative states and have a wide variation in symptoms. These data indicate limitations in the usefulness of the discrete diagnosis of FM. Symptom severity, as opposed to diagnosis, appears to be more clinically reliable and relevant. The fluctuating nature of FM diagnosis has important implications for clinical care and treatment indications.

Disclosure: B. Walitt: None; **W. Häuser:** None; **A. Hassett:** None; **R. S. Katz:** None; **F. Wolfe:** None.

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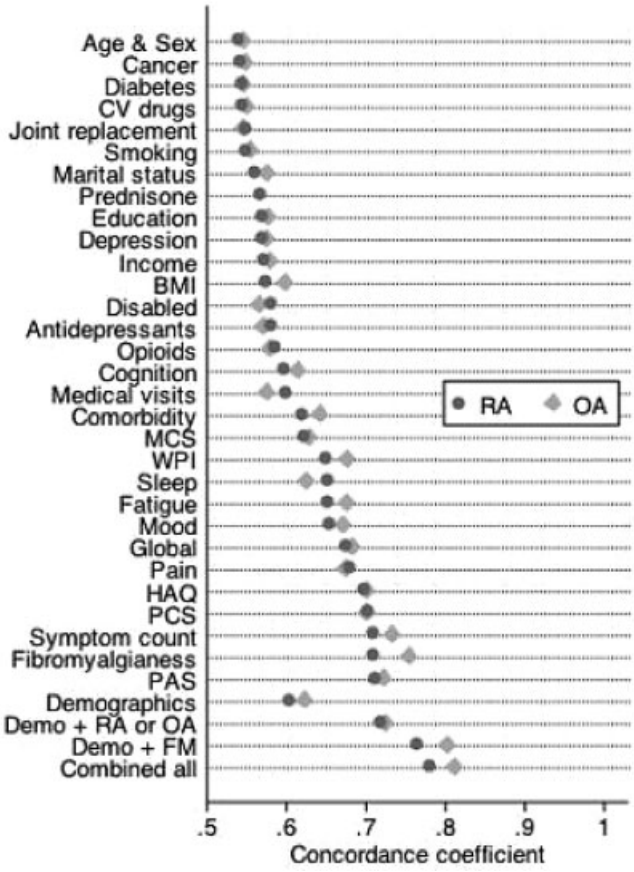
The Development of Fibromyalgia: Examination of Rates and Predictors in Patients with Osteoarthritis (OA). Frederick Wolfe[1] and Winfried Häuser[2]. [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]Technische Universität München, Munich, Germany

Purpose: Using modified ACR 2010 fibromyalgia (FM) criteria, we have reported that in 9,739 rheumatoid arthritis (RA) patients without FM, a series of demographic, RA, FM, and psychological variables predict FM development. However, it is possible that RA damaged joints or systemic illness may interfere with FM measurements and predictors, and prediction and predictive strength might be different in RA compared with regional rheumatic disorders such as osteoarthritis (OA). To examine this possibility, to compare FM in RA and OA, and to confirm our prediction models, we analyzed predictors of FM in OA.

Methods: After excluding patients with FM and those with high levels of FM symptoms (fibromyalgianess score >10), we studied the FM development in 1,888 OA patients during 6,892 patient-years of follow-up over a mean follow-up time of 4.3 (SD 3.5) years (range, 5 to 11). We defined FM using a modification of the ACR 2010 FM diagnostic criteria. We used Cox regression to predict future FM, and examined the discriminatory power and accuracy of predictions using Harrell's C concordance coefficient.

Results: At the last observation, 6.0% of OA compared with 7.4% of RA patients satisfied FM criteria, although 18.8% of OA and 19.8% with RA did so at some point during follow-up, for an OA FM incidence rate of 5.0 (95% CI 4.2, 5.3) and an RA rate of 5.3 (5.1, 5.6) per 100 pt-years. The rate in women was 5.5 (4.9, 6.2) and was 3.5, (4.7, 5.5) in men. Among those satisfying criteria, half of follow-up time after diagnosis was FM criteria (+), and was associated with markedly abnormal OA and FM variable scores. C-statistics, adjusted for age and sex, are shown in Figure 1.



The discriminatory power of variables was similar in OA and RA, except that FM variables were slightly more predictive in OA than RA. In multivariable analyses, demographics were weak predictors of FM (OA C = 0.623, RA C=0.604). Stronger predictors were demographics plus OA (C = 0.725) compared with demographics plus RA variables (C= 0.720), and demographic plus FM variables (OA C = 0.803, RA C = 0.765), and all predictors (OA C = 0.812) (RA C= 0.782) in the multivariable model shown below.

Variable	*H.R (95% CI)*	*z*	*P*-value
Widespread pain index (0–19)	1.28 (1.21, 1.36)	8.41	<0.001
HAQ (0–10)	2.06 (1.67, 2.54)	6.81	<0.001
Symptom count (0–34)	1.10 (1.07, 1.13)	6.45	<0.001
Fatigue (0–10)	1.26 (1.17, 1.35)	6.40	<0.001
Mood (0–10)	1.11 (1.02, 1.21)	2.50	0.013
Opioid use	1.29 (0.99, 1.67)	1.87	0.062
Comorbidity			
None			
1	1.34 (0.97, 1.84)	1.8	0.072
2	1.72 (1.25, 2.37)	3.35	0.001
3	1.70 (1.15, 2.49)	2.69	0.007
4–9	1.35 (0.86, 2.12)	1.29	0.196

Clinically important HRs were noted for cognition, depression, comorbidity and high levels of OA and FM continuous variables.

Conclusions: FM is predicted similarly in patients with OA and RA. Multiple factors contribute to FM development, including socio-demographic disadvantage, comorbidity, psychological distress, drug and service utilization, FM symptoms (particularly somatic symptom reporting), and functional status; but there is little evidence of the effect of underlying causes.

Disclosure: F. Wolfe: None; **W. Häuser:** None.

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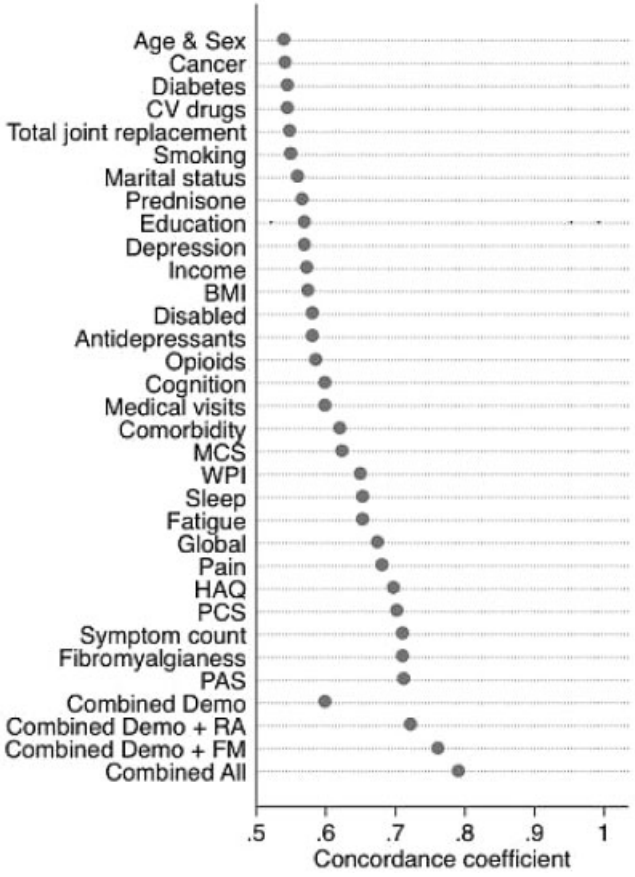
The Development of Fibromyalgia: Examination of Rates and Predictors in Patients with Rheumatoid Arthritis (RA). Frederick Wolfe[1], Winfried Häuser[3], Afton L. Hassett[4], Robert S. Katz[2] and Brian T. Walitt[5]. [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]Rush University Medical Center, Chicago, IL, [3]Technische Universität München, [4]University of Michigan Medical School, [5]Washington Hospital Center, Washington, DC

Purpose: There are no prospective studies of the development of criteria-based fibromyalgia (FM) that consider multiple risk factors. The purpose of the study was to determine rates and predictors of future development of FM in patients with rheumatoid arthritis (RA). We studied FM in RA because of its intrinsic interest and because RA patients provided a substrate of patients that were unselected, particularly with respect to FM characteristics. In addition an extensive set of demographic and severity covariates were available.

Methods: After excluding patients with FM and those with high levels of FM symptoms (fibromyalgianess score >10), we studied the development of FM in 9,739 RA patients during 42,591 patient-years of follow-up. We defined FM using a modification of the ACR 2010 FM diagnostic criteria. We used Cox regression to predict future FM, and examined the discriminatory power and accuracy of predictions using Harrell's C concordance coefficient.

Results: At the last observation, 7.4 % of patients satisfied criteria, although 19.8% satisfied criteria at some point during follow-up, for an incidence rate of 5.3 (95% CI 5.1, 5.6) per 100 patients-years, and at rates that were similar in men (7.0%) and women (8.1%). Among those satisfying criteria, during 11,363 years of follow-up from the time of first fibromyalgia diagnosis, approximately half of follow-up time was fibromyalgia+ and was associated with markedly abnormal RA variable and FM variable scores. C-statistics for individual variables, adjusted for age and sex, are shown in the Figure.



In multivariable analyses, demographic factors were weak predictors of fibromyalgia (C=0.604). Stronger predictors were demographic plus RA variables (C= 0.720) and demographic plus fibromyalgia variables (C= 0.765), and all predictors (C= 0.782). Clinically important hazard ratios were noted for cognition, depression, comorbidity and high levels of RA and FM continuous variables. Using a z score of ≥5 as a cut point, the most important independent predictors for the multivariable prediction of FM were antidepressant use, HAQ, fatigue, widespread pain index and the symptom count.

Conclusions: FM can be predicted with clinically available variables. Multiple correlated factors contribute to the development of fibromyalgia. These factors include socio-demographic disadvantage, comorbidity, psychological distress, drug and service utilization, fibromyalgia symptoms (particularly somatic symptom reporting), and functional status; but there is little evidence of the effect of underlying causes. After diagnosis, patients move in both directions across the diagnostic criteria cut point.

Disclosure: F. Wolfe: None; **W. Häuser:** None; **A. L. Hassett:** None; **R. S. Katz:** None; **B. T. Walitt:** None.

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The Effect of Duloxetine on Cognition in Patients with Fibromyalgia. Philip J. Mease[3], Lesley Arnold[4], Fujun Wang[1], Jonna Ahl[1], Richard Mohs[1], Paula Gaynor[1] and Madelaine Wohlreich[2]. [1]Eli Lilly and Company, [2]Lilly USA, LLC, [3]Seattle Rheumatology Associate, Seattle, WA, [4]Women's Health Research Program, Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati, OH

Background: Cognitive difficulties are common complaints among patients with fibromyalgia and include perceived deficits in attention, concentration and memory. Cognitive testing was conducted in a subset of patients participating in a randomized, double-blind, placebo-controlled trial of duloxetine in fibromyalgia.

Methods: At selected sites, patients eligible for the main study were asked if they would like to participate in the cognitive testing and provided separate informed consent for this testing. Patients were ≥18 years of age, met ACR criteria for fibromyalgia, and ≥4 score on the Brief Pain Inventory (BPI) 24-h average pain severity item. Patients who consented to cognitive testing were randomized to duloxetine (n=80) or placebo (n=76) for 24 weeks of double-blind treatment. The primary endpoint was at Week 12, after which placebo patients were switched to double-blind treatment with duloxetine. The results presented here are for the first 12 weeks. Verbal learning and memory was tested using the 15 word Verbal Learning and Recall Test (VLRT); speed of processing, visual attention and executive function were tested using the Symbol Digit Substitution Test (SDST), the Two Digit Cancellation Test (2DCT), and the Trailmaking Test (Trails A and B). Change from baseline to endpoint (last-observation-carried-forward) was analyzed by an analysis of covariance model, which included baseline, treatment, investigator and treatment-by-investigator interaction.

Results: Most of the patients (N=156) were Caucasian (89%) women (92%), ranging in age from 21 to 88 years, 23% had comorbid major depressive disorder (MDD), and 8% had comorbid generalized anxiety disorder (GAD). Cognitive test scores at baseline were close to published scores[1–4] for the general population indicating no impairment. Baseline-to-endpoint changes in cognitive scores did not differ significantly between treatment groups.

Conclusion: Impairment in cognitive function in patients with fibromyalgia was not evident on VLRT, SDST, 2DCT, or Trails A and B. Overall, treatment with duloxetine did not have a positive or negative effect on cognition when measured with these tests.

Disclosure: P. J. Mease: Cypress Pharmaceutical, Inc., 2, 5, 8, Cypress Pharmaceutical. Inc., 2, 5, 8, Eli Lilly and Company, 2, 5, 8, Forest Pharmaceuticals, Inc, 2, 5, 8, Jazz Pharmaceuticals, Inc., 2, 5, 8, Pfizer Inc, 2, 5, 8; **L. Arnold:** Allergan, 2, 5, Boehringer Ingelheim, 2, 5, Cypress Biosciences, Inc., 2, 5, Eli Lilly and Company, 2, 5, 8, Forest Laboratories, 5, Forest Pharmaceuticals, Inc, 2, NIH, 9, Organon Pharmaceuticals USA, 5, Pfizer Inc, 2, 5, 8, sanof; **F. Wang:** Eli Lilly and Company, 1, 3; **J. Ahl:** Eli Lilly and Company, 1, 3; **R. Mohs:** Eli Lilly and Company, 1, 3; **P. Gaynor:** Eli Lilly and Company, 1, 3; **M. Wohlreich:** Eli Lilly and Company, 1, 3.

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The Effectiveness of Botulinum Toxin Type-A and Prilocaine Injections in Myofascial Pain Syndrome. Mehmet Zeki Kiralp, Baki Ozdemir, Engin Cakar, Oguz Durmus, Levent Tekin and Umit Dincer. Gülhane Military Medical Academy, Haydarpasa Training Hospital, Department of Physical Medicine and Rehabilitation, Istanbul, Turkey

Objective: The objective of this study was to compare the effectiveness of botulinum toxin-A (Btx-A) and prilocaine injections in the treatment of myofascial pain syndrome (MAS).

Methods: Forty-six eligible patients who had diagnosed as MAS were recruited and were randomized into two treatment groups namely Btx group

(n=23) and prilocaine group (n=23). The injections were made to most painful maximum three trigger points of the patients. 10 IU of Btx-A in Btx group and 2ml prilocaine in the prilocaine group were injected to each points. All of the patients were trained about the stretching exercises and instructed to do at home regularly. Clinical assessment parameters were visual analog scale (VAS) for pain during function, pain score (PS) during digital pressure, short form-36 (SF-36) for quality of life and Beck depression inventory (BDI) for general well-being. The assessments were performed at baseline and at 2nd and 6th weeks after the injections.

Results: There were no statistical differences between the groups at baseline. The study was finished with 38 patients (19 patients in each group). Both of the groups' VAS, PS, BDI scores at 2nd and 6th weeks and all of the subscale scores of SF-36 at 6th week improved according to baseline. In inter-group comparison it was seen that the VAS score at 2nd and 6th weeks and PS at 6th week improved statistically better in Btx group than prilocaine group ($p<0.05$). In addition, all of the subscale scores of SF-36 except physical functioning were statistically better in Btx-A group ($p<0.05$) at 2nd and 6th weeks.

Table 1. The intra-group and inter-group comparisons of the treatment effects of Btx-A and prilocaine

	Baseline		2nd week		6th week	
	mean ± SD	p**	mean ± SD	p**	mean ± SD	p**
VAS						
Prilocaine	**8.95 ± 1.13**		4.26 ± 1.41		3.74 ± 1.66	
%			−52		−58	
p*		0.16	<0.0001	0.012	<0.0001	0.001
Btx-A	**8.37 ± 1.38**		3.21 ± 1.03		2 ± 0.88	
%			−62		−76	
p*			<0.0001		<0.0001	
PS						
Prilocaine	**2.89 ± 0.32**		1.68 ± 0.58		1.42 ± 0.61	
%			−42		−51	
p*		0.11	<0.0001	0.16	<0.0001	0.01
Btx-A	**2.68 ± 0.48**		1.42 ± 0.51		1 ± 0.33	
%			−47		−63	
p*			<0.0001		<0.0001	

* : p score of intra-group changes according to baseline
** : p score of inter-group changes
% : the percentage of change according to baseline

Conclusions: Both Btx-A and prilocaine injections combined with appropriate exercise program were beneficial treatment choices in MAS management. It was also seen that Btx-A injections have better effects especially in regard to pain and health quality in short to medium term. It was noticeable that there was no difference between the groups at 2nd week in regard to PS, but Btx group's PS scores were statistically better at 6th week control. This might be interpreted as the progressive cumulative effect of Btx-A.

These outcomes were the preliminary results of an ongoing follow-up study. Further studies are needed for the clarification of the long term effects of Btx-A injections in MAS management.

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The Patient Specific Functional Scale Outperforms the Fibromyalgia Impact Questionnaire Physical Function Scale. Chad S. Boomershine[1], Kim A. Edwards[2], Jennifer Y. Hong[2] and Kenneth A. Wallston[2]. [1]Vanderbilt University, Nashville, TN, [2]Vanderbilt University

Background: Fibromyalgia (FM) is a disease defined by chronic widespread pain and tenderness that causes functional impairment in many patients. The FM impact questionnaire physical function scale (FIQPFS) has been the standard used by rheumatologists to measure functional impairment in FM patients. However, its clinical utility is limited due to its length (11 questions), complex scoring, and assessment of rarely performed activities. The patient specific functional scale (PSFS) is a brief (3 question) functional impairment measure that assesses difficulty with patient-selected activities on an easily scored 0 to 10 numeric rating scale (NRS) commonly used by physical therapists. We hypothesized that the PSFS is a more clinically useful functional measure than the FIQPFS due to its brevity, ease of scoring and patient-specific nature. However, performance of the PSFS has never been compared to the FIQPFS. We compared baseline psychometric properties of the PSFS and the FIQPFS and the ability of both scales to measure global change in patients treated with physical therapy (PT).

Methods: Patients (N=340) sent for PT treatment were assessed at baseline and after treatment for 1 month. Baseline and follow-up evaluations included demographics, a pain NRS, regional pain scale (RPS), fatigue problem scale (FPS), disease-neutral FIQPFS, PSFS, and patient global impression of change (PGIC). Baseline pain NRS scores ≥4 identified pain patients. FM survey criteria (RPS ≥8 and FPS ≥6) at baseline identified FM patients. Spearman rank correlations were used to compare questionnaire scores. Statistical methods were performed using PASW Statistics 17.

Results: At baseline, the PSFS had lower floor effects for all patients (n=340) compared to the FIQPFS (0.9% vs 17.3%, respectively). In patients with pain (n=249), the PSFS also had lower floor effects compared to the FIQPFS (1.2% vs 8.8%, respectively). In FM patients (N=82), the PSFS had no floor effects whereas the FIQPFS had 7.3%. Ceiling effects were negligible for both scales in all patient groups (<1%). PSFS scores were normally distributed for all patient groups, while FIQPFS scores were not normally distributed for any group. At follow-up, PGIC scores significantly correlated with change in PSFS scores for all patients ($\rho=0.52$, $p<0.001$), pain patients ($\rho=0.52$, $p<0.001$) and FM patients ($\rho=0.91$, $p<0.001$).

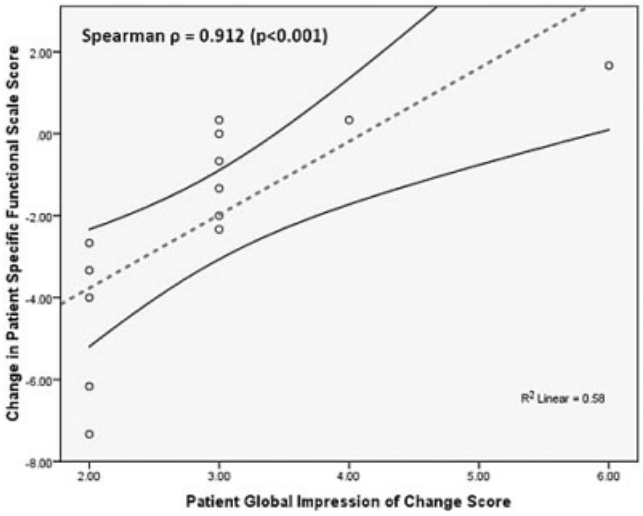

Figure 1. Patient global impression of change score correlates with change in patient specific functional scale score in fibromyalgia patients.

PGIC scores did not correlate significantly with change in FIQPFS scores for any patient group [all patients ($\rho=0.13$, $p=.314$), pain patients ($\rho=0.09$, $p=0.548$), or FM patients ($\rho=0.272$, $p=.347$)].

Conclusions: The PSFS has superior psychometric properties compared to the FIQPFS and significantly correlates with PGIC scores in patients treated with PT. Our results indicate the PSFS may be a better questionnaire to evaluate functional impairment and response to therapy than the FIQPFS in many patient groups including FM patients.

Disclosure: C. S. Boomershine: Eli Lilly and Company, 8, Forest Pharmaceuticals, Inc, 8, NIH, 2, Pfizer Inc, 2, 8; **K. A. Edwards:** None; **J. Y. Hong:** None; **K. A. Wallston:** None.

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The Revised Version of the Fibromyalgia Impact Questionnaire: Association with Physical Function and Quality of Life. Seong-Rye Seo[1], Sung-Ji Lee[3], Tae-Jong Kim[3], Yong-Wook Park[3] and Shin-Seok Lee[2]. [1]Chonnam Natl Univ Med School, Gwangju, Republic of Korea, [2]Chonnam Natl Univ Med School, Gwangju, Korea, Republic of, [3]Chonnam Natl Univ Med School

Purpose: Despite its shortcomings, the Fibromyalgia Impact Questionnaire (FIQ) is widely used to assess clinical symptoms and measure therapeutic changes in patients with fibromyalgia (FM). Recently, the updated version (FIQR) was released. In this study, we validated the Korean version of the FIQR and evaluated whether the revised version is superior to the original one in reflecting the physical function and quality of life of these patients.

Methods: After translating the FIQR into Korean, the FIQR was administered to 50 FM patients to assess its comprehensibility. Next, 76 patients who met the American College of Rheumatology (ACR) criteria for

FM were invited to complete a questionnaire that included the original FIQ, FIQR, Multidimensional Health Assessment Questionnaire (MDHAQ), Rheumatology Attitudes Index (RAI), and Medical Outcome Study Short-Form 36 (SF-36) and were examined for tender points using thumb palpation.

Results: The test-retest reliability was assessed in 53 patients after 1 week, and the correlation coefficients were between 0.604 and 0.825 (Cronbach's alpha = 0.961). The total score on the FIQR was closely correlated with that on the original FIQ ($r = 0.869$, $p < 0.001$), and each of the three FIQR domains was also significantly correlated with the three related FIQ domains (all $p < 0.001$). The FIQR was significantly correlated with tender point counts and scores, pain visual analogue scale (VAS), fatigue VAS, RAI, MDHAQ, and the physical and mental component summary scores of the SF-36 (all $p < 0.001$). The FIQR was more strongly associated with the MDHAQ and SF-36 than with the original FIQ.

Table. Comparison of FIQR and FIQ with symptoms, physical function, and quality of life.

				SF-36	
	Pain	Fatigue	MDHAQ	Physical component	Mental component
FIQR					
1) Function	0.634***	0.635***	0.789***	−0.527***	−0.462***
2) Impact	0.666***	0.637***	0.656***	−0.563***	−0.418***
3) Symptom	0.665***	0.733***	0.568***	−0.385***	−0.501***
Total scores	0.724***	0.755***	0.736***	−0.523***	−0.502***
FIQ					
1) Function	0.457***	0.420***	0.611***	−0.488***	−0.168***
2) Impact	0.677***	0.608***	0.613***	−0.534***	−0.410***
3) Symptom	0.646***	0.676***	0.515***	−0.282***	−0.517***
total scores	0.713***	0.714***	0.612***	−0.426***	−0.498***

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Conclusion: Our study showed that the updated FIQR is a reliable, valid instrument for assessing FM patients and performs better at predicting physical function and health status than does the original FIQ.

Disclosure: S.-R. Seo: None; **S.-J. Lee:** None; **T.-J. Kim:** None; **Y.-W. Park:** None; **S.-S. Lee:** None.

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Treatment with FDA Approved Therapies in Patients with Fibromyalgia. Brian T. Walitt[3], Robert S. Katz[2] and Frederick Wolfe[1]. [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]Rheumatology Associates, Chicago, IL, [3]Washington Hospital Center, Washington, DC

Purpose: Usual treatment for fibromyalgia (FM) is generally considered to be unsatisfactory. Recently, the US Food and Drug Administration approved several drugs specifically for treatment of FM based on controlled clinical trials that showed modest improvement compared to placebo. These treatments include pregabalin, duloxitine, and milnacipram. The treatments are now widely advertised and available in the US. However, whether such treatments are superior to prior conventional FM therapy, as used in the community, is not known. In this study we compare the new therapies to usual therapy to determine the degree to which they improve patients with FM.

Methods: We compared clinical status in patients who received at least one of the 3 therapies when they were receiving the treatments compared with when they were not receiving any of the treatments. Patients were assessed longitudinally at 6 month intervals. We assessed 611 patients during 4,415 observations, 1,895 of which (42.9%) were on treatment and 2,520 (57.1%) were not. To assess treatment effect we used generalized estimating equations (GEE), controlling for age, sex and baseline fibromyalgia severity. The study outcome variables included visual analog scales for pain, fatigue and global, HAQ, SF-36 PCS, MCS and mood, and fibromyalgia severity—using a severity measure from the American College of Rheumatology 2010 fibromyalgia criteria.

Results: The mean age (SD) of treated patients was 56.5 (10.7), and 97% were women. Table 1 shows the adjusted means by treatment category.

Variable	Treatment	Mean (95% CI)	P-value
FM severity	Off Rx	19.9 (19.5, 20.2)	< 0.001
	On Rx	19.2 (18.9, 19.6)	
Pain	Off Rx	6.4 (6.2, 6.5)	0.002
	On Rx	6.2 (6.0, 6.3)	
Fatigue	Off Rx	6.8 (6.7, 7.0)	0.203
	On Rx	6.7 (6.6, 6.9)	
Global	Off Rx	5.4 (5.2, 5.6)	0.403
	On Rx	5.5 (5.3, 5.6)	
Mood	Off Rx	3.9 (3.7, 4.0)	0.152
	On Rx	3.9 (3.8, 4.1)	
HAQ	Off Rx	1.3 (1.2, 1.3)	0.146
	On Rx	1.3 (1.2, 1.3)	
MCS	Off Rx	30.7 (30.1, 31.3)	0.216
	On Rx	31.0 (30.4, 31.6)	
PCS	Off Rx	40.8 (40.0, 41.7)	0.441
	On Rx	40.6 (39.7, 41.5)	

As shown in the table, most variables were not significantly different by treatment class. The 0–10 pain scale was minimally improved by 0.22 units and the 0–31 fibromyalgia severity scale by 0.63 units. We also analyzed the effect of each drug separately. In none of the separate analyses was a significant treatment effect detected.

Discussion: Each of the treatments studied has been shown to be superior to placebo in randomized controlled trials. While our data cannot address treatment effect versus placebo, because there is no true placebo in clinic care, the data does not suggest that treatment is superior to conventional treatments used by fibromyalgia patients. The new treatments are expensive and heavily promoted. But patients in this study did not appear to have additional benefits benefit from the therapies.

Disclosure: B. T. Walitt: None; **R. S. Katz:** None; **F. Wolfe:** None.

ACR Poster Session A
Imaging of Rheumatic Disease I: X-ray, CT and MRI
Monday, November 8, 2010, 9:00 AM–6:00 PM

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A Novel Tool for Fully Automatic Quantification of MRI Synovitis in Rheumatoid Arthritis Is More Sensitive to Change Than the Current Standard Semi-Quantitative Assessment. Michael A. Bowes[1], Jane E. Freeston[4], Edward J. Vital[4], Graham Vincent[2], Gwenael Guillard[2], Paul Bird[5], Paul Emery[3] and Philip G. Conaghan[4]. [1]Imorphics Ltd, Manchester, United Kingdom, [2]Imorphics Ltd, [3]rrrpe@leeds.ac.uk, [4]Section of Musculoskeletal Disease, University of Leeds, UK, [5]University of NSW, Sydney, Australia

Background: Current MRI evaluation in rheumatoid arthritis (RA) employs a semi-quantitative tool (OMERACT RAMRIS). Fully automated quantification of change in MRI pathology remains a highly desirable outcome for clinical trials and practice. 3D statistical appearance models have been used in osteoarthritis to detect very small physical changes in bone, cartilage and soft tissue.

Objectives: To determine the responsiveness of a novel 3D automated measurement of MRI synovitis in the MCP and wrist joints of RA subjects in an open label study and to compare this with the RAMRIS synovitis assessment.

Methods: 3T VIBE MR images pre- and post-contrast of 47 established RA patients who had recently commenced the same biological therapy were evaluated. Subjects were imaged at baseline and regular intervals after 6 months. 3D models or 'masks' of the joints assessed by RAMRIS were created from a separate dataset of RA images. Masks were created for the MCP joints, the radio-carpal joint, the radio-ulnar joint, and a mask for the carpal bones. These masks were fitted to each pre-contrast image and then subtraction images were created using a shuffle transform method. Synovitis volume (in mm^3) was calculated automatically from the enhancing voxels within each mask. RAMRIS scoring was performed by a single experienced reader, blinded to time point.

Results: Mean age of patients was 54.7 years, 88% women, 88.9% RF positive, mean number of previous DMARDs 2.88, 22/55 patients had received previous anti-TNF [10 1TNF, 9 2TNFs, 3 3TNFs] therapy. The numbers of patients with scans available at each time point were: 46 (6 months), 35, 15, 21, and 14 (14 months). At the group level, significant

changes in automated synovitis volume were demonstrated at all time points except 10 months (where the size of the cohort was 15 individuals). RAMRIS scoring showed a similar pattern of change but with no significant change at any time point (Figure 1).

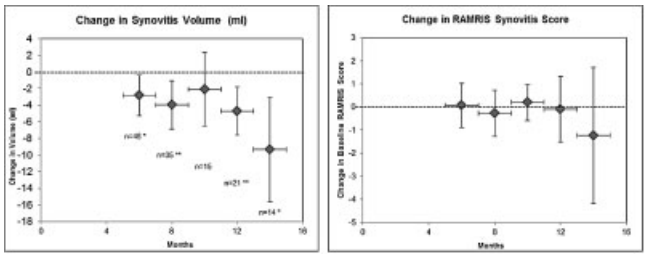

Figure 1. Change in synovitis volume (ml) and RAMRIS scores from baseline, with 95% confidence limits. Cohort size at each time point is shown on left hand graph. RAMRIS synovitis change scores did not achieve statistical significance at any time point. * = $p<0.05$, ** = $p<0.005$.

Conclusions: Fully automated quantitative synovitis measurement is now feasible and practical, and in this observational study proved to be more responsive than semi-quantitative scores. This method could also be applied to clinical practice as well as clinical trials, as synovial volume is measured at the individual joint level.

Disclosure: M. A. Bowes: Imorphics Ltd, 1; **J. E. Freeston:** None; **E. J. Vital:** None; **G. Vincent:** Imorphics Ltd, 1; **G. Guillard:** None; **P. Bird:** None; **P. Emery:** Abbott Immunology Pharmaceuticals, 2, 8, Bristol-Myers Squibb, 8, Centocor, Inc., 8, Merck Pharmaceuticals, 8, Novartis Pharmaceuticals Corporation, 8, Pfizer Inc, 2, 8, Roche, 8, UCB, Inc., 8; **P. G. Conaghan:** AstraZeneca, 8, BioIberica, 8, Bristol-Myers Squibb, 8, Centocor, Inc., 8, Merck Pharmaceuticals, 8, Novartis Pharmaceuticals Corporation, 8, Pfizer Inc, 2, 8, Roche, 8.

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Application of High-Resolution Peripheral Quantitative Computed Tomography (HR-pQCT) To Quantify Bony Damage in Rheumatoid Arthritis. Cheryl C. M. Barnabe[1], Liam Martin[1], Steven K. Boyd[2] and Susan G. Barr[1]. [1]University of Calgary, Calgary, AB, Canada, [2]University of Calgary

Background: High-resolution peripheral quantitative computed tomography (HR-pQCT) (isotropic voxel size of 82 μm) provides three-dimensional information on bone microarchitecture. We investigated the ability of HR-pQCT to provide quantitative assessments of features of RA bony damage, and diagnostic performance.

Methods: Fifteen patients with established RA and damage of the MCP or PIP joints and 15 age- and sex-matched control patients were recruited and scanned by HR-pQCT (XtremeCT; Scanco Medical, Switzerland). A semi-automated segmentation method identified bone mineral based on changes in the gray-scale, with manual correction of any errors made by the program. These images were used to create a three-dimensional reconstruction of the joint. The minimum joint space width was calculated by counting the number of voxels between articular surfaces (Image Processing Language). The number and location of erosions were assessed visually from the two-dimensional images. Quantitative measures of bone density were obtained for the 2nd, 3rd and 4th MCP joints. Diagnostic test performance for HR-pQCT compared to the clinical diagnosis of RA was calculated. Reproducibility was assessed by re-contouring a subset of the images.

Results: Joint space narrowing was detected in RA patients compared to controls (Table 1). In RA, the majority of erosions occurred at the proximal bone surface (mean 23.6 (SD 17.6)). Some controls were found to have erosions, mainly in the IP and PIP joints. Quantitative assessment of bone density parameters did not reveal significant differences between RA patients and controls (Table 2). The best test performance for the clinical diagnosis of RA was determination of an erosion in MCP2 (sensitivity 76.9%, specificity 93.3%, ROC area 0.851, positive likelihood ratio 11.5 (95%CI 1.7–78.4)). Reproducibility was good for bone density parameters (all root square mean coefficients of variance were under 1%), but less so for joint space measurements (17%), perhaps related to difficulties in contouring angulated joints.

Table 1. Relative (and standard deviation) joint space of controls compared to RA patients (positive value indicates the control has a wider joint space).

	PIP 2	PIP 3	PIP 4	PIP 5	MCP 2	MCP 3	MCP 4	MCP 5
Difference (μm)	71 (171)	167 (247)	−68 (181)	44 (196)	131 (535)	262 (502)	106 (406)	145 (287)

Table 2. Relative (and standard deviation) bone density parameters of controls compared to RA patients (positive value indicates that the parameters is higher in controls).

Parameter	MCP 2	MCP 3	MCP 4
Whole bone density (mg/cm^3)	.07 (66)	−8.91 (46)	−24.6 (96)
Cortical density (mg/cm^3)	21.05 (60)	14.21 (53)	−19.55 (90)
Trabecular density (mg/cm^3)	6.13 (48.6)	−1.19 (33.8)	−18.34 (67.3)
Average cortical thickness (mm)	.007 (.047)	−.004 (.037)	−.015 (.046)
Average trabecular number (mm^{-1})	−.04 (.20)	−.01 (.21)	−.36 (1.16)
Average trabecular thickness (mm)	−.004 (.03)	−.002 (.03)	−.010 (.02)
Average trabecular spacing (mm)	.003 (.07)	−.014 (.06)	.006 (.06)

Conclusions: We have developed methods to provide quantitative measurements of bony damage in established RA using HR-pQCT. Differences in joint space width are most pronounced at the MCP joints. Erosions at MCP2 are highly specific for RA, but erosions were detected in controls unrelated to clinical disease. A larger sample size may reveal detectable differences in bone density parameters between subjects with active inflammatory arthritis and those without. In this preliminary study, HR-pQCT demonstrated good performance characteristics for RA diagnosis.

Disclosure: C. C. M. Barnabe: None; **L. Martin:** None; **S. K. Boyd:** None; **S. G. Barr:** None.

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Baseline CRP Predicts Early Improvement in Synovitis, Osteitis, and Erosion on MRI in RA Patients Treated with Tocilizumab: Results from the ACT-RAY MRI Substudy. Orrin M. Troum[6], Charles G. Peterfy[4], Jeffrey L. Kaine[3], Carol Chung[1], Andrew Anisfeld[1], Ewa Olech[2] and Philip G. Conaghan[5]. [1]Genentech, a Member of the Roche Group, South San Francisco, CA, [2]Oklahoma University Health Sciences Center, Oklahoma City, OK, [3]Sarasota Arthritis Research Center, Sarasota, FL, [4]Spire Sciences and Synarc, San Francisco, Kentfield, CA, [5]University of Leeds, Leeds, United Kingdom, [6]University of Southern California, Santa Monica, CA, Santa Monica, CA

Purpose: IL-6R inhibition with tocilizumab (TCZ) inhibits progression of radiographic joint damage in patients (pts) with RA within 6 months. However, clinical and biochemical markers of disease activity, including CRP, and bone and cartilage turnover markers show improvement 2–4 weeks after TCZ initiation. Synovitis (SYN), particularly osteitis (OST), on magnetic resonance imaging (MRI) and elevated CRP levels have been shown to be strong predictors of radiographic progression of joint damage in patients with RA. This analysis examined early effects of TCZ on SYN, OST, and erosion (ERO) in pts with erosive RA who were inadequate responders to methotrexate (MTX-IR).

Methods: As part of a randomized, double-blind, phase 3b study (ACT-RAY) in MTX-IR pts, 63 RA pts on stable MTX were randomly assigned to continue stable MTX or to receive placebo, both in combination with TCZ 8 mg/kg IV every 4 weeks. In this substudy, 0.2T extremity MRI of one hand (metacarpophalangeal joints [MCP] 1–5) and wrist was acquired at baseline and at weeks 2 and 12. MR images were quality controlled and scored by two radiologists using a RAMRIS method blinded to visit order. In this interim analysis, blinded data from both TCZ arms were pooled and analyzed. CRP values were measured at baseline and every 4 weeks.

Results: By week 2, SYN scores improved in 44% of pts and improved ≥ smallest detectable change (SDC) in 7% of pts. By week 12, SYN and OST scores improved ≥SDC in 32% and 28% of patients, respectively. Median ERO score did not change at either time point, but 10 pts showed ERO score change ≥SDC (7 regressed [12%], 3 progressed [5%]) at week 12. Baseline CRP levels were variable, with a mean of 1.2 mg/dL (range 0.1–10.3); 93% of patients achieved normal CRP levels by week 12. Exploratory analysis stratifying MRI RAMRIS subscores by baseline CRP levels revealed that mean baseline SYN, OST, and ERO scores were numerically higher in patients with baseline CRP ≥1.0 than in those with CRP ≤0.3, or 0.3–1.0. Pts with high baseline CRP (≥1.0) were 1.7-, 7.2-, and 3.2-fold more likely to achieve improvements ≥SDC in SYN, OST, and ERO, respectively, at week 12 than were pts with normal baseline CRP levels (≤0.3) (Table).

Conclusions: TCZ reduced synovitis in only 2 weeks and pre-erosive OST within 12 weeks of treatment initiation. Pts with baseline CRP levels ≥1.0 mg/dL were more likely than pts with baseline CRP levels <1 mg/dL to achieve improvements in MRI measures of inflammation and erosive activity, indicating that CRP may have the potential to predict which pts will

experience the greatest MRI improvements after treatment with TCZ. Analysis of the upcoming 52-week visit from this study will offer an opportunity to confirm this observation. MRI evidence of early improvement with TCZ is in line with prior demonstration of inhibition of X-ray joint damage at 1 year and the observation that baseline CRP predicts radiographic progression.

		Baseline CRP, mg/dL			
		≤0.3	>0.3−<1.0	≥1.0	Total
Mean baseline RAMRIS score	n	19	22	22	63
	SYN	6.6	6.5	9.4	7.5
	OST	3.9	5.3	16.2	8.7
	ERO	13.6	20.4	22.3	19.0
Pts with week-12 improvement ≥ SDC, %	n	16	20	21	57
	SYN	25[a]	25	43[a]	32
	OST	6[b]	30	43[b]	28
	ERO	6[c]	10	19[c]	12

SDC: SYN = 1.7, OST = 3.0, ERO = 2.2.
[a] 43 is 1.7-fold greater than 25, [b]43 is 7.2-fold greater than 6. [c]19 is 3.2-fold greater than 6.

Disclosure: O. M. Troum: Abbott Laboratories, 2, 5, 8, Amgen Inc., 2, 5, 8, Bristol-Myers Squibb, 2, 8, Centocor, Inc., 2, 5, Novartis Pharmaceuticals Corporation, 2, Pfizer Inc, 2, 5, 8, Proctor and Gamble, 8, Roche, 2, 5, 8, Takeda, 5, 8, UCB, Inc., 2; **C. G. Peterfy:** Abbott Laboratories, 5, Amgen Inc., 5, Biogen Idec, 5, Bristol-Myers Squibb, 5, Celgene, 5, Centocor, Inc., 5, Crescendo, 1, 3, 4, 5, Genentech, 1, 3, 4, 5, Lilly USA, LLC., 5, Novartis Pharmaceuticals Corporation, 5, Pfizer I; **J. L. Kaine:** Amgen Inc., 8, Bristol-Myers Squibb, 8, Novartis Pharmaceuticals Corporation, 8, UCB, Inc., 8; **C. Chung:** Genentech, 3; **A. Anisfeld:** Genentech, 3; **E. Olech:** Biogen Idec, 2, 8, Bio-rad, 2, 5, 8, Bristol-Myers Squibb, 8, Centocor, Inc., 2, Crescendo, 2, 5, 8, Genentech, 2, 5, 8, Pfizer Inc, 5, Roche, 2, 5, UCB, Inc., 2, 5, 8, Vertex, 2; **P. G. Conaghan:** AstraZeneca, 8, Bioiberica, 8, Bristol-Myers Squibb, 8, Centocor, Inc., 8, Merck Pharmaceuticals, 8, Novartis Pharmaceuticals Corporation, 8, Pfizer Inc, 2, 8, Roche, 8.

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Bone Density Measurement in Osteoarthritis Using Digital Radiographic Procedures. M. B. Kinds[2], L. W. Bartels[1], A. C. A. Marijnissen[3], K. L. Vincken[1], H. W.A.M. de Jong[1], M. A. Viergever[1] and F. P. J. G. Lafeber[3]. [1]Image Sciences Institute, University Medical Center Utrecht, The Netherlands, [2]Rheumatology & Clinical Immunology, Image Sciences Institute, University Medical Utrecht, The Netherlands, Utrecht, The Netherlands, [3]Rheumatology & Clinical Immunology, University Medical Center Utrecht, The Netherlands

Background: Dual energy X-ray Absorptiometry (DXA) is the method of choice for quantifying bone density (BD). In clinical practice however, BD is commonly subjectively assessed on standard radiographs for the evaluation of bone changes (sclerosis) in osteoarthritis (OA). The transition from conventional radiography to digital radiography needs reevaluation whether BD can be quantified on radiographs. The objective of this study was to evaluate whether actual BD (hydroxylapatite in g/cm^2) can be reliably related to grey value in digital radiographs, and to study whether an aluminum step wedge can be used as a reference for BD (in mm aluminum equivalent: mmAl) to make the measurement independently of radiographic settings.

Methods: A bone density standard (BDS) was created consisting of predefined amounts of hydroxylapatite (eight cups ranging from 0 to 5.75 g/cm^2). The BDS was validated by use of DXA (R^2=0.99). Digital radiographs of the BDS were acquired (Philips Digital Diagnost) with different settings. Peak voltage (kVp), milliampere seconds (mAs), position of the BDS in the radiographic field, and filtration were varied. Also the default clinical post-processing module, which is introduced with the development of digital radiography, was compared with post-processing switched off. In all cases a human (cadaver) knee joint was added to simulate clinical conditions. For analysis of BD an aluminum step wedge (40×200mm) consisting of 20 steps with increasing thickness of 2mm was added in all radiographs as a reference. A modified version of Knee Images Digital Analysis (KIDA)[1] was used to express the grey values in the BDS in mmAl by comparison with the grey values in the step wedge. The grey values in the step wedge were represented by a linear or a third order polynomial function. The relation between actual BD (g/cm^2) and BD in mmAl was evaluated with linear regression analysis. The effects of the different radiographic settings were evaluated as well.

Results: The relation between actual BD and BD in mmAl was most importantly influenced by regular clinical post-processing settings. Specifically switching off the post-processing module during acquisition improved the linear relation from R^2=0.82 to R^2=0.93. When a third order polynomial representation of the step wedge was used, the relation improved to R^2=0.95 with clinical post-processing and to R^2=0.98 when post-processing was off. Variation in the other radiographic settings (kVp, mAs, position, and filter) moderately influenced the linearity: R^2=0.71–0.87.

Conclusion: Bone density evaluation on digital radiographs is hampered by the default post-processing as used in clinical practice. By use of an aluminum reference step wedge and by using a third order polynomial function in KIDA, BD on digital radiographs can be reliably expressed in mmAl equivalents.

Reference:

[1]Marijnissen, et al. OA&C. 2008 Feb;16(2):234–243

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Bone Marrow Lesion (BML) Size in Osteoarthritic Knees Correlates with Extent of Cartilage Damage and Predicts Longitudinal Cartilage Loss. Jeffrey B. Driban[3], Grace H. Lo[1], Ji Yeon Lee[2], Robert J. Ward[3], Eric Miller[5] and Timothy E. McAlindon[4]. [1]Tufts Medical Center, Houston, TX, [2]Tufts Medical Center, Brookline, MA, [3]Tufts Medical Center, Boston, MA, [4]Tufts Medical Center Box 406, Boston, MA, [5]Tufts University

Purpose: Although BMLs appear to be associated with cartilage damage in knee osteoarthritis (OA), the nature of the relationship is unclear. Prior studies have used semi-quantitative BML scales which limit analyses of longitudinal relationships and measurements of BML change. Therefore, our aim was to evaluate the cross-sectional and longitudinal relationships between BML size and the extent of cartilage damage using quantitative 3-dimensional measurements (BML size; cartilage volume, thickness and area of denudation).

Methods: The sample comprised 44 knees (baseline Kellgren Lawrence score ≥ 2) from participants in a clinical trial who had sagittal and coronal intermediate-weighted fat-suppressed (IW FS) and DESS MRIs at baseline and 2 years (Siemens Magnetom Avanto 1.5T). Knees were selected that had areas of full thickness cartilage loss. We defined BMLs as regions of high-signal intensity on IW FS images located within 1.0 cm of hyaline cartilage and present on ≥ 2 sagittal or coronal images and classified them within 2 regions: index femur or tibia. Two rheumatologists defined the index compartment as the compartment (medial or lateral) with greater pathology based on radiograph and MRI findings. We measured the maximal anterior-posterior, medial-lateral, and vertical dimensions of each BML. Their product represented the volume of each BML (intra-tester ICC =.96). When multiple BMLs were present in a region their volumes were summed to calculate regional volume. Cartilage measurements were determined by manual segmentation of registered DESS images using Analyze© (intra-tester ICC >.99).

Results: Participants were 65 ± 9 years of age (m ± sd), 52% female, and body mass index of 29.8 ± 5.8 kg/m2. Among femurs, 91% had full thickness cartilage loss at baseline (baseline = 11.0 ± 10.4% of subchondral bone; 2 incident knees; change = 1.5 ± 1.8% of subchondral bone) and 91% had baseline BMLs (baseline = 15.3 ± 16.0 cm3; 1 incident knee; change = 1.6 ± 12.4 cm3). Among tibias, 66% had full thickness cartilage loss at baseline (baseline = 16.3 ± 18.6% of subchondral bone; 3 incident knees; change = 2.1 ± 4.2% of subchondral bone) and 85% had BMLs (baseline = 30.7 ± 31.5 cm3; 2 incident knees; change = 3.9 ± 14.8 cm3).

Table 1 demonstrates intra-region correlations among BML and cartilage. Baseline BML volume had direct associations to area of full thickness cartilage loss (baseline and change). There was also a direct association between tibia BML volume change and tibia cartilage volume change (r =.32, p =.047, n = 39). There were no other correlations between BML volume change and cartilage parameters (baseline or change).

Table 1. Spearman Coefficients among Baseline BML and Cartilage Parameters

	Femur BML Volume: Baseline (n = 40)	Tibia BML Volume: Baseline (n = 37)
Cartilage Volume: Baseline	−.06	−.31*
Cartilage Thickness: Baseline	.02	−.37*
Area of Full Thickness Cartilage Loss: Baseline	.33*	.63**
Cartilage Volume: Change	.03	.16
Cartilage Thickness: Change	−.11	−.13
Area of Full Thickness Cartilage Loss: Change	.48**	.43**

* significant findings ($p \leq .05$)
** significant finding after Bonferroni corrections (18 multiple comparisons; $p < .003$)

Conclusion: In knees with cartilage denudation, BML size indicates the level of risk for further full thickness cartilage loss.

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Decreased Incidence of Synovitis, Osteitis, and Erosion in Early RA Patients Treated with Adalimumab Plus Methotrexate Compared to Those with Methotrexate Alone: High-Field MRI Analysis from OPTIMA. Charles Peterfy[4], Boulos Haraoui[5], Patrick Durez[3], Kaushik Patra[2] and Hartmut Kupper[1]. [1]Abbott GmbH & Co. KG, Ludwigshafen, Germany, [2]Abbott Laboratories, Abbott Park, IL, [3]Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium, [4]Spire Sciences, San Francisco, CA, [5]University of Montreal Hospital Centre, Hopital Notre Dame, Montreal, QC, Canada

Background: Combination therapy with adalimumab (ADA) and methotrexate (MTX) has been shown to reduce X-ray progression of joint damage in rheumatoid arthritis (RA). Magnetic resonance imaging (MRI) is more sensitive than X-ray for bone erosion and also visualizes pre-erosive synovitis and osteitis.

Objective: To determine the proportion of early RA patients showing progression or improvement in synovitis, bone erosion, and osteitis on high-field MRI after 26 weeks of therapy with ADA+MTX or MTX monotherapy in a substudy of OPTIMA (**O**ptimal **P**rotocol for **T**reatment **I**nitiation With **M**ethotrexate and **A**dalimumab Combination Therapy in Patients With Early Rheumatoid Arthritis).

Methods: OPTIMA is an ongoing 78-wk study with 26- and 52-wk periods including MTX-naive patients with RA <1 year, DAS28>3.2, ≥6 SJC, ≥8 TJC, ESR ≥28 mm/h or CRP ≥1.5 mg/dL, and ≥1 of the following: >1 joint erosion, RF+, or anti-CCP+. Patients were randomized to ADA (40 mg every other wk)+MTX (titrated to 20 mg/wk by wk 8) or placebo (PBO)+MTX. Fifty-nine patients had 1.5-Tesla MRI of metacarpophalangeal and wrist joints before and after i.v. gadodiamide. Of these, 23 patients had baseline MRI after the first dose of study drug; 19 (83%) within 7 days of dosing. This analysis reports results at baseline and wk 26. Synovitis, erosions, and osteitis were scored by 2 independent blinded readers using the OMERACT-RAMRIS scoring system. Progression or improvement of MRI scores were defined as positive or negative change from baseline ≥ smallest detectable change (SDC)[1], respectively.

Results: Mean (SD) baseline MRI scores for PBO+MTX (N=32) and ADA+MTX (N=27) were comparable for synovitis: 6.8 (4.33) and 6.2 (4.18), P=0.63; for erosions: 4.1 (5.85) and 6.1 (7.43), P=0.26; and for osteitis: 3.3 (4.74) and 5.4 (7.93), P=0.25. Subjects in the PBO+MTX and ADA+MTX groups, respectively, had mean changes in synovitis of −2.0 and −3.6 (P=0.003), in erosion of 1.4 and −0.8 (P=0.004), and in osteitis of 0.0 and −4.0 (P=0.006), indicating that joint inflammation and damage were significantly alleviated by ADA+MTX. Clinical responses to treatment (ACR20/50/70 and DAS28) were correspondingly greater in the ADA+MTX group. The SDC values for synovitis, erosion, and osteitis were 1.8, 1.2, and 3.8, respectively. Subjects receiving ADA+MTX were more likely to exhibit improvements in synovitis, erosion, and osteitis ≥SDC; only one subject in the ADA+MTX group showed progression of bone erosion ≥SDC, compared with 12 subjects in the PBO+MTX group (Table). A similar pattern was seen among the 36 patients who received MRI prior to the first dose of study drug (data not shown).

Table. Proportion of subjects demonstrating progression or improvement ≥SDC in 26 weeks

n (%) subjects	PBO+MTX (N = 32)	ADA+MTX (N = 27)	P value[a]
Progression			
Synovitis	2 (6%)	0	0.50
Erosion	12 (38%)	1 (4%)	0.002
Osteitis	4 (13%)	0	0.12
Improvement			
Synovitis	14 (44%)	20 (74%)	0.03
Erosion	3 (9%)	6 (22%)	0.28
Osteitis	3 (9%)	8 (30%)	0.09

[a] for comparison between treatment groups, based on Fisher's exact test

Conclusion: Treatment of early RA with ADA+MTX for 26 weeks yielded better MRI profiles than did treatment with MTX alone; the improvements in joint inflammation and damage corresponded with enhanced clinical outcomes.

References:

[1] Bruynesteyn K et al. *Ann Rheum Dis* 2005;64:179–82.

Disclosure: C. Peterfy: Abbott Laboratories, 5, Amgen Inc., 5, Biogen Idec, 5, Bristol-Myers Squibb, 5, Celgene, 5, Centocor, Inc., 5, Crescendo, 3, 5, Genentech and Biogen IDEC Inc, 5, Lilly USA, LLC., 5, Novartis Pharmaceuticals Corporation, 5, Pfizer; **B. Haraoui:** None; **P. Durez:** None; **K. Patra:** Abbott Laboratories, 1, 3; **H. Kupper:** Abbott Laboratories, 1, 3.

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Detection of Radiographic Progression in Early Knee Osteoarthritis (CHECK): Sensitivity to Change of Knee Images Digital Analysis Compared to Altman Grading. M. B. Kinds[3], S. M. A. Bierma-Zeinstra[1], A. C. A. Marijnissen[5], M. A. Viergever[2], J. W. J. Bijlsma[5], P. M. J. Welsing[4] and F. P. J. G. Lafeber[5]. [1]General Practice, Erasmus University Rotterdam, the Netherlands, [2]Image Sciences Institute, University Medical Center Utrecht, The Netherlands, [3]Rheumatology & Clinical Immunology, Image Sciences Institute, University Medical Center Utrecht, The Netherlands, [4]Rheumatology & Clinical Immunology, Julius Center for Health Sciences & Primary Care, University Medical Center Utrecht, The Netherlands, [5]Rheumatology & Clinical Immunology, University Medical Center Utrecht, The Netherlands

Background: In the detection of radiographic progression in osteoarthritis, semi-quantitative measurement commonly results in low sensitivity to change. Quantitative measurement of separate radiographic OA features using Knee Images Digital Analysis (KIDA)[1] theoretically enables more precise measurement and greater sensitivity to change. In the longitudinal Cohort Hip & Cohort Knee (CHECK) radiographic progression is evaluated early in OA. The objective of this study was to determine whether the sensitivity to change of separate radiographic features of OA can be improved by using digital analysis (KIDA).

Methods: Knee radiographs (PA semiflexed) were evaluated for the OA parameters: joint space narrowing (JSN; lateral and medial), osteophytes (lateral and medial femur, lateral and medial tibia), and bone density (BD; lateral femur and medial tibia) by quantitative measurement with KIDA and by semi-quantitative grading according to the Altman atlas[2]. For KIDA measurement sensitivity to change was determined by calculation of the smallest detectable difference (SDD), which accounts for the variability of the radiographic procedure and digital analysis. SDD was determined in a subset of unchanged knees from baseline to 2 year follow-up based on an Altman grade of 0 for all parameters at both time points (313, 303, and 213 pairs of knee radiographs for JSN, osteophyte area, and BD parameters respectively). Next, of all 1002 participants in CHECK available baseline and follow-up knee radiographs were evaluated. The percentage of knees changing on the radiographic parameters was determined for KIDA, defined as a change larger than the SDD, and for the Altman atlas defined as a change of at least one grade. Further, for each parameter knees with a change on KIDA and/or Altman were evaluated for agreement using cross-tabulations.

Results: The SDD for the OA parameters in the different compartments ranged from 0.96 to 2.63mm for JSN, 1.30–4.89mm^2 for osteophyte area, and 10.92–12.96mmAl equivalents for BD. Using KIDA, OA progression was found in 2.4–10.2% (JSN), 6.0–9.2% (osteophyte), and 2.2–4.8% (BD) of knees. Using Altman, OA progression was found in 4.1–11.0% (JSN), 3.3–10.6% (osteophyte), and 0.9–1.3% (BD) of knees. According to both KIDA and Altman, in two years of follow-up only in a limited number of knees radiographic progression occurred: e.g. 3% for JSN medial, and 2% for osteophytes at medial tibia. In 82% and 84% of knees no change occurred. In 15% of cases disagreement existed between knees changing according to KIDA measurement and the Altman atlas.

Conclusion: Sensitivity to change for the detection of radiographic progression in early OA is not improved by using KIDA. Quality of acquisition of radiographs seems to be at least as important as quality of analysis.

References:
[1]Marijnissen, et al. OA&C. 2008 Feb;16(2):234–243; [2]Altman, et al. OA&C. 2007;15(suppl A):A1–56

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Discriminative Power of Different Combinations of Bones and Joints for Assessing Change in Rheumatoid Arthritis with MRI: Results Based on Pooled Data from Four Multisite Clinical Trials. Charles G. Peterfy[8], Peter Countryman[7], Julie DiCarlo[7], Annarita Gabriele[4], Tim M. Shaw[3], Andrew Anisfeld[5], Wayne H. Tsuji[1], Ewa Olech[6] and Norman B. Gaylis[2]. [1]Amgen, Seattle, WA, [2]Arthritis & Rheumatic Disease, Aventura, FL, [3]F Hoffmann La-Roche, Ltd, Welwyn Gladen City Herts, United Kingdom, [4]F Hoffmann La-Roche, Ltd, Italy, [5]Genentech, a Member of the Roche Group, [6]Oklahoma Medical Research Foundation, Oklahoma City, OK, [7]Spire Sciences, LLC, San Francisco, CA, [8]Spire Sciences, LLC, Kentfield, CA

Background: We previously showed that different combinations of bones and joints in the hand and wrist varied in their ability to discriminate significant change in synovitis, osteitis and erosion with MRI in patients wtih RA in a multicenter clinical trial[1]. In this study, we corroborated these findings using pooled data from 4 multisite clinical trials.

Methods: A total of 522 RA patients from 4 clinical trials were included in the analysis. Three of these studies (459 patients) included 1.5T MRI, and 2 studies (118 patients) included 0.2T MRI. All scans used a hand frame to ensure reproducible positioning, and were read by the same 2 radiologists. Metacarpophalangeal joints (MCP) 1–5 and all bones and joints in the wrist were scored using the RAMRIS scale[2] for erosion and osteitis in all 4 trials and synovitis in all but one of the 1.5T trials. Six combinations (RAMRIS, 23 bones and 7 joints in original RAMRIS; RAMRIS+, RAMRIS + MCP1; V-Sharp, MCP1–5 + 6 wrist bones in van der Heijde-Sharp X-ray score; G-Sharp, MCP1–5 + 5 wrist bones in Genant-Sharp X-ray score [V-Sharp – lunate]; MCPs, MCP1–5; Wrist, 15 bones and 3 joints in RAMRIS) were compared for percentages of patients changing (increase or decrease) ≥ smallest detectable change (SDC)[3] at week 12 or 24.

Results: Frequency of involvement at baseline varied by location (Fig.1), but showed a similar pattern in all 4 studies and between patients with early (<2y) RA and those with established (>10y) RA (data not shown). Inter-reader agreement, expressed as intraclass correlation coefficient (ICC), also varied among locations (median = 0.84, 0.88 and 0.81, for erosion, osteitis and synovitis, respectively.) Percent of patients changing ≥SDC at 12 or 24 weeks varied among the different combinations (Fig. 2). Adding MCP-1 to RAMRIS (RAMRIS+) increased discrimination for erosion and synovitis. G-Sharp showed the highest discrimination for osteitis and synovitis, and was equivalent to RAMRIS for erosion. Excluding all wrist locations (leaving only MCPs) actually increased discrimination for erosion over that with RAMRIS, but decreased discrimination for osteitis or synovitis.

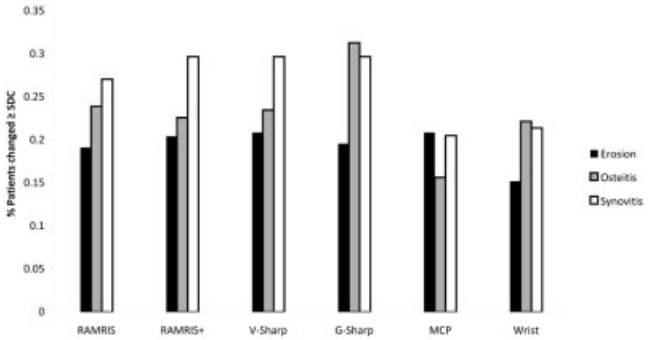

Figure 1. Frequency of involvement of different bones and joints of MCPs and wrist with erosion, osteitis and synovitis (RAD, radius; ULN, ulna; SCAP, scaphoid; TRIQ, triquetrum; PIS, pisiform; TPM, trapezium; TPD, trapezoid; CAP, capitate; HAM, hamate; PMC, proximal metacarpal; DMC, distal metacarpal; PP, proximal phalanx; DRU, distal radioulnar joint; RC, radiocarpal joint; ICMC, intercarpal and carpometacarpal 2-5.)

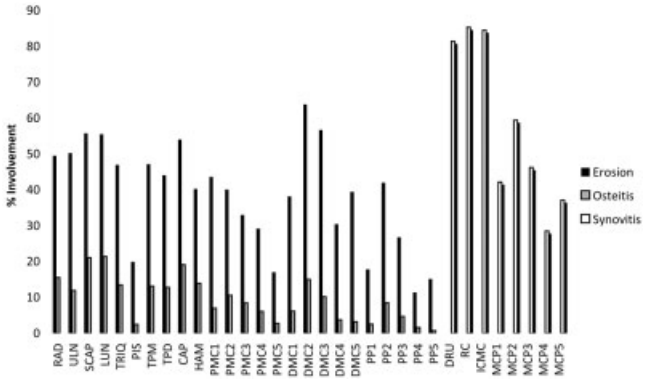

Figure 2. Proportion of patients showing change (increase or decrease) from baseline in erosion, osteitis or synovitis scores ≥ ±SDC for different combinations.

Conclusions: Filtering out noisy and infrequently involved bones and joints may improve discriminative power of RAMRIS. Determining the combination that optimally balances functional relevance with reading reliability requires further investigation.

1. Peterfy C, et al. EULAR 2010
2. Ostergaard M, et al. Ann Rheum Dis 2005;64(Suppl1):i3–i7
3. Bruynesteyn K et al. Ann Rheum Dis 2005;64:179–82

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Giant Cell Arteritis and MRI Evaluation of the Cranial Arteries. Marie I. Clements-Baker[1], Samir Patel[4], Ryan Rebello[2], George Ionnadis[5] and Nader Khalidi[3]. [1]St Joseph's Healthcare Hamilton Ontario, Canada McMaster University, Hamilton, ON, Canada, [2]St Joseph's Healthcare Hamilton, Mcmaster University, Hamilton, ON, Canada, [3]St. Joseph's Healthcare Hamilton, McMaster University, Hamilton, ON, Canada, [4]St. Joseph's Healthcare Hamilton, Mcmaster University, [5]St. Joseph's Healthcare Hamilton. McMaster University

Objective(s): To evaluate whether high field Magnetic Resonance Imaging (MRI) can demonstrate mural edema and inflammation within the superficial temporal artery and other intra- and extracranial arteries and how it compares to temporal artery biopsy results in patients who meet American College of Rheumatology (ACR) criteria for giant cell arteritis (GCA).

Method(s): 49 patients meeting ACR criteria for GCA, and 6 patients otherwise suspicious of GCA were examined by 3T MRI using a head coil. The MRI protocol matured over the course of the study but, in general, high-resolution fluid-sensitive and Gadolinium enhanced images of the clinically-affected STA were obtained, in addition to larger field of view sequences to visualize the other scalp arteries. The images were graded according to protocols reported in recently published studies. All patients except 1 underwent temporal artery biopsy. Images and biopsy were obtained as soon as possible after initiating corticosteroid therapy.

Result(s): Overall 23/55 patients had postive scalp artery MRI findings and 8/55 patients had positive biospy findings. Of these positive biopsies, MRI was reported as positive in 7 with evidence of STA inflammation present in 6 and the seventh patient demonstrating only cavernous carotid artery inflammation. One false negative occured but an inadvertent protocol deviation had occurred with suboptimal image resolution obtained for that patient. The average biopsy length was 2.79 cm. The average number of days from corticosteroid to MRI was 3.9 days and the average number of days to biopsy was 8.98 days.

Other important MRI findings in patients who had negative artery inflammation included 1 case ipsilateral pachymeningitis, 1 cortical infarct, 1 bone lesion questionable for metastatic disease, 1 ipsilateral pansinusitis and 1 case of multiple meningiomas requiring neurosurgical referral.

Conclusion: In patients meeting ACR criteria for GCA, MRI demonstrates evidence of STA inflammation in 43% of patients. This appears superior to our biopsy positive rate of 13%. These results support previous studies and suggest that MRI could replace or complement biopsy as an effective and non-invasive way to diagnose GCA. The MRI protocol and image resolution are crucial components in MRI evaluation of scalp artery

inflammation. MRI is clearly useful in diagnosing other pathologies that may clinically mimic giant cell arteritis.

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High-Field MRI and Powerdoppler Sonography—Supplementary Imaging Techniques in Assesing Disease Activity in Patients with Psoriasis Arthritis (PsA) and Rheumatoid Arthritis (RA) in Sustained Clinical Remission. Maria Hoehle Rheumatologic Practice, Hamburg, Germany

Background: Patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA) responding to anti-TNF therapy show a rapid decrease in inflammatory parameters as well as sustained improvement of clinical signs and symptoms. However inflammatory activity, e.g. synovitis, tenosynovitis, edema still can persist at the joints in patients with clinical remission. These rheumatic processes can be monitored using modern imaging techniques such as high-field MRI and powerdoppler sonography (PD-US).

Objectives: To evaluate whether MRI and US are helpful to stratify patients in clinical and imaging remission for discontinuation of anti-TNF treatment, 41 patiens were followed-up for six years.

Methods: 41 patients (30 women) with RA (35) and PsA (6) starting therapy with adalimumab in 2004 were followed-up for six years. Every six months patients were monitored by standard routine diagnostics as well as by high-field MRI and PD-US. Thereby, the clinically dominant joint was evaluated using RAMRIS and semiquantitative PD-US-score (0–3). Clinical remission was defined as DAS28<2,6. Imaging remission was defined as no detectable synovitis at the clinically dominant joint using MRI and PD-US (RAMRIS synovitis = 0, PD-US synovitis score = 0) (Ref 1,2).

Results: In sixteen patients (16) with early RA (disease duration < 2 years, mean DAS28 = 3,9, mean RAMRIS synovitis = 2,8, mean PD-US synovitis score 2,9) responding to anti-TNF therapy with adalimumab in combination with methotrexat by showing sustained clinical remission (mean DAS28 = 1,5) and imaging remission of at least 12 months adalimumab was discontinued. Clinical and imaging remission persisted in the follow-up period.

In twenty-five patients (25) with established inflammatory rheumatic disease (RA (19), PsA (6), disease duration > 2 years, mean DAS28 = 3,8, mean RAMRIS synovitis = 2,9, mean PD-US synovitis score 2,7) responding to anti-TNF therapy with adalimumab in combination with methotrexat by showing sustained clinical remission (mean DAS28 = 1,4) subclinical synovitis persisted (mean RAMRIS synovitis = 2,1, mean PD-US synovitis score 2,1). Combination therapy was continued in the follow-up period.

In both groups flares of disease activity, erosive progression at hands, severe infections e.g. tuberculosis infections, reactivation of tuberculosis infections or malignoma were not observed since 2004.

Conclusion: According to current evidence patients with RA and PsA should be monitored clinically (DAS28) as well as by modern imaging modalities in a tight and continuous fashion. Early use of adalimumab in the course of the rheumatic disease may allow discontinuation of anti-TNF treatment in true responders as both clinical and imaging remission persisted for five years in the early treatment group. MRI and PD-US seem helpful to stratify patients for discontinuation of biologics.

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Disclosure: M. Hoehle: None.

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Inflammatory Osteophyte Formation Is Different from Degenerative Osteophyte Formation. Stephanie Finzel, Christian Ernet, Christian Stach, Klaus Engelke, Matthias Englbrecht and Georg Schett. University of Erlangen-Nuremberg

Objectives: To investigate the differences in the pattern of periarticular oteophyte formation in patients with psoriatic arthritis and hand osteoarthritis by a high-resolution micro-computed tomography scanner (μCT) designed to visualize bone architecture. Both psoriatic arthritis (PSA) and osteoarthrits (OA) lead to joint destruction via deforming osteophytic proliferation but may differ substantially in their periarticular bone changes.

Methods: 24 patients with PSA and 24 patients age- and sex-matched with OA received a micro- computed tomography scan of the dominantly affected hand to compare structural bone changes in the metacarpophalangeal joints. Number, size and distribution of osteophytes were recorded.

Results: Number and size of osteophytes in PSA were comparable to OA. However osteophytes in OA were exclusively found at the palmar and dorsal sites of the MCP-joints. Moreover, in OA patients the metacarpal heads were by far more affected than the phalangeal bases. In contrast, osteophyte formation in PSA did also involve skeletal sites which are normally spared in OA patients, such as the radial and ulnar sites, usually leading to affection of the entire circumference of the periarticular bone surface ("bony corona"). Also significant affection of the phalangeal bases was observed in PSA in contrast to OA.

Conclusions: High-resolution μCT imaging shows profound differences in periarticular bone changes between PSA and HFE. The differential pattern of osteophyte formation between PSA and OA patient suggest different mechanisms to be involved in bone spur formation in consequence of inflammatory and degenerative arthritis of the finger joints. In particular the wide spread corona- shaped osteophyte formation in PSA suggests a profound involvement of the insertion sides of the tendons which is also supported by a far more severe affection of the phalangeal bases. Theses data suggest that it is possible to differentiate between inflammatory and degenerative osteophyte formation by advanced imaging technology.

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Magnetic Resonance Elastography for the Evaluation of Liver Fibrosis in Patients with Rheumatoid Arthritis Receiving Methotrexate. Deana D. Hoganson[1], Jun Chen[2], Richard L. Ehman[2], Jayant A. Talwalkar[2], Clement J. Michet[1], Meng Yin and Eric L. Matteson[1]. [1]Mayo Clinic, Rochester, MN, [2]Mayo Clinic

Background: Hepatic magnetic resonance elastography (MRE) allows for noninvasive assessment of liver fibrosis. The purpose of this study was to evaluate the usefulness of MRE in detecting and quantifying liver fibrosis in patients with rheumatoid arthritis (RA) who have received methotrexate (MTX).

Methods: Patients receiving MTX for > 5 years or with an abnormal serum AST value in the two years preceding the study onset were evaluated with MRE. Logistic regression and linear regression models with and without adjustment were used to assess the association between mean liver stiffness value as determined by MRE and variables of interest. Prior analyses have shown that a diagnostic cut-off value of 2.9 kilopascals (kPa) can predict all stages of liver fibrosis when compared to normal liver with a sensitivity and specificity of 98% and 99%, respectively. Study participants with an abnormal liver stiffness were subsequently offered evaluation in the hepatology clinic and the decision for a liver biopsy was made based on clinical judgment.

Results: Sixty-five RA patients were enrolled. Mean liver stiffness value by MRE was abnormal in 7 patients, suggestive of hepatic injury. As a result of findings from the MRE, biopsies were performed in 5 patients and all correlated with elevated liver stiffness values (Table). The biopsies revealed chronic inflammation in all subjects; 4 individuals had evidence of fibrosis. There was a significant association between elevated mean liver stiffness and abnormal AST values ever and in the preceding 2 years prior to the scan ($p=0.035$ and $p=0.031$, respectively). Elevated mean liver stiffness values were associated with body mass index (BMI) (OR= 1.18 per 1 kg/m^2; 95% CI: 1.03, 1.36; $p=0.017$), and this remained significant following adjustment for MTX dose, MTX treatment duration, diabetes mellitus, hyperlipidemia, and impaired fasting blood glucose. Neither the total MTX dose nor the duration of MTX treatment was associated with mean liver stiffness value ($p=0.51$ and $P=0.20$, respectively). Eleven patients reported using alcohol more than once a month. Alcohol use was not associated with abnormal mean liver stiffness values ($p=0.96$).

Conclusions: MRE provides a reliable, non-invasive assessment of liver fibrosis in patients with RA receiving MTX. Patients with RA receiving MTX who have an elevated BMI may be at increased risk for chronic hepatic injury, regardless of MTX cumulative dose or duration of treatment.

Table. Abnormal Hepatic Magnetic Resonance Elastography (MRE) Scans in Patients receiving Methotrexate for Treatment of Rheumatoid Arthritis.

Patient	Age (years)	Sex	BMI (kg/m^2)	Total MTX dose (mg)	Frequency abnormal AST 2 years prior to MRE	Mean liver stiffness value (kPa)	Liver biopsy findings
1	71	F	31.1	14235	4/9	3.36	Mildly active (grade 1 of 3) steatohepatitis with focal pericellular fibrosis and mild portal fibrosis (stage 1 of 4)
2	65	F	37.9	2950	1/13	3.46	Mild reactive hepatitis with mild portal fibrosis (stage 1 of 4)
3	57	F	42.1	11880	0/15	3.23	Mildly active steatohepatitis without fibrosis.
4	46	F	44.9	6875	5/7	2.92	Moderately active steatohepatitis, grade 2 (of 3) with portal, periportal, and pericellular fibrosis, stage 2 (of 4).
5	65	F	27.4	6340	1/8	3.26	Not pursued; repeat MRE showed results within a normal range
6	66	M	37.3	3680	0/10	3.13	Mild fatty change with mild portal fibrosis.
7	62	F	31.8	9295	7/17	3.15	Discontinued MTX; no biopsy performed

Abbreviations:
AST-aspartate aminotransferase; BMI-body mass index; MTX-methotrexate; kPa-kilopascal

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Magnetic Resonance Imaging (MRI) of the Spine May Be Useful in Patients with Non-Radiographic Axial Spondyloarthritis (NRASpA) without Active Sacroiliitis on MRI. Guillaume Direz[1], Manuel Couchot[2], Philippe Cotty[1], Denis Mulleman[3] and Philippe M. Goupille[1]. [1]University Hospital, Tours, Tours, France, [2]University Hospital, Tours, Tours, France, [3]University Hospital, Tours, Tours, France

Background: MRI of the sacroiliac joints (SIJ) is useful for the diagnosis of axial spondyloarthritis (SpA) in patients who don't fulfil the modified New York criteria (1). However, about 25 to 30 % of patients with NRASpA have no active sacroiliitis on MRI, according to ASAS/OMERACT criteria (2). MRI of the spine may show lesions such as Romanus and fatty Romanus which, when multiple or severe, may be highly suggestive of the diagnosis of axial SpA.

Objective: To assess, in a NRASpA cohort without active sacroiliitis on MRI, the prevalence of spine lesions on MRI highly suggestive of axial SpA.

Methods: Retrospective analysis of the MRI of SIJ and of the thoracic and lumbar spine, performed between 2005 and 2009, in patients with NRASpA. Blind analysis was performed by two independent radiologists (SIJ and spine were independently assessed). Active sacroiliitis on MRI was defined according to ASAS/OMERACT criteria, and a positive spinal MRI was defined according to the presence of highly suggestive lesions (Romanus, fatty Romanus, Andersson spondylitis, inflammatory posterior lesions) and the experience of the two radiologists (study performed before the definition of a positive spinal MRI by the ASAS group).

Results: MRI of 93 NRASpA patients were analysed. Mean age was 39.4 years, mean disase duration was 4.5 years; 39% of the patients were HLA B27 positive, all patients fulfilled ASAS criteria or Amor criteria of SpA and had a diagnosis of NRASpA by their rheumatologist. Thirty-eight of 93 patients (40.8%) had active sacroiliitis on MRI, 25/93 (26.8%) had sacroiliitis and spine lesion highly suggestive of SpA, 10/93 (10.7%) had a normal MRI of SIJ and spine, 10/93 (10.7%) had some inflammatory lesions of SIJ and/or spine not sufficient for the diagnosis of SpA.

Ten of 93 patients (10.7%) had spine lesion highly suggestive of SpA without active sacroiliitis on MRI (6/10 had other lesions of the SIJ (enthesitis, erosions, sclerosis) suggestive of inflammatory involvement). Eight of these 10 patients fulfilled the recently presented ASAS criteria of positive spinal MRI (3) because they had at least 3 Romanus lesions. Therefore, according to new ASAS criteria, 8/93 patients (8.6%) had a positive spinal MRI without active sacroiliitis. More interesting, on 30/93 patients without active sacroiliitis on MRI, 8/30 (26.6%) had at least 3 Romanus lesions on spinal MRI, leading to the diagnosis of axial SpA. There was no significant association between the presence of psoriasis, uveitis, disease duration, HLA B27 or increased CRP and isolated positive spinal MRI.

Conclusions: In NRASpA patients, only 10% had isolated positive spinal MRI. However, in case of suspicion of SpA without active sacroiliitis on MRI, spine MRI may allow the diagnosis of SpA in about 25% of patients.

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Disclosure: G. Direz: None; **M. Couchot:** None; **P. Cotty:** None; **D. Mulleman:** None; **P. M. Goupille:** None.

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Malalignment of the Knee Is Associated with an Increased Risk for Incident and Enlarging Subchondral Bone Marrow Lesions in the More Loaded Compartments: The MOST Study. Daichi Hayashi[3], Martin Englund[5], Frank Roemer[4], Jingbo Niu[1], Leena Sharma[6], Neil Segal[9], Cora Lewis[8], David T. Felson[2], Michael C. Nevitt[7] and Ali Guermazi[4]. [1]Boston University, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]Boston University School of Medicine, Boston, MA, [4]Boston University School of Medicine, [5]Lund University, Sweden, [6]Northwestern University, Chicago, IL, [7]UCSF, San Francisco, CA, [8]University of Alabama at Birmingham, [9]University of Iowa

Purpose: Malalignment of the lower limb influences the load distribution across the articular surfaces of the knee joint. We hypothesized that subchondral bone marrow lesions (BML) result from increased mechanical loading. The aim of this study was to assess if malalignment is associated with incident and enlarging BML in the more loaded compartments of the tibiofemoral (TF) joint.

Methods: The Multicenter Osteoarthritis Study (MOST) is an NIH-funded longitudinal observational study of individuals who have or are at high risk for knee OA. Full limb radiographs of both legs were taken at baseline and hip-knee-ankle mechanical axis was measured (varus $<179°$, neutral 179–181° and valgus $>181°$). MRI was performed on a 1.0T extremity system. MR images were assessed semiquantitatively in known order using the WORMS system. BML was scored on a 0–3 scale at baseline and at 30 months in 5 TF regions of the medial and lateral compartment, respectively. Outcome was defined as any increase in BML score, including within-grade change not fulfilling the criteria of a full-grade change. Relative risk of an increase in BML score in the medial and lateral compartments in relation to malalignment was estimated using a log linear regression model with the Poisson assumption. Adjustments were made for age, sex, body mass index and physical activity level. We also combined analyses for the more loaded compartments (i.e. medial BML in varus + lateral BML in valgus knees). In secondary analyses results were stratified by ipsilateral meniscal and cartilage status at baseline (i.e. no meniscal or cartilage pathology; meniscal damage present; cartilage loss present; both meniscal and cartilage pathology present) and also by compartments with or without pre-existing BML (i.e. 'incident' if no BML at baseline or 'enlarging' if pre-existing BML).

Results: 1,782 knees from 1,338 subjects were included (62% women, mean age 62.2 ± 7.9 years, mean BMI 29.9 ± 4.8 kg/m^2). Compared to neutral alignment, baseline varus alignment was associated with increased BML scores in the medial compartment (adjusted RRs [95%CI] 1.8 [1.5–2.3]) and valgus alignment with BML score increases in the lateral compartment (2.4 [1.7–3.4]). Increase in BML score was more likely in the more loaded compartments (2.2 [1.8–2.6]) in malaligned knees compared to neutral knees. After stratification, this association remained in knees with ipsilateral meniscus damage (4.9 [1.1–22.6]), cartilage loss (1.4 [1.1–2.0]), or both (1.6 [1.2–2.0]) but not in knees without any ipsilateral meniscal or cartilage pathology (1.8 [0.9–3.4]). Both incident BML (1.8 [1.4–2.4]) and enlarging BML (1.8 [1.4–2.3]) were more likely to occur in the more loaded compartments in malaligned knees compared to neutral knees.

Conclusion: Knee malalignment is associated with increased risk of incident and enlarging BMLs in the more loaded compartments of the TF joint over 30 months. Further longitudinal studies are needed to explore whether malalignment is a primary trigger of structural damage or a secondary phenomenon due to underlying structural damage. BML may be a

marker of increased mechanical load experienced by overlying cartilage in a compartment-specific manner.

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MRI and X-Ray Measured Changes in Joint Space Narrowing Are Closely Associated in Early RA Patients: A Pilot Study. Siri Lillegraven[2], Pernille Bøyesen[2], Mikkel Østergaard[3], Sølve Sesseng[2], Tore K. Kvien[1] and Espen A. Haavardsholm[2]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]Hvidovre University Hospital, Hvidovre, Denmark

Background: Magnetic Resonance Imaging (MRI) is commonly used to assess erosions, synovitis, tenosynovitis and bone marrow edema in rheumatoid arthritis (RA) patients. During the development of the OMERACT RA MRI score (RAMRIS) joint space narrowing (JSN) was tested, but left out due to insufficient image resolution. However, MRI image quality has now improved, and a MRI JSN score with encouraging inter-reader reliability was presented at the 2010 OMERACT meeting.

Objectives: To investigate the intra- and inter-reader reilability of the OMERACT JSN score in a longitudinal setting, and to assess the association with X-ray changes.

Methods: 10 patients were selected from a cohort of early RA patients (disease duration less than one year at baseline) with 5-year follow-up. The patients were examined by X-ray of both hands and MRI of the dominant wrist (GE Signa 1.5 T MRI scanner). The 10 patients were chosen according to 5-year change of van der Heijde Sharp JSN score (hands only), with two patients selected from the two lowest quartiles, and three patients from each of the two highest quartiles. The MRI images were assessed on coronal T1-weighted sequences by two readers (PB and SL), both familiar with the RAMRIS score and with experience from previous JSN exercises. 18 joint sites in the wrist were scored 0 (no JSN) - 4 (ankylosis/total loss of joint space). The images were assessed twice on consecutive days, with anonymization and randomization between the readings. Intra-class correlation coefficients were calculated for intra-reader (single measures), inter-reader (average measures) reliability and association to X-ray (average measures).

Results: The median (25th percentile, 75th percentile) age was 54 (47, 67) years, disease duration 98 (48, 139) days, 8 were female and 4 were anti-ccp positive. 5-year change in van der Heijde Sharp JSN score ranged from 0 to 20, with a median of 4. Table 1 shows the intra-reader ICCs, inter-reader ICCs and comparison of MRI scorings and X-ray for each reader.

Table 1. Intra-reader ICCs, inter-reader ICCs and comparison of MRI and X-ray JSN score.

	Intra-reader ICC		Inter-reader	MRI vs. X-ray ICC	
	Reader 1	Reader 2	ICC	Reader 1	Reader 2
Baseline	0.60	0.75	0.67	0.68	0.40
5 year	0.87	0.91	0.95	0.85	0.82
Change	0.90	0.97	0.99	0.91	0.94

The figure shows an example patient with x-ray and MRI images.

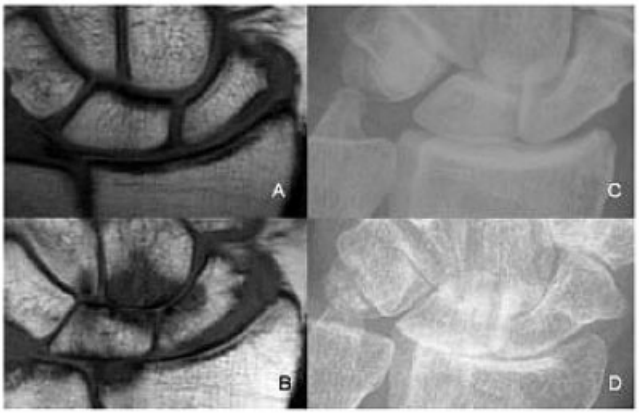

Figure. Patient example with development of JSN at several wrist joints: MRI images from baseline (A) and 5-year follow-up (B) left, X-ray images from baseline (C) and 5-year follow-up (D).

Few of the patients had much change in JSN assessed by MRI, with a median change (range)[25th percentile, 75th percentile] for scorer 1 of 0 (0–30) [0, 1.25] and for scorer 2 1.5 (0 – 28) [0.75, 3.5].

Conclusion: This small study shows promising results for the assessment of JSN on MRI, with strong association between change in JSN on MRI and X-ray. However, these results need to be confirmed in other cohorts, especially including patients with more JSN.

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MRI Bone Edema Is an Independent Predictor of Development of Rheumatoid Arthritis in Patients with Early Undifferentiated Arthritis. Anne Duer-Jensen[7], Kim Hørslev-Petersen[10], Merete L. Hetland[1], Lene Bak[5], Bo J. Ejbjerg[9], Michael S. Hansen[6], Julia S. Johansen[3], Hanne M. Lindegaard[8], Henrik Vinterberg[11], Jakob M. Møller[4] and Mikkel Ostergaard[2]. [1]Copenhagen Univ Hosp Hvidovre and Glostrup, Hvidovre, Denmark, [2]Copenhagen University Hospitals at Hvidovre and Glostrup, Hvidovre, Denmark, [3]Dept of Oncology, Copenhagen University Hospital at Herlev, [4]Dept of Radiology, Copenhagen University Hospital at Herlev, [5]Dept of Radiology, Sygehus Lillebælt, Kolding, [6]Dept of Rheumatology, Copenhagen University Hospital at Gentofte, [7]Dept of Rheumatology, Copenhagen University Hospital at Glostrup and Hvidovre, Denmark, [8]Dept of Rheumatology, Odense University Hospital, [9]Dept of Rheumatology, Slagelse Hospital, [10]King Christian Xth Hospital for Rheumatic Diseases, Gråsten, [11]Rheumatology Clinic, Amagerbrogade, Copenhagen

Objectives: To study magnetic resonance imaging (MRI) as a tool for early diagnosis of rheumatoid arthritis (RA) in patients with early undifferentiated arthritis (UA).

Methods: 116 patients without a specific rheumatological diagnosis, but with ≥2 tender and/or swollen metacarpophalangeal, proximal interphalangeal, wrist or metatarsophalangeal (MTP) joints for >6 weeks but <24 months, underwent clinical, biochemical, conventional radiography and MRI examinations (qualitatively assessed for various pathologies and according to the OMERACT RAMRIS scoring method (CMC1 and MTP1 joints excluded)) and were followed for >12 months for final RA/non-RA diagnosis.

Based on univariate analyses, clinical, biochemical and imaging parameters were selected as explanatory variables in multiple logistic regression analysis with development of RA as dependent variable.

Results: 27 patients (23.3%) developed RA. The gender distribution and median age in the RA/non-RA groups were 81.5/76.4% women and 50 yrs (range 21–80)/47 yrs (19–82), respectively, and the symptom duration 4 mth (2–18)/7 mth (1.5–24). The final prediction model, consisting of presence of hand arthritis, positive rheumatoid factor (RF), morning stiffness >1 hour and OMERACT sum score of bone edema in MTP and wrist joints, correctly identified 82% of patients, who eventually developed RA or not RA (sensitivity/specificity: 81%/82%) (table, model 1). An alternative model (table, model 2), in which OMERACT sum score of bone edema in MTP and wrist joints was replaced by OMERACT sum score of bone edema in MTP, wrist and PIP joints, confirmed bone edema as independent predictor.

Table. Baseline predictors of development of rheumatoid arthritis (logistic regression analysis)

	Model 1			Model 2		
Variable	Coefficient	OR (CI)	p-value	Coefficient	OR (CI)	p-value
Arthritis of the hand	2.367	10.7 (2.9–39.7)	<0.001	2.309	10.1 (2.7–37.4)	0.001
Rheumatoid factor positive	0.881	6.6 (2.0–22.0)	0.001	1.889	6.6 (2.0–21.0)	0.002
> 1 hour of morning stiffness	1.997	7.4 (2.3–24.1)	0.001	1.944	7.0 (2.3–22.9)	0.001
OMERACT bone edema sum score in wrist+MTP joint areas (per unit)	0.365	1.4 (1.0–2.0)	0.035	—	—	—
OMERACT bone edema sum score in wrist+MTP+PIP joint areas (per unit)	—	—	—	0.348	1.4 (1.0–2.0)	0.046

Abbreviations: MTP=met at arsophalangeal, PIP=proximal interphalangeal, OR=Odds Ratio, CI=Confidence interval for OR.

Conclusion: MRI bone edema in MTP and wrist joints is an independent predictor of future RA in patients with early UA. A prediction model,

including clinical hand arthritis, morning stiffness, positive RF and MRI bone edema score in MTP and wrist joints correctly identified the development of RA or non-RA in 82% of patients.

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MRI Inflammation in the Sacroiliac Joints Is Associated with CTX-II and Changes in Systemic Inflammation during TNFα Inhibitor Therapy.

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Objectives: To investigate the relation between inflammation in the sacroiliac joints (SIJ) on magnetic resonance imaging (MRI) and biomarkers of inflammation (C-reactive protein (CRP), interleukin-6 (IL-6), YKL-40), angiogenesis (vascular endothelial growth factor (VEGF)), cartilage turnover (CTX-II, matrix metalloproteinase 3 (MMP3), total aggrecan, cartilage oligomeric matrix protein (COMP)) and bone turnover (CTX-I, total osteocalcin) in patients with axial spondyloarthritis (SpA) treated with TNFα inhibitors.

Methods: Forty-three patients (34 men, 9 women; median age 40 yrs (range 21–62); disease duration 14 yrs (1–45)) initiated treatment with TNFα inhibitors (infliximab (n=31), etanercept (n=9) and adalimumab (n=3)) and were followed for 46 weeks. MR images were evaluated according to the Berlin SIJ inflammation scoring method at baseline, week 22 and 46. Biomarker levels of the patients were compared to these scores and biomarker levels of healthy subjects.

Results: The patients had a pretreatment MRI SIJ score of median 5 (range: 0–23) and SIJ inflammation was seen in 33 (77%) patients. The SIJ scores correlated with CTX-II (rho=0.57, p<0.0001) and COMP (inversely, −0.36, p=0.02), whereas no correlations were seen with the other 8 biomarkers. Compared to patients without pretreatment SIJ inflammation, patients with SIJ inflammation (MRI score ≥1) had higher baseline urine CTX-II levels (median 490 ng/mmol (IQR: 396–766) vs. 245 (128–345), p=0.003), and higher time-integrated mean concentrations of CTX-II from baseline to week 22 (461 ng/mmol (313–665) vs. 311 (185–404), p=0.04) and to week 46 (418 ng/mmol (286–610) vs. 214 (175–306) p=0.009) and lower YKL-40 from baseline to week 46 (41 μg/l (25–62) vs. 69 (46–106), p=0.03). After 22 weeks of anti-TNFα therapy 17 (52%) patients with SIJ inflammation on baseline MRI decreased in score, whereas 16 (48%) patients were unchanged or increased in score. A decrease in SIJ scores after 22 weeks was associated with larger percentage decreases in CRP (-84% (−94;−67) vs. −45% (−65;−18), p=0.008) and IL-6 (−76% (−88;−73) vs. −43% (−84;15), p=0.03) but not with any other biomarker as compared to unchanged/increased SIJ score. CRP and IL-6 frequently normalized after 22 weeks (i.e. CRP ≤8 mg/l and IL-6 ≤3.3 ng/l) in patients with a decrease in SIJ score as compared to patients with unchanged/increased SIJ score (Table 1).

Table 1. Changes in biomarkers of inflammation (CRP and IL-6) versus change in Berlin MRI inflammation score

	SIJ Inflammation score		
Changes from baseline to week 0–22	**Decreased N=17**	**Unchanged/Persistent N=16**	**p-value**
CRP decreased to ≤8 mg/l	12 (71)	5 (29)	
CRP remained >8 mg/l	1 (0)	7 (100)	0.01†
CRP remained ≤8 mg/l	4 (50)	4 (50)	NS§
IL-6 decreased to ≤3.3 ng/l	15 (79)	4 (21)	
IL-6 remained >3.3 ng/l	1 (14)	6 (86)	0.005†
IL-6 remained ≤3.3 ng/l	1 (14)	6 (86)	0.005§

Number (%). Chi² test and Fisher's Exact test. †Normalization vs. persistently increased biomarker levels. §Normalization vs. normal levels at baseline

Conclusion: Inflammation in SIJ on baseline MRI was associated with higher urine levels of the cartilage degradation biomarker CTX-II. Decrease in MRI inflammation during treatment with TNFα inhibitors was associated with decrease in systemic inflammation.

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Quantitative Characterization of Bone Marrow Edema in Patients with Rheumatoid Arthritis.

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Objective: When assessed qualitatively or semi-quantitatively, bone marrow edema (BME) pattern, the hyperintense region within trabecular bone/bone marrow on T2-weighted fat-suppressed magnetic resonance imaging (MRI), predicts radiographic erosion progression in rheumatoid arthritis (RA). The goal of this study was to develop quantitative measures of BME, including volume, signal intensity and perfusion parameters, in the wrist using 3 Tesla (3T) MRI.

Methods and Materials: 10 patients (56.8 ± 12.9 years, 7 females) who fulfilled ACR classification criteria for RA and 3 healthy controls (36.2 ± 17.2 years, 2 females) were recruited. All patients were on disease-modifying anti-rheumatic drugs with (n=2) or without (n=8) biological agents. All MRI data were acquired with a 3T GE Signa scanner using an 8-channel wrist coil. Coronal T2-weighted fast spin-echo (FSE) images (TR/TE=3500/50ms, in plane resolution = 0.2 mm, slice thickness = 2 mm) were acquired using iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL) sequences. Coronal 3D dynamic contrast enhanced images were acquired during Gd-DTPA injection (TR/TE = 6.4/2.1ms, in plane resolution = 0.4 mm, slice thickness = 3 mm, temporal resolution 12 s, 32 time points). A semi-automatic algorithm was developed to segment BME in T2-weighted IDEAL FSE images. Volume, and signal intensity change of BME compared to normal bone marrow (NBM), defined as (SIBME – SINBM)/SINBM, were calculated automatically. Perfusion parameters were calculated based on the signal-time curve obtained from DCE-MRI, including slope (S) = (SImax-SIbase)/(SIbase* Tmax) and maximum enhancement (E) = (SImax-SIbase)/SIbase. Two subjects were scanned twice and coefficients of variation (CV) of BME quantification were calculated for evaluating reproducibility. Spearman correlation coefficients between imaging measures and clinical evaluation (DAS28, ESR, and C-reactive protein, CRP) were calculated. Perfusion measures within BME were compared to outside BME using a paired t-test.

Results: The mean DAS28, ESR and CRP was 3.23 ± 1.43, 18 ± 17 mm/h, and 2.9 ± 2.3 mg/l, respectively. Nine patients had BME. The mean volume and signal intensity change of BME was 0.89 ± 1.05 cm3 and 6.09 ± 1.51, respectively. Quantification of BME volume showed good reproducibility (mean CV 6.9%). The maximum enhancement and slope were significantly higher in BME compared to normal bone marrow (1.5 ± 1.2 vs. 1.1 ± 0.6, p<0.001; 1.8 ± 0.5 vs. 0.9 ± 0.3, p<0.001), indicating increased perfusion in areas of BME. BME quantification did not correlate significantly with DAS28, ESR, or CRP. BME was detected in 3 of the 4 RA patients who had DAS28<2.6.

Conclusions and Discussion: BME quantification using IDEAL sequences was highly reproducible. In this preliminary study, there were discrepancies between BME burden and clinical measures of disease activity, with BME present in the majority of patients in remission by DAS28. Quantifying BME may provide a useful parameter to assess the adequacy of therapeutic response on the

individual patient level. Future work will examine the relationship between BME quantification and disease progression.

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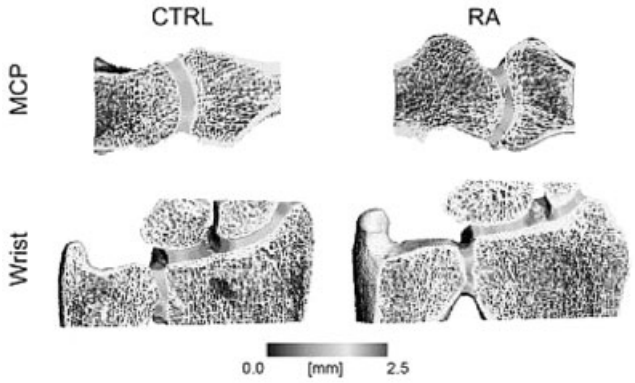
Quantitative In Vivo HR-pQCT Imaging of 3D Radiocarpal and Metacarpophalangeal Joint Space Distances in Rheumatoid Arthritis. Andrew J. Burghardt[2], Christina Kurhanewicz[3], John B. Imboden[1], Sharmila Majumdar[3], Thomas M. Link[3] and Xiaojuan Li[2]. [1]Department of Medicine, University of California, San Francisco and Division of Rheumatology, San Francisco General Hospital, [2]Musculoskeletal Quantitative Imaging Research Group, Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, CA, [3]Musculoskeletal Quantitative Imaging Research Group, Department of Radiology and Biomedical Imaging, University of California, San Francisco

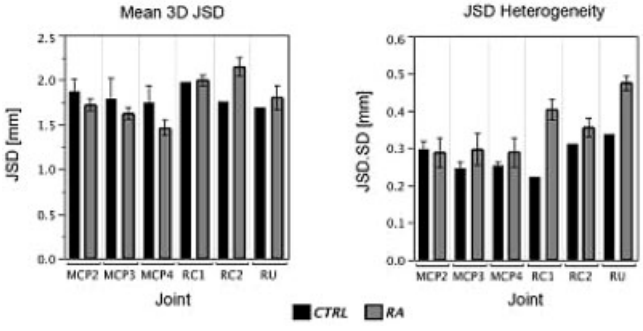
Purpose: In this technique development study, high-resolution peripheral quantitative computed tomography (HR-pQCT) was applied to non-invasively image the radioulnar (RU), radiocarpal (RC) and metacarpophalangeal (MCP) joints of patients with established rheumatoid arthritis (RA). Automated image processing methods were developed to quantify 3D MCP joint space morphology.

Methods: HR-pQCT imaging (82μm isotropic resolution) of the dominant hand was performed in patients with diagnosed rheumatoid arthritis (RA, N=7, age:54±14) and young healthy controls (CTRL, N=2, age:36±17). An automated segmentation technique was developed to individually segment the articulating joint space in the RU, two RC, and the 2nd to 4th MCP joints. The 3D distance transformation approach was applied to spatially map joint space distance and was summarized by the mean joint space distance (JSD) and standard deviation (JSD.SD) – a measure of joint space heterogeneity. The *in vivo* precision for each measure was characterized using root mean square coefficient of variation (RMSCV%) from repeat acquisitions performed on two RA patients.

Results: The *in vivo* reproducibility was high for JSD (RMSCV: 1.3%) and moderate for JSD.SD (RMSCV: 9.4%) despite one repeat measure with substantial motion artifacts. Qualitatively, the HR-pQCT images and JSD maps showed global joint space narrowing as well as focal defects in RA patients compared to CTRL (Fig 1).



In a modest number of subjects there was a general trend for decreased JSD at the MCP and comparable or greater JSD at the radial joints in RA subjects compared to CTRL. Joint space heterogeneity (JSD.SD) all tended to be greater in RA patients compared to CTRL (Fig 2).



Conclusions: This study has established the feasibility of *in vivo* quantification of 3D joint space morphology in RA using HR-pQCT. This technology has the potential to provide a highly resolved, longitudinal assessment of joint morphology, which could provide new insights into clinical research studies of early disease progression and the efficacy of therapeutic interventions.

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Radiographic Severity of Knee Osteoarthritis Predicts Quantitative Bone Marrow Lesions on MRI. Svetlana Krasnokutsky[4], Ravinder Regatte[2], Jenny Bencardino[2], Leon Rybak[2], Ilana Belitskaya-Lévy[2], Jonathan Samuels[1], Mukundan Attur[3] and Steven B. Abramson[4]. [1]New York University Hospital for Joint Disease, New York, NY, [2]NYU Langone Medical Center, [3]NYU Langone Medical Center, NYU Hospital for Joint Diseases, [4]NYU Langone Medical Center, NYU Hospital for Joint Diseases, New York, NY

Objective: To evaluate the relationship of quantitative assessment of Bone Marrow Lesions (BML) with knee OA severity by radiographic findings.

Methods: 58 OA patients (mean age 62±10, mean BMI 27±3, 59% female) underwent standardized nonfluoroscopic fixed-flexion knee radiographs. Two radiologists read the X-rays for KL grade, joint space width (JSW), and, using the OARSI atlas, joint space narrowing (JSN) and osteophytes; inter-reader agreement was assessed using Kappas and concordance correlation coefficients. Linear and logistic regression analysis was performed to assess associations while controlling the effects of age, sex and BMI. 3T-MRI included sagittal T2-weighted fat saturated spin-echo images (TR/TE=4000ms/75ms, FOV=15cm, matrix=256×128, slice thickness=3.0mm, receiver bandwidth 130Hz/pixel) and in/out of phase of FLASH images. Compartment-wise (medial tibial, lateral tibial, medial femur, lateral femur) BML volumes were quantified with T2-weighted fat saturated images and in/out of phase images respectively. BML volumes were dichotomized for statistical analysis.

Results: KL score was a significant predictor of total BML volume (OR = 8.41, p = 0.0235). Medial tibial JSW, OARSI medial JSN, and medial tibial plateau osteophytes approached significance as predictors of BML volume at the medial tibia (OR = 0.71, p = 0.0551; OR = 2.16, p = 0.0597; and OR = 2.68, p = 0.0875, respectively). OARSI lateral JSN was a significant predictor of BML volume at the lateral tibia (OR = 3.62, p = 0.0169). Lateral tibial plateau osteophytes were predictors of total BML volume (OR = 4.58, p = 0.0299) and of BML volume at the lateral tibia (OR = 2.31, p = 0.0685). Lateral femoral condyle osteophytes approached significance as a predictor for BML at the lateral femur (OR = 2.25, p = 0.0651). Furthermore, quantitative BML volume strongly correlated with total quantitative synovial volume measured on MRI (β = 0.22, p = 0.0003).

Conclusions: Our data indicate that BML volume on MRI is a characteristic feature of progressive stages of OA, which not only correlates with JSN and osteophytes, but does so in a compartment-specific way. The data suggest that the altered mechanical forces that promote compartmental disease in OA lead to BML, JSN and osteophyte formation. Whether BML further contribute to cartilage loss, and are therefore targets of therapeutic intervention, remains to be determined.

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REMISSION^{PLUS}: Multicenter Evaluation of Low-Field MRI for Monitoring Treatment Response in Rheumatoid Arthritis Patients. Ben Ostendorf[8], Sabine Kamp[8], Birthe Koerbl[2], Dorothea Reichelt[1], Klaus Strassburger[2], Axel Scherer[1], Sabine Blaschke[9], Edmund Edelmann[6], Ino Gao[7], Gernot Keyβer[11], Hans-Martin Lorenz[5], Ulf Müller-Ladner[10], Hans-Georg Pott[3], Marisa Walther[4] and Matthias Schneider[8]. [1]Department of Radiology, Heinrich-Heine-University Düsseldorf, Düsseldorf, NRW, Germany, [2]German Diabetes Center at the Heinrich-Heine-University Düsseldorf, Leibniz Center for Diabetes Research, Institute of Biometrics and Epidemiology, Düsseldorf, NRW, Germany, [3]Rheumatology Center, Hannover, Hannover, Germany, [4]Rheumatology Clinic, Berlin-Buch, Berlin, Germany, [5]Rheumatology Department, Heidelberg University Hospital, Heidelberg, Germany, [6]Rheumatology Office, Bad Aibling, Bad Aibling, Germany, [7]Rheumatology Office, Heidelberg, Heidelberg, Germany, [8]Rheumatology, Department of Endocrinology, Diabetology and Rheumatology, Rhine-Ruhr Rheumatology Center, Heinrich-Heine-University Düsseldorf, Düsseldorf, NRW, Germany, [9]Rheumatology, Göttingen University Hospital, Göttingen, Germany, [10]Rheumatology, Kerckhoff Clinic, Bad Nauheim, Germany, [11]Rheumatology, Martin Luther University, Halle-Wittenberg, Halle, Germany

Objective: Multicenter evaluation of low-field MRI as a tool for monitoring treatment response in patients with rheumatoid arthritis (RA) on the REMISSION PLUS pilot project.

Methods: RA patients initiating treatment with a DMARD or biologic at 9 sites throughout Germany underwent low-field MRI (C-scan, Esaote, 0.2 T) of the clinically dominant hand at time points T0 (baseline), T1 (3 months) and T2 (6 to 12 months). The images were evaluated semiquantitatively using the RAMRIS scoring system and correlated with clinical and lab chemistry markers.

Results: 206 RA patients (T0), 58 = m, 148 = f, age (years): (mean=55.87, min.19, max. 84), time since diagnosis: (median=20.32 months, min. 0.2 months, max. 45 years), DAS28 (mean = 4.83, 2.1 – 8), rheumatoid factor positive n = 118, CCP antibody positive n = 118, treatment naive: n = 64, switching treatments: n = 187; MRI follow-up at 3 months (T1) and at 6 to 12 months (T2); T0 and T2: n=96; T0, T1 and T2: n=55. RAMRIS (T0-T1-T2): 41.58-29.62-21.91; MCP: 13.31-8.76-6.38; wrist: 28.19-20.74-15.50; synovitis score (MCP): 5.11-3.06-1.60; wrist: 4.47-3.64-2.54; edema score (MCP): 2.85-1.74-0.91; wrist: 10.04-5.60-2.91; erosion score (MCP): 5.35-4.13-3.87; wrist: 13.68-11.49-10.06; SRM (standardized response mean (> 0.5 moderate potential to detect changes)) T0-T2 synovitis: 0.999 (MCP); 0.709 (wrist), edema: 0.702 (MCP); 0.792 (wrist); p-correlations T0-DAS28 for synovitis: 0.010 (MCP); 0.037 (wrist); for edema: 0.507 (MCP); 0.049 (wrist); T0-CRP for synovitis: 0.538 (MCP); 0.276 (wrist); for edema: 0.154 (MCP); 0.011 (wrist).

Conclusions: Low-field MRI is a sensitive imaging method and RAMRIS a practicable scoring system for morphological and semiquantitative evaluation of therapeutic response to real-life rheumatologic care in significant correlation to clinical and lab data. The added benefit of low-field MRI is that it provides in-depth information on the severity of synovitis, edema (significant reduction on treatment) and erosion during follow-up, hence enabling early identification of responders/non-responders and providing a basis for individual prediction of prognosis and optimal disease management.

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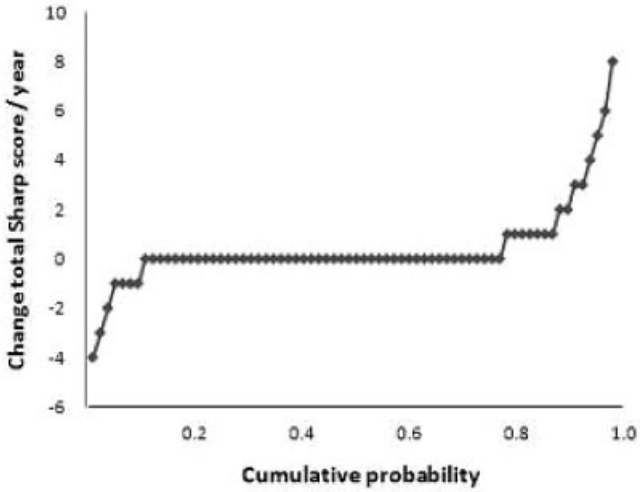
Repair of Bone Erosions in Patients Treated with TNF Antagonists in the Real World. Kaoru Takase[2], Kouji Kobayashi[3], Kayo Terauchi[3], Toshiyuki Watanabe[3], Reikou Watanabe[3], Maasa Hama[3], Rhusuke Yoshimi[3], Hiroshi Kobayashi[3], Atsushi Ihata[3], Atsuhisa Ueda[3], Mitsuhiro Takeno[3], Haruko Ideguchi[1], Shigeru Ohno[1] and Yoshiaki Ishigatsubo[2]. [1]Center for Rheumatic Diseases, Yokohama City University Medical Center, [2]Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan, [3]Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine

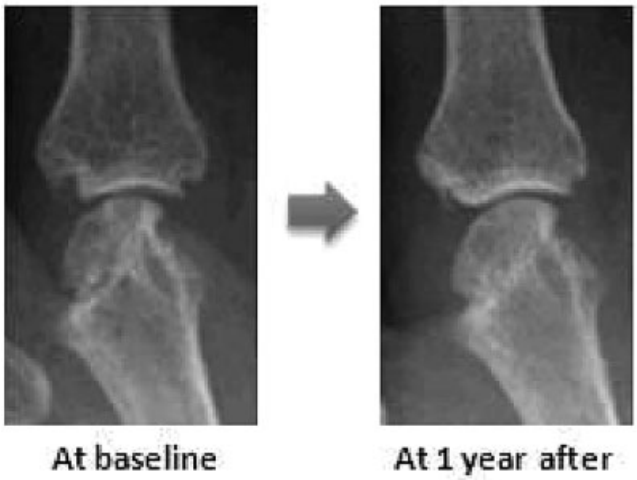
Objectives: A number of clinical studies have shown that TNF antagonists suppress not only clinical symptoms but also the progression of joint destructions in patients with RA. Moreover, the therapeutic effects are accompanied by repair of bone erosions in some patients, though the prevalence is uncertain in the real world. We have previously reported that repair of bone erosions was found in 10.7% of RA patients treated with nonbiologic DMARDs. This study investigated the frequency of repair in RA patients receiving TNF antagonists and characterized clinical features in the patients.

Methods: Seventy RA patients (63 female, 7 male; age range, 28–76 years) who fulfilled the 1987 ACR classification criteria and received TNF antagonists for longer than one year were enrolled in this study. Radiographs of hands and feet were evaluated before the initiation of the TNF antagonists including infliximab, etanercept, and adalimumab, and thereafter annually according to the van der Heijde modified Sharp score. Bone erosion was defined as a discrete interruption of the cortical surface, based on standard plain film radiograph criteria. Evaluators assessed the findings without clinical information and chronological orders of radiographs in the same patient. The patients who had repair of bone erosion in any joints were defined as the repaired group, while the others were into the non-repaired group.

Results: Mean yearly progression of total Sharp score was 0.39 in all subjects. The score was increased in 15, decreased in 7, and unchanged in 48 patients after one year.



Progression of bone erosions in any joints were observed in 10 patients, while 6 patients (8.6%) having repair were categorized into the repaired group. Representative images are shown.



Therapies in the repair group were as follows; etanercept + MTX + PSL 2, etanercept + MTX 1, etanercept + PSL 1, etanercept alone 1, and infliximab + MTX + PSL 1. Three of them were concurrently treated with MTX. There were no differences in Stage, Class, and DAS28 before the initiation of TNF antagonists. The repaired group showed more favorable clinical responses to TNF antagonist therapy compared with the non-repair group. Most patients had a good response according to EULAR criteria. DAS28 was statistically more reduced in the repaired group than that in non-repaired group during the first one year of TNF antagonist therapy ($P<0.05$).

Discussions: The present study showed that repair of bone erosion is associated with good response to treatment with TNF antagonists. Well controlled disease activity is a precondition for structural recovery, irrespective of therapeutic agents.

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Responsiveness to Change and Reliability of Radiographic Joint Space Width in Osteoarthritis of the Knee: A Systematic Review. William M. Reichmann[2], Jean Francis Maillefert[4], David J. Hunter[5], Jeffrey N. Katz[1], Philip G. Conaghan[3] and Elena Losina[2]. [1]Brigham & Womens Hosp, Boston, MA, [2]Brigham and Womens Hospital, Boston, MA, [3]Chapel Allerton Hospital, Leeds, United Kingdom, [4]Dijon University Hospital, Dijon, France, [5]University of Sydney, Boston, MA

Introduction: The quest for disease modifying OA drugs is anchored on the availability of responsive and reliable methods of measuring structural progres-

sion. The goal of this systematic review was to report the responsiveness to change and reliability of joint space width (JSW) measured on conventional knee radiographs.

Methods: We searched the PubMed and Embase databases using the following search criteria: (osteoarthritis [MeSH]) AND (knee) AND (x-ray OR radiography OR diagnostic imaging OR radiology OR disease progression) AND (joint space OR JSW or disease progression). The search was not limited by publication date and the last search occurred in January 2009. We assessed responsiveness by calculating the standardized response mean (SRM), defined as the mean change in JSW divided by the standard deviation of change. An SRM that is greater than 0.4 is considered to have moderate responsiveness. We assessed reliability using intra- and inter-reader intra-class correlation (ICC; higher ICCs indicate more reliable estimates) and coefficient of variation (CV, calculated as standard deviation/mean; higher CVs indicate less reliable estimates). The I-squared statistic was used to assess heterogeneity of study estimates (0=no heterogeneity; 1= complete heterogeneity). Random-effects models were used to pool results from multiple studies. Results were stratified by technique for obtaining radiographs, measurement method, design, and study duration.

Results: 998 articles were identified using the search terms. Of these, 32 articles (43 estimates) reported data on responsiveness and 24 articles (50 estimates) reported data on reliability. For studies assessing responsiveness the I-squared statistic was 0.82, indicating substantial heterogeneity. The overall pooled SRM was 0.33 (95% CI: 0.26, 0.41). Responsiveness to change in JSW was substantially greater in studies of greater than 2 years duration (SRM=0.57; 95% CI: [0.39, 0.75]; see Table). The pooled intra-reader ICC was estimated at 0.97 (95% CI: 0.92, 1.00) and the intra-reader CV at 3.0% (95% CI: 2.0%, 4.0%). The pooled inter-reader ICC was estimated at 0.93 (95% CI: 0.86, 0.99) and the inter-reader CV at 3.4% (95% CI: 1.3%, 5.5%).

Table. Results of random-effects pooling for studies that reported estimates of responsiveness by different study characteristics

	Number of Estimates	Mean Sample Size	Pooled SRM (95% CI)
Overall	43	100	0.33 (0.26, 0.41)
Knee Flexion			
Extended	16	102	0.32 (0.26, 0.37)
Flexed	27	99	0.34 (0.22, 0.45)
Use of Fluoroscopy			
Fluoroscopy used	23	104	0.38 (0.27, 0.48)
Fluoroscopy not used	20	96	0.28 (0.17, 0.39)
Measurement Method			
Manual	18	97	0.38 (0.26, 0.50)
Computerized	24	104	0.31 (0.20, 0.41)
Study Type			
RCT	19	135	0.30 (0.20, 0.40)
Cohort	24	73	0.36 (0.24, 0.49)
Follow-up Time			
1-year or less	21	71	0.24 (0.15, 0.32)
1–2 years	10	144	0.25 (0.13, 0.37)
Greater than 2 years	12	115	0.57 (0.39, 0.75)

Conclusions: There was considerable heterogeneity in estimates of responsiveness to change of quantitative JSW measured on conventional radiographs. Studies of greater than 2 years duration provided the greatest responsiveness, while methods of obtaining and measuring radiographs did not have a large impact on responsiveness. Measurement of radiographic JSW is reliable. These data will be useful in planning RCTs that use change in minimum JSW as the outcome of interest.

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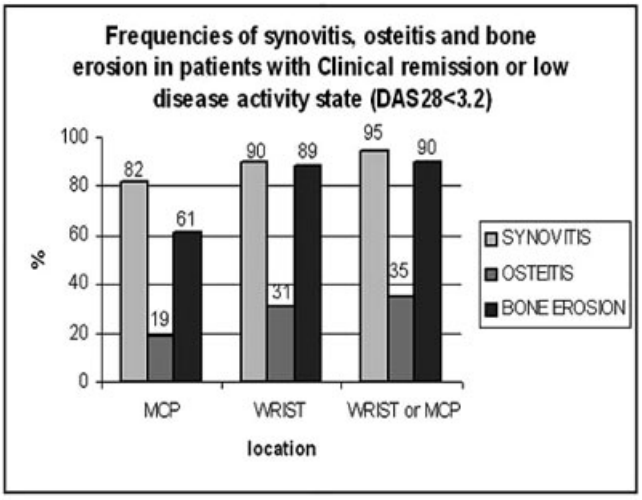
Synovitis and Osteitis Is Very Frequent in Rheumatoid Arthritis (RA) Patients in Clinical Remission: Results from a MRI Study of 300 RA Patients in Clinical Remission or Low Disease Activity State. Frederique Gandjbakhch[5], Philip G. Conaghan[12], Bo Ejbjerg[2], Espen Haavardsholm[3], Violaine Foltz[6], Andrew Brown[12], Uffe Moller Dohn[11], Marissa Lassere[9], Jane Freeston[12], Pernille Bøyesen[3], Paul Bird[4], Bruno Fautrel[6], Merete Lund Hetland[2], Paul Emery[1], Pierre Bourgeois[6], Kim Hørslev-Petersen[8], Tore Kvien[3], Fiona M. McQueen[10] and Mikkel Østergaard[7] [1]Chapel Allerton Hospital, Leeds, United Kingdom, [2]Copenhagen University Hospitals at Hvidovre and Glostrup, Denmark, [3]Diakonhjemmet Hospital, University of Oslo, Oslo, Norway, [4]Division of Medicine, University of NSW, Sydney Australia, [5]Hôpital Pitié-Salpétrière, Université PARIS VI - UPMC, Paris, France, [6]Hôpital Pitié-Salpétrière, Université PARIS VI-UPMC, Paris, France, [7]Hvidovre University Hospital, Hvidovre, Denmark, [8]King Christian X's Hospital for Rheumatic Diseases, University of Southern Denmark, [9]St. George Hospital, University of NSW, Sydney, Australia, [10]Univ of Auckland Sch of Med, Auckland, New Zealand, [11]University Hospitals at Hvidovre and Glostrup, Denmark, [12]University of Leeds, Leeds, UK

Background: The OMERACT rheumatoid arthritis magnetic resonance imaging score (RAMRIS) has been validated for RA monitoring and has been demonstrated to be reliable, sensitive to change and discriminative. Structural progression may occur despite clinical remission. However, remission and low disease activity (LDA) are defined on clinical criteria, and MRI may reveal subclinical inflammation.

Objective: To determine MRI characteristics of RA patients in clinical remission or LDA state.

Materials and Methods: Databases issued from 6 different cohorts were collected from 5 centres. RA patients in clinical remission or LDA state (defined as DAS28-CRP < 3.2) with available MRI data were included. MRIs were assessed according to RAMRIS. Data were analysed using SAS software, version 9.1.

Results: 300 patients in clinical remission (219 patients) or LDA state (81 patients) were included. Patient characteristics: 69% female, age: median 55(IQR 43–63) years, disease duration 2.4(0.7–5.1) years, DAS28-CRP 2.2(1.7–2.6), SDAI: 3.9(1.9–6.5), CDAI: 3.1(1.5– 5.8), RF/anti-CCP positivity: 56%/54%, presence of radiographic erosions: 67 %. Wrist and MCP-MRI data were available for 287 patients and 247 patients respectively. MRI inflammatory activity was observed in the majority of patients, as synovitis and bone edema (osteitis) were observed in wrist or MCP joints in 95 % and 35% of the patients, respectively (figure1). The median (IQR) RAMRIS score for synovitis was 6(3–9) and for osteitis was 0(0–2).



The occurrence of synovitis and bone edema was not significantly different between patients in DAS28-clinical remission (synovitis/osteitis 96%/35%) and patients in LDA but not remission (synovitis/osteitis 91%/36%)(p=0.15/0.87). A trend towards lower frequencies of synovitis and osteitis in patients fulfilling more stringent remission criteria (SDAI and CDAI) was observed (data not shown).

Conclusion: Subclinical inflammation was revealed by MRI in the majority of RA patients in clinical remission or LDA state. This may explain structural progression in such patients. It should be considered whether future remission criteria should include modern imaging.

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The Intra- and Inter-Reader Reliability of the Oslo Hand Osteoarthritis (HOA) Magnetic Resonance Imaging (MRI) Score. Ida Kristin Haugen[2], Siri Lillegraven[2], Barbara Slatkowsky-Christensen[2], Espen Haavardsholm[2], Sølve Sesseng[2], Tore K. Kvien[1], Desiree M. Van Der Heijde[3] and Pernille Bøyesen[2]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Diakonhjemmet Hospital, [3]Leiden University Medical Center, Meerssen, The Netherlands

Background: HOA is increasingly recognized to involve the whole joint, incl. articular cartilage, subchondral bone, synovium, capsule and ligaments. MRI has a unique advantage to depict all joint components, and may be useful in evaluation of emerging treatments.

Objectives: To examine if pathological HOA features can be reliably assessed by testing the intra- and inter-reader reliability of the proposed Oslo HOA MRI score [1].

Methods: The exercise was performed using MRI scans from 10 patients (9 women) with mean (SD) age of 69.5 (6.1) years from the Oslo HOA cohort [2]. The patients were selected from quintiles of radiographic severity. The dominant hand was anchored in a cylindrical coil (diameter 100 mm), and the distal (DIP) and proximal interphalangeal (PIP) joints of the 2nd-5th fingers were examined using a high-field extremity MRI unit (1.0 T). Coronal, sagittal and axial T1w fat-suppressed pre-and postgadolinium images were reproduced from a 3D dual echo Dixon technique (TR 20 ms, TE 5 ms, 1 mm slice thickness), in addition to coronal and axial Short T1 Inversion Recovery (STIR) images (TR 2850/3150 ms, TE 16.3/21 ms, 2/3 mm slice thickness). A training session and two exercises were arranged prior to this study. The images were read by three assessors (IKH, SL, PB) in accordance to the proposed MRI score of the DIP and PIP joints in HOA: Synovitis (grade 0–3), flexor tenosynovitis (grade 0–3), erosions (grade 0–3), cysts (grade 0–1), osteophytes (OP) (grade 0–3), joint space narrowing (JSN) (grade 0–3), malalignment (grade 0–1 in frontal and sagittal plane), bone marrow lesions (BML) (grade 0–3) and collateral ligament (CL) presence (grade 0–1), and BML at CL insertion sites (grade 0–1). The readers were blinded for patient characteristics. The images were read twice with one week interval, and were anonymised and rearranged prior to the last scoring session. Mean scores for all features across the three readers were calculated. The intra- and inter-reader reliability of the individual subscales was assessed by intra-class correlation coefficients (ICCs) (two way mixed effect model, single and average measure).

Results: Table shows mean (min, max) scores and ICCs for intra- and inter-reader reliability. The range of each feature is reported in brackets. Inter-reader reliability was good to excellent for synovitis, tenosynovitis, erosions, OP, JSN, malalignment, BML and CL presence. The median intra-reader reliability was good to excellent for most features except synovitis, tenosynovitis and cysts.

Table

DIP and PIP joints	Mean (min, max)	Inter-reader AvmICC	Intra-reader SmICC median (min, max)
Synovitis [0–24]	11.6 (6.3–15.0)	0.84	0.48 (0.09–0.70)
Flexor tenosynovitis [0–24]	5.9 (1.7–10.3)	0.64	0.51 (0.49–0.65)
Erosions [0–48]	13.1 (2.3–29.0)	0.94	0.92 (0.91–0.96)
Cysts [0–16]	0.4 (0.0–2.0)	0.59	0.21 (0.00–0.57)
Osteophytes [0–48]	22.7 (7.3–34.0)	0.91	0.88 (0.86–0.89)
Joint space narrowing [0–24]	10.8 (0.7–15.3	0.99	0.97 (0.93–0.99)
Malalignment frontal [0–8]	0.9 (0.0–2.3)	0.95	0.79 (0.77–1.00)
Malalignment sagittal [0–8]	0.0 (0.0–0.3)	0.00	*
BMLs [0–48]	4.2 (0.3–9.7)	0.83	0.89 (0.65–0.89)
CL presence [0–16]	10.0 (3.0–14.3)	0.79	0.81 (0.61, 0.81)
BML at CL insertion sites [0–32]	2.4 (0.0–5.0)	0.42	0.81 (−0.07,0.82)

AvmICC=Average measure ICC, SmICC=single measure ICC, BMLs=bone marrow lesions, CL=collateral ligaments, *=no variance

Conclusion: The proposed Oslo HOA MRI score could reliably assess key features of HOA. Further validation of the system to clinical and radiological findings should be performed.

References:
1. Haugen IK. Abstract EULAR 2010
2. Slatkowsky-Christensen B. A&R 2007

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Validity and Responsiveness to Change of Radiograph-Based Joint Space Narrowing Metric Measurement: A Systematic Review. Delphine Chu Miow Lin[6], William M. Reichmann[2], Laure Gossec[4], Elena Losina[1], Philip G. Conaghan[5] and Jean-Francis Maillefert[3]. [1]Department of Orthopaedic Surgery, Brigham and Women's Hospital, Boston, MA, [2]Department of Orthopaedic Surgery, Brigham and Women's Hospital, Boston, MA and 3. Department of Biostatistics, Boston University School of Public Health, Boston, MA, [3]Department of Rheumatology, Dijon University Hospital, Dijon, F-21078, France, University of Burgundy, Dijon, F-21079, France, INSERM U887, Dijon, F-21079, France, [4]Paris Descartes University, Medicine Faculty; UPRES-EA 4058; APHP, Rheumatology B Department, Cochin Hospital, Paris France, [5]Section of Musculoskeletal Disease, University of Leeds & NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK, [6]Tours Medicine Faculty; Department of Rheumatology, Tours University Hospital, Tours, France

Introduction: The quest for disease modifying Osteoarthritis (OA) drugs is anchored on the availability of responsive and reliable methods of measuring structural progression. The goal of this systematic review was to report the responsiveness to change and reliability of conventional hip radiographic joint space width (JSW). We performed a systematic analysis of the literature on the concurrent validity, predictive validity and responsiveness of radiographic metric measurement of coxo-femoral joint space in hip OA.

Method: We searched studies reporting any data on 1- hip OA patients in whom a metric measurement of the coxo-femoral JSW on X-rays was performed and 2- on correlations with clinical symptoms and/or with further symptomatic state, joint space loss or joint replacement, and/or JSW change over time. We searched the PubMed and Embase databases using the following search terms ((Osteoarthritis[MeSH] and (hip)) AND (x-ray OR radiography OR diagnostic imaging OR radiology OR disease progression) AND (joint space OR JSW OR disease progression). Pooled SRM were evaluated using data obtained in articles in which the SRM were available or could be calculated from the mean change and standard deviation of change. For randomized clinical trials (RCTs), only the placebo arms were entered. Pooled SRMs were obtained for minimum JSW metric measurement. Additional analyses restricted to cohorts and RCTs, to intention to treat (ITT) and completer analyses, to measurement of joint space performed with manual and computer-based methods, were performed.

Results: Twenty four studies were identified. Five suggested an association between JSW and symptoms in the general population. Two evaluated the correlations between the coxofemoral JSW and symptoms in hip OA patients, with heterogeneous results. Two suggested that joint symptoms are moderately correlated to further joint space loss. Five demonstrated that minimal JSW is predictive of further hip joint replacement. Responsiveness (11 studies, see table) was good, but tended to be lower in randomized clinical trials than in cohort studies, using an intention to treat rather than a completer analysis, and using computer-based rather than manual measurement.

Table. Summary of hip responsiveness from radiographs using random-effects pooling of the standardized response mean (SRM) of the minimum joint space narrowing.

Analysis	Number of Studies	Mean Sample Size	SRM	95% Confidence Interval
Overall	11	164	0.66	0.41–0.91
Study design				
RCT	4	111	0.35	0.12–0.57
Cohort	7	194	0.83	0.49–1.16
Analysis				
Completers	8	176	0.80	0.50–1.10
ITT	3	132	0.30	0.06–0.55
Measurement Technique				
Computer	4	40	1.12	0.64–1.59
Manual	7	234	0.47	0.31–0.62

RCT = randomized controlled trial, ITT = intention-to-treat

Conclusion: There is some evidence of a weak association with symptoms and evidence of at least moderate responsiveness of metric measurement of JSW and symptoms in hip OA.

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ACR Poster Session A
Metabolic and Crystal Arthropathies—Therapeutics and Outcomes I
Monday, November 8, 2010, 9:00 AM–6:00 PM

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A Single Cohort, Dose Escalation Phase 1 Study of Intravenous Infusion of Pegsiticase (Formerly Uricase-PEG 20), a Drug for Managing Hyperuricemia in Refractory Gout. Tony Fiorino[3], Alan J. Kivitz[1], Patricia Pardo[5], Rocelle Flores[2], Zhihua Zhang[2] and John S. Bomalaski[4]. [1]Altoona Arthritis & Osteo Ctr, Duncansville, PA, [2]EnzymeRx, [3]EnzymeRx, Paramus, NJ, [4]EnzymeRx, Wayne, PA, [5]Miami Research Associates, Miami, FL

Background: The enzyme uricase, found in most mammals but not humans, metabolizes uric acid into the highly soluble allantoin and represents a potential treatment for patients suffering from tophaceous and refractory gout. As a foreign protein, uricase is highly immunogenic and not suited for

chronic use. Pegsiticase is a pegylated recombinant uricase designed to have an extended half life and reduced that has been previously studied as a single intramuscular dose in a phase 1 study in gout patients. It has not yet been studied as an intravenous agent.

Methods: This was an open label, single dose escalation phase 1 study in healthy volunteers and gout patients. Subjects of age 40–75 with screening plasma uric acid ≥ 6 mg/dL for men and ≥5 mg/dL for women were eligible to participate. The study enrolled five cohorts (4 subjects per cohort) at doses of 0.05, 0.1, 0.2, 0.3, and 0.4 mg/kg, respectively. Pegsiticase was administered via intravenous infusion over one hour without premedication, and subjects were followed for 24 days. The primary endpoint was safety and tolerability and the secondary endpoints were pharmacodynamics (plasma uric acid), and pharmacokinetics (serum uricase activity). Adverse events were graded according to the Common Toxicity Criteria for Rheumatology, version 2.0.

Results: Pegsiticase was well tolerated in this study. No serious or grade 3 adverse events were observed, and no infusion or allergic reactions were observed in any subjects. The only observed grade 2 toxicities were gout flares. Plasma uric acid level decreased upon infusion of pegsiticase, with the rate of uric acid decrease exhibiting dose-dependence At 0.05 mg/kg, uric acid levels decreased from a baseline of 8.3 mg/dL to almost undetectable levels within 24 hours of the infusion, whereas at the highest dose (0.4 mg/dL), plasma uric acid decreased from a mean of 7.8 mg/dL to undetectable levels within 3 hours. All subjects responded to pegsiticase, and the duration of uric acid suppression below 2 mg/dL ranged from 7 to 24 days, in a dose-dependent manner. In the highest dose cohort, all four subjects maintained plasma uric acid at or near the limit of detection for the entire 24 day follow-up period.

Conclusions: A single intravenous infusion of pegsiticase was safe and well-tolerated in these 20 subjects, and was capable of profoundly suppressing uric acid levels for up to 24 days. Further study of intravenous pegsiticase as a chronic therapy in gout patients is warranted.

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Canakinumab (ACZ885) Relieves Pain and Controls Inflammation Rapidly in Patients with Difficult-To-Treat Gouty Arthritis: Comparison with Triamcinolone Acetonide. A. So[6], M. De Meulemeester[4], A. Pikhlak[2], A. E. Yücel[1], U. Arulmani[3], D. Richard[3], V. Murphy[3], P. Sallstig[3] and N. Schlesinger[5]. [1]Baskent University, Ankara, Turkey, [2]Moscow State University of Medicine and Dentistry, Moscow, Russian Federation, [3]Novartis Pharma AG, Basel, Switzerland, [4]Private Practice, Gozée, Belgium, [5]UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, [6]University of Lausanne, Lausanne, Switzerland

Purpose: Monosodium urate (MSU) crystals stimulate the production of interleukin (IL)-1β, a potent inflammatory cytokine. Targeted IL-1β blockade with canakinumab, a fully human monoclonal anti-IL-1β antibody, is a novel treatment for gouty arthritis. Its effects on pain and inflammation in acute gouty arthritis flares were compared with triamcinolone acetonide (TA). TA has been shown to be effective in the treatment of acute gouty arthritis flares[1].

Methods: This was an 8-week, dose-ranging, multicenter, blinded, active-controlled trial. Patients ≥18 to ≤80 years with an acute gouty arthritis flare, refractory to or contraindicated to NSAIDs and/or colchicine were randomized to 1 subcutaneous dose of canakinumab (10, 25, 50, 90, or 150 mg; n=143) or 1 intramuscular dose of TA (40 mg; n=57). Primary outcome was pain intensity at 72 hours post dose on VAS scale (0–100 mm). Secondary outcomes included C-reactive protein (CRP), serum amyloid A (SAA), and physician's assessment of tenderness, swelling and erythema of target joint at 72 hours, 7 days, 4- and 8-weeks post dose.

Results: 191/200 patients completed the study. Canakinumab showed a statistically significant dose response at 72 hours. The 150 mg dose group reached superior pain relief compared to TA group starting from 24 hours as previously reported[2]. At 72 hours post dose, 78% of canakinumab 150 mg treated patients achieved ≥75% and 96% achieved ≥50% reduction in pain from baseline. In contrast, 45% and 61% of patients treated with TA achieved ≥75% and ≥50% pain reduction, respectively. Median CRP/SAA levels were normalized by Day 7 for all canakinumab doses above 10 mg and remained below the Upper Limit of Normal [(ULN): CRP 3.0 mg/L; SAA 6.7 mg/L)] for rest of the study. In TA group, median CRP levels remained above the ULN throughout the study while median SAA levels decreased below ULN only 28 days after first dose. At 72 hours post dose, canakinumab 150 mg group was 3.2 (95% CI, 1.27–7.89) times more likely to have less joint tenderness and 2.7 (95% CI, 1.09–6.5) times more likely to have less joint swelling than TA group ($p<0.05$). At 72 hours post dose, erythema disappeared in 74.1% of patients receiving canakinumab 150 mg and 69.6% of patients receiving TA. At 7 days post dose, erythema was absent in 96.3% of canakinumab 150 mg treated patients vs. 83.9% of patients receiving TA. The overall incidence of AEs was similar for canakinumab (41%) and triamcinolone acetonide (42%). Serious AEs (canakinumab treatment groups n=4, TA n=1) were not considered treatment related by investigators. No discontinuations occurred due to AEs.

Conclusions: Canakinumab 150 mg provided superior pain relief compared to TA for acute flares in difficult-to-treat gouty arthritis patients. Canakinumab provided rapid normalization of markers of inflammation accompanied by reduction of clinical signs and symptoms of inflammation.

Reference:

1. Alloway et al. J Rheumatol 1993;20:111–3; 2. So et al. Arthritis Rheum 2010. DOI 10.1002/art.27600

Disclosure: A. So: Abbott Laboratories, 5, Bristol-Myers Squibb, 5, Essex, 5, MSD, 5, Novartis Pharma AG, 5, Pfizer Inc, 5, Roche, 5, UBC, 5, Wyeth Pharmaceuticals, 5; **M. De Meulemeester:** None; **A. Pikhlak:** Novartis Pharma AG, 2; **A. E. Yücel:** None; **U. Arulmani:** Novartis Pharma AG, 1, 3; **D. Richard:** Novartis Pharma AG, 1, 3; **V. Murphy:** Novartis Pharma AG, 1, 3; **P. Sallstig:** Novartis Pharma AG, 1, 3; **N. Schlesinger:** EnzymeRx, 8, 9, Novartis Pharmaceuticals Corporation, 2, 5, 9, Savient Pharmaceuticals, 9, Takeda, 8, 9, URL Pharma, 9.

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Change in Uric Acid Level Is Associated with Change in Patient Reported Outcomes in the Context of a Clinical Trial for Chronic Gout. Will Taylor[1], Steve Hamburger[2], Lisa K. Stamp[5], Zebulun D. Horowitz[3] and Nicola Dalbeth[4]. [1]Department of Medicine, University of Otago Christchurch, New Zealand, [2]Savient Pharmaceuticals, Inc., E. Brunswick NJ, [3]Savient Pharmaceuticals, Inc., E. Brunswick NJ, Baskingridge, NJ, [4]Univ Auckland, Auckland, New Zealand, [5]University of Otago Christchurch, Christchurch, New Zealand

Background: Serum uric acid (SUA) is an important endpoint for clinical trials of gout therapy. It is strongly endorsed by rheumatologists as the most important indicator of response in the context of a clinical trial for chronic gout. It fulfils most of the OMERACT biomarker criteria as a biomarker for patient reported outcomes (PRO), except that change in SUA has never been shown to be independently associated with change in PRO.

Methods: Data from 2 replicate Phase 3 randomised controlled trials of pegloticase were analysed for the association between change in uric acid levels from baseline to final follow-up (6 months) and change in PRO scores (pain, patient global, HAQ-DI, SF-36 MCS and SF-36 PCS). In this study, plasma uric acid levels were measured (PUA). For each PRO, a linear regression model was developed that incorporated final value of PUA, age and sex and a separate model that incorporated the change in PUA, age and sex. Change and final value of PUA were not incorporated together in the same model because of collinearity (correlation - 0.815).

Results: Change in PUA and also final value of PUA was significantly associated with changes in all PRO except the mental health summary score of SF-36. The magnitude of the beta coefficients for change and final value in PUA were similar. The magnitude of the association is weak.

Table 1. Regression models for each PRO by change in PUA and final PUA (all models adjusted for age and sex)

	p-value	Beta coefficient	Overall model r^2
As a predictor of ΔHAQ-DI			
Change in PUA	0.012	0.201	0.055
6 month PUA	0.002	−0.25	0.074
As a predictor of Δpatient global			
Change in PUA	<0.001	−0.299	0.096
6 month PUA	<0.001	0.357	0.129
As a predictor of Δpain			
Change in PUA	0.041	0.164	0.027
6 month PUA	0.004	−0.233	0.051
As a predictor of ΔSF36-PCS			
Change in PUA	0.002	0.247	0.078
6 month PUA	0.003	−0.236	0.070
As a predictor of ΔSF36-MCS			
Change in PUA	0.921	0.008	0.055
6 month PUA	0.702	−0.031	0.056

Conclusion: Although weak, the association of changes in PUA with changes in PRO help confirm that uric acid is a valid biomarker for outcomes of direct relevance for people with chronic gout.

Disclosure: W. Taylor: None; **S. Hamburger:** Savient Pharmaceuticals, 3; **L. K. Stamp:** None; **Z. D. Horowitz:** None; **N. Dalbeth:** None.

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Chronologic Age, Renal Function, and Comorbid Conditions (Physiologic Age) of Patients with Gout Did Not Increase Likelihood of Adverse Events (AEs): AGREE Study Post Hoc Analyses. Daniel E. Furst[1], Paul Maranian[1], Matthew W. Davis[3], Suman Wason[3], Dinesh Khanna[1] and Robert Terkeltaub[2]. [1]University of California Los Angeles, Los Angeles, CA, [2]University of California San Diego, San Diego, CA, [3]URL Pharma, Inc, Philadelphia, PA

Background: Typical patients with gout have multiple comorbidities such as metabolic and cardiovascular (CV) disorders, hypertension, and kidney disease; concern for these conditions can make gout treatment conditions complex. This post hoc analysis was conducted to examine the relationship of age and comorbidities (renal, hepatic, CV function, and body mass index [BMI]) on the adverse event (AE) profile of patients with acute gout who were treated with colchicine.

Methods: A phase 3 multicenter, randomized placebo-controlled trial (AGREE) compared safety and tolerability of 2 different colchicine regimens, low dose (2 × 0.6 mg initially, then 0.6 mg 1 hr later to 1.8 mg/day total) and high dose (2 × 0.6 mg initially, then 0.6 mg/hr to 4.8 mg/day total) versus placebo in patients with gout (N = 185). Data were pooled for the low-dose and high-dose groups. For the present analyses, logistic regression was undertaken using presence or absence of AEs as the dependent variable and the following as independent variables: creatinine clearance (≥60 mL/min); alanine aminotransferase and aspartate aminotransferase ([ALT, AST] above upper limit of normal [ULN]); albumin (≤3.5 g/L); alkaline phosphatase (>ULN); gout duration (years); BMI (>30); age (years); and presence or absence of CV history (eg, myocardial infarction, CV or cerebrovascular illness). Odds ratios (OR) were reported and compared. A Pearson chi-square P value <0.05 was used as the measure of statistical significance.

Results: At baseline, patients had a mean age of 51.5 (standard deviation [SD] = 11.1) years, with a diagnosed gout duration of 10.5 (SD = 8.9) years, a BMI of 33.0 (SD = 5.7), and serum uric acid level of 8.8 (SD = 1.8) mg/dL, and had experienced ≥2 acute gout flares in the 12 months before enrollment. Across the study, 83 patients (~45%) experienced an AE; most of these were mild to moderate gastrointestinal AEs (~73%). Incidence of AEs in patients treated with colchicine was not significantly affected by any of the independent variables analyzed in this study (Table). Additional sensitivity analyses using cutoffs of 3 × ULN for AST (n = 0), ALT (n = 0), and alkaline phosphatase (n = 1), and 3.0 g/L for albumin (n = 0), were not performed because numbers of patients meeting these criteria were negligible.

Table

Independent baseline variables analyzed	Patients, n (%)	Odds ratio	95% Confidence interval	*P* value
Age (continuous)	185 (100.0)	1.00	0.97, 1.03	0.999
BMI >30	125 (67.6)	1.22	0.63, 2.37	0.548
Gout duration >8 years	91 (49.2)	1.24	0.68, 2.25	0.476
Cardiovascular history (yes/no)	107 (57.8)	1.13	0.60, 2.10	0.707
Creatinine clearance ≥60 mL/min	161 (87.0)	0.87	0.34, 2.22	0.778
AST > ULN	12 (6.5)	1.19	0.31, 4.61	0.805
ALT > ULN	31 (16.8)	0.57	0.23, 1.44	0.236
Albumin ≤3.5 g/L	0	—	—	—
Alkaline phosphatase > ULN	2 (1.1)	1.04	0.06, 19.01	0.976

Conclusions: In these regression analyses of 185 patients with gout in a randomized phase 3 study, there was no effect of chronologic age, gout duration, renal function (indicated by creatinine clearance), liver function (as assessed by AST, ALT, albumin, and alkaline phosphatase), presence of CV history, or obesity with the incidence of AEs following colchicine treatment (inclusive of all doses). Although additional studies would be needed to corroborate these results, these data offer reassurance regarding the safety of colchicine in patients with several comorbid conditions.

Disclosure: D. E. Furst: None; **P. Maranian:** None; **M. W. Davis:** URL Pharma, 1, 3, 9; **S. Wason:** URL Pharma, 1, 3; **D. Khanna:** Savient Pharmaceuticals, 2, 5, Takeda Pharmaceuticals North America, 8; **R. Terkeltaub:** BioCryst, 5, Celgene, 5, Novartis Pharmaceuticals Corporation, 5, Pfizer Inc, 5, Regeneron Pharmaceuticals, Inc., 5, Savient Pharmaceuticals, 5, Takeda Pharmaceuticals North America, 5, UCB, Inc., 5, URL Pharma, 5.

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Colchicine Use Is Associated with Decreased Diagnosis of Myocardial Infarction (MI) and Trend toward Reduction of All-Cause Mortality and C-Reactive Protein (CRP) Levels: Insights from the NY VA Gout Cohort. Aaron Lehmann[5], Laura Schneck[5], Robert T. Keenan[2], William O'Brien[6], Daria B. Crittenden[6], Kristen Lee[6], Rekha Tadoori[6], Jeffrey D. Greenberg[1], Bruce N. Cronstein[3], Steven Sedlis[4] and Michael H. Pillinger[5]. [1]Millburn, NJ, [2]Duke University, Durham, NC, [3]New York Univ Med Ctr, New York, NY, [4]NYU Langone Medical Center, [5]NYU Langone Medical Center, NYU Hospital for Joint Diseases, New York, NY, [6]NYU Langone Medical Center, NYU Hospital for Joint Diseases

Statement of Purpose: Inflammatory mechanisms contribute to the pathogenesis of cardiovascular (CV) disease, and some drugs that reduce CV risk (ex, statins) also reduce inflammatory markers such as CRP. Patients with some chronic inflammatory diseases (ex, rheumatoid arthritis) have increased CV risk that may improve with immune modulation. Gout is a chronic/intermittent inflammatory condition driven by hyperuricemia and uric acid crystal formation, and associated in some studies with increased CV risk. Gout is frequently managed with colchicine, an agent that modulates inflammatory mechanisms of potential relevance to CV disease (leukocyte adhesion molecules expression, IL-1 expression, etc), including lowering CRP even in patients without gout. We tested whether colchicine use alters MI rate, all-cause mortality and CRP levels among patients with gout.

Methods: Using the electronic medical record system (EMR) of the New York Harbor Healthcare System (N=40,107), we identified all patients receiving an ICD-9 gout code at the Manhattan, Brooklyn and St Albans Veterans Affairs Hospitals in New York City between August 2007 and August 2008. Demographics, cardiovascular co-morbidities and endpoints were collected by chart review, including review of each patient's EMR problem list and note review as appropriate. Primary (MI) and secondary (all-cause mortality, CRP level) outcomes were analyzed based on presence/absence of colchicine use. Using ICD-9 codes, patients with osteoarthritis (OA) but no gout were identified to serve as controls for the first phase of the study.

Results: 1,288 gout patients were identified, and 1,288 patients with OA/no gout were randomly selected from among 3,300 to serve as controls. OA and Gout patients were similar in mean age (71 each group) and other demographics, but gout patients had more CV disease (23 vs 31%) and all-cause mortality (2 vs 4.5%), consistent with reports that gout conveys increased CV risk. Gout patients were then divided according to ever or never use of colchicine. Colchicine (N=576) and no colchicine (N=712) groups were similar in age, sex, race, BMI, HTN, blood pressure, smoking, diabetes, kidney disease, hyperlipidemia, peripheral vascular disease, stroke, and serum uric acid. Incidence of MI diagnosis was 2.6% in the no colchicine vs 1.2% in the colchicine group (p=0.04, Fisher's exact test). All-cause mortality rates were 5% (no colchicine) vs 3.9% (colchicine) (n.s.). CRP levels were 4.53 (no colchicine) vs 2.49 (colchicine) mg/dl (n.s.). Use of allopurinol was not associated with reduced MI in either group.

Conclusion: In this retrospective study, gout patients ever vs never treated with colchicine had similar rates of atherosclerosis and fixed cardiovascular disease. Nonetheless, gout patients treated with colchicine demonstrated decreased diagnosis of MI, and trends toward lower CRP levels and all-cause mortality. These data suggest a possible protective effect of colchicine on the incidence of acute coronary syndromes.

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Effect of Multiple Doses of Febuxostat on the Pharmacokinetics of a Single Dose of Theophylline. Max Tsai, Jingtao Wu, Lhanoo Gunawardhana and Himanshu Naik. Takeda Global Research & Development Center, Inc., Deerfield, IL

Background: Theophylline is metabolized by cytochrome P-450 (CYP) to 1-methylxanthine, 3-methylxanthine, and 1, 3-dimethyluric acid. Further,

metabolism of 1-methylxanthine to 1-methyluric acid is mediated by xanthine oxidase (XO). Febuxostat is not expected to have any inhibitory effect on the CYP isozymes involved in metabolism of theophylline. However, since febuxostat is a nonpurine selective inhibitor of XO, it could affect the XO-mediated metabolism of theophylline and potentially alter the clearance of theophylline. Since theophylline is a low therapeutic index drug and coadministration with high doses of the XO inhibitor allopurinol results in decreased clearance of theophylline, this study was performed to evaluate the effect of febuxostat and its metabolites at steady-state on the pharmacokinetics of theophylline.

Methods: This was a Phase 1, double-blind, randomized, 2-period crossover study. Twenty-four subjects (12 male and 12 female) were enrolled in the study and were randomly assigned in a 1:1 ratio to receive febuxostat or matching placebo for 7 days. On Day 5 of each period, 400 mg of theophylline was administered followed by collection of plasma and urine pharmacokinetic samples until 72 hours postdose.

Results: Theophylline was absorbed with median T_{max} value of 6 hrs and eliminated with a mean $T_{1/2}$ of 9.69 hrs following oral administration of theophylline 400 mg with placebo or febuxostat. Mean theophylline C_{max} values were 4.14 and 4.39 μg/mL when subjects were coadministered placebo and febuxostat, respectively. Mean theophylline $AUC_{0\text{-}tlqc}$ values were 115 and 122 μg·hr/mL when subjects were coadministered placebo and febuxostat, respectively. Likewise, mean $AUC_{0\text{-}inf}$, $T_{1/2}$, CL/F, and V_z/F values were also comparable between regimens. The mean amount of theophylline excreted in the urine over a 72-hour interval was comparable between the 2 regimens. The mean amounts of 1,3-dimethyluric acid and 3-methylxanthine was also similar between the 2 treatment arms. In contrast, the amount of 1-methyluric acid decreased and 1-methylxanthine increased in subjects following administration of theophylline with febuxostat compared to placebo. The changes in the amounts of metabolites excreted in urine have little or no clinical significance, as neither of these metabolites has pharmacological activity.

The point estimate for the ratio of theophylline C_{max} central values following administration of theophylline with febuxostat or placebo, and corresponding 90% confidence intervals (CIs) were 1.03 and (0.917, 1.149), respectively. The point estimate for the ratio of theophylline $AUC_{0\text{-}tlqc}$ central values following administration of theophylline with febuxostat or placebo, and corresponding 90% CIs were 1.04 and (0.927, 1.156), respectively. Both 90% CIs fell within the *no-effect* range of 0.8 and 1.25.

Conclusions: Coadministration of febuxostat with theophylline has no effect on the pharmacokinetics of theophylline. No dose adjustment for theophylline is required when coadministered with febuxostat.

Disclosure: M. Tsai: Takeda Global Research and Development Center, Inc., 3; **J. Wu:** Takeda Global Research and Development Center, Inc., 3; **L. Gunawardhana:** Takeda Global Research and Development Center, Inc., 3; **H. Naik:** Takeda Global Research and Development Center, Inc., 3.

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Effects of a Purine Nucleoside Phosphorylase Inhibitor, BCX4208, on the Serum Uric Acid Concentrations in Patients with Gout. David Fitz-Patrick[2], Waymon Drummond[4], John Pappas[3] and Alan S. Hollister[1]. [1]BioCryst Pharmaceuticals, Inc., Durham, NC, [2]East-West Medical Research Institute, Honolulu, HI, [3]Kentucky Medical Research Center, Lexington, KY, [4]Renaissance Clinical Research, Dallas, TX

Purine nucleoside phosphorylase inhibitors (PNPi) are a novel approach to lowering serum uric acid (sUA) in patients with gout. The specific PNPi, BCX4208, has a 0.52 nM K_i for human PNP. This compound was studied in a randomized, placebo-controlled, double blind three week trial using oral doses of 40, 80, and 120 mg daily in 60 gout patients whose sUA was >8 mg/dL at baseline. Eligible subjects were followed weekly for sUA, safety labs (including lymphocyte subsets), and adverse events during treatment and for 4 weeks of follow-up.

56 males and 4 females (39W, 6B, 5 Pacific Islander, 4 Asian, 6 Other) meeting the ARA criteria for the diagnosis of gout completed the study. Mean (SD) age was 51 (12) years; mean weight was 108 (25) kg. Trial endpoints were: absolute reduction in sUA at 3 weeks, proportion of subjects with sUA <6.0 mg/dL, frequency of gout flares, safety, tolerability, and abbreviated first dose BCX4208 pharmacokinetics.

After 3 weeks of therapy, sUA was reduced by −2.7, −3.3, and −3.4 mg/dL in the 40, 80, and 120 mg/d dose groups of BCX4208, respectively, compared to −0.4 mg/dL in the placebo group ($p<0.001$). No placebo-treated subject achieved a sUA <6.0 mg/dL, whereas 33%, 36%, and 31% of the subjects on BCX4208 at 40, 80, and 120 mg/d, respectively, met this goal at 3 weeks ($p<0.05$). 33%, 57%, and 56% of the BCX4208-treated subjects met this goal at least once during the 3 weeks of treatment ($p<0.001$), and 38%, 60%, and 100% of subjects with baseline sUA <10 mg/dL met this goal at least once during therapy with the 3 respective dose levels ($p<0.001$). One gout flare (1/16) occurred in a subject on 120 mg/d, and two gout flares (one placebo- and one 80 mg/d-treated subject) occurred during the 4 week follow-up period. Lymphocyte subsets (CD4+, CD8+, CD20+, and CD56+ cells) were reduced 30 to 70% by all doses of BCX4208, without a clear dose-response relationship. No subject met pre-defined stopping criteria for lymphocyte subset cell counts during the treatment period. All subjects completed the study and adverse events were evenly distributed in the BCX4208 and placebo arms. There were no serious adverse events. Abbreviated pharmacokinetics on the first day of treatment with BCX4208 showed a dose-proportional increase in C_{max} and AUC_{0-24}.

BCX4208 at 40, 80, and 120 mg/day produced a prompt reduction in sUA in gout patients and achieved the therapeutic goal of < 6.0 mg/dL in up to one-half of the patients during a 3 week trial. The drug produced moderate reductions in lymphocyte subsets, but was well tolerated. PNP inhibition may represent a novel approach to the treatment of gout.

Disclosure: D. Fitz-Patrick: BioCryst Pharmaceuticals, Inc., 2; **W. Drummond:** BioCryst Pharmaceuticals, Inc., 2; **J. Pappas:** BioCryst Pharmaceuticals, Inc., 2, Takeda Pharmaceuticals North America, 8; **A. S. Hollister:** BioCryst Pharmaceuticals, Inc., 3.

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Efficacy and Tolerability of Celecoxib in the Treatment of Moderate to Extreme Pain Associated with Acute Gouty Arthritis: A Randomized Controlled Trial. H. Ralph Schumacher[4], Manuela Berger[3], Julie Li-Yu[5], Fernando Perez-Ruiz[1], Ruben Burgos Vargas[2] and Chunming (Mark) Li[3]. [1]Hospital de Cruces, Baracaldo, Spain, [2]Hospital General de México, México City, Mexico, [3]Pfizer Inc., New York, NY, [4]University of Pennsylvania VA Medical Center, Philadelphia, PA, [5]University of Santo Tomas Hospital, Manila, Philippines

Background: Although nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin are widely used for the treatment of acute gouty arthritis, adverse events (AEs) have limited their use to date. This study was performed to evaluate the efficacy and tolerability of various doses of the cyclooxygenase (COX)-2 selective NSAID celecoxib in the treatment of moderate to extreme pain and inflammation associated with acute gouty arthritis.

Methods: Multinational, randomized, double-blind, double-dummy, active-controlled trial in patients (aged ≥ 18 y) with acute gouty arthritis (onset of pain ≤48 h prior to enrollment). Patients were required to have moderate to extreme pain in the index joint over the previous 24 h (5-point Patient's Assessment of Pain Intensity) and to be candidates for daily therapy with NSAIDs and/or analgesics. Patients with polyarticular (> 4 joints affected)/chronic gout, or other form of arthritis (except mild to moderate osteoarthritis not affecting the index joint) were excluded. The study consisted of an 8-day treatment period followed by 1-week follow-up. Patients were randomized 1:1:1:1 to receive: 1) celecoxib 50mg bid, 2) celecoxib 400mg followed by 200mg on Day 1 and then 200mg bid for 7 days, 3) celecoxib 800mg followed by 400mg on Day 1 and then 400mg bid for 7 days and 4) indomethacin 50mg tid. The primary objective was to evaluate the analgesic efficacy of a high-dose celecoxib regimen (800/400mg) compared with a low-dose regimen (50mg bid) in the treatment of moderate to extreme pain at Day 2. Secondary objectives included the evaluation of the analgesic and anti-inflammatory effects of different celecoxib doses compared with indomethacin 50mg tid; safety and tolerability were also assessed.

Results: Of 443 patients screened, 402 patients were randomized and 400 received treatment. Baseline demographics were comparable between treatments. For the primary end point, patients receiving high-dose celecoxib (800/400 mg) experienced a significantly greater reduction in patients' assessment of pain intensity on Day 2 compared with low-dose celecoxib (50 mg bid; least squares [LS] mean difference −0.46, $P=0.0014$). For high-dose celecoxib 800/400mg, the change in pain scores from baseline to Day 2 was comparable to indomethacin 50mg tid (LS mean difference 0.11, $P=0.4331$). Compared to indomethacin 50mg tid, celecoxib 400/200mg and 50mg bid produced small reductions in pain (LS mean difference 0.33 [$P<0.05$] and 0.57 [$P<0.0001$], respectively). Secondary efficacy and safety findings are presented below.

Table

	Celecoxib 50 mg bid (n = 101)	Celecoxib 400/200 mg bid (n = 99)	Celecoxib 800/400 mg bid (n = 98)	Indomethacin 50 mg tid (n = 102)
Physician's Assessment of Tenderness of the Index Joint (measure of inflammation on Day 5-change from Baseline)				
vs Celecoxib 50mg bid				
LS mean Difference (SE)	—	−0.08 (0.11)	−0.20 (0.11)	—
95% CI		−0.29, 0.14	−0.42, 0.02	
P value		0.4743	0.0737	
vs Indomethacin 50 mg tid				
Ls Mean Difference (SE)	0.26 (0.11)	0.18 (0.11)	−0.06 (0.11)	—
95% CI	0.04, 0.47	−0.04, 0.39	−0.16, 0.27	
P value	0.0200	0.1050	0.0737	
Safety, number (%) of Patients				
Number of AEs	59	43	51	80
AEs	33 (32.7)	27 (27.3)	28 (28.6)	44 (43.1)
Headache	5 (5.0)	4 (4.0)	3 (3.1)	4 (3.9)
Diarrhea	3 (3.0)	2 (2.0)	2 (2.0)	5 (4.9)
Dizziness	2 (2.0)	1 (1.0)	2 (2.0)	6 (5.9)
Upper Abdominal Pain	1 (1.0)	0	1 (1.0)	5 (4.9)
Severe AEs	5 (5.0)	3 (3.0)	2 (2.0)	1 (1.0)
Discontinuations due to AEs	5 (5.0)	3 (3.0)	1 (1.0)	9 (8.8)
Deaths	0	0	0	0

SE=standard error; CI=confidence interval

Conclusions: High-dose celecoxib (800/400 mg) is significantly more effective than low-dose celecoxib (50 mg bid) in the treatment of moderate-to-extreme pain and inflammation associated with acute gouty arthritis. Furthermore, this regimen is comparable in efficacy to indomethacin 50 mg tid and appears to offer an improved tolerability profile.

Disclosure: H. R. Schumacher: Pfizer Inc, 5; **M. Berger:** Pfizer Inc, 1, 3; **J. Li-Yu:** Pfizer Inc, 8; **F. Perez-Ruiz:** Ardea Biosciences, 5, 8, Menarini, 5, 8, Novartis Pharmaceuticals Corporation, 8, Pfizer Inc, 5; **R. Burgos Vargas:** Abbott Laboratories, 5, 8, Bristol-Myers Squibb, 5, 8, Merck Pharmaceuticals, 5, 8, Pfizer Inc, 5, 8, Roche, 5, 8; **C. M. Li:** Pfizer Inc, 1, 3.

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Evaluation of Rilonacept for Prevention of Gout Flares during Initiation of Urate-Lowering Therapy: Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial. Robert Terkeltaub[6], H. Ralph Schumacher[5], Kenneth G. Saag[4], James Clower[7], William Jennings[1], Robert R. Evans[2], Jian Wang[3], Shirletta King-Davis[3] and Steven P. Weinstein[2]. [1]Radiant Research, San Antonio, TX, [2]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [3]Regeneron Pharmaceuticals, Inc., [4]University of Alabama-Birmingham, Birmingham, AL, [5]VA Medical Center and UPenn, Philadelphia, PA, [6]VA Medical Ctr, San Diego, CA, [7]Westside Center for Clinical Research, Jacksonville, FL

Background: The present study evaluated the efficacy and safety of rilonacept (IL-1 Trap) for the prevention of gout flares (GFs) during initiation of urate-lowering therapy (ULT) with allopurinol. While attaining target serum levels is critical to the long-term management of gout, ULT can elicit or prolong acute attacks during the initial months of therapy. This paradoxical finding may be attributable to remodeling of crystal deposits during dissolution.

Methods: This North American multicenter trial included adults with gout (ARA criteria), urate levels ≥7.5 mg/dL, and self-reported history of ≥2 GFs in the previous year. Eligible patients were initiated on allopurinol 300 mg daily (or lower dose in those with renal dysfunction, with subsequent titration to achieve urate <6 mg/dL) and randomized to receive treatment with weekly subcutaneous (SC) injections of placebo (Pbo; n=80), rilonacept 80 mg (R80; n=80), or rilonacept 160 mg (R160; n=81) (loading dose on Day 1). GFs were reported by the patient via interactive voice response diary and treated, as appropriate, with NSAIDs or oral glucocorticoids while continuing study treatments. Efficacy endpoints included the number of GFs, % of patients with 1 or more flares, and number of flare days. Safety and tolerability were also assessed.

Results: Baseline characteristics were similar among treatment groups; 92.9% were male, the mean ± SD age was 52.3±12.6 years, and the number of flares reported in the prior year was 4.6 ± 3.3. Fewer patients on Pbo completed the 16-wk treatment period (72.5%) compared with those receiving active treatment (80.0% R80; 86.4% R160). Observed serum urate levels decreased similarly in all 3 groups. Through wk 16, the mean number of GFs per patient (primary endpoint) was significantly lower in both R groups relative to Pbo: 1.06 (84 flares) for Pbo; 0.29 (23 flares) for R80, and 0.21 (17 flares) for R160 (95% CI, 0.22 to 0.46; p<0.0001 vs Pbo). One or more flares were reported by 46.8% Pbo, 18.8% R80, and 16.3% of R160 patients (p<0.0001). The number of flare days per patient was significantly lower with rilonacept: 5.52, 2.36, and 0.98 for Pbo, R80, and R160, respectively (p<0.0001 vs Pbo). From day 1 to wk 16, the proportion of patients who experienced multiple flares was 31.6% Pbo (95% CI, 21.6 to 43.1) vs 5.0% R80 (95% CI, 1.4 to 12.3) vs 3.7% R160 (95% CI, 0.8 to 10.6; p<0.0001 for both comparisons), resulting in an 84% and 88% reduction in the respective R groups. The overall incidence of adverse events (AE) was similar between Pbo (60.8%) and rilonacept (63.4%). Injection site reactions were the most frequent AE with rilonacept (14.3% vs 1.3%). Other common AEs, reported by ≥5% of patients, were respiratory infections, musculoskeletal system disorders, and headache, and rates were generally similar among the treatment groups. Three patients in each group experienced serious AEs; no rilonacept-related SAEs, deaths, or serious infectious AEs were reported.

Conclusions: This phase 3 trial confirmed that IL-1 blockade with rilonacept markedly reduced the occurrence of gout flares during initiation of urate lowering therapy. Rilonacept demonstrated an acceptable safety and tolerability profile.

Disclosure: R. Terkeltaub: BioCryst, 5, Celgene, 5, Novartis Pharmaceuticals Corporation, 5, Regeneron Pharmaceuticals, Inc., 5, Savient Pharmaceuticals, 5, Takeda Pharmaceuticals North America, 5, UCB, Inc., 5, URL Pharma, 5; **H. R. Schumacher:** Regeneron Pharmaceuticals, Inc., 5, Savient Pharmaceuticals, 5, Takeda Pharmaceuticals North America, 2, 5; **K. G. Saag:** None; **J. Clower:** None; **W. Jennings:** None; **R. R. Evans:** Regeneron Pharmaceuticals, Inc., 2, 3; **J. Wang:** Regeneron Pharmaceuticals, Inc., 1, 3; **S. King-Davis:** Regeneron Pharmaceuticals, Inc., 1, 3; **S. P. Weinstein:** Regeneron Pharmaceuticals, Inc., 1, 3.

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Evaluation of Rilonacept in Patients with Gouty Arthritis Experiencing an Acute Gout Attack. Robert Terkeltaub[6], H. Ralph Schumacher[5], Craig Curtis[1], Neil Patterson[2], Robert R. Evans[3], Jian Wang[4], Shirletta King-Davis[4] and Steven P. Weinstein[3]. [1]Compass Research, Orlando, FL, [2]Private Practice, Oviedo, FL, [3]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [4]Regeneron Pharmaceuticals, Inc., [5]VA Medical Center, Philadelphia, PA, [6]VA Medical Ctr, San Diego, CA

Background: The role of IL-1β as a central mediator of acute gouty inflammation has been confirmed by animal models and gout prevention studies in patients initiating urate lowering therapy. Although IL-1 appears to trigger gout flares (GFs), available data on IL-1 inhibition in the treatment of GFs is limited to case reports and a single dose-ranging study.

Objective: To report initial findings from SURGE (Study of Rilonacept in Gout Exacerbations), a large phase 3, randomized, double-blind, double-dummy, active-controlled study of the IL-1β and IL-1α blocker rilonacept for the treatment of acute GFs, conducted at approximately 80 sites in North America.

Methods: Eligible patients with gout aged ≥18 to ≤70 y presenting within 48 hrs of onset of a GF with at least moderately severe pain, evidence of swelling and tenderness in the gouty index joint (most painful joint), and who had not initiated treatment for GF symptoms were randomized to 1 of 3 regimens: SC placebo (Pbo) at baseline (BL), plus oral indomethacin (IN) for at least 3 days (d) [50 mg TID × 3 d, then 25 mg TID × 9 d] (IN group); SC rilonacept 320 mg at BL, plus IN for at least 3 d (R+IN group); or SC rilonacept 320 mg at BL, plus oral Pbo for at least 3 d (R group). Patient assessment of pain intensity in the gouty index joint was recorded using a 5-point Likert scale (0= none; 4=extreme) at BL (pre-dose) and 4, 8, 12, 24,

48, and 72 h after administration of SC study drug, and then daily up to 12 d via electronic diary. The primary efficacy endpoint was change from BL pain score to the averaged values at 24, 48 and 72 h. Sequential testing of 2 primary endpoints was planned: R+IN vs IN group, followed by R vs IN group, with the second comparison contingent upon $p<0.05$ for the first. Secondary efficacy analyses included change from BL in pain scores at 24, 48 and 72 hours under the same conditions.

Results: 225 patients with an acute GF were randomized to treatment (IN n=76; R+IN n=74; R n=75). Baseline characteristics were similar among groups. IN resulted in a statistically significant ($p<0.0001$) within-group reported reduction from BL in pain intensity similar to that reported in previous studies of IN. Although a numerically greater reduction in pain intensity was observed with R+IN compared with IN alone (mean ± SD change R+IN −1.55±0.92 vs IN −1.40±0.96), the difference was not statistically significant (95% CI, −0.44 to 0.15; $p=0.33$). Therefore, comparison of the IN with the R group (mean change ± SD R −0.69± 0.97 from baseline) was not performed, per the analysis plan.

Treatment with rilonacept was generally well-tolerated, with 3 patients reporting serious adverse events in the R+IN group, none considered drug-related. Adverse events reported at an incidence of at least 5% in any group were headache and dizziness.

Conclusions: Under conditions in which the reduction of acute gout flare pain in the indomethacin alone group was similar to published reports, inhibition of IL-1 with rilonacept did not provide additional pain relief within 72 hours of flare onset. In comparison with prior studies, the results suggest that blockade of IL-1 for treatment of an early, established acute gout flare is less effective clinically than for acute gout flare prophylaxis.

Disclosure: R. Terkeltaub: BioCryst, 5, Celgene, 5, Novartis Pharmaceuticals Corporation, 5, Regeneron Pharmaceuticals, Inc., 5, Savient Pharmaceuticals, 5, Takeda Pharmaceuticals North America, 5, UCB, Inc., 5, URL Pharma, 5; **H. R. Schumacher:** Regeneron Pharmaceuticals, Inc., 5, Savient Pharmaceuticals, 5, Takeda Pharmaceuticals North America, 2, 5; **C. Curtis:** None; **N. Patterson:** None; **R. R. Evans:** Regeneron Pharmaceuticals, Inc., 1, 3; **J. Wang:** Regeneron Pharmaceuticals, Inc., 1, 3; **S. King-Davis:** Regeneron Pharmaceuticals, Inc., 1, 3; **S. P. Weinstein:** Regeneron Pharmaceuticals, Inc., 1, 3.

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Febuxostat Versus Allopurinol in the Treatment of Gout in Subjects ≥65 Years of Age: A Subgroup Analysis of the CONFIRMS Trial. Eswar Krishnan[1], Patricia A. MacDonald[2], Barbara Hunt[2] and Robert Jackson[2]. [1]Stanford University, Stanford, CA, [2]Takeda Global Research & Development Center, Inc., Lake Forest, IL

Purpose: Efficacy and safety of urate-lowering therapy (ULT) in an older gout population has been infrequently reported. Febuxostat is a novel, non-purine, selective inhibitor of xanthine oxidase for the treatment of hyperuricemia in patients with chronic gout. This is a subset analysis of 374 elderly subjects (≥65 years of age) from a total of 2269 subjects treated with febuxostat (FEB) or allopurinol (ALLO) for 6 months from the CONFIRMS study.[1]

Methods: Subjects with gout and serum urate levels (sUA) ≥8.0 mg/dL were randomized to FEB 40 mg, FEB 80 mg, or ALLO (200/300 mg based on renal function) once daily. Gout flare prophylaxis (colchicine or naproxen) was provided for the entire study duration. The outcomes of interest were percent of elderly subjects with sUA <6.0 mg/dL by renal functional status and safety in this at-risk population.

Results: The 374 subjects were predominately male (86%), Caucasian (85%), and obese (51% with body mass index [BMI] ≥30 kg/m^2), with a mean age of 71 years. Baseline characteristics and comorbidities were similar across groups; 82% had hypertension, 25% diabetes, 24% coronary artery disease, 21% cardiac arrhythmia, and 11% previous myocardial infarction. The three treatment groups were similar in age, gender, race, and duration of gout. Mean duration of gout was 15 years with a baseline sUA 9.4 mg/dL, with history of tophi (19%) and kidney stones (20%); 98% of subjects had some degree of renal impairment. Urate-lowering therapy use, at some time prior to study entry, was reported by 71% of subjects (ALLO 63% and 15% FEB). The proportions of subjects whose final sUA was <6.0 mg/dL were 62% (71/115), 82% (105/128), and 47% (62/131) in the FEB 40 mg, FEB 80 mg, and ALLO groups, respectively. Results by renal function status are presented in the table. The most frequently reported AEs irrespective of treatment were diarrhea (10%) and upper respiratory infection (8%). The majority were transient and resolved while on treatment. Serious AEs were reported by 8% in the FEB 40 mg, 6% in the FEB 80 mg, and 11% in the ALLO group. The most common serious AEs were cardiac disorders, 1%, 2%, and 3%, and lower respiratory tract infections, 1%, 0%, and 2%, in the FEB 40 mg, FEB 80 mg, and ALLO treatment groups, respectively. There were no hypersensitivity reactions. Overall response rates were similar to those seen in the combined CONFIRMS population.

Percent of Subjects Achieving sUA <6 mg/dL	FEB 40 mg n/N (%)	FEB 80 mg n/N (%)	ALLO 200/300 mg n/N (%)
Normal (CLcr ≥90 mL/min)	2/3 (67)	1/2 (50)	1/1 (100)
Mild (CLcr ≥60 to 89 mL/min)	33/45 (73)	39/44 (89)*	31/50 (62)
Moderate (CLcr >30 to 59 mL/min)	36/67 (54)	65/82 (79)*,**	30/80 (38)

* $p<0.05$, FEB 80 mg vs ALLO; **$p<0.05$, FEB 80 vs FEB 40 mg.

Conclusions: Treatment with FEB reduced sUA to <6.0 mg/dL in this elderly population with significant cardiovascular comorbidities and was well tolerated. Response in the elderly moderately renally impaired population was statistically significantly better with either dose of FEB vs ALLO.

Reference:

1. Becker MA, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. *Arthritis Res Ther* 2010;12:R63.

Disclosure: E. Krishnan: ARDEA Biosciences, 9, Savient Pharmaceuticals, 1, Takeda Pharmaceuticals North America, 2; **P. A. MacDonald:** Takeda Global Research & Development Center, Inc, 3; **B. Hunt:** Takeda Global Research & Development Center, Inc, 3; **R. Jackson:** Takeda Global Research & Development Center, Inc, 3.

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Healthcare Utilization and Productivity at Home and Work Place in Tophaceous vs. Non-Tophaceous Gout. Puja Khanna[3], Jay Persselin[1], Ron Hays[2], Daniel Furst[2], Harold Paulus[2], Paul Maranian[2] and Dinesh Khanna[2]. [1]Greater Los Angeles VA, [2]UCLA, [3]UCLA and Greater Los Angeles VA

Objective: Gout is a painful inflammatory arthritis that causes debilitating acute attacks and is associated with increased resource utilization. Retrospective claims data has shown economic impact of gout on both direct and indirect medical costs including office visits, emergency room visits, medications, and time lost from work. However, there is lack of prospective data in a well-defined gout cohort. In addition, no study has reported the impact of gout on productivity. We assessed the impact of gout on health care utilization and productivity at home and work place.

Methods: Patients with tophaceous and non-tophaceous gout were recruited at VA and University medical centers. Productivity was assessed using Work Productivity Survey (*Osterhaus, J, Arthritis Research & Therapy 2009*). Patients indicated whether or not they were employed outside of the home, how many days in last month they missed work (employment or household work) due to gout, how many days/month productivity was decreased 50% due to gout, and how much gout interfered with work/household chores (0–10 scale), days/month they missed family and social activities, and days/month they required outside help. Health care utilization was assessed using UCSD Health Care Utilization Questionnaire (HCU). HCU asked about resource utilization during past 3 months on office/ hospital visits, surgeries, medical supplies, prescription and OTC medications due to their ongoing medical conditions (not just gout).

Results: Of 71 patients, 45 (63%) patients had non-tophaceous gout. There were no statistical differences in demographics between tophaceous and non-tophaceous gout. On average, patients were 68.2 years old, 96% were male, 70% were Caucasian. Patient with tophaceous gout had similar disease duration, serum uric acid and Charlson comorbidity index; patients with tophi had worse HAQ-DI score (1.1 vs. 0.7, $p=0.06$). Only 20% of patients were employed. Patients missed an average of 3.7 days of work at home or work place per month, had work or home productivity reduced by more than 50% in 3 days per month, had 3 days with reduced family and social activities, and had 1.4 days where they required outside help to do work at home. Tophaceous gout was associated with greater loss of productivity at home and work place compared to non-tophaceous gout (Table). Resource utilization was not significantly different between the 2 groups.

Patient Characteristics	Total Population (N=71)	Non-Tophaceous (N=45)	Tophaceous (N=26)
Age (years), mean (SD)	68.2 (10.0)	67.5 (10.1)	68.7 (9.9)
Charisons Comorbidity index, mean (SD)	3.0 (2.6)	3.0 (2.7)	13.1 (2.4)
Severity of Gout scale, 0–10 mean (SD)	3.0 (2.9)	2.1 (2.3)	4.7 (3.2)
Productivity			
Employed, N (%)	14 (19.7)	8 (17.8)	8 (23.1)
Days missed due to gout, mean (SD)	3.7 (8.1)	3.2 (7.5)	4.5 (9.1)
Days with reduced productivity due to gout, mean (SD)	3 (7.1)	2.4 (6.1)	4.2 (8.6)
Gout interfered (0–10), mean (SD)	3.3 (3.6)	2.8 (3.4)	4.4 (3.7)*
Days with reduced family and social activities, mean (SD)	3 (6.8)	1.6 (3)	5.6 (10.4)
Days requiring outside help due to gout, mean (SD)	1.4 (5.3)	0.4 (1.7)	3.1 (8.4)
UCSD Health Care Utilization (in last 3 months), mean (SD)			
Health care professional visit	5.1 (5.8)	5.2 (6.8)	4.8 (3.4)
Phone calls to healthcare professional	2 (3.1)	1.9 (3.5)	2.1 (2.3)
Triage or urgent care	0.7 (1)	0.7 (1)	0.7 (0.9)
Health care visit to home	0.6 (2.6)	0.8 (3.1)	0.4 (1.4)
Hospital admissions	3 (11.4)	14 (14.2)	1.3 (2.9)
Prescription medications	8.7 (4.7)	8.5 (4.8)	9.1 (4.6)
Non-prescription medications	2.4 (2.8)	2.8 (3.3)	1.6 (1.5)

* $p<0.05$ for comparison between tophaceous and non-tophaceous gout

Conclusions: Tophaceous gout negatively impacts work place and home productivity. The lack of significant differences in utilization in patients with and without non-tophaceous gout is likely due to similar comorbidity profiles.

Disclosure: P. Khanna: ACR REF, 2; **J. Persselin:** None; **R. Hays:** None; **D. Furst:** None; **H. Paulus:** None; **P. Maranian:** Savient Pharmaceuticals, 5; **D. Khanna:** Savient Pharmaceuticals, 2, 5.

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Patient Knowledge and Beliefs Concerning Gout and Its Treatment. Leslie R. Harrold[4], Kathleen M. Mazor[2], Daniel Peterson[3], Cassandra Firneno[3] and Robert A. Yood[1]. [1]Fallon Clinic, Worcester, MA, [2]Meyers Primary Care Insitute/UMass Medical School, [3]Meyers Primary Care Institute, [4]UMass Medical Schl, Worcester, MA

Objectives: We sought to examine patients' knowledge and beliefs concerning gout and its treatment to order to identify ways to improve gout care.

Methods: We identified all members (≥18 years of age) of a group-model health maintenance organization (HMO) with documentation of at least one health care encounter associated with a gout diagnosis during the period 2008–2009 (n=1346). From this population a random sample of 500 subjects were sent a questionnaire assessing knowledge with regard to gout, beliefs about prescription medications used to treat gout, satisfaction with physician-patient communication, and trust in the physician.

Results: Two hundred and forty patients returned surveys and research authorization forms (response rate of 51% after excluding patients who reported never having gout). The majority of patients were male (80%), white (94%), and aged 65 and older (66%). Only 14 (6%) patients were cared for by a rheumatologist. The vast majority of patients were aware that gout was related to uric acid and flares were the result of crystals inducing inflammation. Many participants were unaware of foods that may lead to a gout flare. Specifically, more patients reported vegetables (58%), chicken (55%) and legumes (39%) as triggers as compared to seafood (23%), beef (22%) and pork (7%). Only 43% reported beer could increase the chances of a gout flare. Awareness of dietary triggers was not greater among those with more encounters for gout or chronic gout (identified by use of urate-lowering drugs [ULDs]). For the management of acute flares, nonsteroidal anti-inflammatory drugs were considered easy to take (86%) and effective in decreasing pain (78%) with only 22% having side effects to the agents. Among colchicine users, colchicine was considered easy to take (91%) and effective (76%) but 37% reported side effects to the medication. There were 101 patients prescribed a ULD of whom 21% reported forgetting to take their medication in the past month. Only a minority of ULD users (12%) were aware of the risk of flare when initiating treatment with this medication class. The majority of patients reported high levels of trust in their physician and good patient-provider communication.

Conclusion: In this gout patient population cared for mostly by primary care providers, we identified several knowledge deficits that may worsen disease management including lack of knowledge regarding dietary triggers and lack of awareness of the risk of gout flare with initiation of ULDs. In addition, providers should explore with their patients reasons for missed doses of ULDs in order to improve adherence.

Disclosure: L. R. Harrold: Takeda Pharmaceuticals North America, 2; **K. M. Mazor:** Takeda Pharmaceuticals North America, 2; **D. Peterson:** Takeda Pharmaceuticals North America, 2; **C. Firneno:** Takeda Pharmaceuticals North America, 2; **R. A. Yood:** Takeda Pharmaceuticals North America, 2.

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Progressive Reduction in Tophus Burden with Pegloticase Therapy in Patients with Chronic Gout Refractory to Conventional Therapy. Herbert Baraf[1], Sergio R. Gutierrez-Urena[4], Janitzia Vazquez-Mellado[5], Claudia Rehrig[6], Faith Ottery[6], John S. Sundy[2] and Robert A. Yood[3]. [1]Arthritis & Rheumatism Association, Wheaton, MD, [2]Duke University Medical Center, Durham, NC, [3]Fallon Clinic, Worcester, MA, [4]Hospital Civil de Guadelajara, Guadalajara, Mexico, [5]Hospital General de México, México City, [6]Savient Pharmaceuticals, Inc

Purpose: To evaluate the effect of up to 30 months of i.v. pegloticase therapy on tophi in patients (pts) with treatment refractory chronic gout.

Methods: Pts completing one of two 6-month, randomized, double-blind, placebo-controlled Phase 3 trials (RCT) of pegloticase were eligible for continued therapy in an open label extension study (OLE). Treatment in RCT was pegloticase (PGL) 8 mg (q2wk or q4wk) or placebo (PBO) and in OLE was PGL (q2wk or q4wk). OLE pts could switch dose arms after 6 months. Primary response endpoint in RCT was plasma uric acid (PUA) <6.0 mg/dL 80% of the time in months 3 and 6. Secondary outcomes included treatment effects for tophus, flares, other rheumatologic variables and pt reported outcomes. Tophus response was assessed using **CAPER (C**omputer-**A**ssisted **P**hotographic **E**valuation in **R**heumatology) methodology (Abstract 1111, ACR 2009) with blinded central readers of standardized serial digital photos taken of hands, feet (accounting for maximum of 5 target tophi for serial assessment) and up to 2 other tophus sites at RCT baseline and throughout RCT and OLE. While PGL effect on tophi was analyzed in a number of ways using CAPER, this analysis addresses individual target tophus response. Complete response (CR) for each target tophus was defined as 100% decrease in the area (or disappearance) of the tophus from baseline.

Results: At RCT baseline, 154 of 212 (73%) dosed pts had ≥1 tophus; 107 had ≥1 tophus entering OLE. 151/157 (96%) of RCT completers enrolled in the OLE (82 q2wks, 67 q4wks, 2 observation). 50 of 60 RCT PUA-responders maintained serum UA <6 mg/dL during OLE. Tophus response was related to UA-responder status, with tophus progression during OLE in 13 RCT nonresponders and 0 RCT responders. Individual target tophus complete response data for pts on pegloticase in both RCT+OLE are summarized below. In addition, 12 of 28 pts with ≥1 tophus on PBO in RCT had their first target tophus CR in the OLE (data not shown).

Complete Responses (CR) for Target Tophi in Patients on Pegloticase in Both RCT and OLE

Total number of patients with baseline target tophi, N	79
Total # target tophi	308
Total number of patients having ≥ 1 tophus CR, n/N (%)	53/79 (67%)
• Pts having 1st CR for target tophi during RCT, n/N (%)	29/79 (37%)
• Pts having 1st target tophus CR during OLE, n/N (%)	24/79 (30%)
Total # of target tophi CRs during RCT + OLE	180 (58%)
• Number of tophi undergoing CR in RCT	85/308 (28%)
• Additional tophi undergoing CR in OLE in pts who had their	42/308 (14%)
• Number of tophi undergoing CR in OLE in pts who had their first CR during OLE	53/308 (17%)

Conclusion: Pegloticase has a remarkable effect on tophus resolution in pts with chronic gout refractory to conventional therapy. Approximately 28% of baseline target tophi assessed by digital photography completely resolved during the first 6 months of pegloticase therapy. Resolution continued during pegloticase therapy for up to 30 months with a total of 58% of baseline target tophi eliminated.

Disclosure: H. Baraf: Investigator, 9, Savient Pharmaceuticals, 5, 9, Takeda Pharmaceuticals North America, 8; **S. R. Gutierrez-Urena:** Savient Pharmaceuticals, 9; **J. Vazquez-Mellado:** Savient Pharmaceuticals, 9; **C. Rehrig:** Savient Pharmaceuticals, 3; **F. Ottery:** Savient Pharmaceuticals, 3; **J. S. Sundy:** Alnara, Anadys, Array BioPharma, Pharmos, 5, 9, Ardea Biosciences, 5, 9, CME through Duke University, 5, 9, Genentech and Biogen IDEC Inc, 9, Managing Partner, 5, 9, Regeneron Pharmaceuticals, Inc., 9, Roche, 5, Savient Pharmace; **R. A. Yood:** Savient Pharmaceuticals, 9, Takeda Pharmaceuticals North America, 2.

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Safety and Efficacy of Febuxostat (FEB) Treatment in Subjects with Gout and Severe Allopurinol (ALLO) Adverse Reactions. Saima Chohan and Michael A. Becker. University of Chicago, Chicago, IL

Background: ALLO, a purine base analogue inhibitor of xanthine oxidase (XO) activity, remains the standard for pharmacologic urate-lowering (UL) management of gout. ALLO is efficacious and safe in most patients, but intolerance is estimated to occur in up to 10% of treated patients. Severe or life-threatening ALLO adverse reactions (AEs) precluding re-challenge with the drug occur much less frequently (~0.1 to 0.4% of treated patients), and include severe cutaneous ALLO reactions (SCAR), vasculitis, and/or a multisystem ALLO hypersensitivity syndrome (AHS). During clinical development of FEB, a recently approved non-purine analogue inhibitor of XO, subjects with severe ALLO intolerance were excluded from randomized double-blind FEB/ALLO comparative trials.

Methods: In this retrospective study, safety and UL efficacy of FEB was assessed in13 successively encountered gout patients (8 men, 5 women; age range, 52 to 85 years) with prior documented severe ALLO reactions: SCAR only, 10 patients; multisystem involvement, 3 patients, including skin (2 patients), acute or acute on chronic renal insufficiency (3), hepatitis (1) and/or hematologic abnormalities (2). All patients had impaired baseline renal function: eCLcr 60–89 ml/min, 4; 30–59 ml/min, 5; 15–29 ml/min, 4. FEB treatment was initiated at 40 mg/day in 12 patients and 20 mg/day in 1. FEB dose was titrated, if permitted by safety and renal function monitoring, to achieve and maintain serum urate levels (sUA) $<$6.0 mg/dL.

Results: All 13 patients were hyperuricemic (range: sUA 7.5 to 14 mg/dL) prior to FEB therapy. FEB was well tolerated in 12 patients, each of whom remains on treatment (mean FEB exposure 10 months; range 1.5 to 15 months). sUA decreased from 25 to 59% in these 12 patients: 6 remain on the initial FEB dose (20 mg/day, 1 patient; 40 mg/day, 5 patients), and 10 patients have maintained sUA $<$6.0 mg/dL on FEB doses from 20 to 80 mg/day. In 2 patients, sUA remains $>$6.0 mg/dL despite 32% and 38% sUA reductions from baseline, respectively, on FEB 40 mg/day and 80 mg/day. One patient (an 85 year old woman), previously hospitalized with documented exfoliative erythroderma during ALLO treatment, developed biopsy-confirmed cutaneous leukocytoclastic vasculitis after 4 days exposure to FEB 40 mg/day. No evidence for other organ system involvement was detected, and the rash resolved promptly after FEB withdrawal. This patient had also received seasonal influenza vaccination on day 1 of FEB treatment. None of the other 12 patients treated with FEB showed rash, worsening hepatic function, blood cytopenia or eosinophilia. One patient with baseline moderate CKD, progressed to severe CKD; renal biopsy showed focal segmental glomerulosclerosis.

Conclusion: In 12 of our 13 gout patients with previously documented severe ALLO AEs, FEB treatment was safe; in 10, goal range sUA was achieved and maintained over a mean treatment period of 10 months. However, the development of a hypersensitivity type cutaneous vasculitis (likely but not definitively FEB-related) early in treatment mandates caution, careful dose escalation, and close monitoring when FEB UL therapy of ALLO-intolerant patients is considered.

Disclosure: S. Chohan: Takeda Pharmaceuticals North America, 5; **M. A. Becker:** Ardea, 5, BioCryst, 5, Regeneron Pharmaceuticals, Inc., 5, Savient Pharmaceuticals, 5, Takeda Pharmaceuticals North America, 5, URL/Mutual, 5.

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Serum Urate Levels Have an Impact on Renal Function in Patients with Gout Withdrawing Urate-Lowering Therapy (ULT). Fernando Perez-Ruiz[1], Ana M. Herrero-Beites[2] and Miguel A. Gonzalez-Gay[3]. [1]Hospital de Cruces, Jopelana, Spain, [2]Hospital de Górliz, [3]Hospital Univesitario Marqués de Valdecilla

Objective: to evaluate whether serum urate levels have an impact on renal function in patients with gout.

Methods: patients who gave consent to withdraw ULT after 5-yr treatment (for non-tophaceous) or 5-yr after disappearance of tophi were included in an ongoing observational study of recurrence of flares (Perez-Ruiz F, Arthritis Rheum 2006, Arthritis Rheum 2009-abstract). Renal function was estimated with clearance of creatinine at baseline and treatment, and with MDRD formula after withdrawing ULT. Outcome measure for renal dysfunction was considered as MDRD renal function estimation $<$ 60 ml/min at last observation of follow-up. Patients with recurrence of gout were started on ULT, and stopped for follow-up in this cohort. Kaplan-Meier survival analysis (log rank test) was used to identify variables associated with outcome, including age, time from onset of gout, tophi, serum urate at baseline, withdrawal (average) and follow-up (average), time on ULT, clearance of creatinine at baseline and withdrawal, urate-lowering drugs, hypertension, diabetes, hyperlipidemia, vascular episodes, proteinuria ($>$ 500 mg/day). Multivariant Cox proportional hazard regression analysis was used to study those variables associated with the outcome as survival variable.

Results: from a 202 patient cohort, 179 had all variables to estimate renal function with MDRD equation at last observation, and were included in analysis. Mean age at ULT withdrawal was 61$\pm$11 (35–89), time on treatment was 65$\pm$6 months (60–116), time on follow-up 34$\pm$23 months (1–124). Serum urate was 8.91$\pm$1.31, 4.90$\pm$0.83, and 8.53$\pm$1.45 at baseline, withdrawal and follow-up. Tophi were present at baseline in 25%, 49% received allopurinol, and 51% benzbromarone. Hypertension (37%), diabetes (14.9%), diuretics (13.7%), hyperlipidemia (49.7%), and vascular events (17.1%) were common in this hospital-based cohort. Renal dysfunction was present in 24 (13.4%), 33 (18,4%), and 39 (21.8%) patients at baseline, withdrawal and follow-up respectively, 8 patients showing proteinuria. Multivariant Cox regression analysis showed three variables to be independently and significantly associated with renal dysfunction: lower clearance of creatinine at withdrawal, presence of proteinuria, and increasing serum urate levels during follow-up, but only for the two upper quartiles of the distribution (median 8.45 mg/dl).

Variables	Hazard ratio	95% CI limits	p
Proteinuria ($>$500 mg/day)	4.423	2.021–9.675	0.000
CrClearance (ml/min)	0.922	0.902–0.941	0.000
Serum urate ($>$8.45 mg/dl)	3.853	1.866–7.956	0.000

Conclusions: renal function and proteinuria, but also the highest quartiles of serum urate levels, are independently associated with poor renal outcome after ULT withdrawal.

Disclosure: F. Perez-Ruiz: None; **A. M. Herrero-Beites:** None; **M. A. Gonzalez-Gay:** None.

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The Combination of Tranilast with Allopurinol Results in Enhanced Urate Lowering. John S. Sundy[4], Michael M. Kitt[5], Sue G. Griffith[1], Randall R. Stoltz[2] and Ronald Goldblum[3]. [1]ClinPharma Resources, San Diego, CA, [2]Covance, Evansville, IN, [3]CPC Inc, Carlsbad, CA, [4]Duke University Medical Center, Durham, NC, [5]Nuon Therapeutics, Inc., San Mateo, CA

Background: Reduction of serum urate (sUA) can be achieved with uricosuric drugs, which enhance excretion of uric acid, or with inhibitors of xanthine-oxidase, which interrupt the enzymatic cascade converting xanthine to urate. Combination therapy utilizing both mechanisms may be useful in producing lower sUA levels and higher responder rates than a single mechanism in patients with hyperuricemia and gout.

Study Design: A double-blind, 5-treatment period, crossover Phase 2 study evaluated co-administration of tranilast and allopurinol in patients with hyperuricemia. Subjects were randomized 1:1:1 in an initial 3-treatment crossover phase to 300 mg tranilast (T_{300}), 300 mg allopurinol (A_{300}), or a combination of A_{300} + T_{300} (C_{300}). At end of the third period, patients were randomized 1:1 in a 2-treatment crossover phase of allopurinol 400 mg (A_{400})

or a combination of A_{400} + T_{300} (C_{400}). Each period within a phase was 14 days in duration with 7 days treatment orally once daily (Days 1–7), followed by a 7-day washout interval. sUA levels were obtained each day of dosing and 24 hours after last dose. Plasma concentrations of tranilast, allopurinol, and oxypurinol (allopurinol's active metabolite) were evaluated over the 24-hour interval after last dose of each 7-day period. The primary objective was to compare % change from baseline sUA of the combination with tranilast or allopurinol alone.

Results: Twenty male patients were enrolled with mean age 43 years, BMI 29.7 kg/m^2, and baseline sUA 8.1 mg/dL. Combination treatment resulted in greater percentage decrease in sUA than tranilast or allopurinol alone (see table). With $C_{400,}$ 61% of patients achieved sUA levels <4.0 mg/dL, which was significantly greater than the 11% achieved with C_{300} or A_{400} alone (p=0.0027).

	T_{300} N=19	A_{300} N=19	C_{300} (T_{300} + A_{300}) N=18	A_{300} N=19	C_{300} (T_{300} + A_{300}) N=18
Mean % sUA Change from Baseline[a]	−14%	−35%	−43%[b]	−38%	−49%[c]
Responders <6 mg/mL sUA	28%	94%	100%	94%	100%
Responders <4 mg/mL sUA	0%	6%	11%	11%	61%

[a] 24 h after Day 7 dose
[b] *P*-value for LSMean difference between T_{300} or A_{300} and C_{300}; ≤0.0002.
[c] *P*-value for LSMean difference between A_{300} and C_{300}; ≤0.0001.

Coadministration of allopurinol with tranilast did not affect plasma tranilast C_{max} or AUC. Although tranilast had no effect on plasma allopurinol pharmacokinetics, tranilast decreased plasma oxypurinol C_{max} and AUC by ~25–30%, which was an expected interaction, as uricosurics such as tranilast inhibit the reabsorption of both uric acid and oxypurinol in the renal tubules. All treatment regimens were well-tolerated.

Conclusion: In patients with hyperuricemia, combining tranilast 300 mg with allopurinol 400 mg is more effective in reducing sUA to normal levels than allopurinol alone.

Disclosure: J. S. Sundy: Academic Partners for Medical Education, 2, 4, 5, 8, Alnara, 2, 4, 5, 8, Anadys, 2, 4, 5, 8, Ardea, 2, 4, 5, 8, Array, 2, 4, 5, 8, Genentech and Biogen IDEC Inc, 2, Neopharm, 2, 4, 5, 8, Nuon Therapeutics, Inc, 2, 4, 5, 8, Pharmo; **M. M. Kitt:** Nuon Therapeutics, Inc, 3; **S. G. Griffith:** Nuon Therapeutics, Inc, 5; **R. R. Stoltz:** Covance, 1, 3; **R. Goldblum:** Nuon Therapeutics, Inc, 5.

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The Effect of Allopurinol on Renal Function in Patients with Hyperuricemia: A Case-Control Study. Aneesa Krishnamurthy[1], Deana M. Lazaro[5], David R. Blumenthal[4], Donald A. Gerber[2] and Peter L. Flom[3]. [1]SUNY Downstate Medical Center, Kew Garden Hills, NY, [2]SUNY Downstate Medical Center, Brooklyn, NY, [3]SUNY Downstate Medical Center, [4]VA New York Harbor Healthcare System, Short Hills, NJ, [5]VA New York Harbor Healthcare System and SUNY Downstate Medical Center, Brooklyn, NY

Purpose: Animal models and human studies suggest that hyperuricemia has a deleterious effect on renal function, although the effect of lowering serum uric acid on renal function in humans is unclear. The objective of this study is to determine the effect of allopurinol, a uric acid lowering agent, on kidney function in a male veteran population.

Methods: This was a retrospective case-control study using pharmacy, medical and laboratory records from October 2000 to November 2006 of veterans enrolled at the VA New York Harbor Healthcare System. Cases were patients with hyperuricemia defined as a serum uric acid greater than 7 mg/dl who were newly started on allopurinol for any reason and who had evidence of treatment compliance. Controls were patients with hyperuricemia who were not treated with allopurinol or any other uric acid lowering agent. Control patients were matched to cases for race, gender, age, length of follow-up and creatinine clearance (CrCl). Exclusion criteria were treatment with hemodialysis, prior uric acid lowering therapy and acute kidney failure during the observation period. The average length of follow-up was 3.4 years.

Results: The study included 50 cases and 50 controls (100% male, mean age 65.3 years for cases and 64.8 years for controls, 56% African American, average CrCl for cases 70.4 ml/min for cases and 70.7 ml/min for controls). The mean final serum uric acid for the allopurinol group, treated with an average dose of 221 mg/day, was 6.35 mg/ml versus 8.93 mg/ml for the untreated control group (p<0.001). The mean final CrCl for the allopurinol group was 83.23 ml/min, with an average improvement of 12.87 ml/min. There was a significant improvement in CrCl at the end of the observation period in the cases compared with the controls (p=0.037). Adverse events were seen in 3 treated cases: one episode of elevated liver function tests, one patient who experienced diarrhea and another patient with nausea.

Conclusion: Treatment of hyperuricemic patients with allopurinol over an average of 3.4 years resulted in a significant improvement of kidney function in this male cohort from the VA Healthcare system. Clinicians should consider this potential benefit of allopurinol in the treatment of patients with hyperuricemia.

Disclosure: A. Krishnamurthy: None; **D. M. Lazaro:** None; **D. R. Blumenthal:** None; **D. A. Gerber:** None; **P. L. Flom:** None.

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The Impact of Deficits in Gout Care on Hospitalizations. Prachaya Nitichaikulvatana[1], Katherine Upchurch[2] and Leslie Harrold[2]. [1]University of Massachusetts Medical School, Worcester, [2]University of Massachusetts Medical School

Objective: To identify hospital admissions and complicated hospital stays due to gout and examine the contribution deficits in gout care had on hospitalizations.

Methods: We performed a retrospective chart review of all hospitalized patients between January 1, 2008 and December 31, 2009 in whom a rheumatology consultation was requested and a diagnosis of gout was made by the treating rheumatologist. We included only the first inpatient consultation on each patient. Deficits in gout care were identified based on published gout treatment recommendations and quality of care indications. Descriptive statistics were performed.

Results: A total of 700 rheumatology inpatient consultations were performed during the study period of whom 120 patients were diagnosed with gout and met inclusion criteria. At the time of hospitalization, 33 (28%) had no prior diagnosis of gout, although tophi were present in 7 (21%). In the 87 patients with a prior diagnosis of gout, 32 (27%) were crystal proven while in 55 (46%) the diagnosis was made clinically. The majority of patients were Caucasian (82%) and male (78%). The mean age was 69 years. Comorbidities such as hypertension (71%) and renal disease (54%) were common, as well as outpatient use of diuretics (56%) and low dose aspirin (40%). Deficits in pre-hospital gout care were found in 29%. Specifically, urate lowering drugs were not used in the setting of tophi, radiographic erosive changes presumed to be secondary to gout or recurrent gouty attacks. Therefore, acute gout episodes in these settings were considered preventable. Patients with non-crystal proven gout were found to have the most pre-hospitalization deficits of care (21 out of 35). Thirty two patients had a prior evaluation by a rheumatologist (27%). Previous outpatient rheumatology management of gout improved the quality indicators of gout care (P value < 0.02 in patients with a history of gout).

Nine patients (8%) among the study group were rehospitalized due to gout or complications related to gout during the two year study period. Five out of nine (56%) were not treated with urate lowering agents when indicated during their initial hospitalizations.

Table 1. Identification of potential gout triggers stratified by gout diagnosis prior to admission.

	Prehospitalization Diagnosis of Gout			
	Crystal proven gout N = 32	Non-crystal proven gout N=55	No previous history of gout N = 33	Total N=120
Prevention predisposing factors				
Lack of ULD use when indicated	7	21	7	35 (29%)
Nonadherence to ULD treatment	0	2	0	2 (2%)
Nonpreventable predisposing factors				
Worsening renal function	5	11	6	22 (18%)
Aggressive diuretic use	1	8	1	10 (8%)
Fluid shifts from surgery	2	2	2	6 (5%)

Conclusion: This study demonstrates that both outpatient and inpatient deficits in gout quality of care occur commonly and were associated with both complicated hospitalizations and inpatient admission. Addressing gout quality of care in order to reduce the frequency and intensity of acute flares has the potential to reduce the frequency of hospitalizations, and hospital length of stay.

Disclosure: P. Nitichaikulvatana: None; **K. Upchurch:** None; **L. Harrold:** None.

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The Safety and Efficacy of Anakinra in the Treatment of Acute Gout in Hospitalized Patients. Michael Cho[1], Pradipta Ghosh[3], Gurpreet Hans[4], Julia J. Rhiannon[2], Gregory C. Gardner[1] and Peter A. Simkin[1]. [1]University of Washington, Seattle, WA, [2]University of Washington, Seattle, WA, [3]University of Washington, Lake Forest Park, WA, [4]University of Washington, Kirkland, WA

Background: The management of acute gout in the hospital setting can be a difficult clinical problem due to co-morbidities that may limit the use of traditional anti-inflammatory medications. The anti-IL1 receptor antagonist, anakinra, has been successful in the treatment of acute/chronic gout in two published series and 4 case reports totaling 24 patients. The purpose of this study was to review our use of anakinra in acute gout in the hospital setting for efficacy of single and multiple courses of anakinra and to investigate any potential safety concerns.

Methods: We reviewed our consult records over the past three years to identify patients with acute gout treated with anakinra while hospital inpatients. Data extracted from the charts included age, gender, BMI, co-morbidities, uric acid level, results of arthrocentesis, number of anakinra courses, joint(s) and soft-tissue sites involved, anakinra dosing, time to initial improvement, time to complete resolution of signs and symptoms of inflammation, and any possible side effects in particular infection or leukopenia.

Results: We identified 15 patients with acute gout who had received 22 courses of anakinra. The group consisted of 13 males and 2 females, mean age of 53 years (range 32–72 yrs). The major co-morbidities, often in combination, were CKD in 10 patients, DM in 5, CHF in 5, post-solid organ transplant in 2, acute leukemia in 2, and systemic infection in 1. Seven patients had tophaceous disease. The mean BMI was 34.9 (range 22.8–57.8).

Reasons for choosing anakinra were failure of prophylactic low dose colchicine and therapeutic steroids (oral, IV or IA) to reduce pain and inflammation in 14 courses of anakinra and co-morbid disease limitations in 8. Dosing of anakinra was generally 100 mg subcutaneously daily for 3 days. In 18 of the 22 courses, joint involvement was pauci-polyarticular. Ten patients received 1 course of anakinra and 5 patients had 2–4 courses during different hospital stays. In 19/22 anakinra courses, patients reported pain improvement (often dramatic) in 1 day or less. In 3/22 courses pain improvement was noted by day 2. In 9/22 courses patients had complete resolution in 5 or less days, 11/22 in 6–10 days, and in 1/22 it took $>$10 days for the gouty attack to completely resolve. There was no decrement in response to multiple courses separated by time. There were no cases of anakinra-associated leukopenia but one patient developed a post-operative wound infection 5 days after starting an anakinra course.

Conclusion: Anakinra is an effective therapy for acute gout in hospitalized patients with multiple co-morbidities. It was successful in 14 courses where the patients had no apparent response to steroids. It also appears to be effective in multiple courses in the same patient. Dosing strategies, length of therapy, and positioning of anakinra therapy in this setting are areas that will continue to be investigated. The post-operative wound infection is of concern but of uncertain significance. Use of anakinra in the post-operative period should be considered with caution.

Disclosure: M. Cho: None; **P. Ghosh:** None; **G. Hans:** None; **J. J. Rhiannon:** None; **G. C. Gardner:** None; **P. A. Simkin:** None.

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Tranilast Inhibits Urate Transport Mediated by URAT1 and GLUT9. Asim Mandal[3], Daniel Emerling[1], Tito Serafini[1] and David B. Mount[2]. [1]Nuon Therapeutics, Inc., San Mateo, CA 94403, [2]Renal Division, VA Boston Healthcare System and Brigham & Women's Hospital, Harvard Medical School, Boston, MA, [3]Renal Division, VA Boston Healthcare System and Brigham & Women's Hospital, Harvard Medical School, Boston, MA 02115

Background: Gout is a disease first described nearly five millennia ago that still has a large unmet need and a growing incidence. Gout occurs when crystals of monosodium urate (MSU), deposited in joints and soft tissues, lead to acute as well as chronic, local and systemic inflammation. Treatment of gout has focused on chronic treatment of the underlying hyperuricemia that leads to MSU crystal deposition. The kidney mediates two thirds of urate elimination, excreting urate as the net sum of absorption and secretion in the proximal tubule. In humans, proximal tubular urate reabsorption of urate from the glomerular filtrate requires the apical urate-anion exchanger URAT1; basolateral exit is accomplished by GLUT9. Loss of function in either protein is a genetic cause of renal hypouricemia; more common variants in GLUT9 exert a significant effect on serum uric acid. Tranilast, the active ingredient of a drug marketed in Japan and South Korea, has recently been shown both to lower serum uric acid in humans via a uricosuric mechanism and to suppress MSU crystal-mediated inflammatory responses in a animal model of gouty inflammation. Given the critical roles of GLUT9 and URAT1 in urate homeostasis, we determined the effect of tranilast on these two transporters.

Objectives: To determine if tranilast can inhibit urate transport mediated by the two key reabsorptive urate transporters, URAT1 (SLC22A12) and GLUT9 (SLC2A9).

Methods: Urate transport assays were established in *Xenopus* oocytes, injecting cRNA transcribed *in vitro* from expression constructs in the pGEMHE vector. Constructs were generated from full-length cDNAs encoding the long form of human GLUT9 (Genbank sequence BC110414) and human URAT1 (BC053348). [14C]Uric acid was used to monitor transport. Tranilast was prepared in a DMSO stock solution and diluted immediately prior to use. Benzbromarone was utilized as a positive inhibition control for both GLUT9 and URAT1.

Results: Urate transport was robust in *Xenopus* oocytes injected with GLUT9 and URAT1 cRNAs, with urate uptakes as much as 45-fold and 26-fold higher, respectively, than in buffer-injected controls. Urate transport via GLUT9 in this system was inhibited by tranilast with an IC50 of approximately 16 microM. Likewise, tranilast inhibited urate transport mediated by URAT1, with an IC50 of approximately 24 microM.

Conclusions: Tranilast can inhibit urate transport through both GLUT9 and URAT1 proteins, with an IC50 consistent in each case with the level of exposure in humans resulting from doses that produce a uricosuric effect. This suggests that the uricosuric activity of tranilast is due to inhibition of these reabsorptive urate transporters in the kidney.

Disclosure: A. Mandal: None; **D. Emerling:** Nuon Therapeutics, 3; **T. Serafini:** Nuon Therapeutics, 3; **D. B. Mount:** None.

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Urate-Lowering (UL) Efficacy and Safety of Febuxostat (FEB) and Allopurinol (ALLO) in Women with Gout, an Older Subset of Gout Subjects with Increased Comorbidity. Saima Chohan[3], Michael A. Becker[3], Patricia A. MacDonald[1], Solomon Chefo[2] and Robert Jackson[2]. [1]Takeda Global R&D Inc, Lake Forest, IL, [2]Takeda Global Research & Development Center, Inc, Deerfield, IL, [3]University of Chicago, Chicago, IL

Background: Although the incidence and prevalence of gout is increasing in the older population of both genders, literature on women with gout confirms later mean onset of the disease in women than men (averaging a decade or more after menopause) and suggests that the frequent comorbidities (renal impairment, cardiovascular disease, metabolic syndrome components, diuretic use) accompanying hyperuricemia/gout in men may be even more common in women. Given this background, we evaluated the UL efficacy and safety of therapy with FEB or ALLO in the subset of women enrolled in a series of randomized controlled clinical trials (RCTs) comparing these xanthine oxidase inhibitors.

Methods: 4101 subjects (3875 men/226 women) participated in the 12-month FACT or the 6-month APEX or CONFIRMS trials. This post-hoc subset analysis focuses on female subjects with gout and serum urate levels (sUA) $\geq$8.0 mg/dL who were randomized (study specific) to daily PBO (n=11 subjects), FEB (n=139), or ALLO (n=76). Baseline renal functional status was assessed by estimated creatinine clearance (eCLcr) calculated using the Cockcroft-Gault formula. UL efficacy results are reported according to study drug and dose administered and stratified by baseline renal function.

Results: The 5.5% women subjects in these RCTs had a mean age of 62 y (vs 52 y men), and 74% had BMI ≥30 kg/m^2 (62% men). Comorbid history (women vs men), was significant for hypertension (81% vs 48%), diabetes (26% vs 10%), hyperlipidemia (46% vs 37%) and renal impairment (64% eCLcr <60 mL/min vs 13%). Gout history: 19% of women and 21% of men had tophi; 86% and 85%, respectively, had experienced a gout flare in the prior year, and mean disease duration was 8 y women and 12 y men. Mean sUA at baseline was 9.7 mg/dL for both men and women. Proportions of women subjects with final visit sUA <6.0 mg/dL are presented by renal functional status in the Table.

Table. Proportions of Women Subjects With Final Visit sUA <6.0 mg/dL

Baseline Renal Function (eCLcr)	PBO n/N (%)	FEB 40 mg n/N (%)	FEB 80 mg n/N (%)	FEB 120 mg (n/N (%)	FEB 240 mg n/N (%)	ALLO 100/200/ 300 mg* n/N (%)
Normal (≥90 mL/ min)	0/1 (0)	1/2 (50)	7/7 (100)	1/1 (100)	NA	1/2 (50)
Mid (≥60–<90 mL/min)	0/5 (0)	8/10 (80)	21/25 (84)	4/5 (80)	3/3 (100)	9/18 (50)
Moderate or severe (17–59 mL/min)	0/5 (0)	10/23 (44)	35/42 (83)	12/15 (80)	4/4 (100)	24/54 (44)

* 2 subjects with CLcr <80 mL/min received ALLO 100 mg and 32 received ALLO 200 mg NA=not applicable

The most frequently reported AEs among women were: URI (16%), diarrhea (11%), and musculoskeletal/connective tissue (11%). The majority of AEs were transient and resolved while on treatment. The most common serious AEs were cardiac disorders: FEB (all doses 2%) and ALLO (4%).

Conclusions: In this female population with gout and significant comorbidities, including renal impairment, UL with FEB 80 mg and FEB 120 mg were both superior to that of ALLO ($p<0.05$). This is the largest number of female hyperuricemic gout subjects treated in RCTs with either FEB or ALLO. Treatment with febuxostat was effective in reducing sUA to <6.0 mg/dL, independent of renal function, and was well tolerated.

Disclosure: S. Chohan: Takeda Global Research & Development Center, Inc., 5; **M. A. Becker:** Ardea, 5, BioCryst, 5, Regeneron, 5, Savient Pharmaceuticals, 5, Takeda Global Research & Development Center, Inc., 5, URL Pharma, 5; **P. A. MacDonald:** Takeda Global Research & Development Center, Inc, 3; **S. Chefo:** Takeda Global Research & Development Center, Inc, 3; **R. Jackson:** Takeda Global Research & Development Center, Inc, 3.

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Use of Pegloticase in Chronic Gout Refractory to Conventional Therapy Is Associated with Significant Clinical Benefit: Tender Joint and Swollen Joint Counts and Patient Global Assessment (Health Assessment Questionnaire).

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Purpose: To assess the therapy response of pegloticase for a spectrum of non-flare, non-tophus, gout-related rheumatologic variables in patients (pts) with treatment refractory chronic gout (TRCG) in 2 replicate Phase 3, randomized, double-blind, placebo-controlled trials (RCTs).

Methods: TRCG was defined as: ≥3 flares in the previous 18 months, or ≥1 tophus, or gouty arthropathy; serum urate >8.0 mg/dL; and prior failure of maximum medically appropriate dose of allopurinol or contraindication to allopurinol. 212 pts were treated with IV pegloticase or placebo (PBO) in the Phase 3 RCTs. Pts were randomized to PGL 8 mg q2wk (n=85), 8 mg q4wk (n=84), or PBO (n=43) and were infused every 2 weeks for 6 months in a blinded fashion. Primary response endpoint was plasma uric acid (PUA) <6.0 mg/dL 80% of the time in months 3 and 6. Data were pooled for secondary endpoints: reduction of tophus size, gout flare incidence, swollen joints (SJ), tender joints (TJ), pt-reported outcomes by SF-36 and Health Assessment Questionnaire (HAQ). Change from baseline for each secondary rheumatologic variable was compared by regimen and PUA responder status.

Results: Baseline characteristics: 82% male; mean age 55 yrs; high degree of comorbidity: hypertension (71%), chronic kidney disease (43%), cardiovascular disease (31%), and diabetes (22%). As previously reported at ACR 2008, both pegloticase groups were significantly superior to PBO for the primary efficacy endpoint in both studies. Tender joint or swollen joint counts (Table 1) and HAQ-Patient Global Assessment (Table 2), assessed for change from baseline to last visit (last observation carried forward) or week 25, were significant for pooled PGL vs PBO (≤0.001). Changes within each pegloticase group were consistently better in PUA responders® vs non-responders (NR).

Table 1. Tender Joint and Swollen Joint Counts

Swollen Joint Count	Peglotlcase q2wk R	Peglotlcase q2wk NR	Peglotlcase q2wk Total	Peglotlcase q4wk R	Peglotlcase q4wk NR	Peglotlcase q4wk Total	Placebo
Baseline, n	36	49	84	29	54	83	43
Baseline, mean (SD)	10.5 (11.7)	7.7 (10.6)	8.9 (11.1)	10.3 (11.5)	9.9 (9.2)	10.1 (10.0)	13.2 (13.7)
Week 25, n	36	25	61	29	34	63	38
Week 25, mean Δ(SD)	−8.6 (10.3)	−3.4 (9.4)	−6.4 (10.2)	−8.0 (9.3)	−3.4 (5.3)	−5.6 (7.78)	−2.1 (12.2)
Final visit, n	35	43	78	29	48	77	43
Final visit, mean Δ(SD)	−8.6 (10.3)	−3.0 (10.0)**	−6.5 (10.5)	−8.0 (9.3)	−3.3 (6.20)**	−6.1 (7.8)	−2.6 (11.6)
p-value [1]							0.001
Tender Joint Count							
	Peglotlcaseq2wk R	Peglotlcaseq2wk NR	Peglotlcaseq2wk Total	Peglotlcase q4wk R	Peglotlcase q4wk NR	Peglotlcase q4wk Total	Placebo
Baseline, n	36	49	84	29	54	83	43
Baseline, mean (SD)	11.7 (13.3)	11.6 (12.8)	11.7 (13.0)	12.3 (15.3)	10.4 (12.6)	11.1 (13.5)	14.1 (14.8)
Week 25, n	36	25	61	29	34	63	38
Week 25, mean Δ(SD)	−8.9 (12.0)	−7.7 (12.1)	−8.4 (11.9)	−9.9 (12.8)	−3.9 (8.89)	−6.7 (11.2)	−0.9 (12.8)
Final visit, n	35	43	78	29	48	77	43
Final visit, mean Δ(SD)	−8.9 (12.0)	−6.1 (11.9)**	−7.4 (12.0)*	−9.9 (12.8)	−3.9 (8.5)**	−6.1 (10.6)*	−1.2 (12.3)
p-value [1]							<0.001

Week 25 = 14 days after dose 12
[1] P-value for pooled PGL vs PBO.
* P-value significant or comparison of corresponding peglotlcase group vs. placebo.
** P-value significant or comparison of with in group P vs. NR

Table 2. HAQ Patient Global Assessment

	Pegloticase q2wk R	Pegloticase q2wk HR	Pegloticase q2wk Total	Pegloticase q4wk R	Pegloticase q4wk HR	Pegloticase q4wk Total	Placebo
Baseline, n	33	40	73	25	53	78	40
Baseline, mean (SD)	42.7 (26.1)	42.2 (24.0)	42.4 (24.8)	49.6 (25.2)	49.9 (25.0)	49.8 (24.9)	51.6 (24.9)
Week 25, n	32	20	52	25	33	58	35
Week 25, mean (SD)	23.3 (20.7)	33.1 (24.6)	27.1 (2.6)	26.2 (19.6)	41.4 (26.3)	34.9 (24.7)	53.4 (25.5)
A from BL	−20.0 (27.0)	−13.2 (21.1)**	−17.5 (24.9)*	−23.4 (24.8)	−6.2 (23.7)**	−13.6 (25.5)*	4.2 (20.2)
P-value [1]							<0.001
Final visit, n	33	36*	69	25	47	72	40
Final visit, mean (SD)	22.8 (20.7)	37.5 (27.2)	30.4 (25.2)	26.2 (19.6)	42.9 (25.3)	37.1 (24.7)	52.4 (26.2)
A from BL	−19.94 (26.5)	−4.2 (27.6)**	−11.9 (28.0)*	−23.4 (24.8)	−6.9 (26.6)**	−12.6 (27.0)*	0.8 (25.0)
P-value [1]							<0.001

[1] P-value for pooled PGL vs PBO.
*P-value significant for comparison of corresponding pegloticase group vs. placebo
**P-value significant for comparison of within group R vs. NR
§Change from baseline only includes 19 (or 35) subjects based on lacking baseline for one subject

Conclusions: Successful pegloticase therapy in patients with chronic gout refractory to conventional urate-lowering therapy (defined as UA < 6 mg/dL 80% of the time in months 3 and 6 during replicate Phase 3 trials), is associated with improvement in tender joint and swollen joint counts and Patient Global Assessment.

Disclosure: D. R. Mandel: Amgen, Abbott, BMS, Lilly, Pfizer, Takeda, 8, Savient Pharmaceuticals, 9; **H. Baraf:** Investigaotr, 9, Savient Pharmaceuticals, 5, 9, Takeda Pharmaceuticals North America, 8; **C. Rehrig:** Savient Pharmaceuticals, 3; **Z. D. Horowitz:** Savient Pharmaceuticals, 9; **F. D. Ottery:** Savient Pharmaceuticals, 3; **R. A. Yood:** Savient Pharmaceuticals, 9, Takeda Pharmaceuticals North America, 2.

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A Specific Chemokine Expression Pattern Is Associated with Synovial Inflammation and Symptoms in Patients with Traumatic Knee Injury Undergoing Arthroscopic Meniscectomy. Carla R. Scanzello[7], Brian McKeon[6], Bryan H. Swaim[6], Edward DiCarlo[5], Eva Umoh[4], Veero Kanda[8], Anjali Nair[8], David M. Lee[2], John C. Richmond[6], Jeffrey N. Katz[1], Mary K. Crow[3] and Steven R. Goldring[3]. [1]Brigham & Womens Hosp, Boston, MA, [2]Brigham and Womens Hospital, Boston, MA, [3]Hospital for Special Surgery, New York, NY, [4]Hospital for Special Surgery, New York NY, [5]Hosptial for Special Surgery, New York NY, [6]New England Baptist Hospital, Boston MA, [7]Rush University Medical Center, Chicago, IL, [8]Rush University Medical Center, Chicago IL

Objective: In established OA, the presence of synovitis is associated with pain and progression, but a relationship between synovitis, symptoms and meniscal pathology in isolated meniscal disease has not been previously investigated. The present studies were undertaken to characterize synovial pathology in patients with traumatic knee injuries associated with meniscal tears, and to determine the relationship between synovial inflammation, meniscal and cartilage pathology, and symptoms. Furthermore, the synovial gene expression patterns were analyzed to gain insight into the gene products and molecular pathways that may contribute to development of meniscal pathology and synovial inflammation in these patients.

Methods: Patients without clinical or radiographic evidence of OA undergoing athroscopic menisectomy for traumatic knee injuries were recruited. Pain and function were assessed preoperatively utilizing the Lysholm score (a patient-administered questionnaire measuring knee-specific symptoms and dysfunction); meniscal and cartilage abnormalities were documented at the time of surgery. Inflammation was scored histologically on synovial biopsies and associations between inflammation and Lysholm scores determined. Microarray analysis of synovial tissue was performed and expression patterns in patients with or without inflammation compared. The microarray results were confirmed by real-time pcr.

Results: Synovial inflammation was present in 42% of the patients and was associated with worse pre-operative Lysholm scores, independent of age, gender, or pre-existing cartilage pathology. Microarray analysis and real-time PCR revealed a chemokine signature in synovial biopsies with increased inflammation scores. Increasing synovial transcript levels of the chemokine/receptor pair CCL19/CCR7, identified by microarray and quantitated by real-time PCR, were significantly associated with worse Lysholm scores (Spearman $r = -0.86$ and -0.79 respectively, $p = 0.002$).

Conclusion: In patients with traumatic meniscal injury without clinical or radiographic evidence of OA undergoing arthroscopic menisectomy, synovial inflammation was a frequent finding and was associated with increased pain and dysfunction. Synovium with inflammatory infiltrates exhibited a chemokine signature, and expression levels of CCL19 and its receptor CCR7 were strongly associated with symptoms measured by the Lysholm score. Chemokines play a role in the development of synovial inflammation in patients with meniscal pathology and represent potential therapeutic targets to reduce inflammatory symptoms and potentially modulate the long-term risk for the development of OA.

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A Systematic Review and Meta-Analysis of the Impact of Total Shoulder Arthroplasty on Health-Related Quality of Life. Michael J. Carter[1], Ted R. Mikuls[1], Smita Nayak[2], Edward V. Fehringer[1] and Kaleb D. Michaud[1]. [1]Univ of Nebraska Med Ctr, Omaha, NE, [2]University of Pittsburgh, Pittsburgh, PA

Background: Total shoulder arthroplasty (TSA) is becoming more common as an arthritis treatment. However, the effect of TSA on health related quality of life (HRQoL) has not been established. The goal of this systematic review and meta-analysis was to characterize the change in HRQoL as a result of TSA. A quantitative value would establish the potential benefit from the procedure, and also help to evaluate future modifications to the TSA procedure.

Methods: We identified published studies that showed preoperative and postoperative HRQoL outcomes for patients receiving TSA. Articles were included if: 1) patients received primary TSA with an unconstrained prosthesis, with synthetic humeral and glenoid components, and 2) preoperative and postoperative HRQoL measures with at least 6 months of follow-up were reported. Reports were examined to identify all HRQoL measures reported, and meta-analysis was used to calculate standardized mean differences (SMD, reflective of the effect size) and 95% confidence intervals (CI) for each scale.

Results: There were 20 studies (1576 total shoulders) examining TSA outcomes meeting criteria for inclusion in the meta-analysis. Nearly all shoulders had treatment indications of primary osteoarthritis (n=1499) and rheumatoid arthritis (n=60). The most commonly examined HRQoL outcome measures included the Short Form-36 (SF-36), the visual analog scale for pain (VAS), and three shoulder specific measures: Constant score, American Shoulder and Elbow Surgeons score (ASES), and Simple Shoulder Test (SST). Effects of TSA on study outcomes are summarized in the Table, with the average follow-up at 45.2 months:

HRQoL Outcome (number of studies reporting)	Standardized Mean Difference (95% CI)	Mean Difference in Outcome Measure (SD)
SF-36 physical component score (n = 4)	0.69 (0.52 to 0.86)	7.02 (1.78)
SF-36 mental component score (n = 4)	−0.04 (−0.20 to 0.13)	−0.10 (3.56)
Constant score (n = 11)	2.67 (2.55 to 2.79)	38.1 (19.9)
ASES (n = 5)	2.61 (2.43 to 2.80)	53.6 (25.3)
SST (n = 3)	2.20 (1.96 to 2.44)	6.51 (2.60)
Pain VAS (n = 5)	−2.63 (−2.86 to −2.40)	−5.79 (2.58)

Conclusions: Total shoulder arthroplasty is efficacious, offering significant improvement in both function and pain. Shoulder-specific measures demonstrate far greater changes postoperatively than does the global SF-36 instrument. However, the change in SF-36 physical component score is statistically significant, and an SMD of 0.69 is a moderate to large effect size. Because most patients receive TSA on an elective basis, establishing the effect of TSA on HRQoL measures via systematic review and meta-analysis has important implications for both patients and payers.

Disclosure: M. J. Carter: None; **T. R. Mikuls:** None; **S. Nayak:** None; **E. V. Fehringer:** Tournier, 7; **K. D. Michaud:** None.

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Cane Use in Hip Osteoarthritis. Karen L. Perell-Gerson[1], Constance Heiney[4], Nancy D. Harada[4], Jennifer M. Yentes[2], Sulabha Masih[4] and Meika A. Fang[3]. [1]Georgia Gwinnett College, Lawrenceville, GA, [2]University of Nebraska at Omaha, [3]VA Greater Los Angeles Healthcare System, Los Angeles, CA, [4]VA Greater Los Angeles Healthcare System, Los Angeles, CA

Purpose: Symptomatic hip osteoarthritis (OA) affects ~5% of the population over the age of 60 years, is often highly disabling and progressive, and accounts for most total hip replacements in Western countries. Although canes are often prescribed as part of the therapy for hip OA, little information is available regarding the impact of canes on pain, function, and gait characteristics. The aim of this pilot study was to evaluate the effects of walking aids on hip OA by testing the hypothesis that the use of a single-point cane would alter gait characteristics, decrease pain and improve function in hip OA patients.

Methods: Fourteen male participants with symptomatic hip OA (mean Kellgren-Lawrence grade 2.6) were given a single point cane to use contra-lateral to the painful limb for four weeks. All participants underwent gait assessment with and without a cane at baseline and after four weeks of cane use via a three-dimensional motion capture system (Motion Analysis Corp., Santa Rosa, CA) and an in-shoe dynamic pressure distribution system (Novel Electronics, St. Paul, MN). OA-related pain, stiffness, and function were assessed with the Western Ontario and McMaster Universities Osteoarthritis Index. Participants also completed a questionnaire regarding frequency of cane use, falls, and their opinions regarding cane use.

Results: Fourteen male participants (mean age 67.5 ±5.8 years) completed the study. At the baseline visit, mean cadence was 99 steps/min when subjects ambulated without a walking aid and the cadence decreased to 85 steps/min when they walked with a cane contralateral to the painful limb

($p<0.001$). They also walked slower when using a cane compared to walking unaided with the gait speed decreasing from 80 to 68 cm/sec ($p<0.005$). The decrease in cadence and gait speed when walking with a cane compared to walking unaided persisted in these participants after using the cane for four weeks. Step length and stride length did not differ when participants walked without a cane and with a cane contralateral to the painful limb. Force (%BW) and pressure (%BW) on the whole foot were decreased on the painful limb compared to the unaffected limb when walking with and without a cane. There were no significant changes in OA pain, function, and stiffness after using the cane for four weeks. Eight of the participants reported using the cane six or more times a week. Most of them (13/14) noted that using the cane prevented them from losing their balance and half of the participants reported a history of falls or near falls prior to enrolling in the study.

Conclusion: This pilot study suggests that decreased gait speed and cadence when walking with a cane may be one strategy people with symptomatic hip OA adopt to improve gait stability. However, cane use may not be as effective in relieving hip pain for some people and this may be due in part to insufficient offloading of the affected limb and to intermittent use of the cane during ambulation.

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Comorbid Subjective Health Complaints in Patients with Sciatica, a Prospective Study Including Comparison with the General Population. Lars Grøvle[2], Anne J. Haugen[2], Camilla Ihlebaek[5], Anne Keller[1], Bård Natvig[4], Jens I. Brox[6] and Margreth Grotle[3]. [1]Department of Physical Medicine and Rehabilitation, Oslo University Hospital, Ullevaal, [2]Department of Rheumatology, østfold Hospital Trust, Fredrikstad, Norway, [3]FORMI (Communication Unit for Musculoskeletal Disorders), Oslo University Hospital, Ullevaal, [4]National Resource Centre for Rehabilitation in Rheumatology, Diakonhjemmet Hospital & Department of General Practice and Community Medicine, ASAM, University of Oslo, [5]Research Group of Nature, Health and Quality of Life, Norwegian University of Life Sciences, Aas, [6]Section for Back Surgery and Physical Medicine and Rehabilitation, Orthopaedic Department, Oslo University Hospital, Rikshospitalet

Background: Chronic nonspecific low back pain is accompanied by high rates of comorbid mental and physical conditions. The aims of this study were to investigate if patients with specific back pain, that is, sciatica caused by lumbar herniation, reported higher rates of subjective health complaints (SHC) than the normal population, and if there is an association between change in sciatica symptoms and change in subjective health complaints over a 12-month period.

Methods: A multicenter cohort study of 466 sciatica patients was conducted with follow-up by mailed questionnaires at 3, 6 and 12 months. All patients had radiating pain or paresis below the knee, and a lumbar disc herniation verified by an MRI or CT scan of the corresponding level and side. SHCs were measured by 27 items of the SHC inventory which is a list of common somatic and psychological complaints. The SHC number in each patient was calculated by summing all complaints present. Items directly related to sciatica were not included. Sciatica severity was measured by the Maine Seattle Back Questionnaire. Patient recovery was assessed by a 7 point sciatica global change scale. Odds ratios for each SHC, with adjustments for age, sex and education, were calculated with comparison to a general population sample (n = 928) by logistic regression. Change in the SHC number between baseline and 1 year as function of patient recovery was calculated by Wilcoxon's matched pairs signed-rank sum test or paired *t*-tests.

Results: At baseline, the sciatica patients reported a mean (SD) SHC number of 7.5 (4.4), compared to 5.2 (4.4) in the reference population ($p < 0.01$). The ORs for reporting SHCs for the sciatica patients were significantly higher in 15 of the 27 items. The most prevalent complaints were sleep problems (OR= 8.3 [95% CI= 6.3–10.8]), constipation (OR=5.8 [95% CI 4.1–8.2]), sadness/depression (OR=5.3 [95% CI 4.1–6.8] and heat flushes (OR= 4.6 [95% CI 3.3–6.4]). During the one-year follow-up period, the mean number of SHCs remained stable while the sciatica severity improved. Spearman's correlation coefficient between the change in the SHC number and the change in the MSBQ was − 0.25. Of those patients who at 1 year follow-up rated their sciatica as *completely gone* (n=61), the mean SHC number was significantly reduced from 6.3 (*SD* = 4.2) at baseline to 4.6 (*SD* = 4.0) at 1 year (mean difference= –1.8 [95% (CI) = –0.8 to –2.8], $p < 0.01$). Of those who rated their sciatica as *unchanged* or *worse* (n=74), the mean number of SHCs increased significantly from 8.0 (*SD* = 4.8) to 9.4 (*SD* = 5.5) (mean difference = 1.4 [95% CI = 0.4–2.3], $p < 0.01$).

Conclusion: Among those patients who fully recovered from their sciatica, the number of SHC was reduced to the level of the general population. Among those with persisting or worsening sciatica, the number of complaints increased to a level almost double that of the general population.

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Early Progressive Rehabilitation Following Total Knee Arthroplasty Improves Outcomes. Michael J. Bade[2], Tami Struessel[2] and Jennifer E. Stevens-Lapsley[1]. [1]University of Colorado Denver, Aurora, CO, [2]University of Colorado Denver

Background: Although total knee arthroplasty (TKA) reliably reduces pain, research indicates that current rehabilitation methods do not adequately rehabilitate patients to the level of their healthy peers. The purpose of this study was to assess the initial efficacy of a progressive rehabilitation program (PROG) compared to a standard rehabilitation program (historical controls).

Patients: Eight patients (PROG group) undergoing a unilateral, primary TKA for end-stage osteoarthritis participated(65.3 ± 11.5 years; 5 women, 3 men). Patients were compared to a historical cohort of 37 patients (64.9 ± 8.6 years; 19 women, 18 men). Patients from both groups were excluded if they had uncontrolled hypertension, uncontrolled diabetes, body mass index >35 kg/m2, contralateral knee pain, other significant lower extremity orthopaedic problems, or neurological impairments.

Methods: Active range of motion (AROM) was measured by goniometry. Maximum isometric quadriceps strength was assessed using an electromechanical dynamometer and normalized to body weight. Activation was assessed using a doublet twitch interpolation technique. Functional performance was assessed using the 6-minute walk test (6MW), timed up and go test (TUG), and timed stair climbing test (SCT). All measures were assessed preoperatively, 1 month, 3 months, and 6 months after surgery.

Rehabilitation: The historical cohort completed a previously published standard rehabilitation program. The PROG group completed a rehabilitation program that differed in several key ways: a longer duration of treatment (12 weeks vs. 10 weeks); a higher frequency of treatment (28 vs. 18 sessions); the use of single-leg, machine-based resistive exercise; and an emphasis on higher level functional exercises (e.g. lunges, step-downs).

Results: There were no differences in baseline demographics between groups (age, BMI or sex). Compared to historical controls at one month after surgery, the PROG group walked 78.3 m farther on the 6MW, were 3.5s faster on the TUG, were 10.1s faster on the SCT, demonstrated 57.4% greater quadriceps strength, and 17.4% better quadriceps activation. At 3 months, the PROG group walked 47.2 m further on the 6MW, were 1.4s faster on the TUG, were 1.9s faster on the SCT, demonstrated 33.9% greater quadriceps strength, and 7.8% better quadriceps activation than controls. At 6 months after surgery, the PROG group walked 67.0 m further on the 6MW, were 1.1s faster on the TUG,1.2s faster on the SCT, demonstrated 35.5% greater quadriceps strength, and 9.3% better quadriceps activation than controls. Although there were baseline differences on AROM, at 6 months the PROG group demonstrated better knee extension (-1.9° vs. 1.2°) and better flexion (120° vs. 113°).

Conclusions: A progressive program of rehabilitation which includes higher frequency, longer duration, and higher level of exercise leads to improved outcomes compared to a standard rehabilitation program. This higher intensity rehabilitation did not impair ROM and did not result in any increased incidence of injury.

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Disclosure: M. J. Bade: None; **T. Struessel:** None; **J. E. Stevens-Lapsley:** None.

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Facet Joint Injections for Low Back Pain Improve Quality of Life. Cecilia Mercieca[2], Stefania Chetcuti Zammit[2], Josef Lauri[1] and Andrew Albert Borg[2]. [1]Department of Mathematics, University of Malta, Malta, [2]Department of Rheumatology, Mater Dei Hospital, Msida, Malta

Aim: To ascertain whether facet joint injections improve Quality of Life in chronic low back pain. Secondary endpoints studied included procedure efficacy and safety.

Patients and Methods: 40 patients suffering from low back pain due to facet joint disease [1] were recruited. All patients had degenerative changes in

their facet joints on radiographs. Severity of back pain was assessed at baseline and after one month. Patients were asked about any improvement in back pain, activities of daily living (ADLs) and walking ability they expected as a result of the procedure. These responses were measured using 10mm VAS and correlated with the actual outcomes one month after injection. The Roland-Morris disability (RDQ) [2] and the Oswestry [3] questionnaires were also administered at baseline and one month after the intervention.

Results: 40 patients underwent facet joint injection (11 males, 29 females). There was significant improvement in pain and disability according to the RDQ. The mean score at baseline was 13.1 (CI 12.33–17.76) while after one month it was 10.4 (CI 9.63–15), p=0.008. No significant improvement was found using the Oswestry questionnaire (p=0.9). There was a strong correlation between high expectations of improvement at baseline and actual improvement at one month in ADLs (r=0.7; p=0.001), improvement in back pain (r=0.37; p=0.026), but not for walking ability (r=0.25; p=0.132). Gender, BMI, age and severity of back pain did not influence outcomes.

The lack of correlation between severity of back pain at baseline and the actual improvement in back pain at one month suggests that the degree of improvement depended more on the individual's expectation of benefit rather than the actual back pain severity.

More than 70% felt the procedure helped and 60% of them were willing to undergo the procedure again. Prior to the procedure over 60% expected complications although none occurred, confirming that the procedure is safe.

Conclusions: Evaluating treatment outcome for low back pain has always generated considerable interest. This study shows that facet joint injections reduce disability as measured by the RDQ with a clinically significant change of nearly three points in the scale. This study further suggests that the two disability measures studied should not be used uncritically as their complexity varies and the domains that they cover are different.

Additionally, the patient's expectation of improvement from the facet joint injection was a better predictor of improved outcome than the initial severity of back pain reinforcing the concept of a multifactorial aetiology for the pain. Patients with very low expectations of benefit from this procedure tended to have poorer outcomes and little improvement in quality of life. This is relevant when selecting patients for facet joint injection. Facet joint injections are a safe and useful adjunct in the treatment of low back pain.

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3. Fairbank JCT and Pynsent PB. Spine 2000;25:2940–2953.

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Fat Mass Is a Predictor of Disabling Foot Pain: A Cross-Sectional Study. Stephanie Tanamas[4], Anita Wluka[4], Patricia Berry[4], Hylton Menz[2], Boyd Strauss[4], Miranda Davies-Tuck[4], Joseph Proietto[5], John Dixon[1], Graeme Jones[3] and Flavia Cicuttini[4]. [1]Baker IDI Heart and Diabetes Institute, [2]La Trobe University, [3]Menzies Research Institute, [4]Monash University, [5]University of Melbourne

Background: To examine the relationship between body composition and disabling foot pain as assessed by the Manchester Foot Pain and Disability Index (MFPDI).

Methods: 137 subjects aged 25–62 years were recruited as part of a study examining the relationship between obesity and musculoskeletal health. Disabling foot pain was determined from the MFPDI and defined as current foot pain and pain in the last month, and recording ≥ 1 disability item on the MFPDI (an MFPDI score of ≥ 1). Body composition was measured using dual x-ray absorptiometry.

Results: The BMI in this population was normally distributed around a mean of 32.2 kg/m^2.The prevalence of foot pain was 54.7%. In multivariate modelling, there was a positive association between BMI and disabling foot pain (OR 1.11, 95% CI 1.05, 1.17). Similarly, the risk of disabling foot pain was positively associated with total body fat mass (OR 1.05, 95% CI 1.02, 1.08) adjusted for age, gender, strenuous physical activity, and skeletal muscle mass. Total body fat mass was also positively associated with functional limitation, foot pain intensity and self consciousness regarding feet/footwear, independent of skeletal muscle mass.

Conclusions: Fat mass, but not muscle mass, is associated with foot pain. This suggests that obesity may affect foot pain not only through increased loading but also act via a systemic mechanism through increased adiposity. Further work is needed to clarify the mechanisms for this effect and the importance of reducing body fat rather than simple weight loss in the reduction of foot pain.

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Is There an Association between Living Situation and Pain Severity at the Time Patients Choose Total Hip Replacement? Yvonne C. Lee[1], Huong T. Do[3] and Lisa A. Mandl[2]. [1]Brigham and Women's Hospital, Boston, MA, [2]Hospital for Special Surgery, New York, NY, [3]Hospital for Special Surgery

Background: Living situation is an important measure of social support and could influence when patients choose to undergo total hip replacement (THR). We examined whether living situation is associated with pain severity, the main reason patients decide to undergo THR, and whether living situation is a potential effect modifier of the relationship between sociodemographic variables and pain.

Methods: This single center study evaluated a cohort of 3079 patients over 40 years of age who decided to undergo primary unilateral THR between May 2007 and September 2009. Participants with a systemic inflammatory disease were excluded. Living situation was categorized as: 1) those who lived alone and 2) those who lived with others. Education was dichotomized as < college or some college or more. Self-reported pain after scheduling THR surgery was assessed using the WOMAC pain score. Univariate associations between clinical variables and pain were assessed using two sample t-tests. Variables associated with pain with P-value < 0.01 were considered for inclusion in the multivariable model, in which pain at time of THR was the dependent variable. The final multivariable model was obtained using a backward selection process. Stratified analyses were performed to assess the role of living situation as an effect modifier.

Results: Mean age was 62.5 ± 11.0 years. Fifty percent were female. Ninety-four percent were Caucasian. In univariate analyses, living situation was significantly associated with pain at the time of THR (P-value= 0.01). In multivariable analyses adjusted for age and sex, living situation was not significantly associated with pain severity at the time of THR. Race, education level, Elixhauser comorbidity index, fatigue and vitality were significantly associated with pain severity. In analyses stratified by living situation, age, sex, fatigue and vitality remained significantly associated with pain severity in both models. Non-Caucasian race was more strongly and significantly associated with greater pain at the time of THR (B = 5.3, P-value = 0.03) among patients living alone (N = 659) than among patients living with others (N = 2383) (B = 2.1, P-value = 0.18). Less education was more strongly and significantly associated with more severe pain (B = 4.6, P-value < 0.0001) among patients living with others than among patients living alone (B = 2.9, P-value = 0.16).

Conclusions: Although living situation is not independently associated with pain severity at the time of THR, it appears to act as an effect modifier. This raises the possibility that living situation could influence how much pain patients are willing to tolerate before choosing THR. While statistical significance is dependent on sample size, these differential relationships should be explored further.

Disclosure: Y. C. Lee: Merck Pharmaceuticals, 1, Novartis Pharmaceuticals Corporation, 1; **H. T. Do:** None; **L. A. Mandl:** None.

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OMERACT Responder Analysis of Patients Treated with Duloxetine for Chronic Low Back Pain. Vladimir Skljarevski[1], Matthew J. Bair[2], Melissa J. Ossanna[1], Eli Frakes[1], Shuyu Zhang[1] and Karla Alaka[1]. [1]Eli Lilly and Company, [2]Roudebush VA Medical Center

Background: There are no standardized outcome measures to assess treatment effect in chronic low back pain (CLBP) clinical trials. The OMERACT (Outcome Measures in Rheumatology) group proposed a preliminary approach to assessing treatment responders in CLBP trials (Simon et al, 2007). This current analysis utilizes the OMERACT approach to measure response in trials of duloxetine for the treatment of CLBP.

Methods: We analyzed three randomized, double-blind, placebo-controlled clinical trials of duloxetine in the treatment of adult patients with

CLBP. Duloxetine treatment dose was 60 mg daily, 120 mg daily or flexible doses of 60–120 mg daily over 12 or 13 weeks. OMERACT treatment response was a composite outcome defined as a ≥30% reduction in Brief Pain Inventory average pain, a Patient Global Impression score PGI-I ≤2 ("much improved") at endpoint and Roland Morris Disability Questionnaire (RMDQ) total score reduction from baseline ≥2.

Results: In Study 1, 35.4% of patients taking duloxetine 60–120 mg (N=99) met the defined response criteria versus 18.1% of patients assigned to placebo (N=105; p=0.007). In Study 2, response criteria was met by 36.1% of patients taking 60 mg duloxetine (N=83) and 34.1% of patients taking 120 mg duloxetine (N=82), versus 27.2% of patients taking placebo (N=92; p=0.254 and p=0.328, respectively). In Study 3, 37.9% of patients taking duloxetine 60 mg (N=177) responded versus 26.8% of those taking placebo (N=179; p=0.031).

Conclusions: Our analysis demonstrates that duloxetine was more efficacious than placebo in 2 out of 3 separate trials of patients with chronic low back pain, as assessed by the OMERACT composite outcome, including pain severity, patient perception of improvement and functional limitations. These findings suggest that duloxetine may be helpful in the clinical armamentarium for the treatment of chronic low back pain.

Reference:

Simon LS, Evans C, Katz N, Bombardier C, West C, Robbins J, Copley-Merriman C, Markman J, Coombs JH. Preliminary Development of a Responder Index for Chronic Low Back Pain. J Rheumatol. 2007;34:1386–91

Disclosure: V. Skljarevski: Eli Lilly and Company, 3; **M. J. Bair:** None; **M. J. Ossanna:** Eli Lilly and Company, 3; **E. Frakes:** Eli Lilly and Company, 3; **S. Zhang:** Eli Lilly and Company, 3; **K. Alaka:** Eli Lilly and Company, 3.

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The Clinical Benefit of Joint Distraction in Treatment of Advanced Ankle OA May Be Partly Explained by Subchondral Bone Changes. F. Intema[1], T. P. Thomas[2], D. D. Anderson[2], J. Elkins[2], S. C. Mastbergen[1], F. P. J. G. Lafeber[1], T. D. Brown[2], A. Amendola[2] and C. L. Saltzman[3]. [1]Rheumatology & Clinical Immunology, University Medical Center Utrecht, The Netherlands, [2]The University of Iowa, Iowa City, IA, [3]The University of Utah, Salt Lake City, UT

Background: In osteoarthritis (OA), it has long been understood that cartilage degeneration is accompanied by sclerosis of subchondral bone. The subsequent stiffening of the bone decreases its capacity to absorb mechanical impact energy, which might play a role in the development and/or progression of cartilage degeneration. Joint distraction as a treatment for advanced ankle OA has been shown to provide pain relief and improve clinical function, with some evidence accruing that cartilage repair is involved. However, the underlying mechanism(s) remain unclear. This study evaluated whether long-term changes in subchondral bone density are associated with extended joint distraction.

Methods: Twenty-six patients with advanced post-traumatic ankle OA were treated with joint distraction for three months using an Ilizarov frame. Follow-up was two years, and clinical outcome was assessed using the ankle OA scale (AOS).

Dual-contrast CT scans were obtained at baseline (before treatment), and at one- and two-year follow-ups after treatment, to analyse joint space width and bone density. The tibia and talus bones were manually segmented at each time point, and the bone segmentations from the two follow-up CT scans were registered to the baseline scans for each patient. The resulting spatial transformations were then used to bring all CT datasets for a given patient into a common spatial reference frame, using purpose-written MATLAB code. Changes in bone density (Hounsfield Units (HU), relative to baseline) were calculated at a number of discrete locations beneath the tibial and talar weight-bearing regions. The measurement grid covered a subchondral patch of nominally 650 mm2, with ~4000 point measurements per surface (~0.17mm2/point). Bone density calculations were performed at 1 mm intervals beneath the bone surface, along the surface normals and extending subchondrally up to 8 mm (total of roughly 30,000 sampled point locations for each bone).

Results: Joint distraction resulted in a statistically significant long-term decrease in pain (mean value decreased from 60 to 35, on a scale of 100; p<0.01) and function (mean decreased from 67 to 36; p<0.01) at two years post-treatment. These clinical changes were accompanied by changes in bone density. The initial subchondral bone density was 569±14 HU for the tibia, and 490±19 HU for the talus. The average decrease in density was 133±17 HU (p<0.01) for the tibia and 95±17 HU (p<0.01) for the talus, one year after treatment. These density changes persisted two years after treatment (124±16 HU; p<0.01, and 88±18 HU; p<0.01, for tibia and talus, respectively), and they were not significantly different from the bone density one year after treatment (p=0.11).

Conclusion: Treatment of advanced post-traumatic ankle OA with three months of joint distraction produced decreases in subchondral bone density that persisted for at least two years of follow-up. This could lead to a more physiologically normal distribution of mechanical stresses by the less dense bone, encouraging cartilage repair activity. As such, these prolonged bone changes may in part explain the clinical benefits of joint distraction.

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The Safety and Patient Acceptability of Suprascpular Nerve Block. E. Michael Shanahan[2], Kieran Ross Shanahan[2], Catherine Hill[1], Malcolm Smith[2] and Michael John Ahern[2]. [1]Adelaide University, Adelaide, South Australia, Australia, [2]Flinders University, Adelaide, South Australia, Australia

Background: Suprascapular nerve block is an effective therapy for shoulder pain from arthritis. To date however, the safety of the procedure has not been fully validated. This is because the numbers of patients in the trials to establish the efficacy of the treatment are far smaller than those required to establish its safety. Since 2003 the rheumatologists at the Repatriation General Hospital Flinders Medical Centre and the Queen Elizabeth Hospital have been regularly performing this procedure for the relief of shoulder pain.

The safety and patient satisfaction of their experience with this procedure has now been assessed.

Aim: To audit the safety and patient satisfaction of patients receiving at least one suprascapular nerve block performed by rheumatologists in South Australia between 2003 and 2009.

Methods: All nerve blocks performed between 2003–2009 were included in the study. The interventions were sourced through an electronic search of the medical records. In all, 1005 individual procedures were reviewed. Case note reviews of all the procedures were performed and each patient contacted. Case notes were audited for patient demographics, and recorded complications. Patients were surveyed for complications and also satisfaction using the Patient Satisfaction Questionnaire in Musculoskeletal Care. Supplementary questions were added to enquire specifically about satisfaction for the nerve block procedure.

Results: 1005 nerve block were performed on 293 patients (mean age 78, 75% with one or more co morbidities). 6 minor complications (presyncope, transient arm weakness and facial flushing) were reported or recorded. There were no major complications, giving a maximum significant complication rate of 0.3%. The overall response rate to the satisfaction survey was 55%. 87% of respondents were satisfied with the results of the nerve block.

Conclusion: Suprascapular nerve block is a safe procedure which is well tolerated by patients, even those with multiple co morbidities. Patients rate the procedure highly in terms of the ease of procedure and the pain relief that it confers.

Disclosure: E. M. Shanahan: None; **K. R. Shanahan:** None; **C. Hill:** None; **M. Smith:** None; **M. J. Ahern:** None.

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Using the Patient Generated Index (PGI) To Measure Personalized Quality of Life (QoL) in Patients Undergoing Total Knee Arthroplasty (TKA). Maria A. Lopez-Olivo[2], Michael A. Kallen[2], Chong H. Pak[2], Sherwin J. Siff[1], Glenn C. Landon[1], David Edelstein[1], Kausha C. Robinson[2] and Maria E. Suarez-Almazor[3]. [1]St. Luke's Episcopal Health System, Houston, TX, [2]The University of Texas M.D. Anderson Cancer Center, Houston, TX, [3]University of Texas, MD Anderson Cancer Center, Houston, TX

Background: Personalized respondent-generated measures such as the Patient-Generated Index (PGI) can be used as an adjunct to other measures to assess individual quality of life, to improve patients' outcomes through interventions aimed at targeting patients' values for health, and to identify changes in individual responses. The objective of this study was to assess how patients redefine their components of quality of life after a total knee arthroplasty (TKA) during the first six months of recovery.

Methods: We interviewed 122 patients with knee osteoarthritis (OA) at baseline, 12 and 24 weeks post TKA. PGI, a semi-quantitative instrument that

allows patients to select the areas of their lives that are most affected by their disease, and to rate them using ranking and ordinal scores. The PGI is made up of three stages; each stage is linked to the other stages in sequence: i) the first stage focuses on those areas of life affected by the patients' health; ii) the second stage rates how badly patients are limited by their condition; and iii) the third stage reduce ambiguity in the weighting of life areas by rating the relative importance of potential improvements in the area.

Results: 66% of the patients were female; mean age was 65 (8.9) yrs. 63% were married, 70% were White and 25% African American. At baseline, patients were able to select the areas of their lives that were most affected by their knee OA. Patients presented with different combinations problem areas. To reduce the amount of possible combinations, we use the same areas reported at baseline for the 12 and 24 weeks assessments. Five major areas were identified as the most salient: (i) family—this included relationships with family; (ii) physical function—e.g. walking, kneeling, activities of daily living; (iii) health—sleep, fatigue, personal care; (iv) professional life—work and school; and (v) spirituality—church, religious activities. There was a statistically significant difference between observed PGI total scores pre and post TKA: 2.5±1.2 at baseline, 4.2±1.4 at 12 weeks ($p<0.001$), and 4.3±1.4 at 24-weeks ($p=<0.001$). Mean score for each area are shown in table 1. Substantial variation was observed in the areas that patients described as affected. Additionally, we observed that the perception of the area that is most affected by the knee OA changed over the time in each patient.

Table 1. Weighted mean PGI scores specific to each domain – 6 months.

	Baseline		12 weeks		24 weeks		24 weeks (fresh)	
	n(%)	*score*	*n(%)*	*score*	*n(%)*	*score*	*n(%)*	*score*
Family	29%	2.8	31%	4.5	34%	4.5	14%	4.1
Physical function	36%	2.5	36%	4.2	31%	4.1	52%	4.7
Gen health	12%	2.5	8%	4.2	11%	4.9	14%	4.9
Professional life	11%	2.2	7%	0.4	8%	4.3	15%	4.2
Spirituality	7%	2.5	7%	4.7	5%	3.8	3%	3.5
Other areas	5%	2.4	11%	4.2	11%	4.3	2%	4.2

Conclusion: Physical function and interference with family life were the most frequent areas identified by patients as detrimental to their QoL. The PGI was responsive to changes in patient's chosen domains for QoL.

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ACR Poster Session A
Osteoarthritis - Clinical Aspects: Biomechanics, Function, and Imaging I
Monday, November 8, 2010, 9:00 AM–6:00 PM

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Adiponectin but Not Leptin and Resistin, Is Associated with the Progression of Hand Osteoarthritis. Erlangga Yusuf[1], Andreea Ioan-Facsinay[2], Jessica Bijsterbosch[2], Joanneke Kwekkeboom[2], P. Eline Slagboom[2], Tom W. J. Huizinga[2] and Margreet Kloppenburg[2]. [1]LUMC, Leiden, The Netherlands, [2]LUMC, The Netherlands

Purpose: The link between obesity and osteoarthritis (OA) may be explained by the increased joint stress accompanying obesity. However, it does not explain why being obese is also associated with OA in non-weight-bearing joints, such as the hands. It is suggested that systemic products of fat with systemic metabolic activity (adipokines) may influence the onset and/or progression of osteoarthritis. We investigated here the association between three most common adipokines: leptin, adiponectin and resistin and the progression of hand OA.

Methods: We selected patients with radiographic hand OA from a cohort consisted of Caucasian sibs with symptomatic OA at multiple sites. We defined hand OA as Kellgren and Lawrence score ≥2 in at least two from 20 hand joints (four proximal interphalangeal joints (PIP's), four distal interphalangeal joints (DIP's), one interphalangeal (IP-1) and one carpometacarpal (CMC-1) on each hand). Using the Osteoarthritis Research Society International atlas, the baseline and 6-years follow-up radiograph were assessed for the joint space narrowing (JSN, grade 0 to 3: 0 normal, 3: severe narrowing) of 20 joints (four DIP's, four PIP's, one IP-1 and one CMC-1) per patient. JSN reflects articular cartilage damage. The radiographs were assessed by two readers in consensus and the intra-class correlation coefficient for intra-reader reproducibility based on 25 randomly selected pairs of radiographs was high (0.87). Progression was defined as a change in JSN above the smallest detectable change (SDC) of 2, reflecting change above measurement error. Baseline serum adiponectin concentration was measured by Bio-Plex Pro Assay (Bio-Rad, USA). With logistic regression analysis odds ratios of hand OA progression were computed and transformed to risk ratio (RRs). Adjustments for confounders as age, sex, body mass index (BMI) and family effect were made. We categorized all adipokines in tertiles.

Results: Complete follow-up data were available from 164 patients out of 248 included patients, (66%, mean age [SD]: 60 [7] years, 81% female, mean BMI [SD]: 27 [5] kg/m^2). Fifety-five patients showed hand OA progression. BMI was positively correlated with leptin (Pearson's correlation coefficient, r=0.3) and resistin (r=0.2) and negatively correlated with adiponectin (r=-0.2). Leptin, adiponectin and resistin did not significantly correlate to each other. BMI was not associated with radiographic hand OA progression (β-regression coefficient −0.04 (95% confidence interval −0.08 to 0.05). The association between adipokines and progression of hand OA is shown in the Table.

Adiponectin	Risk Ratio (95% Confidence Interval)	Risk Ratio (95% Confidence Interval) after adjustment for age, sex, BMI and family effect
Leptin (ng/mL)		
<4.4	1 (reference)	1 (reference)
4.41 to 8.2	0.7 (0.3 to 1.6)	0.7 (0.3 to 1.5)
>8.2	1.1 (0.5 to 2.3)	1.2 (0.4 to 2.5)
Adiponectin (μg/mL)		
<16.6	1 (reference)	1 (reference)
16.6 to 28.4	0.3 (0.1 to 0.7)‡	0.2 (0.1 to 0.5)‡
>28.4	0.3 (0.1 to 0.6)‡	0.2 (0.1 to 0.5)‡
Resistin (ng/mL)		
<0.8	1 (reference)	1 (reference)
0.8 to 1.4	1.0 (0.4 to 2.1)	0.9 (0.4 to 1.8)
>1.4	0.8 (0.4 to 1.7)	0.7 (0.3 to 1.5)

‡ Statistical significant at $p<0.05$

Conclusions: We show for the first time a substantial inverse association between serum adiponectin levels and radiographic worsening of hand OA. Further studies on the use of adiponectin as biological markers for OA progression and studies on the biological role of adiponectin in OA are needed.

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Association of Knee, Ankle, and Midfoot Osteoarthritis and Physical Performance. Gary McDaniel[1], Jordan B. Renner[2], Richard Sloane[1] and Virginia B. Kraus[1]. [1]Duke University Medical Center, Durham, NC, [2]University of North Carolina School of Medicine

Purpose: The direct measurement of the ability to perform physical tasks yields information about factors contributing to poor function and insights into strategies for preventing disability. The Short Physical Performance Battery (SPPB) measures walking speed, balance, and the ability to rise from a chair. Previous studies evaluating the contribution of knee to physical function have relied solely on the Kellgren-Lawrence (KL) grading system, whereas studies of the ankle's contribution to physical function have failed to assess the association of radiographic ankle or midfoot OA. Our goal was to evaluate the relationship of SPPB with specific radiographic features of osteoarthritis (OA), joint space narrowing (JSN) and osteophyte (OST), of the knee, ankle, and midfoot.

Methods: SPPB was performed by 138 [101 females, 37 males, mean age 66 (SD 11.6) years and BMI 31.3 (SD 6.9)] participants of a longitudinal observational study of knee OA progression (POP study). Radiographic features of OA severity, joint space narrowing (JSN, a surrogate for cartilage loss) and osteophyte formation (OST) were assessed for the knee, ankle, and midfoot. The association of SPPB with radiographic OA was evaluated using non-parametric Spearman correlation analysis, adjusted for age, gender, BMI, and number of comorbidities.

Results: Knee, ankle tibiotalar joint (TTJ), ankle subtalar joint (STJ), and midfoot talonavicular joint (TNJ) radiographic features of OA were negatively associated with specific SPPB tests: walking speed was associated with knee JSN (Spearman rho=-0.20, p=0.02), balance with ankle (subtalar joint)

JSN (-0.22, 0.01), and chairs stands with midfoot (talonavicular joint) JSN (-0.18, 0.04).

Table 1. Associations of knee and ankle/foot osteoarthritis with physical performance measures (unadjusted and adjusted for age, gender, BMI, number of comorbidities).

Joint Site		OA Feature	Gait Velocity (m/sec) (higher better)	SPPB Standing Balance (higher better)	SPPB Chair Stand (higher better)	SPPB Total (higher better)
			Spearman Correlation Coefficients: r unadjusted (or r adjusted for age, BMI, number of comorbidities, and gender)			
Knee		JSN	−0.19* (−0.20*)	−0.04 (−0.03)	−0.07 (−0.05)	−0.09 (−0.08)
		OST	−0.16 (−0.16)	−0.01 (−0.01)	0.01 (0.02)	0.001 (0.01)
		KL	−0.12 (−0.12)	−0.02 (−0.01)	−0.07 (−0.06)	−0.07 (−0.06)
Ankle	TTJ	JSN	−0.06 (0.01)	−0.15 (−0.06)	−0.19* (−0.12)	−0.19* (−0.09)
Ankle	STJ	JSN	−0.12 (−0.09)	−0.29*** (−0.22**)	−0.19* (−0.11)	−0.24** (−0.17*)
Ankle	TTJ	OST	0.03 (0.06)	−0.03 (<0.01)	−0.02 (0.03)	<−0.01 (0.05)
Ankle	STJ	OST	−0.03 (−0.16)	−0.10 (−0.01)	−0.04 (0.02)	−0.06 (0.01)
Ankle	TTJ	KL	−0.01 (−0.04)	−0.19* (−0.12)	−0.21** (−0.13)	−0.20* (−0.12)
Midfoot	TNJ	JSN	−0.06 (−0.05)	−0.15 (−0.16)	−0.16* (−0.18*)	−0.18* (−0.21*)
Midfoot	TNJ	OST	−0.16 (−0.16)	−0.04 (−0.02)	0.07 (0.13)	0.03 (0.08)

OA = osteoarthritis; p values; * <0.05, **≤0.01, *** ≤ 0.001

These relationships remained significant upon further control for knee and ankle pain.

Conclusions: To our knowledge this is the first study describing a relationship between individual SPPB tests and specific radiographic features of knee, ankle and midfoot OA (JSN and OST). We discovered that ankle OA negatively impacts balance; knee OA slows you down; and midfoot OA negatively impacts chair stands. Structural joint damage due to OA (JSN in contrast to OST) negatively impacted these specific domains of physical performance. These results indicate that radiographic evidence of OA in specific joints may inform strategies targeting specific functional outcomes for early intervention to prevent disability in an older population.

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Associations between Composite Measures of Multi-Joint Osteoarthritis, Gait Speed, and Health Assessment Questionnaire Scores: The Johnston County Osteoarthritis Project.

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Objective: As there is no widely accepted definition of multi-joint osteoarthritis (OA), it is difficult to quantify the effect of multiple joint involvement on OA outcomes. We used factor analysis to create composite variables reflecting multi-joint radiographic OA, and determined associations between these variables and systemic outcomes (gait speed and health assessment questionnaire [HAQ] scores).

Methods: Data were from a cross-sectional sample of the Johnston County OA Project, including individuals with multi-joint radiographs, HAQ, and gait speed (n=1350, 66% women, 33% African Americans, mean age 67 ± 10 years, mean body mass index [BMI] 31 ± 6 kg/m^2). HAQ scores were categorized as 0, 0 to < 1, or ≥ 1. Mean seconds to complete an 8-foot walk were converted to gait speed in m/s. Radiographs of the bilateral hands, tibiofemoral joints (TFJ), and hips were read for Kellgren-Lawrence grade (KL 0–4) at each joint. Lateral lumbosacral spine (LS) films were read for osteophytes (OST 0–3) and disc space narrowing (DN 0–3) at 5 levels, and patellofemoral joint (PFJ) radiographs were read for OST (0–3), using the Burnett atlas. During factor analysis using these scores, the hip and LS variables did not load onto factors and were assessed separately (Hip OA if KL ≥ 2 at either hip, LS OA if OST and DN ≥ 1 at a single level). Linear and partial proportional odds regression models for gait speed and HAQ, respectively, were used to determine associations between OA variables and outcomes, adjusting for age, BMI, gender, and race.

Results: Factor analysis produced 3 factors. The 1st consisted of the 1st interphalangeal (IP) joints, distal IP joints 2–5, and proximal IP joints 2–5 (IP factor, α=0.96); the 2nd included the metacarpophalangeal joints 2–5 (MCP factor, α=0.81); the 3rd included TFJs and PFJs (Knee factor, α=0.87). The mean gait speed in the sample was 0.7 ± 0.2 m/s. Proportions by HAQ categories were 30% (0), 24% (> 0 to < 1) and 46% (≥ 1). Gait speed was negatively associated with hip OA and the 3 factors, but the associations were greatly attenuated after adjustment (Table). For HAQ, a 1-SD increase in either the IP or knee factor resulted in 18% and 16% increased odds, respectively, of being in a higher HAQ category after adjustment (IP factor cumulative odds ratio [cOR]=1.18 [95% CI 1.03–1.36]; knee factor cOR 1.16 [95% CI 1.03–1.30]).

Association between composite factors representing multi-joint OA and functional outcomes.

OA variable[c]	HAQ[a] Unadjusted[d] cOR	95% CI	Adjusted[e] cOR	95% CI	Gait speed[b] Unadjusted[d] Beta	95% CI	Adjusted[e] Beta	95% CI
IP factor	1.45	1.29, 1.64	1.18	1.03, 1.36	−0.025	−0.038, −0.012	−0.003	−0.016, 0.010
MCP factor	0.94	0.84, 1.06	1.15[f]	0.96, 1.35	−0.014	−0.026, −0.001	−0.006	−0.018, 0.006
Knee factor	1.24	1.11, 1.39	1.16	1.03, 1.30	−0.030	−0.043, −0.018	−0.010	−0.022, 0.002
Hip OA	1.23	0.98, 1.53	1.12	0.89, 1.40	−0.044	−0.070, −0.019	−0.015	−0.038, 0.009
LS OA	1.11	0.90, 1.37	1.02	0.82, 1.27	−0.016	−0.041, 0.006	−0.001	−0.024, 0.022

HAQ: Health Assessment Questionnaire; cOR: cumulative odds ratio; CI: confidence interval; DIP: distal interphalangeal joint; PIP: proximal IP joint; MCP: metacarpophalangeal joint; TFJ: bibotemoral joint; PFJ: patellofemoral joint; Hip OA-KL grade 82 in either hip; LS OA-Lumbosacral spine OA, defined as an osteophyte 81 and disc narrowing at the same level.
a. Partial proportional odds regression model
b. Linear regression model
c. Factor scores are the standardized average of the radiographic scores of the included joints (average/std deviation)
d. Unadjusted results are for aI OA variables only.
e. Adjusted for age, BMI, gender, and race, with all OA variables in the model.
f. Factor 2 does not meet proportional odds assumption for categories of HAQ: the given OR is for the lowest category of HAQ (0) vs. the higher 2, for the lower 2 vs. the highest, OR 0.93 (95% CI: 0.81, 1.05)

Conclusions: Composite factors representing multi-joint OA involvement were associated with reduced gait speed and higher HAQ scores, although the estimates were attenuated by covariates, particularly age and BMI. Such composite factors can represent multiple joints in a single variable, reducing dimensionality and allowing more precise estimation of the effects of multi-joint OA involvement in models.

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Associations between Radiographic Hand Osteoarthritis and Femorotibial Cartilage Thickness and Thinning in Subjects with Prevalent or at High Risk of Knee Osteoarthritis—Data from OAI.

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Introduction: Hand osteoarthritis (HOA) may represent generalized OA and a predisposition for knee OA. Previous studies have suggested that HOA is a risk factor for incident and progressive knee OA, but the relationship between HOA and MRI-based knee cartilage thickness has not been previously studied.

Aim: To evaluate whether radiographic HOA features are associated with knee cartilage thickness (cross-sectionally) and/or 1-year cartilage thinning.

Methods: We studied 765 knees from 765 OAI participants (455 women, mean (SD) age 62.5 (9.4) years) with prevalent or at high risk of knee OA. The dominant (n=467) or both hands (n=298) were imaged at baseline. One investigator scored the x-rays for presence of osteophytes (OP) and joint space narrowing (JSN) (grade 0–3) in the DIP, PIP, MCP and CMC-1 joints. If both hands were imaged, the hand with the highest total score was used for analyses. Total scores for OP (range 0–45) and JSN (range 0–45) were calculated. Femorotibial cartilage thickness (ThCtAB) was measured quantitatively from coronal FLASHwe images (0.E.1, 1.E.1) by Chondrometrics GmbH. In the cross-sectional analyses (linear regression), ThCtAB in the medial femorotibial compartment (MFTC) was the primary outcome. In the

longitudinal analyses (logistic regression), the ordered values (OV) of subregional cartilage thickness changes were used to define the outcome. OV1 represented the knee subregion with greatest cartilage thinning. The cut-off between progressors (cartilage thinning) and non-progressors (no/less cartilage thinning) was set to the median OV1 value. In the primary models, we evaluated the associations between radiographic HOA feature scores and ThCtAB with adjustment for age, sex and BMI. In the secondary models, separate analyses were done with knees grouped into two strata of knee OA at baseline (Kellgren-Lawrence grade (KLG) 0–2 and KLG 3–4)

Results: Most patients had mild HOA with median (quartiles) scores of 3 (1–6) for OP and 8 (5–12) for JSN. Hand JSN and OP scores were significantly associated with reduced ThCtAB in MFTC at baseline after adjustment for covariates (table). The associations were greater in KLG 3–4 than KLG 0–2. The risk of 1-year cartilage thinning was inversely related to higher hand JSN score in the total sample, while not significant for the hand OP score or in the stratified analyses (table).

Table. Associations between hand features and ThCtAB in MFTC (cross-sectionally) and 1-year cartilage thinning in OV1 (longitudinally) (beta (p value)).

	All patients (n = 765)	KLG 0–2 (n = 364)	KLG 3–4 (n = 401)
Cross-sectionally (MFTC)			
Hand OP score	−0.01 (0.05)	−0.002 (0.81)	−0.02 (0.06)
Hand JSN score	−0.02 (<0.001)	−0.01 (0.007)	−0.03 (<0.001)
Longitudinally (OV1)			
Hand OP score	0.01 (0.74)	−0.02 (0.45)	0.02 (0.35)
Hand JSN score	−0.03 (0.05)	−0.03 (0.23)	−0.03 (0.14)

Conclusion: Radiographic HOA features were significantly associated with reduced knee cartilage thickness cross-sectionally, assessed by quantitative MRI. This may support an endogenous and generalized susceptibility for OA. In contrast, we found no consistent association between HOA and 1-year knee cartilage thinning, and re-evaluation of the sample after a longer period of follow-up is warranted.

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Change in Weight over 10 Years Is Associated with Bone Marrow Lesions in a Population-Based Cohort Study of Adult Women. Sharon Brennan[1], Flavia Cicuttini[1], Julie Pasco[1], Margaret Henry[2], Yuanyuan Wang[1], Mark Kotowicz[2], Geoffrey Nicholson[2] and Anita Wluka[1]. [1]Monash University, [2]University of Melbourne

Background: Although obesity is a modifiable risk factor for knee osteoarthritis (OA), the effect of change in weight on knee structure in young and healthy adults has not been examined. The aim of this study was to examine the relationship between body mass index (BMI), and change in BMI over the preceding 10-year period, and knee structure [cartilage defects, cartilage volume and bone marrow lesions (BMLs)] in a population-based sample of young to middle-aged females.

Methods: One hundred and forty two healthy, asymptomatic females (range 30–49 years) in the Barwon region of Victoria, Australia, underwent magnetic resonance imaging (MRI) during 2006-08. BMI measured 10 years prior (1994-97), current BMI and change in BMI (accounting for baseline BMI) over this period, was assessed for an association with cartilage defects and volume, and BMLs.

Summary of the Results: After adjusting for age and tibial plateau area, there was a trend for a 1 unit increase in current BMI to be associated with cartilage defects (OR 1.06 [95%CI 1.00, 1.13] p=0.05), and for a 1 unit increase in BMI over 10 years to be associated with reduced cartilage volume (–17.8ml [95%CI –39.4, 3.9] p=0.1). BMLs were associated with baseline BMI (OR 1.14 [95%CI 1.03, 1.26] p=0.009), current BMI (OR 1.13 [95%CI 1.04, 1.23] p=0.005), and per 1 unit increase in BMI (OR 1.14 [95%CI 1.03, 1.26] p=0.01). Results remained similar after excluding those with osteophytes.

Conclusions: This study provides longitudinal evidence for the importance of avoiding weight gain in women in during early to middle adult-hood as this is associated with adverse structural changes at the knee. Avoiding weight gain even in early adulthood may play an important role in the prevention of knee OA.

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Comorbidity and Health Status in Early Osteoarthritis of Hip and Knee; CHECK Cohort. J. Wesseling[2], S. M. A. Bierma-Zeinstra[1], J. Dekker[4], K. J. Gorter[3], J. W. J. Bijlsma[3] and on Behalf of the CHECK Group. [1]Erasmus University Medical Center Rotterdam, [2]Rheumatology & Clinical Immunology, University Medical Center Utrecht, Utrecht, The Netherlands, [3]University Medical Center Utrecht, [4]VU University Medical Center Amsterdam

Background: Osteoarthritis (OA) is the most common diagnosis made in elderly patients with knee or hip pain. Like OA the prevalence of many other disabling conditions increases with age and many chronic conditions can be found together with OA. The objective of the present study is to describe the relationship between comorbidity (count as well as the presence of specific comorbidities) and complaints (like pain and limitation in activity) and the physical and mental status of participants with complaints of early osteoarthritis.

Methods: In the Netherlands a prospective 10-year follow-up study was initiated by the Dutch Arthritis Association in participants with early OA related complaints of hip and/or knee: the CHECK study, to study the onset and progression of OA. Individuals were eligible if they had pain and/or stiffness of knee and/or hip, were aged 45–65 years, and had never or not longer than 6 months ago visited the general practitioner for these symptoms for the first time. The WOMAC was utilized to measure pain and limitations in activity. Physical functioning and mental functioning were measured bij SF36. Comorbidity is assessed with a self-reported health module of the Agency of Statistics in the Netherlands with consists of 24 chronic diseases. Linear regression analysis was used to determine the influence of the 'comorbidity count' on the outcome variables pain, and physical and mental functioning.

Results: In CHECK 1002 participants were included, mean age of 56 years, mean BMI of 26 kg/m^2 and 79% female. Over 67% of the total study population had comorbidity: disorders of neck, shoulder, elbow, wrist or hand (23%), hypertension (20%) and back disorders (18%) were most prevalent. The results indicate that the pain score and physical function score on the WOMAC deteriorates with about 3 and 4 points respectively with every (extra) comorbidity. The physical and mental status of the SF36 deteriorates with respectively about 2 and 1 point with every (extra) comorbidity. Results of the final model (controlling for age, gender, Kellgren & Lawrence grade) show that severe back disorders have the most negative effect on WOMAC pain, physical functioning and one of the most negative effects on physical status of SF36. The presence of this disorder increases WOMAC pain score on average with 7 points, WOMAC function score with 8 points, and SF36 PCS score with 4 points. The mental status was negatively influenced by the presence of duodenal/gastric, thyroid disease, and migraine or regular headache.

Conclusions: In the early stage of osteoarthritis the effect of the presence of especially diseases in the locomotor system have negative effect on complaints and health status. The clinical implications are that to improve the physical health of participants with early OA of knee and/or hip not only the complaints related to OA have to be treated but also the additional diseases, especially back, neck, shoulder, elbow, wrist or hand disorders or obesity. Apart from the physical status also the mental status is affected in the early stage of OA by the presence of comorbidity and this is a further reason to take comorbidity into account in the management of early OA.

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Do Bony Enlargements Correlate with Radiological Findings in Hand Osteoarthritis (HOA)? Roshan Dhawale[3], Niveditha Mohan[2], Michael J. Hannon[4] and C. Kent Kwoh[1]. [1]Univ of Pittsburgh, Pittsburgh, PA, [2]Univ of Pittsburgh Arth Inst, Pittsburgh, PA, [3]University of Pittsburgh, Pittsburgh, PA, [4]University of Pittsburgh

Purpose: Symptomatic Hand Osteoarthritis (HOA) affects 20% of patients above the age of 55 years, a large proportion of whom have bony enlargements. The relationship between bony enlargements and radiological findings of HOA is unclear and has not been well-studied. We assessed the correlation between bony enlargements and radiological findings and whether all patients with bony enlargements had radiological evidence of HOA.

Methods: The study utilized data from the Osteoarthritis Initiative, a community-based cohort aged 49–75 years with symptomatic knee OA or with risk factors for developing knee OA. Dominant hand films of 200

women were read by two independent trained investigators using the ICRS/OARSI Radiographic Atlas. The 1st carpometacarpal (CMC), 2nd-5th distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints were assessed for joint space narrowing (JSN) and osteophytes (OST) on a scale of 0–3 and the presence of central erosions (CE) and lateral deviation (LD)(>15 degrees) was read. Trained study personnel assessed the presence of nodal enlargements. Grades 2 and 3 JSN and/or OST were considered as definite radiological evidence of HOA. Statistical analysis was performed by logistic regression adjusted for clustering by person with age over 65, race, BMI, smoking and family history of OA as covariates.

Results: The sample was predominantly Caucasian (83.5%); mean age was 61.6 ± 9.2 years. Three subjects had LD at the 1st CMC and 1 had LD at the 5th DIP. Thirty-six central erosions were found in 20 subjects, of which 86% were at the 1st CMC and DIP joints. Fifteen and 6 subjects had JSN and 3 and 2 subjects had OST in all four DIPs and PIPs respectively. One hundred and twenty-two subjects (61%) had bony enlargements on exam. Of 792 DIP joints, 101 had both bony enlargements and radiological evidence (JSN or OST). Having a bony enlargement was highly predictive of finding radiological evidence for OST (OR 23.03, 95% CI 9.62–55.18) and JSN (OR 9.73, 95% CI 5.43–17.44). When adjusted for covariates, the association was maintained for OST (OR 13.26, 95% CI 4.98–35.31) and JSN (OR 7.0, 95% CI 3.68–13.27). Only 27 subjects had radiological findings without bony enlargements on examination, but 182 subjects, a significantly higher number, had a bony enlargement without any radiological evidence of OA.

Table 1. Distribution of HOA

	JSN (Grade 1)		JSN (Grades 2,3)		OST (Grade 1)		OST (Grades 2,3)	
Joint	*n*	**(%)**	*n*	**(%)**	*n*	**(%)**	*n*	**(%)**
CMC	99	49.5	41	20.5	73	36.5	41	20.5
DIP 2	65	32.5	26	13	34	17	24	12
DIP 3	66	33	26	13	20	10	15	7.5
DIP 4	65	32.5	31	15.5	7	3.5	8	4
DIP 5	79	39.5	33	16.5	39	19.5	20	10
PIP 2	70	35	9	4.5	24	12	10	5
PIP 3	86	43	15	7.5	20	10	7	3.5
PIP 4	97	48	19	9.5	11	5.5	8	4
PIP 5	89	44.5	15	7.5	21	10.5	7	3.5

Conclusion: The presence of bony enlargement strongly correlates with radiological evidence of HOA, but having a bony enlargement does not always predict having radiological findings. A possible explanation for why a large number of patients had bony enlargements without radiological evidence of hand OA may be because we excluded Grade 1 JSN and OST from our analysis. However, it appears that radiological evidence is more specific for HOA. Our study suggests that radiological evaluation is an inexpensive diagnostic tool to confirm HOA.

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Frailty and 3-Year Mobility Outcome in Persons with or at Higher Risk for Knee Osteoarthritis. September Cahue[4], Karen W. Hayes[2], Jing Song[4], Dorothy D. Dunlop[3], Joan S. Chmiel[4], Marc C. Hochberg[5], Carmelita J. Colbert[1] and Leena Sharma[3]. [1]Northwestern University, LaGrange, IL, [2]Northwestern University, Downers Grove, IL, [3]Northwestern University, Chicago, IL, [4]Northwestern University, [5]University of Maryland, Baltimore, MD

Purpose: Frailty has been examined in the context of aging, but little is known about its role in health outcomes in persons with knee osteoarthritis (OA). Risk of knee OA increases with age, and knee OA is a leading cause of chronic disability in older individuals; however, how best to identify persons who are likely to decline and/or benefit from intervention is unknown. The Osteoarthritis Initiative (OAI) cohort represents the continuum of knee OA from the stage of high risk prior to radiographic change through advanced disease and is uniquely suited to our goals: 1) determine the prevalence of frailty in this population; and 2) evaluate whether frailty at baseline predicts subsequent 3-year mobility outcome.

Methods: OAI data from public release data set 0.2.2 were used. We adapted the frailty index of Ensrud et al (Arch Int Med 2008), including inability to rise five times from a seated position without using arms and self-reported exhaustion (CES-D) (but not the weight criterion due to varied implications of weight loss in this population and because BMI was the basis of enrollment for a subset of the OAI cohort). Mobility outcomes were: baseline-to-3-year increase in difficulty in WOMAC mobility items (walking, ascending stairs, descending stairs); poor SF12 physical component outcome (persons were grouped by quintile of baseline function, and "poor" defined as moving into a worse quintile group or remaining in the worst 2 groups at 3 years). We used logistic regression to analyze the relationship between frailty at baseline (≥ 1 item) (vs. not frail, reference) and baseline-to-3-year outcome, adjusting for age, gender, race, education, comorbidities, and K/L grade (worse of the two knees) in the overall sample and in BMI strata.

Results: In 4138 persons, mean age was 61 years, mean BMI was 28, and 58% were women. At baseline, 14% of women and 11% of men were frail. Frailty was also associated with being African-American, having a lower education level, and poorer self-assessed health. By three years, 35% had worse WOMAC mobility, and 52% had poor SF12 physical component outcome. In the overall sample (Table), frailty at baseline was associated with worse 3-year WOMAC mobility and poor SF12 physical component outcome in adjusted analyses. These results persisted in the normal weight and overweight strata but were not significant in the obese stratum (Table).

Table. Frailty and 3-Year Mobility Outcome, Odds Ratios (OR) (95% CI)

	WOMAC Mobility Item Worsening OR (95% CI)		Poor SF12 Physical Component Outcome OR (95% CI)	
	Unadjusted	**Adjusted***	**Unadjusted**	**Adjusted***
Overall N = 4138**	*1.73 (1.44, 2.08)*	*1.56 (1.29, 1.89)*	*1.79 (1.48, 2.17)*	*1.63 (1.34, 1.99)*
BMI Categories	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Normal (BMI <25) N = 1027**	*2.06 (1.36, 3.11)*	*1.79 (1.16, 2.75)*	*1.55 (1.02, 2.37)*	1.48 (0.96, 2.28)
Overweight (25≤BMI<30) N = 1027**	*1.91 (1.42, 2.57)*	*1.71 (1.25, 2.32)*	*2.30 (1.67, 3.17)*	*2.21 (1.59, 3.08)*
Obese (BMI ≥30) N = 1483**	*1.33 (1.00, 1.76)*	1.27 (0.94, 1.70)	*1.39 (1.03, 1.88)*	1.23 (0.89, 1.68)

*Adjusted for age, gender, race, education, comorbidities, K/L grade
**SF-12 outcome sample sizes; Overall n = 3968; BMI Categories; Normal n = 967; Overweight n = 1569; Obese n = 1432

Conclusion: A simple frailty index, easily usable in a clinical setting, was independently associated with worse 3-year mobility in persons at high risk for or with knee OA. These results also suggest that a frailty index may not function similarly across BMI strata in this population. Further work to refine the ability to capture the frailty phenotype—decreased reserve and resistance to stressors—should occur, as a simple but potentially powerful means of ultimately aiding the prevention of adverse outcomes in persons with knee OA.

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Greater Burden of Disease in Erosive Hand Osteoarthritis. Mariko L. Ishimori[1], Roy D. Altman[4], Myles J. Cohen[2], Jerome I. Rotter[2] and Michael H. Weisman[3]. [1]Cedars Sinai Medical Center, Los Angeles, CA, [2]Cedars-Sinai, [3]Cedars-Sinai Medical Center, Los Angeles, CA, [4]UCLA, Agua Dulce, CA

Purpose: The goal of our study was to evaluate relationships between patients with erosive vs. non-erosive hand osteoarthritis (OA) by radiography and features such as extent of joint involvement, body mass index (BMI), and pain, stiffness, and physical disability as assessed by the Australian/Canadian (AUSCAN) Hand Osteoarthritis Index.

Methods: Consecutive patients with clinical and radiographic hand OA were evaluated by examination, BMI, radiography, and AUSCAN as part of The Genetics of Hand Osteoarthritis Study (GHOST). Radiographs were scored by radiographic atlas and analyzed for relationship to degree of joint involvement, BMI and AUSCAN subscales. Subjects were grouped as 1) erosive involvement of distal interphalangeal (DIP), proximal interphalangeal (PIP) and interphalangeal (IP) joints with hand OA, 2) non erosive (nodal) involvement of DIP, PIP and IP joints with hand OA, and 3) non-erosive involvement of 1st carpo-metacarpal (CMC) joints only. Subjects with any one joint with erosive change were classified as having erosive hand OA. Two scores were generated: 1) Total Count—number of selected joints with osteophytes and 2) Total Score—Sum of osteophytes scores from selected joints (DIP, PIP, IP, CMC).

Results: A total of 279 subjects were enrolled with a mean age of 68.7 years. The majority of study subjects were women (90.7%) and Caucasian (91.0%). The breakdown of radiographic findings was as follows: 105 (37.6%) with erosive changes, 124 (44.4%) with non-erosive (nodal) involvement and 50 (17.9%) with non-erosive CMC involvement. The group of subjects with erosive hand OA had greater Total Score ($p<0.0001$) and Total Count ($p=0.001$) than subjects with non-erosive (nodal) hand OA or CMC involvement. The AUSCAN subscore of stiffness was significantly greater in erosive hand OA ($p<0.0003$) and nodal hand OA ($p=0.027$) than in subjects with CMC only involvement (Wilcoxon rank sum). Within the erosive hand OA group, increasing number of joints involved with HOA correlated with worsening Stiffness ($p=0.0099$) and Physical Function ($p=0.0175$) subscales of the AUSCAN index (Spearman's correlation).

Conclusion: In a cross-sectional analysis of clinical and radiographic hand OA, subjects with erosive hand OA generally had a greater burden of joints involved that the non-erosive (nodal) group. This may be related to erosive OA potentially being a more severe manifestation and a different group than traditional non-erosive (nodal) OA, suggesting genetic differences. Within the erosive hand OA group, greater Stiffness and worse Physical Function by AUSCAN index correlated with increasing numbers of joints involved with hand OA. This occurred even when there were very few or only one joint with erosive change. The concepts of nodal versus erosive IP arthritis may represent distinct clinical and etiologic groups, and not two sides of a spectrum, reflecting the heterogenity of hand OA which may have implications for genetic studies. Future studies need to include careful descriptions of disease phenotypes, particularly in relation to genetic investigations.

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Image Processing and Machine Learning Methods Applied to MRI Trabecular Morphometry in Knee Osteoarthritis. Jason Nochlin[4], Eric Miller[4], Grace H. Lo[2], Anna Tassinari[1] and Timothy E. McAlindon[3]. [1]Tufts Medical Center, Boston, MA, [2]Tufts Medical Center, Houston, TX, [3]Tufts Medical Center Box 406, Boston, MA, [4]Tufts University, Medford, MA

Purpose: We can image periarticular bone in vivo, a tissue involved in the pathology of knee osteoarthritis (OA). In digital images such as MRIs, *texture* refers to patterns in pixel intensity. Using texture filters, the original image is transformed into a new image where the value of each pixel corresponds to how well the region around that pixel "matches" the pattern encapsulated in a filter. Such techniques are used to characterize regions of an image. In a natural scene, though the image may not resolve single blades of grass, the pixel patterns formed by these structures infer information about the individual components. In this instance where individual trabeculae are not resolved in images of the periarticular bone, our hypothesis is that variations in texture correlate with relative periarticular bone mineral density (paBMD), a known correlate of structural OA severity.

Methods: Using a sample of 39 right knees from an ancillary study to the Osteoarthritis Initiative, we analyzed 3T MRIs (Trio, Siemens) coronal 3D FISP trabecular sequences. From each of 20 central slices, a region of interest (ROI) in the periarticular tibia was extracted by identifying the top edge of the bone and selecting a region of 24mm wide by 8mm high. 24 texture filters (8 Gabor and 16 Laws' Masks) were applied to each ROI. All pixels in each transformed slice's ROI formed a data array for that filter. With each Laws' Mask, pixel values were squared to form a new data array, totaling data arrays (20 slices $\times$ 2) for each knee MRI. On each array we computed mean, standard deviation, skewness, entropy, and kurtosis. Knee DXAs were obtained using a GE Lunar scanner to calculate measures of the medial:lateral tibial paBMD. The 200 statistics from the 40 data arrays were used as regressors for predicting medial:lateral tibial paBMD. The regression problem was solved using kernel-Support Vector Regression. A wrapper approach was used to limit the number of regressors in solution to 15. All computations were done using MATLAB r2007b.

Results: Thirty-nine patients were studied, 53% males; age 68 ($\pm$9.3); BMI 27.8 ($\pm$4.6). The predictive model estimated the medial:lateral paBMD ratio for each patient in a cross-validation scheme, a regression coefficient of.870 was found between the predicted and actual values, (p-value of $p<.0001$).

Of the 15 selected regressors, several patterns were found. The most prominent textures were Laws' Masks derived from a 1mm (5 pixel) *wave* or *ripple* pattern. The wave pattern roughly corresponds to texture with frequent, large changes in contrast (brightness highs and lows nearby each other). The ripple pattern corresponds to texture where the maxima are extremely prominent. Gabor Filters, which match sine wave patterns in the texture, with a wavelength of.8mm (4 pixels) with various orientations were also significant differentiators.

Conclusion: Using image processing and machine learning techniques, we developed a novel method for analyzing bone structure MRI images that correlate well to paBMD. Further development of such tools will help in better understanding of the periarticular bone pathology in those with knee OA. Future studies are needed to validate these measures against histopathology.

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Knee Confidence and Physical Function Outcome in Persons with Knee Osteoarthritis. Carmelita J. Colbert[1], Jing Song[4], Dorothy D. Dunlop[3], Joan S. Chmiel[4], Karen W. Hayes[2], September Cahue[4], Kirsten Moisio[4], Alison H. Chang[3] and Leena Sharma[3]. [1]Northwestern University, LaGrange, IL, [2]Northwestern University, Downers Grove, IL, [3]Northwestern University, Chicago, IL, [4]Northwestern University

Purpose: Given the central role of the knee in all weightbearing activity, confidence in the knees may be a proximal factor influencing activity choices and self-efficacy, factors thought critical to function and disability. We evaluated whether knee confidence at baseline was associated with physical function outcome over the subsequent two years in persons with knee OA, and whether any relationship persisted after adjusting for other factors.

Methods: Osteoarthritis Initiative (OAI) participants have or are at risk for developing knee OA. Knee confidence was assessed using the KOOS item (How much are you troubled with lack of confidence in your knees?) and function assessments included the WOMAC function scale and chair stand test performance. We grouped participants with knee OA ($K/L \geq 2$) by quintile of baseline function; poor outcome was defined as moving into a worse quintile group or remaining in the 3 worst groups at 24 months. To evaluate the relationship between baseline confidence and poor outcome, logistic regression was used, sequentially adjusting for nested groups of covariates: 1) age, gender, race; 2) previous covariates + depression, comorbidity, falls; 3) all previous + BMI; 4) all previous + physical activity, alcohol use; 5) all previous + hip, ankle, foot pain; 6) all previous + knee injury, knee surgery; and 7) all previous + knee pain severity, knee OA severity, extensor strength.

Results: Among 2243 OAI participants (mean age 62 years, BMI 29, 57% women) with knee OA, the percentage with poor outcome increased with worse baseline knee confidence category (Table 1).

Table 1. Proportion of Persons with Poor Baseline-to-2-Year Function Outcome by Baseline Confidence Level

	Percent with Poor Baseline-to-2-Year Function Outcome of Persons within Baseline Knee Confidence Category	
Knee Confidence Category	Poor WOMAC Physical Function Outcome	Poor Chair Stand Outcome
Not troubled by lack of confidence (n = 923 persons)	32.9%	47.6%
Mildly troubled by lack of confidence (n = 692)	48.8%	50.5%
Moderately troubled by lack of confidence (n = 422)	56.9%	51.9%
Severely or extremely troubled by lack of confidence (n = 206)	69.4%	59.3%

As shown in Table 2, compared to persons not lacking confidence, the odds of a poor WOMAC outcome and a poor chair stand outcome increased with worse knee confidence category resulting in significant trend tests. For the WOMAC outcome, this held for all intermediate nested covariate groups (not shown) and in the final fully adjusted analysis (Table 2). In contrast, the relationship between confidence and poor chair stand outcome was weaker and significance did not persist in the fully adjusted analysis (Table 2). For

both outcomes, the reduction in the odds ratio was most pronounced after further adjustment for the final covariate group.

Table 2. Odds Ratios and 95% Confidence Intervals (CIs) Associated with Knee Confidence for Poor Baseline-to-2-Year Function Outcome

	Poor WOMAC Physical Function Outcome		Poor Chair Stand Outcome	
Knee Confidence Category	OR (95% CI)	Adjusted* OR (95% CI)	OR (95% CI)	Adjusted* OR (95% CI)
Not troubled by lack of confidence (reference)	reference	reference	reference	reference
Mildly troubled by lack of confidence	1.94 (1.59, 2.38)	1.67 (1.35, 2.08)	1.12 (0.92, 1.38)	1.08 (0.87, 1.35)
Moderately troubled by lack of confidence	2.69 (2.12, 3.40)	1.90 (1.45, 2.48)	1.19 (0.94, 1.51)	1.02 (0.78, 1.35)
Severely or extremely troubled by lack of confidence	4.62 (3.33, 6.40)	2.59 (1.76, 3.80)	1.61 (1.16, 2.22)	1.23 (0.83, 1.82)
P for trend	< .0001	< .0001	.005	.44

*model including all covariate groups

Conclusion: In persons with knee OA, lower knee confidence at baseline was associated with poor 2-year WOMAC function outcome but not with poor chair stand outcome in adjusted analyses. The role of confidence in the trajectory of physical function decline in knee OA should be further examined; better understanding of its role may empower strategies to reduce the likelihood of poor outcome.

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Lateral Compartment Unloading in People with Medial Knee Osteoarthritis. Deepak Kumar, Katherine S. Rudolph and Kurt Manal. University of Delaware, Newark, DE

Background: It is well known that people with medial knee osteoarthritis (MKOA) exhibit high knee adduction moments (KAM) during walking. Investigators have speculated that a failure to generate sufficient muscle force to counter high external loads could result in the lateral femoral condyle lifting off the tibia. Lateral condular lift-off has not been confirmed by modeling techniques that account for subject specific EMG patterns, kinematics and kinetics. The aims of this study are (1) to estimate articular loads in people with MKOA using an EMG-driven model and, (2) to examine the relationship between passive laxity, varus malalignment, functional knee instability (FKI) and loading patterns.

Methods: 16 MKOA and 12 control (C) subjects walked while kinematic, kinetic and EMG data were collected. Muscle forces and moments were calculated from an EMG-driven model previously described. Loading of the medial and lateral compartments were calculated by balancing the internal/external moments at the knee. One walking trial was used to optimize the model parameters and the average of 3 separate trials was used to predict articular loading during stance. Functional Knee Instability (FKI) was assessed from the Knee Outcome Survey. Stress radiographs were used to assess frontal laxity and long cassette radiographs were used to assess alignment. ANOVAs and Pearson's correlation coefficients comprised the statistical analyses.

Results: MKOA subjects walked more slowly and had greater laxity, static and dynamic varus alignment, less flexion and greater KAM than controls. Loading, when normalized to BW was no different between the groups but MKOA subjects had greater absolute medial load than C and maintained a greater %total load on the medial compartment. Lateral compartment unloading during mid-late stance was observed in 50% of OA subjects which was related to greater KAM, dynamic varus alignment and FKI but not to laxity or static malalignment. MKOA subjects with lateral joint unloading had lower hamstring force and lower force in the lateral muscles.

Discussion: Loading for C subjects matched that measured from instrumented knee prostheses, supporting the veracity of the model. Speculations about greater medial loading in people with MKOA are confirmed with our data, as well as, the phenomenon of lateral condylar lift-off. It was interesting that the unloading did not occur during weight acceptance phase when the loads are greatest but rather occurred during mid-late stance when the knee experiences its greatest varus angulation. The relations between unloading to FKI rather than laxity or malalignment suggest that it is due to a failure of neuromuscular strategies and not only mechanical factors. This was confirmed by the muscle force data where we found that MKOA subjects who showed unloading, had poor quadriceps-hamstring and medial-lateral muscle force balance resulting from lower hamstring and lateral muscle forces. These data support the need for neuromuscular retraining interventions for people with MKOA that address loading and FKI rather than quadriceps strengthening alone.

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Lower Extremity Muscle Function, Quality of Life and Physical Function Outcomes and Their Relation to Subsequent Knee Replacement in a 24 Month Period—Data from the Osteoarthritis Initiative (OAI). Bjoern Buehring[1], Boris Bershadsky[2] and M. Elaine Husni[1]. [1]Cleveland Clinic, Cleveland, OH, [2]Cleveland Clinic

Background: Patients with osteoarthritis (OA) of the knee have functional disability and reduced muscle performance. The impact of lower extremity muscle function and its recovery after total knee arthroplasty (TKA) is largely unknown. In a previous analysis of the OAI database we found that muscle performance is associated with health related quality of life (HRQoL) and physical function in individuals with both evidence of knee OA or at risk for developing OA. We hypothesize that these parameters change over time and that preoperative values can predict the likelihood of TKA.

Methods: Baseline and 24 months data from OAI were examined using three cohorts labeled as: 1) a "progressive" group (PRO) with evidence of knee OA at baseline, 2) an "incidence" group (INC) with risk factors for developing OA, and 3) normal controls. Parameters of interest were isometric upper leg strength, rapid chair-stands, and 20 and 400-meter walks as well as the WOMAC, KOOS, and Study Short Form (SF12) questionnaires. We compared changes between baseline and 24 months data and differences among groups using t-tests. The relation of baseline parameters to TKA within the next 24 months was examined using binary logistic and linear multivariate regression models. This analysis was done separately for persons that received a right TKA, a left TKA and for all TKAs combined.

Results: 4796 volunteers (PRO: 1390, INC: 3284, control 122) from the OAI cohort were included. 41.5% were men and 58.5% women. Muscle power assessed by the 400m walk time worsened by approx 2% whereas chair-stand pace improved by 2% in PRO and INC, 20m walk pace declined in PRO only ($p<0.05$ or lower). Muscle strength worsened in both groups ($p<0.0001$) by 6–10%. WOMAC and KOOS scores improved in PRO and INC (all $p<0.0001$) and varied between 1–9%. SF-12 scores worsened ($p<0.05$ or lower) but changes were small (2%). No changes were found in the control group for any of the measures. At 24 months there were 35 new right and 27 new left TKA. Baseline parameters that best correlated with future TKA were SF12, WOMAC disability score, 400m walk time and right quadriceps strength. Knee specific analysis revealed better prediction ability than if new TKA was assessed for both knees combined. Models remained significant after adjusting for age, BMI and gender. When comparing baseline muscle tests and HRQoL of individuals undergoing a TKA at 24 months to those without, persons with TKA had worse scores in all parameters ($p<0.05$ or lower).

Conclusions: Our analysis demonstrated that both HRQoL and muscle performance tests were able to distinguish between individuals with knee OA and those at risk for OA. WOMAC scores, SF12, 400m walk time and quadriceps strength were able to independently predict the likelihood of subsequent TKA. Side specific knee analysis was better than combined knee (L and R) analysis. Individuals that underwent a TKA within 24 months had worse scores in all HRQoL and muscle performance parameters at baseline suggesting these measures should be included in routine clinical assessment of knee OA patients. Improving muscle function and HRQoL should be a focus of preoperative risk stratification to optimize potential outcomes for TKA patients.

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Morphological Changes in Articular Cartilage and Subchondral Bone in Tibiofemoral and Patellofemoral Joints Following Arthroscopic Partial Medial Meniscectomy. Yuanyuan Wang[2], Alasdair Dempsey[3], David Lloyd[3], Peter Mills[1], Tim Wrigley[4], Kim Bennell[4], Ben Metcalf[4], Fahad Hanna[2] and Flavia Cicuttini[2]. [1]Griffith University, [2]Monash University, [3]The University of Western Australia, [4]University of Melbourne

Background: Although meniscectomy is an important risk factor for tibiofemoral osteoarthritis (OA), there is a paucity of studies examining the

relationship between meniscectomy and patellofemoral OA. This study aimed to examine the morphological changes in articular cartilage and subchondral bone in tibiofemoral and patellofemoral joints in a meniscectomy population.

Methods: 158 patients aged 30–55 years, without evidence of knee OA when undergoing isolated arthroscopic partial medial meniscectomy (APMM), and 38 controls with similar characteristics with APMM patients but without the surgery were recruited. Magnetic resonance imaging (MRI) of the operated knee was obtained at 3 months, 2 years, or 4 years post-surgery. MRI of the randomly assigned knee of the controls was also obtained. Cartilage volume and cartilage defects, bone area or volume were assessed using validated methods in tibiofemoral and patellofemoral compartments.

Summary of Results: Compared with controls, patients undergoing APMM had an increased prevalence of cartilage defects in the medial tibiofemoral (OR = 3.17, 95% CI 1.24 – 8.11, P = 0.02) and patellofemoral (OR = 13.76, 95% CI 1.52 – 124.80, P = 0.02) compartments, and increased medial tibial plateau bone area (B = 143.8, 95% CI 57.4 – 230.2, P = 0.001). Time from APMM was positively associated with the prevalence of cartilage defects in the medial tibiofemoral (OR = 1.02, 95% CI 1.00 – 1.03, P = 0.09) and patellofemoral (OR = 1.04, 95% CI 1.01 – 1.07, P = 0.02) compartments, and medial tibial plateau area (B = 2.5, 95% CI 0.8 – 4.3, P = 0.005), but negatively associated with lateral tibial cartilage volume (B = −4.9, 95% CI −8.4 to −1.5, P = 0.005). The association of APMM and time from APMM with patellar cartilage defects was independent of medial tibial cartilage volume.

Conclusions: Meniscectomy has adverse impacts on both tibiofemoral and patellofemoral joints within 5 years post-surgery. Strategies aimed at preventing the development of OA and reducing morbidity in meniscectomy populations should focus on both tibiofemoral and patellofemoral joints.

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MRI-Defined Risk Factors for Cartilage Loss over a 6 Months Period. Frank W. Roemer[1], C. Kent Kwoh[2], Michael J. Hannon[2], Stephanie M. Green[2], John M. Jakicic[2], Robert Boudreau[2], Michel D. Crema[1] and Ali Guermazi[1]. [1]Boston University, [2]University of Pittsburgh

Purpose: Cartilage morphology may only be directly assessed by MRI. Cartilage loss over short observational periods is rare but not uncommon. Aim of the study was to assess several non-MRI and MRI-features as baseline (BL) risk factors that may predict patello-femoral (PF) and tibio-femoral (TF) cartilage loss over a 6 months follow-up (FU) period.

Materials and Methods: The JOG study is a double-blind randomized trial investigating the effect of oral glucosamine supplementation over a 6 months period. 177 subjects aged 35–65 with chronic, frequent knee pain were included. 3 T MRI of both knees was performed at BL and 6 months FU using the same pulse sequence protocol as in the Osteoarthritis Initiative. Knees were semiquantitatively assessed according to the WORMS system. Cartilage status was scored on a scale from 0–6. A change of +0.5 in any subregion, indicating within-grade progression, was defined as the minimum requirement for cartilage loss. Bone marrow lesions (BMLs) in the same subregion, meniscal damage or meniscal extrusion in the TF compartment, synovitis and effusion were scored in addition and assessed as baseline risk factors.

All MR joint morphologic features were dichotomized into present (≥ 1) vs. absent (0). Logistic regression models were applied to assess the risk of cartilage loss for knees exhibiting risk factors when compared to knees without the risk factor at baseline. We performed a subregion-based analysis using general estimating equations (GEE) to account for the clustering of subregions within a knee and knees within an individual. Multivariate models were adjusted for age, gender, treatment (oral glucosamine) and BMI. In addition MRI-based risk factors were adjusted for each other in a multi-adjusted model.

Results: 51.2 % of participants were men, mean age was 52.3 (± 6.2), mean BMI was 29.1 (± 4.1). Baseline Kellgren/Lawrence grades (for worst knee) were: K/L 0: 37 (20.9%) knees, K/L 1: 14 (7.9%) knees, K/L 2: 26 (14.7%) knees, K/L 3: 81 (45.8%) knees K/L 4: 19 (10.7%). Of the 353 knees, 304 knees (87.9%) and 1,153 subregions (23.8%) exhibited prevalent cartilage damage at baseline. 79 (1.6%) subregions showed incident or worsening cartilage damage at 6 months FU. Predictors for PF cartilage loss at 6 months were baseline presence of effusion and prevalent cartilage damage in the same subregion. Risk factors for TF cartilage loss were baseline ipsi-compartmental meniscal extrusion, prevalent BMLs and cartilage damage in same subregion.

Table 1. Risk factors for patello-femoral and tibio-femoral cartilage loss over 6 months of follow-up

Risk factor	Reference	Adjusted Odds Ratio[3] (95% confidence intervals)
Patello-femoral		
Effusion (WORMS ≥ 1)[1]	Effusion absence (WORMS score = 0)	3.54 (1.30–9.64)*
Synovitis (modified WORMS ≥ 1)[1]	Synovitis absence (modified WORMS score = 0 in both synovitis subregions)	0.79 (0.28–2.07)
Prevalent cartilage damage (WORMS ≥2)[2]	No cartilage damage in subregion (WORMS score = 0 or 1)	4.32 (1.35–13.85)*
BML (WORMS ≥ 1)[2]	No BML in subregion (WORMS score = 0)	1.61 (0.67–3.84)
Tibio-femoral		
Effusion[1] (WORMS ≥ 1)[1]	Effusion absence (WORMS score = 0)	1.79 (0.76–4.23)
Synovitis[1] (modified WORMS ≥ 1)[1]	Synovitis absence (modified WORMS score = 0)	0.68 (0.32–1.45)
Meniscal damage[4]	No meniscal damage	1.98 (0.76–5.15)
Meniscal extrusion[4]	No meniscal extrusion	3.62 (1.29–10.12)*
Prevalent cartilage damage (WORMS ≥ 2)[2]	Absence of cartilage damage in subregion (WORMS = 0 or 1)	15.90 (5.08–49.79)*
BML(WORMS ≥ 1)[2]	No BML in subregion (WORMS = 0)	4.58 (1.08–19.44)*

[1]cartilage loss at 6 months in any of 4 PF/10 TF subregions
[2]cartilage loss or worsening of BML in same subregion at 6 months follow-up
[3]multi-adjusted GEE model accounting for correlations within and between knees, and adjusted for age, gender, BMI, treatment, and the other MR features
[4]cartilage loss in same compartment as meniscal damage or extrusion (5 subregions medial or lateral)
*statistically significant at p ≤ 0.05

Conclusion: Cartilage loss over 6 months is rare, but may be detected semiquantitatively by MRI. The strongest predictors of PF cartilage loss were presence of baseline effusion and prevalent cartilage damage in the same subregion. The greatest predictor of TF cartilage loss was also prevalent cartilage damage, but prevalent BMLs and meniscal extrusion were also significant predictors of compartment-specific TF cartilage loss.

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Neuromuscular Responses to Perturbations during Walking in Knee Osteoarthritis: Influence of Instability, Strength, Proprioception and Stiffness. Deepak Kumar, Darcy Reisman, Charles B. Swanik and Katherine S. Rudolph. University of Delaware, Newark, DE

Background: Neuromuscular interventions that reduce disability and slow disease progression are needed for people with knee osteoarthritis (OA). Effective interventions would depend on the ability of the neuromuscular system to adapt to changing external demands, in spite of the deficits in afferent and efferent pathways seen in people with knee OA. The ability of the neuromuscular system to adapt has been studied through the response to repeated perturbations; however, no studies report mechanisms that may accompany successful neuromuscular adaptation in people with knee OA. The aims of this study are to (1) analyze the responses to repeated perturbations during walking in people with knee OA compared to controls, and (2) to analyze the effect of quadriceps strength, functional knee instability (FKI), proprioceptive loss and altered knee stiffness on the responses to repeated perturbations.

Methods: 43 subjects with medial knee OA and 21 healthy controls (C) participated. Kinematic and EMG data were collected as subjects walked overground (Level) for 10 trials and over a platform that translated laterally (Perturbed) at initial contact (IC), for 30 trials. FKI was assessed from the response to the instability question in Knee Outcome Survey. Isometric quadriceps strength was measured at 90° flexion. Proprioception was assessed using Threshold to Detect Passive Motion and Joint Repositioning Sense techniques at 15° flexion. Knee stiffness (toque/degree motion) was assessed by

a rapid knee flexion from 30°-50° while seated. Walking data were analyzed over- Preactivation (Pre:100 msec before IC), Loading Response (LR: IC to peak knee flexion) and Midstance (MSt: end of LR to peak knee extension) phases. Mixed ANOVAs and Pearson's correlations were used for statistical analyses.

Results: OA had lower quadriceps strength than C. There were no differences in proprioception or stiffness. OA had less motion and higher activation than C across all conditions. All groups showed an increase in activation and decrease in motion in the 1st perturbation trial compared to normal walking. No adaptation was seen during preactivation and LR phases but during MSt, there was increased knee motion and deceasedmuscle activation over the 1st 5 trials. Quadriceps strength, knee stiffness, proprioception and FKI were not related to the rate of adaptation.

Discussion: This is the 1st report of neuromuscular adaptation in people with knee OA, and also for knee stiffness in this population. We found that people with knee OA respond similarly to controls when exposed to repeated lateral perturbations during walking, with an increase in knee motion and decrease in muscle activations. The knee OA related impairments in quadriceps strength, proprioception, stiffness and dynamic stability are not related to the ability to adapt. The results provide evidence that rehabilitation strategies aimed at modifying movement and muscle activation strategies to improve knee stability and reduce joint contact forces may be effective for people with knee OA. Further study is needed to determine the goals and best methods for improving neuromuscular control in this population.

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Peri-Articular Bone Density Is Strongly Correlated with Static Alignment and Varus Thrust.

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Purpose: Knee bone mineral density (BMD) has been associated with radiographic and MRI features of OA. Therefore, we hypothesized that tibial peri-articular BMD (paBMD) would be associated with static and dynamic alignment, both predictors of OA structural progression.

Methods: This is a cross-sectional study of a convenience sample from a randomized controlled trial (RCT) of vitamin D for symptomatic radiographic knee OA. Participants had standing PA semi-flexed knee x-rays read for anatomic alignment, a measure of static alignment. All consenting participants who did not use ambulatory devices and had video recordings of their gait using a standard digital video camera (60 Hz) walking at a self-selected speed were measured for varus thrust (VT), a measure of dynamic alignment. These videos were viewed at separate reading sessions by two rheumatologists trained to evaluate VT. Disagreements were adjudicated by consensus of both readers. Knee DXA scans were obtained using a GE-Lunar scanner and customized regions of interest were placed to calculate the medial:lateral tibial paBMD (ICC = 0.98).

Anatomic alignment measures were modified to reflect mechanical alignment; < 178°, 178° – 182°, and > 182° categorized participants as varus, neutral, or valgus respectively. Low, normal and high tibial paBMD groups were defined using biological cut offs of 1 and 1.25. We ran ANOVAs of medial:lateral paBMD stratified by mechanical alignment and VT groups. We also performed chi-squared tests of mechanical alignment and VT prevalences stratified by tibial paBMD groups.

Results: Participants (N=82) were 60% female, had a mean age 63.0 (±8.5), BMI 30.2 (±5.4), and tibial medial:lateral paBMD 1.19 (±0.21). 49% and 23% had varus and valgus alignment while 31% had VT.

Varus and valgus were associated with higher and lower medial:lateral paBMDs respectively. Mechanical alignment accounted for 59% of the variability in medial:lateral paBMD. (Table 1) VT was associated with higher medial:lateral paBMD. (Table 1).

Table 1. Medial: Lateral paBMD stratified by biomechanical categories.

		Mean Medial: Lateral paBMD	R^2	Overall p-values	Individual p-values
Static Allignment	Varus (n = 40)	1.35	0.59	< 0.0001	<0.0001
	Neutral (n = 23)	1.11			Referent
	Valgus (n = 19)	0.95			0.0014
Varus Thrust	Present (n = 25)	1.33	0.20	< 0.0001	n/a
	Absent (n = 57)	1.13			

The high medial:lateral paBMD had a high varus (93%) and a low valgus (0%) prevalence. (Table 2). The low paBMD group had the opposite findings.

Table 2. Prevalence of biomechanical categories stratified by the medial:lateral paBMD groups.

	VARUS Prevalence		VALGUS Prevalence		Varus Thrust Prevalence	
Medial:Lateral paBMD Groups						
Low	0/16 (0%)	p<0.0001	12/16 (75%)	p<0.0001	1/16 (6%)	p<0.0001
Normal	12/36 (33%)		7/36 (19%)		6/36 (17%)	
High	28/30 (93%)		0/30 (0%)		18/30 (60%)	

Conclusion: Static and dynamic alignment are strongly associated with medial:lateral tibial paBMD, accounting for nearly 60% and 20% of its variability. This may indicate that peri-articular bone responds to biomechanical derangements in those with knee OA. Modification of static or dynamic alignment may therefore lead to a change in peri-articular bone. Alternatively, treatment of bone health may be important in mediating the effects of alignment in knee OA.

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Prediction of Total Knee Replacement in a Two-Year Multi-Centre Clinical Trial in Knee Osteoarthritis: Results from a 4–6 Year Observation.

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Background: The aim of this study was to predict, using data from quantitative magnetic resonance imaging (qMRI), the incidence of total knee replacement (TKR) during the long-term follow-up of knee OA patients who formerly received treatment with licofelone or naproxen.

Methods: Knee OA patients participating in a previous 2-year randomized, double-blind controlled trial evaluating the impact of licofelone (200 mg BID) vs. naproxen (500 mg BID) who had serial MRI acquisitions of the symptomatic knee[1] were recently contacted to evaluate retrospectively the incidence of TKR of the study knee. A sub-group of patients (n=123) who had taken all the study medication and had all the MRI evaluations (according-to-protocol [ATP]) were selected for this post-hoc retrospective analysis. The TKR incidence was assessed blindly to the treatment allocation with a standardized phone interview.

Results: The patients' mean age was 63.5 years, 63.5% were female and the average body mass index (BMI) was 31.9 kg/m^2. A total of 18 TKRs (14.6%) were performed upon this sub-population in the time frame of 4–6 years after completion of the original study. Interestingly, there were significantly more TKRs performed within the naproxen group than the licofelone group (61% vs. 39%, Fischer's exact test p=0.23). Further, we investigated the predictors of long-term TKRs by comparing, within the ATP cohort, the patients who had TKR to those who did not, using data at baseline or the change at 2 years. Data revealed that baseline values of bone marrow lesions (BMLs) of the medial tibial plateau (p=0.0001; Fisher's exact test), medial joint space width (X-ray) (p=0.0008), presence of severe medial meniscal tear (p=0.004), medial meniscal extrusion (p=0.01), and C reactive protein (CRP) level (p=0.05) were strong predictors of TKR. Changes at 2 years also yielded strong predictors including change in the cartilage volume of the medial compartment (p=0.005) and of the global joint (p=0.03), as well as change in WOMAC pain (p=0.009) and function (p=0.02) scores. Logistic regressions that included age, sex, and BMI in the model, yielded that baseline severe medial tear (p=0.006) and the presence of a medial BML (p=0.002) were the strongest independent predictors of long-term TKR.

Conclusion: These data demonstrate that, in a knee OA clinical trial, it is possible to predict a "hard" outcome such as TKR using clinical and qMRI

data. The results are highly encouraging and support the use of qMRI as a surrogate for joint tissue damage upon which a DMOAD may act.

Reference:
[1] Raynauld JP, et al. Ann Rheum Dis 2009;68:938–47.

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Prevalence of MRI-Detected Joint Pathology of the Knee in a Population-Based Sample: Framingham Osteoarthritis Study. Jingbo Niu[3], Yuqing Zhang[1], Ali Guermazi[4], Frank W. Roemer[4] and David T. Felson[2]. [1]Boston Univ School of Medicine, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]Boston University School of Medicine, Boston, MA, [4]Boston University School of Medicine

Magnetic resonance imaging (MRI) allows direct visualization of cartilage and other soft tissues and is becoming a common method to image knees osteoarthritis (OA) in studies. MRI-detected intraarticular pathology may be common in persons without disease. Previous work has shown that meniscal tears are common even in persons without radiographic OA. For other features, this is unknown because little population based data are available on the prevalence of pathologic lesions.

Residents (age ≥ 50) in Framingham, MA were contacted by random-digit telephone dialing advertising a study of health in general and of bone health. Of 1039 subjects recruited, 992 had MRIs (1.5 T) on the knee(s) without contraindication to acquisition and MRI of one knee, right side preferred, was read. MRI features were scored using the WORMS system by two MSK radiologists. Each MRI feature was scored at multiple subregions in a knee. Kappa statistics for inter-rater reliability were 0.51–0.82 depending on feature. The presence of a lesion was defined by the worst score among subregions exceeding a pre-defined cut-point. We estimated sex- and age-specific prevalence of each lesion in the whole knee, then in the tibiofemoral (TF) and patellofemoral (PF) joint separately. We calculated the age-standardized prevalence of each lesion in men and women respectively, using the age distribution in the whole sample as the standard. Finally, we repeated the analysis among subjects without radiographic TF OA (K/L grade 0–1) and without radiographic PF OA, respectively.

Included in the analyses were 992 subjects (57% women, 93% White, mean age: 62.5 years, sd=8.8, range 50–92; mean BMI: 28.6 kg/m^2, sd=5.6). 791 (80%) had no radiographic TF OA, and 895 (90%) had no PF OA. The prevalence of each lesion detected on MRI increased with age among men. However, in women, the prevalence reached a plateau at age 65 then either leveled off or slightly decreased. As shown in the table, age standardized prevalence of MRI features was high and similar between men and women. The prevalence of MRI features in the TF joint was similar to or higher than that in the PF joint except for cartilage lesion in women. Over 70% of knees showed at least erosions of cartilage, about 60% showed at least small bone marrow lesions, roughly 1/4 knees showed at least moderate osteophytes, and over 40% showed synovitis or effusions. In knees without radiographic TF or PF OA, over 40% had cartilage lesion and over 30% had bone marrow lesion.

Pathologic lesions typical of osteoarthritis are common on MRIs among people aged 50 and older drawn from the community, even among subjects without radiographic OA. The prevalence of MRI lesions increased with age and was similar between men and women.

Table age-standardized prevalence of MRI features by gender (as % of knees)

MRI lesion (score range)	definition	Whole knee	TF joint	Med TF	Lat TF	PF joint	Med PF	Lat PF
	Men							
Cartilage morphology (0–6)	≥2 (at least cartilage erosion)	73.6	57.4	47.5	27.4	60.7	56.5	36.5
Ostoephyte (0–7)	≥3 (at least medium size)	27.5	23.0	22.3	9.7	18.1	13.2	10.7
Bone marrow lesion (0–3)	≥1 (at least small lesion)	57.5	43.9	29.0	17.4	36.1	29.4	21.4
Subarticular cyst (0–3)	≥1 (any cyst)	32.3	24.9	14.3	7.6	14.3	10.4	7.6
Meniscal tear (0–3)	≥1 (definite tear)	-	42.0	36.4	10.6	-	-	-
popliteal/Baker's cyst (0–3)	≥1 (bursitis or cyst)	29.9	-	-	-	-	-	-
ansenine bursitis (0–1)	=1 (bursitis)	20.0	-	-	-	-	-	-
patella bursitis (0–1)	=1 (bursitis)	16.0	-	-	-	-	-	-
Synovitis/effusion (0–3)	≥1 (at least small effusion)	44.8	-	-	-	-	-	-
	Women							
Cartilage morphology (0–6)	≥2 (at least cartilage erosion)	75.4	52.2	43.9	28.6	67.2	64.0	45.8
Ostoephyte (0–7)	≥3 (at least medium size)	29.4	25.3	24.4	11.3	19.2	14.5	11.1
Bone marrow lesion (0–3)	≥1 (at least small lesion)	60.2	42.3	29.0	16.6	41.9	35.7	23.5
Subarticular cyst (0–3)	≥1 (any cyst)	33.7	23.8	13.6	7.0	17.6	12.8	10.1
Meniscal tear (0–3)	≥1 (definite tear)	-	28.5	21.6	10.4	-	-	-
popliteal/Baker's cyst (0–3)	≥1 (bursitis or cyst)	32.4	-	-	-	-	-	-
Anserine bursitis (0–1)	=1 (bursitis)	24.2	-	-	-	-	-	-
Patella bursitis (0–1)	=1 (bursitis)	22.6	-	-	-	-	-	-
Synovitis/effusion (0–3)	≥1 (at least small effusion)	45.1	-	-	-	-	-	-

*MRI features with prevalence <5% were not listed.

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Relation of Hand Enthesophytes on Plain Radiographs with Findings of Knee Enthesopathy: Is Osteoarthritis a Generalized Enthesopathy? Nadia Gibson[1], Mary M. Clancy[4], Jingbo Niu[3], Peter Grayson[2], Piran Aliabadi[6], Ali Guermazi[2] and David T. Felson[5]. [1]Boston Medical Center, Boston, MA, [2]Boston Medical Center, [3]Boston University, Boston, MA, [4]Boston University Sch Med, Boston, MA, [5]Boston University School of Medicine, Boston, MA, [6]Brigham's and Women Hospital

Purpose: Enthesopathy, an abnormality at the attachment of a tendon or ligament to bone, has been reported as a feature of osteoarthritis (OA) in the DIP joints. Some patients have central bone marrow lesions (BMLs) on MRI at the insertion sites of the ACL and PCL suggesting enthesopathy in the knee that might be similar to that seen in the hand. We have reported that these central BMLs on MRI are associated with OA (Arthritis Rheum 2008; 58: 130– 136). In this study, we evaluated whether hand enthesopathy was related to this presumed knee enthesopathy and whether in those with knee OA, hand enthesopathy was associated with these central BMLs.

Methods: We studied knee and hand x-rays of subjects from the Framingham Osteoarthritis Study, a population based study. Subjects seen in 2002–2005 had bilateral PA hand x-rays, weight bearing knee x-rays and knee MRI's using a 1.5 T magnet. We used T-2 weighted fat suppressed images to identify central BMLs. Knee x-rays were read for K/L grade. Hand x-rays were read for enthesophytes defined as bony spurs at the juxta-articular nonsynovial areas of MCP, PIP and DIP joints (excluding osteophytes) and midshafts of proximal, middle and distal phalanges. We scored lesions as 0: none, 1:small, 2:moderate, 3:large. The intra-observer kappa was 0.67. To determine whether there was a relation of presence of enthesophytes in either hand with central BML's in the knees (one knee/person), we selected 100 cases of knees withcentral BML's and 100 matched controls without this finding of the same age (2 year categories) and sex. We assessed the association by using conditional logistic regression adjusting for worst K/L grade in the knee. To determine if hand enthesopathy was related to central BMLs in the context of knee OA, further analyses restricted cases and controls to those with knee OA.

Results: Mean age of subjects was 68 years, mean BMI 29.5. Those with enthesophytes of at least one score ≥ 2 at DIP, PIP and/or MCP were less likely to have central BMLs of the knee (OR = 0.49, 95% CI 0.17–1.40), than those without such enthesophytes, although this was not statistically significant (see Table). Similarly, having at least one score ≥2 on the shafts (distal, middle and/or proximal) was not significantly associated with having central knee BMLs (OR=0.59, 95% CI 0.23 –1.51). Considering all hand sites, the number of subjects with at least one score ≥2 was 38 in the cases and 42 in the controls (OR = 0.57, 95% CI 0.26–1.27). Analyses using enthesophyte score ≥ 1 yielded similar results. When we examined only cases and controls with OA, we found similarly null results.

Conclusions: We found no relation between hand enthesophytes and central BML's in the knee. We also found no clear association of hand enthesophytes with central BMLs in patients with established OA. This provides evidence against a generalized enthesopathic disorder in association with knee OA.

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Responsiveness and Reliability of MRI in Osteoarthritis: Analytic Literature Review. David J. Hunter[5], Weiya Zhang[1], Philip G. Conaghan[4], Kelly Hirko, Leo Menashe, William M. Reichmann[2] and Elena Losina[3]. [1]United Kingdom, [2]Brigham and Womens Hosp, Boston, MA, [3]Brigham and Womens Hospital, Boston, MA, [4]Chapel Allerton Hospital, Leeds, United Kingdom, [5]University of Sydney, Sydney, NSW, Australia

Objective: To summarize literature on the responsiveness and reliability of MRI-based measures of osteoarthritis (OA) structural change.

Methods: An online literature search was conducted of the OVID, EMBASE, CINAHL, PsychInfo and Cochrane databases of articles published up to the time of the search, April 2009, with the search entries "MRI", and "osteoarthritis". The abstracts of the 1338 citations received with this search were then preliminarily screened for relevance by two reviewers. Of these, 243 were selected for data extraction for this analysis as well as a distinct analysis on validity. We extracted data on responsiveness and reliability from both longitudinal and cross-sectional studies for all synovial joint tissues as it relates to MRI measurement in OA. Reliability was defined by inter- and intra-class correlation (ICC) and kappa statistics. Higher ICCs and kappa values indicate more reliable estimates. Responsiveness was defined as standardized response mean (SRM)—ratio of mean of change over time divided by standard deviation of change. For the quantitative analysis negative SRMs indicate a loss of cartilage. For the semi-quantitative analysis, loss in cartilage is defined by positive SRMs. Random-effects models were used to summarize data from multiple studies.

Results: The reliability analysis included data from 89 manuscripts. The inter-reader and intra-reader ICC were all excellent (range 0.81–0.94).The inter-reader and intra-reader kappa values for quantitative, semi-quantitative and compositional measures were all moderate to excellent (range 0.52–0.88).

Table 1. Results of random-effects pooling of reliability

Inter-reader intra-class correlations (ICC)	Number of Estimates (Studies)	Mean Sample Size	Pooled ICC	95% Confidence Interval
Quantitative				
Cartilage	10 (4)	196	0.90	0.86, 0.95
Meniscus	2 (1)	291	0.81	0.72, 0.89
Inter-reader kappa	**Number of Estimates (Studies)**	**Mean Sample Size**	**Pooled Kappa**	**95% Confidence Interval**
Semi-Quantitative				
Cartilage	15 (4)	136	0.57	0.44, 0.71
Bone Marrow Lesion	2 (2)	237	0.88	0.79, 0.97
Meniscus	3 (3)	418	0.73	0.63, 0.84
Ligament	3 (3)	209	0.80	0.69, 0.90

The responsiveness analysis included data from 42 manuscripts. The pooled SRM for quantitative measures of cartilage for medial tibiofemoral joint was −0.58 (95%CI −0.75 to −0.41). The pooled SRM for the semi-quantitative measurement of cartilage for the medial tibiofemoral joint was 0.55 (95%CI 0.47 to 0.64).

Table 2. Results of random-effects pooling of standardized response mean

Stratification	Number of Estimates (Studies)	Mean Sample Size	Pooled SRM	95% Confidence Interval
Quantitative Cartilage				
Medial Femoral	54 (12)	118	−0.39	−0.48,−0.30
Medial Tibial	55 (17)	134	−0.33	−0.39,−0.26
Medial Tibio-Femoral	31 (12)	92	−0.58	−0.75,−0.41
Lateral Femoral	32 (8)	151	−0.19	−0.27,−0.11
Lateral Tibial	44 (14)	152	−0.44	−0.51,−0.36
Lateral Tibio-Femoral	14 (5)	110	−0.56	−0.92,−0.20
Patella	13 (9)	131	−0.60	−0.83,−0.37
Semi-Quantitative Cartilage				
Medial Tibial-Femoral	3 (3)	224	0.55	0.47, 0.64
Lateral Tibial-Femoral	3 (3)	224	0.37	0.18, 0.57
Patella	2 (2)	238	0.29	0.03, 0.56
Semi-Quantitative Other				
Synovium	3 (2)	68	0.52	0.28, 0.76
Osteophytes	4 (1)	150	0.36	0.28, 0.44
Bone Marrow Lesion	6 (2)	130	0.19	0.07, 0.30
Meniscus	2 (1)	264	0.27	0.14, 0.40

Conclusion: MRI has evolved substantially over the last decade and its strengths include its ability to visualize individual tissue pathologies, which can be measured reliably using both quantitative and semi-quantitative techniques. Using MRI it is possible to accurately and feasibly measure change in cartilage morphology over 12 months for knee OA. Studies also suggest that cartilage and synovium are responsive measures on semi-quantitative assessment.

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The Effects of Hip Muscle Training on Knee Joint Loading in Medial Knee Osteoarthritis. Julia Daher[1], Joel A. Block[2], Markus Wimmer[1], Dale R. Sumner[1] and Laura E. Thorp[3]. [1]Rush University Medical Center, [2]Rush University Medical Center, Chicago, IL, [3]Rush University Medical Center, Chicago, IL

Objective: The purpose of this investigation was to analyze the effects of a focused hip muscle training program on knee joint loading in subjects with medial compartment knee OA. Specifically, we hypothesized that focused hip musculature training in individuals with mild to moderate knee OA would produce favorable changes in dynamic loading of the medial knee during walking, as evidenced by decreased external knee adduction moments.

Methods: To date, 12 subjects with mild to moderate medial compartment knee OA ranging in age from 35–69 years of age completed the study protocol. Subjects underwent gait analysis at their self-selected normal walking speed and both the peak external knee adduction moment and the knee adduction angular impulse were calculated before and after participation in a 4-week supervised, physical therapy intervention targeted at the hip abductor musculature. Response to treatment was defined as a reduction in either parameter. Additionally, subjects wore an accelerometer-based activity monitor for 7 days after the baseline visit.

Results: 8 of the 12 subjects responded to therapy. For these subjects, the mean percent decreases in the peak external knee adduction moment were −9.6 ± 8.7% and −12.4 ± 7.7% for index and contralateral knees respectively. In the index and contralateral knees, the mean percent decreases in knee adduction angular impulse were −7.1 ± 3.8% and −22.0 ± 8.3% respectively. The magnitude of change in the responders was greater in the contralateral knee than in the index knee. The responders tended to be more active than the non-responders, though this difference was not significant. Nonetheless, when non-responders were included in the analysis, there were no significant changes in either peak adduction moment or adduction angular impulse.

Conclusion: The discrepancy between responders and non-responders is unexplained, though may relate to activity and/or adherence. While more subjects are needed to determine the efficacy of hip muscle training on joint loads in medial compartment knee OA, these preliminary results suggest hip muscle training may have use in prevention of contralateral disease development. It is possible that this type of intervention may be best suited for more active individuals.

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The Relationship between Symptoms of Medial Tibiofemoral Osteoarthritis and Toe-Out Angle during Walking: The MOST Study. K. Douglas Gross[4], Jingbo Niu[3], Yuqing Zhang[1], Michael C. Nevitt[6], Cora E. Lewis[5], James Torner[7] and David T. Felson[2]. [1]Boston Univ School of Medicine, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]Boston University School of Medicine, Boston, MA, [4]MGH Institute of Health Professions, Boston, MA, [5]University of Alabama, Birmingham, Birmingham, AL, [6]University of California, San Francisco, San Francisco, CA, [7]University of Iowa, Iowa City

Background: Many people with symptomatic medial knee osteoarthritis (OA) walk with an increased toe-out angle, an adaptation that can reduce compressive load on the medial tibiofemoral (TF) compartment and offer protection against worsening disease. Despite these advantages, it is not known why some people with medial TF OA spontaneously modify their gait in such a way as to increase toe-out, while others do not. It is possible that the presence and severity of knee pain provides a necessary incentive.

Methods: The Multicenter Osteoarthritis Study (MOST) is a NIH-funded longitudinal study of individuals who have or are at high risk for knee OA. From among participants who completed the 60-month exam, we selected all knees with radiographic medial TF OA (K&L grade >/=2 on fixed flexion x-ray with OARSI medial joint space narrowing score >/=1 and greater medial than lateral JSN). We inquired about knee pain in three ways: 1) presence of 'current knee pain' during the walking exam, 2) presence of 'frequent knee pain' during the past 30 days, and 3) 'knee pain severity' (none, mild, >/= moderate) when walking during the past 30 days. Toe-out angle was measured in degrees between the line of progression and the midline of a footprint at self-selected normal and fast walking speeds using a 14' GAITRite instrumented walkway. Linear regression with generalized estimating equations compared mean toe-out angle between knees with and without pain while adjusting for covariates (baseline age, BMI, sex, race, and mean walking velocity).

Results: 269 participants (mean age 62.9 +/− 8.0 yrs, mean BMI 32.1 +/− 6.7 kg/m2, 34.6% female, 84.0% white) contributed 374 knees (25.4% with current pain, 53.0% with frequent pain, and 51.1% with pain of at least mild severity when walking). Crude mean toe-out angle was 7.0 +/− 5.5 (range −8.2, 24.7) degrees at normal walking speed and 6.2 +/− 5.3 (range −7.9, – 24.4) degrees at fast walking speed. Adjusted mean toe-out angle at normal and fast speeds (respectively) was smaller among knees with current (p=0.09, p=0.05), frequent (p=0.33, p=0.14), and more severe knee pain (p=0.36, p=0.12), although the differences were not statistically significant (see table).

Conclusions: These findings do not lend support to the hypothesis that the presence or severity of knee pain among persons with medial TF OA is associated with greater toe-out angle during walking. On the contrary, because toe-out angle may be diminished among those with current, frequent, or more severe pain, an opportunity exists for gait training to increase toe-out among those with medial TF OA symptoms.

Toe-Out angle and Medial TF OA Pain during Normal and Fast Paced Walking

	N knees	Normal Paced Walking			Fast Paced Walking		
		Adjusted* mean toe-out, degrees (95% CI)	Beta Coefficient (95% CI)	p-value	Adjusted* mean toe-out, degrees (95% CI)	Beta Coefficient (95% CI)	p-value
Current Knee Pain (during walking exam)							
No	279	8 (7, 9.1)	0 (Reference)		7.2 (6.2, 8.2)	0 (Reference)	
Yes	95	6.9 (5.3, 8.4)	−1.2 (−2.50, 0.18)	0.09	5.9 (4.4, 7.3)	−1.31 (−2.64, 0.03)	0.05
Frequent Knee Pain (on most days)							
No	175	8.0 (6.9, 9.2)	0 (Reference)		7.3 (6.2, 8.4)	0 (Reference)	
Yes	197	7.5 (6.2, 8.7)	−0.55 (−1.64, 0.55)	0.33	6.5 (5.3, 7.6)	−0.81 (−1.90, 0.27)	0.14
Knee Pain Severity (when walking)				p trend			p trend
No	183	8 (6.8, 9.2)	0 Reference		7.3 (6.2, 8.5)	0 Reference	
Mild	120	7.4 (6.1, 8.7)	−0.64 (−1.81, 0.53)		6.3 (5.1, 7.6)	−0.99 (−2.18, 0.20)	
≥Mod	71	7.5 (6.2, 8.9)	−0.49 (−1.86, 0.88)	0.36	6.4 (5.1, 7.7)	−0.93 (−2.34, 0.49)	0.12

*Adjusted for baseline age, BMI, sex, race, and mean walking velocity.

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The Relationship between Varus and Valgus Thrust and Meniscal Damage in Persons with Knee Osteoarthritis. Alison H. Chang[4], Ali Guermazi[1], Frank Roemer[1], Kirsten Moisio[5], Jing Song[5], Dorothy D. Dunlop[4], Michael C. Nevitt[6], Carmelita J. Colbert[2], John A. Lynch[7], Karen W. Hayes[3] and Leena Sharma[4]. [1]Boston University, [2]Northwestern University, LaGrange, IL, [3]Northwestern University, Downers Grove, IL, [4]Northwestern University, Chicago, IL, [5]Northwestern University, [6]UCSF, San Francisco, CA, [7]UCSF

Purpose: Varus thrust observed during gait has been shown to be associated with a 4-fold increase in the risk of medial knee osteoarthritis (OA) progression. It is plausible that a varus thrust may trigger or exacerbate medial meniscal damage as a cumulative effect of the acute increase in medial load with each step of walking. A parallel relationship may exist between valgus thrust and the lateral meniscus. We tested the hypotheses: 1) varus thrust is associated with medial meniscal damage (tear, maceration, extrusion); and 2) valgus thrust is associated with lateral meniscal damage.

Methods: The sample included Osteoarthritis Initiative (OAI) participants with symptomatic radiographic knee OA (data from public release data sets version 0.2.2 and 1.2.1 and from an NIH-funded ancillary study). Trained examiners assessed all participants at the 12-month visit for varus and valgus thrust presence by gait observation. The following sequences from the OAI protocol were used for meniscal assessment: sagittal IW 2D TSE FS, sagittal 3D DESS WE, axial MPR of SAG 3D DESS WE, coronal MPR of SAG 3D DESS WE. Meniscal status was scored according to the BLOKS system in the anterior, body and posterior horn of the medial and lateral meniscus. In addition, extrusion was scored from 0–3, with presence defined as > 0. We used logistic regression to specifically evaluate the relationship of varus thrust to medial meniscal damage (tear, maceration, and extrusion) and valgus thrust to lateral meniscal damage, adjusting for age, gender, and BMI.

Results: 496 persons (1 knee/person) (mean age 62 years, BMI 30, 58% women) were examined. Varus thrust was present in 169 knees (34%) and valgus thrust in 31 knees (6%). As shown in Table 1, varus thrust was significantly associated with medial meniscal tear and with medial meniscal maceration.

Table 1. Varus Thrust and Medial Meniscal Damage

Thrust Status (n = 496 knees)	Number of Knees (row %) with Medial Meniscal Tear (238 knees, 48.0%)	Medial Meniscal Tear Adjusted OR (95% CI)	Number of Knees (row %) with Medial Meniscal Maceration (172 knees, 34.7%)	Medial Meniscal Maceration Adjusted OR (95% CI)
No varus thrust (reference) (n = 327 knees)	142 (43.4%)	Reference	99 (30.3%)	Reference
Varus thrust (n = 169 knees)	96 (56.8%)	1.50 (1.01, 2.22)	73 (43.2%)	1.53 (1.02, 2.29)

As shown in Table 2, valgus thrust was significantly associated with lateral meniscal maceration; the association with lateral meniscal tear approached significance.

Table 2. Valgus Thrust and Lateral Meniscal Damage

Thrust Status (n = 496 knees)	Number of Knees (row %) with Lateral Meniscal Tear (121 knees, 24.4%)	Lateral Meniscal Tear Adjusted OR (95% CI)	Number of Knees (row %) with Lateral Meniscal Maceration (77 knees, 15.5%)	Lateral Meniscal Maceration Adjusted OR (95% CI)
No valgus thrust (reference) (n = 465 knees)	109 (23.4%)	Reference	68 (14.6%)	Reference
Valgus thrust (n = 31 knees)	12 (38.7%)	2.12 (0.98, 4.56)	9 (29.0%)	2.38 (1.04, 5.45)

Neither varus thrust nor valgus thrust was significantly associated with meniscal extrusion (not shown).

Conclusion: Varus thrust during ambulation was associated with medial meniscal tear and maceration, but not with extrusion, with similar findings for valgus thrust and lateral meniscal damage. Longitudinal studies may help elucidate the cause-effect relationship between these factors and how they might act in concert to accelerate OA progression.

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Thigh Muscle Quality Correlates with Function, Leg Strength, and Walking Speed, but Not with Alignment in Individuals with Obesity and Knee Osteoarthritis. Rachel W. Holt[3], Richard F. Loeser[5], Cralen Davis[4], Claudine Legault[4], Barb Nicklas[4], Jeffrey Carr[4], David J. Hunter[1] and Stephen P. Messier[2]. [1]New England Baptist Hospital, Boston, MA, [2]Wake Forest Univ, Winston-Salem, NC, [3]Wake Forest Univ., Winston Salem, NC, [4]Wake Forest Univ., [5]Wake Forest University, Winston-Salem, NC

Purpose: The effect of obesity on risk for disease progression in osteoarthritis is mediated by the extent of malalignment but it is not known if adiposity and alignment are related. Adipose tissue in the thigh varies in distribution with some individuals having greater subcutaneous fat and others more between (intermuscular) and within (intramuscular) adipose tissue. In addition, muscle associated triglyceride can be determined by the CT attenuation of muscle and is a measure of muscle quality. The **objective of this study** was to determine the relationship between CT measures of thigh fat and lower extremity alignment and then with measures of pain and function in overweight and obese adults with mild to moderate knee OA.

Methods: Data were collected at baseline from participants entering the Intensive Diet and Exercise for Arthritis (IDEA) study. Inclusion criteria were BMI of 27–40.5 kg/m^2, age>55 years, self reported disability due to knee pain, and radiographic evidence of mild to moderate (K-L score II-III) tibiofemoral OA in at least one knee. Mechanical alignment was measured using full-length lower extremity x-rays and Image J software. Subcutaneous and inter/intramuscular (IM) thigh adipose tissue and thigh muscle quality were measured by CT. Self reported pain and function were evaluated using WOMAC. Strength was measured on a Kin-Con isokinetic dynamometer. Data were analyzed using SAS to calculate Pearson correlation coefficients and ANOVA (for analysis of alignment type).

Results: Data were available on 129 IDEA participants with the following characteristics: 70% female, mean±sd age of 65.9±6.2 years, BMI of 33.2±3.7 units, subcutaneous thigh fat of 876.2±285.9 cm^3, IM thigh fat of 30.4±16.1 cm^3, thigh muscle quality of 52.0±6.2 Hounsfield units, WOMAC function of 23.4 ±10.4, WOMAC pain of 6.0±2.9, concentric extensor strength of 61.2±23.9 Nm and 236.3±83.4 N, and walking speed of 1.2±0.2 m/s. 25% of the subjects had neutral alignment, 25% valgus, and 50% varus. The analysis of muscle quality showed significant negative correlations with age, BMI, IM thigh fat, and WOMAC function and positive correlations with strength and walking speed (Table 1). The analysis of the magnitude of the alignment angle (Table 1) revealed weak but significant correlations with WOMAC pain and function but not the CT measures. Furthermore, the mean thigh muscle quality did not differ significantly between the three alignment types (ANOVA not shown).

		Quadriceps quality		Alignment (angle)	
Variable	N	r	p	r	p
Age	129	−0.31	0.0003	0.02	0.86
BMI	129	−0.19	0.04	0.13	0.15
Subcutaneous thigh fat (cm^2)	129	−0.18	0.04	−0.001	0.99
IM thigh fat (cm^2)	128	−0.31	0.0002	0.02	0.86
Quadriceps quality	129			−0.03	0.71
WOMAC pain	129	−0.04	0.63	0.25	0.01
WOMAC function	129	−0.19	0.03	0.18	0.04
Leg strength (Nm)	102	0.26	0.01	−0.02	0.86
Leg strength (N)	102	0.30	0.003	−0.04	0.67
6 minute walk speed	129	0.20	0.02	−0.13	0.15

Conclusion: These results suggests that reduced thigh muscle quality due to IM fat correlates with age and BMI and has a detrimental effect on strength, speed, and overall function in this population; however, alignment does not appear to have the same impact. Based on posthoc power calculations, a larger sample size would be needed to detect the observed differences of about 1 HU in thigh muscle quality between alignment types.

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Understanding the Individual Burden of Osteoarthritis: Development of a Conceptual Model. Lucy Busija[3], Richard H. Osborne[2] and Rachelle Buchbinder[1]. [1]Cabrini Institute and Monash University, Malvern, Australia, [2]Deakin University, Melbourne, Australia, [3]University of Melbourne

Aims: While the importance of osteoarthritis as a public health burden is well recognised, less is known about the impact of this condition at the individual level. Currently, no unifying framework is available for comprehensively documenting health-related consequences from the individual's perspective as existing frameworks are either not designed to represent the views of people with osteoarthritis or do not capture the full range of osteoarthritis-related consequences. The aim of this study was to develop a conceptual framework for documenting health-related consequences of osteoarthritis in affected individuals.

Methods: Structured concept mapping (SCM) workshops (n=6) were undertaken, three with patients (n=26) and three with health professionals and health policy makers (n=27) in Australia and in Sweden. The participants were asked to generate statements describing the impact of osteoarthritis on individuals with this condition and those around them. The post-workshop analyses used a mix of quantitative (three-dimensional multidimensional scaling analysis) and qualitative (thematic analysis) approaches to indentify major dimensions of the individual burden of osteoarthritis. A relational algorithm was then used to identify the interrelationships among these dimensions and to construct an integrated theoretical model of the Personal Burden of Osteoarthritis (PBO).

Results: A synthesis of the workshops identified 8 potentially independent aspects of PBO, including Physical distress, Fatigue, Physical limitations, Psychosocial distress, Physical de-conditioning, Financial hardship, Sleep disturbances, and Lost productivity. Physical distress was the key influence on individual health and welfare. One of the major effects of physical distress was impaired physical function. In combination, physical limitations and physical distress lead to psychosocial problems, reduced work productivity, financial difficulties, and loss of physical fitness.

Conclusions: The PBO framework was designed to comprehensively capture the consequences of osteoarthritis on individuals with this condition. The framework provides new insight for individual care and program development for people with osteoarthritis.

Disclosure: L. Busija: None; **R. H. Osborne:** None; **R. Buchbinder:** None.

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Vibratory Sense Deficits in Radiographic Knee Osteoarthritis: The Multicenter Osteoarthritis Study (MOST). Najia Shakoor[4], Tuhina Neogi[1], David T. Felson[3], Jingbo Niu[2], Laura Frey Law[7], Cora E. Lewis[6] and Michael C. Nevitt[5]. [1]Boston Univ Schl of Med, Boston, MA, [2]Boston University, Boston, MA, [3]Boston University School of Medicine, Boston, MA, [4]Rush-University Medical Center, Chicago, IL, [5]UCSF, San Francisco, CA, [6]University of Alabama, [7]University of Iowa, Iowa City, IA

Background: Somatosensory abnormalities, including proprioceptive and vibratory sense deficits, have been observed in osteoarthritis (OA) of the knee. Deficits in vibratory sense were associated with the presence of knee and hip OA in two small cross-sectional studies. We examined the association of vibratory sense with radiographic knee OA (RKO) in participants in a large cohort study of knee OA, the Multicenter Osteoarthritis Study (MOST).

Methods: MOST is a NIH-funded longitudinal study of persons with symptomatic knee OA or at increased risk of OA. At the 60-month visit, participants underwent bilateral evaluation of vibratory perception threshold (VPT), using a biothesiometer (Bio-Medical Instrument Co.) operating at a frequency of 120Hz. The applicator tip of the instrument was placed on three anatomical bony prominences: the dorsum of the first MTP joint, the tibial tuberosity and, the radial styloid. The voltage of the biothesiometer was initially set at "0" and then increased by 1 volt/second until the participant acknowledged sensation and this was defined as the VPT. At each study visit, participants had bilateral weight bearing PA and lateral x-rays which were read for Kellgren Lawrence (KL) grade, and defined as RKO if KL grade was ≥2. Those with knee replacement or diabetes were excluded. In light of large differences in VPT between genders and with age, men and women were evaluated separately and divided into age subgroups, <65 years and ≥65 years. A knee-based analysis was performed with three knee groups: 1) RKO (KL ≥ 2); 2) contralateral "normal" knee of unilateral RKO and 3) control knee (no RKO in either knee). Linear regression with GEE was used to compare VPT between groups adjusted for age and BMI and accounting for between knee correlations.

Results: This analysis included 222 men (mean age (SD) of 67±9 years) and 451 women (mean age (SD) of 68±8 years). VPT values for men were significantly (p<0.001 at all sites) higher compared to women adjusted for age and BMI. In men age ≥65, VPT was higher at the MTP and tibial tuberosity in knees with RKO compared to control knees, but this was not significant after age adjustment (Table). VPT in the nonOA knee of those with unilateral RKO was higher than controls, nearly reaching significance at the radial styloid. There were no significant associations of VPT with RKO status in men less than 65 or women in either age group.

		Mean VPT (95% CI) adjusted for BMI	P value (compared to control)	Mean VPT (95% CI) adjusted for BMI and age	P value (compared to control)
Men Age ≥65 years					
MTP	RKO (n = 84)	33.0 (29.5, 36.5)	0.009*	31.9 (28.3, 35.4)	0.056
	Contralateral (n = 28)	30.7 (25.3, 36.1)	0.190	31.1 (26.0, 36.1)	0.198
	Controls (n = 125)	26.5 (23.3, 29.7)		27.2 (24.1, 30.2)	
Tibial tuberosity	RKO (n = 85)	32.6 (29.9, 35.4)	0.011*	31.3 (28.5, 34.1)	0.142
	Contralateral (n = 29)	31.4 (26.3, 36.4)	0.196	31.5 (26.7, 36.1)	0.270
	Controls (n = 126)	27.6 (24.8, 30.3)		27.2 (24.1, 30.2)	
Radial styloid	RKO (n = 85)	12.1 (11.0, 13.3)	0.368	11.5 (10.3, 12.6)	0.807
	Contralateral (n = 29)	13.9 (11.5, 16.3)	0.069	14.0 (11.9, 16.1)	0.072
	Controls (n = 128)	11.3 (9.9, 12.7)		11.7 (10.3, 13.1)	

Conclusions: In this cohort study, an association between RKO and higher VPTs was present only in men ≥65 years of age, which is also the

group with the highest VPTs overall. No associations were observed in women in the current study. The control knees in our study had higher VPT values compared to previous studies, perhaps because this control group consisted of participants at high risk for OA. These results suggest that the association of VPT and knee OA may differ by age and gender.

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ACR Poster Session A
Pediatric Rheumatology—Clinical and Therapeutic Aspects: Juvenile Idiopathic Arthritis I
Monday, November 8, 2010, 9:00 AM–6:00 PM

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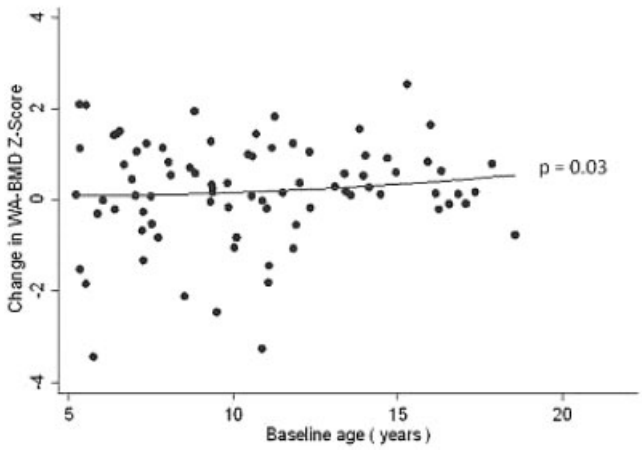
A Critical Appraisal of Lumbar Spine DXA Bone Mineral Density in a Longitudinal Study of Children with JIA. Maureen G. Leffler[1], Justine Shults[6], Sogol Mostoufi-Moab[2], Babette S. Zemel[7], Sarah E. Dubner[5], Mary B. Leonard[4] and Jon M. Burnham[3]. [1]AI duPont Hospital for Children, Thomas Jefferson University, [2]Children's Hospital of Philadelphia, [3]Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Center for Clinical Epidemiology and Biostatistics, Philadelphia, PA, [4]Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Center for Clinical Epidemiology and Biostatistics, [5]Seattle Children's Hospital, University of Washington School of Medicine, [6]University of Pennsylvania School of Medicine, Center for Clinical Epidemiology and Biostatistics, [7]University of Pennsylvania School of Medicine, Children's Hospital of Philadelphia

Background: Juvenile idiopathic arthritis (JIA) is associated with vertebral fractures. Precise screening methods are needed to identify those at-risk. Lumbar spine posterior-anterior (PA) dual x-ray absorptiometry (DXA) areal bone mineral density (aBMD, g/cm^2), obtained in 2D, is confounded by short stature and superimposes trabecular (vertebral body) and cortical (posterior elements) structures. Volumetric imputation using bone mineral apparent density (BMAD) or height Z-score adjustment (HAZ-aBMD) addresses confounding by stature. 3D width-adjusted volumetric BMD (WA-BMD, g/cm^3) pairs PA and lateral scans to isolate the vertebral body, excluding posterior elements. To evaluate the performance of these DXA measures in JIA, we assessed 1) aBMD, BMAD, HAZ-aBMD, and WA-BMD Z-score deficits and their change from baseline to 12 months, and 2) determinants of WA-BMD Z-scores and their change.

Methods: JIA subjects [n=88, 5 –19 yr, 79% F, 21 oligoarticular (OJIA), 35 polyarticular (PJIA), 16 systemic (SJIA), 16 spondyloarthropathy (SpA)] completed two visits. JIA subjects were compared with controls (n = 909, 5–21 yr). DXA PA spine (L1–4) scans (Hologic Delphi) were used to calculate aBMD and BMAD [bone mineral content/(bone area)$^{1.5}$] and paired PA – lateral scans of L3 were used to determine WA-BMD. DXA Z-scores, derived from controls, were age-, sex- and race-specific. HAZ-aBMD Z-score was calculated according to Zemel et al. (J Clin Endocrinol Metab, 2010). T-tests and multivariable linear and logistic regression were used to compare Z-scores and identify predictors of low Z-scores (< -1).

Results: Baseline: Compared with controls, height Z-scores were low in JIA (0.26 vs. -0.06, $p = 0.001$). In JIA, deficits were observed using WA-BMD ($Z = -0.59$, $p < 0.001$), but not aBMD ($Z = -0.23$, $p = 0.05$), HAZ-aBMD ($Z = -0.14$, $p = 0.62$), or BMAD ($Z = -0.13$, $p = 0.27$). WA-BMD deficits were significant in PJIA, SJIA and SpA. Lower WA-BMD Z-scores were associated with low BMI Z-scores (JIA and controls, $p < 0.001$), low height Z-scores (JIA only, p for interaction < 0.04), steroid use, active arthritis, and high CHAQ scores ($p < 0.05$).

Follow Up: No significant changes were noted for JIA using any DXA measure. WA-BMD Z-scores improved in SpA only ($D = 0.46$, $p = 0.02$). aBMD, HAZ-aBMD and BMAD Z-scores improved in SJIA ($D = 0.18 – 0.21$, $p < 0.05$). Adjusting for baseline WA-BMD Z-scores ($b = -0.58$, $p < 0.001$), no clinical predictors of Z-score changes were detected, but older age was associated with significant improvement (Figure).



Conclusions: In JIA, WA-BMD detects spine deficits obscured using aBMD, HAZ-aBMD, and BMAD. Greater baseline deficits were associated with low BMI and height Z-scores, active disease, disability, and steroid use. WA-BMD improvements were greatest in adolescents and those with lower baseline Z-scores. Future studies should use 3D modalities to define which tool best identifies vertebral fragility in JIA.

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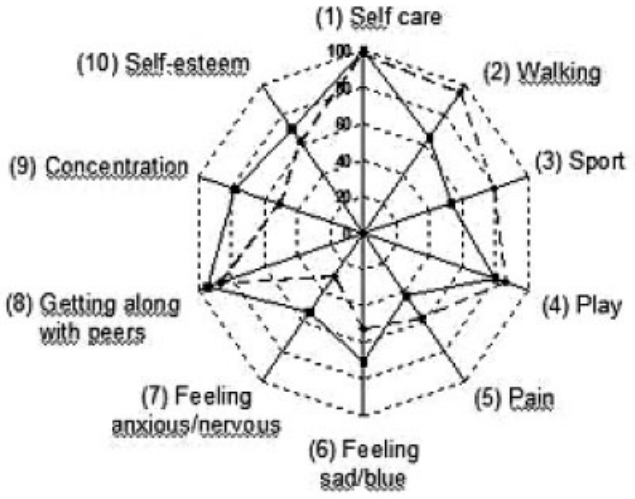
Adolescents with Juvenile Idiopathic Arthritis Currently Followed in a Tertiary Care Hospital Have a Better Psychosocial Well-Being Than Healthy Adolescents. Marta Bertamino[4], Giovanni Filocamo[5], Sara Dalprà[4], Elena Palmisani[4], Nicoletta Solari[4], Silvia Magni-Manzoni[1], Benedetta Schiappapietra[4], Nicolino Ruperto[4], Alberto Martini[3] and Angelo Ravelli[2]. [1]IRCCS Fondazione Policlinico San Matteo, Pavia, Italy, [2]IRCCS G. Gaslini and Università di Genova, Genova, Italy, [3]IRCCS G. Gaslini and Università di Genova, Genova, Italy, [4]IRCCS G. Gaslini, Genova, Italy, [5]Policlinico Sant'Orsola, Bologna, Italy

Background: Assessment of health-related quality of life (HRQL) is increasingly recognized as a fundamental component of the clinical evaluation of children with pediatric rheumatic diseases (PRD). It has been suggested that measurement of HRQL be incorporated into routine pediatric rheumatology care. Several studies have investigated the HRQL of children with PRD. However, comparison with healthy children has seldom been attempted.

Objective: To compare the health-related quality of life (HRQL) of children with juvenile idiopathic arthritis (JIA) and healthy children.

Methods: 472 parents of children with JIA, 232 children with JIA, 801 parents of healthy children, and 796 healthy children completed independently the Pediatric Rheumatology Quality of Life scale (PRQL) (Filocamo et al. Rheumatology 2010). Children with JIA and healthy children who completed the questionnaire were aged > 7–8 years.

Results: As expected, both parents of children with JIA and JIA children provided worse rating on the physical health (PhH) subscale of the PRQL than did parents of healthy children ($p<0.0001$) or healthy children ($p=0.0002$), respectively. However, scores on the psychosocial health (PsH) subscale were comparable between parents of JIA patients and parents of healthy children ($p=0.34$), and were much worse for healthy children than for children with JIA ($p < 0.0001$). Stratification of children by age (< 10 years, 10–13 years, > 13 years) showed that proxy- and self-reported scores on the PsH subscale were much worse for healthy children older than 13 years than for the other age groups. These differences were not related to sex or JIA severity. The figure shows the comparison of the frequency of abnormal values in the 10 items of the PRQL as self-reported by adolescents with JIA (continuous line) and healthy adolescents (dotted line). Items 1 to 5 refer to the PhH, whereas items 6 to 10 refer to the PsH.



Conclusion: To our knowledge, our study is the first to show that psychosocial functioning of adolescents with JIA is better than that of healthy adolescents. This phenomenon may depend, at least partially, on most of the JIA patients attending our clinics for follow-up visits having well-controlled disease with little or no disease activity or disability. This observation deserves further exploration in different populations.

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An International Consensus Survey of the Diagnostic Criteria for Macrophage Activation Syndrome in Systemic Juvenile Idiopathic Arthritis. Sergio Davì[4], Alessandro Consolaro[4], Dinara Guseinova[4], Angela Pistorio[4], Alberto Martini[3], Randy Q. Cron[1] and Angelo Ravelli[2]. [1]Children's Hospital of Alabama and University of Alabama at Birmingham, Birmingham, AL, [2]IRCCS G. Gaslini and Università di Genova, Genova, Italy, [3]IRCCS G. Gaslini and Università di Genova, Genova, Italy, [4]IRCCS G. Gaslini, Genova, Italy

Background: Macrophage activation syndrome (MAS) is a potentially life-threatening complication of systemic juvenile idiopathic arthritis (sJIA). Because MAS is a serious condition that can follow a rapidly fatal course, prompt recognition of its clinical and laboratory features and immediate therapeutic intervention are critical. However, diagnosis of MAS can be difficult and hard to distinguish from sepsis-like syndromes. In addition, subclinical forms of MAS in sJIA underscore the importance of establishing criteria sensitive enough to identify MAS from routine disease flare.

Objective: To select the clinical, laboratory and histopathologic features which are more suitable as diagnostic criteria for sJIA-associated MAS through an international Delphi questionnaire survey.

Methods: All members of the Paediatric Rheumatology International Trials Organisation (PRINTO), the Childhood Arthritis & Rheumatology Research Alliance (CARRA), and the Pediatric Rheumatology Collaborative Study Group (PRCSG) were submitted a questionnaire that listed the 28 most typical features of MAS and were first asked to select the 10 features that they deemed most important in the diagnosis of the syndrome, and then to rank order the 10 selected features by assigning 10 to the most important, and end with 1 as the least important.

Results: Of the 505 pediatric rheumatologists who were contacted, 232 (45.9%) participated in the survey. The table shows, for the features selected by more than 30% of respondents, the percentage of investigators who selected the feature and its median rank.

Results are reported for all respondents and for respondents categorized by geographic area. Falling platelet count, hyperferritinemia, evidence of hemophagocytosis in the bone marrow, increased liver enzymes, and falling leukocyte count were the 5 most frequently selected features. Only evidence of hemophagocytosis in the bone marrow, hyperferritinemia, and persistent fever reached a median rank >7. Overall, investigators from Europe and other parts of the world tended to give more weight to clinical manifestations than North American investigators, whereas North American investigators appeared to rely more on laboratory abnormalities than investigators from Europe and other parts of the world.

Feature	No. (%) of respondents who selected the feature	Median rank	Mean (SD) rank	% of respondents giving rank 8–10 to the feature	% of respondents giving rank 5–10 to the feature
Falling platelet count	201 (86.6)	6.5	6.1 (2.3)	24.6	61.6
Hyperferritinemia	194 (83.6)	7	6.5 (3.0)	39.2	53.9
Bone marrow hemophagocytosis	188 (81.0)	9	6.9 (3.6)	44.8	55.2
Increased liver enzymes	174 (75)	5	5.0 (2.4)	13	40.9
Falling leukocyte count	172 (74.1)	5	5.6 (2.5)	20.3	46
Persistent continous fever ≥ 38°C	158 (68.1)	7	6.0 (3.4)	30.2	40.1
Falling erythrocite sedimentation rate	142 (61.2)	6	5.5 (2.7)	15.9	38.8
Hypofibrinogenemia	142 (61.2)	5	5.4 (2.4)	12.9	36.6
Hypertriglic eridemia	135 (58.2)	5	5.1 (2.7)	16.8	31
Central nervous system dysfunction	104 (44.8)	5	5.0 (2.9)	11.6	23.7
Falling hemoglobin level	100 (43.1)	5	4.8 (2.3)	4.3	23.3
Prolongation of clotting times	81 (34.9)	4.5	4.5 (2.3)	4.7	17.2
Increased D-dimer	76 (32.8)	5	5 (2.6)	7.3	19.4
Hemorragic manifestations	72 (31.0)	5	5.3 (3.0)	10	17.7
Liver enlargement	71 (30.6)	4	4.8 (2.8)	7.3	14.2

Conclusions: We identified the features of MAS that were agreed upon by the majority of international pediatric rheumatologists. The ability of each feature to discriminate MAS from potentially "confusable" conditions and the optimal diagnostic threshold for laboratory tests will be assessed through a large-scale data collection, which is ongoing. Altogether, these processes will lead to the development of a new and robust set of criteria for MAS complicating sJIA.

Disclosure: S. Davì: None; **A. Consolaro:** None; **D. Guseinova:** None; **A. Pistorio:** None; **A. Martini:** None; **R. Q. Cron:** None; **A. Ravelli:** None.

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Anakinra as First-Line Disease Modifying Therapy in Systemic Juvenile Idiopathic Arthritis—Report of 46 Patients from an International Multicenter Series. Peter A. Nigrovic[4], Melissa Mannion[14], Andrew S. Zeft[15], Egla C. Rabinovich[8], Marion A. J. van Rossum[9], Elisabetta Cortis[2], Manuela Pardeo[2], Paivi M. Miettunen[1], Ginger L. Janow[5], James D. Birmingham[10], Aaron T. Eggebeen[10], Erin M. Janssen[3], Andrew I. Shulman[4], Mary Beth F. Son[4], Sandy D. Hong[13], Karla B. Jones[11], Norman T. Ilowite[7], Randy Q. Cron[6] and Gloria C. Higgins[12]. [1]Alberta Childrens Hospital, Calgary, AB, Canada, [2]Bambino Gesù Hospital, Rome, Italy, [3]Children's Hospital Boston, Cambridge, MA, [4]Children's Hospital Boston, Boston, MA, [5]Children's Hospital Montefiore, New York, NY, [6]Children's Hospital of Alabama, Birmingham, AL, [7]Children's Hospital Montefiore, Bronx, NY, [8]Duke University Medical Center, Durham, NC, [9]Emma Children's Hospital, Amsterdam, The Netherlands, [10]Michigan State Univ, Grand Rapids, MI, [11]Nationwide Children's Hospital, Columbus, OH, [12]Nationwide Childrens Hosp, Columbus, OH, [13]U of Iowa Children's Hosp, Iowa City, IA, [14]Univ of Alabama at Birmingham, Birmingham, AL, [15]University of Utah, Salt Lake City, UT

Objective: Chronic active systemic juvenile idiopathic arthritis (sJIA) is one of the most devastating rheumatologic diseases of childhood. We hypothesized that early treatment with anakinra could favorably affect the course of this disease.

Methods: Medical records of children receiving anakinra as first-line therapy for sJIA were reviewed to characterize clinical course.

Results: 46 children from 11 centers in 4 countries received anakinra as part of initial disease-modifying anti-rheumatic drug (DMARD) therapy for sJIA, at a median dose of 1.5 mg/kg/day. Anakinra alone was employed as monotherapy in 10 patients (22%), while corticosteroids and additional DMARDs were employed in 67% and 33% respectively. Median follow-up was 14.5 months. Approximately 60% of patients, including 8 of 10 treated

with anakinra monotherapy, attained clinical remission without further escalation of therapy. Fever and rash resolved within 1 month in over 95%, while C-reactive protein and ferritin normalized within this interval in over 80%. Active arthritis persisted at 1 month in 40%, at 3 months in 27%, and at >6 month follow-up in approximately 10%. Disease characteristics and treatment parameters were similar in partial and complete responders, but partial responders were markedly younger at onset (5.8 vs. 9.8 years, p=0.004). Associated adverse events included bacterial infection in 2 patients and hepatitis in 1 patient.

Conclusions: Anakinra is effective first-line therapy of sJIA, enabling rapid resolution of systemic symptoms while forestalling the development of refractory arthritis in 90% of patients. These results justify further study of IL-1 inhibition as first-line, rather than rescue, therapy in sJIA.

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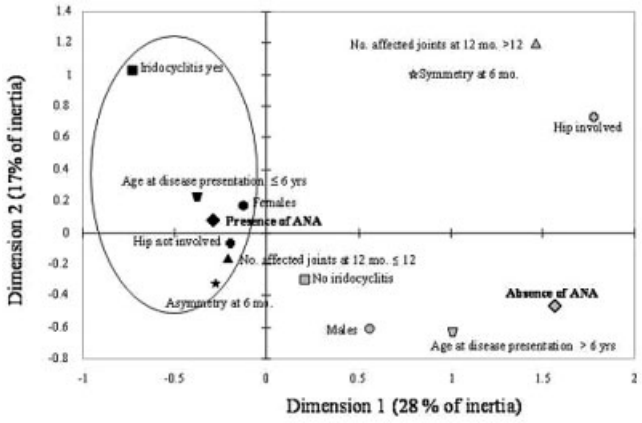
Antinuclear Antibody Positive Patients Should Be Grouped as a Separate Category in the Classification of Juvenile Idiopathic Arthritis. Angelo Ravelli[2], Giulia C. Varnier[4], Sheila K. Oliveira[5], Esteban Castell[4], Olga Arguedas[4], Alessandra Magnani[4], Angela Pistorio[4], Nicolino Ruperto[4], Silvia Magni-Manzoni[1], Bianca Lattanzi[4], Roberta Galasso[4] and Alberto Martini[3]. [1]IRCCS Fondazione Policlinico San Matteo, Pavia, Italy, [2]IRCCS G. Gaslini and Università di Genova, Genova, Italy, [3]IRCCS G. Gaslini and Università di Genova, Genova, Italy, [4]IRCCS G. Gaslini, Genova, Italy, [5]Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

Objective: We hypothesized that in the International League of Associations for Rheumatology (ILAR) classification of juvenile idiopathic arthritis (JIA), patients with similar characteristics are classified into different categories. We sought to investigate whether ANA-positive patients belonging to the ILAR categories of oligoarthritis, rheumatoid factor (RF)-negative polyarthritis, psoriatic arthritis, and undifferentiated arthritis share homogeneous features and to compare these features with those of ANA-negative patients in the same categories.

Methods: We identified all JIA patients who were followed up during a 22-year period. ANA positivity was defined as ≥ 2 positive results at a titer of ≥ 1:160. Demographic and clinical features were recorded retrospectively and compared among ANA-positive and ANA-negative patients.

Results: A total of 1219 patients fulfilled the ILAR criteria for JIA. Patients with systemic arthritis, RF-positive polyarthritis and enthesitis-related arthritis were excluded from the study. The remaining 971 patients belonging to the ILAR categories of oligoarthritis (n=649), RF-negative polyarthritis (n=223), psoriatic arthritis (n=37), and undifferentiated arthritis (n=62) were combined and classified according to their ANA status as follows: 711 (73.2%) were ANA positive, 149 (15.3%) were ANA negative, and 111 (11.4%) had a doubtful ANA status. Patients with a doubtful ANA status were excluded from the analysis. The number of ANA determinations per patient in the 860 patients who had the ANA status specified ranged from 2 to 20 (mean 5.4); the total number of determinations was 4610. All ANA-positive patients were similar in terms of age at disease presentation, female-to-male ratio, and frequency of asymmetric arthritis and iridocyclitis. Compared with ANA-positive patients, ANA-negative patients were older at disease presentation and had a lesser female prevalence, a lower frequency of iridocyclitis and asymmetric arthritis, a greater number of affected joints over time, and a different pattern of arthritis. The close relationship between the presence of ANA and younger age at disease presentation, female predilection, asymmetric arthritis, and development of iridocyclitis was confirmed by multivariate, multiple correspondence, and cluster analysis. The figure shows the 2-dimensional scatterplot of multiple correspondence analysis.



This analysis led to the identification of 2 patient groups with distinct characteristics: the circle identifies the interrelated variables that define the ANA-positive patient profile.

Conclusion: Our findings substantiate the hypothesis that ANA-positive patients classified into different JIA categories by current ILAR criteria constitute a homogeneous patient population, irrespective of the course of joint disease or the presence of psoriatic features.

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Are They Ready for Adult Care? An Assessment of Variables Affecting Patient Autonomy When Transitioning from Pediatric to Adult Rheumatology. Sharon E. Banks[3], Catherine A. Bingham[1] and Brandt P. Groh[2]. [1]Hershey Medical Center, Zionsville, PA, [2]Hershey Medical Center, Hershey, PA, [3]Hershey Medical Center

Background: Transition from a pediatric to adult provider is often difficult for pediatric rheumatology patients and their families. Currently there are no criteria used to determine whom or when to transition. Physicians expect the adolescent to become motivated to be medically independent in caring for his/her own disease without parental influence. However, many adolescents are not ready to assume this role causing a lapse in medical care. We sought to identify factors which, when present, might lead to increased autonomy. Identification of these factors could be used in the clinic to determine which patients would make a more successful transition.

Methods: 69 pediatric and young adult rheumatology patients between the ages of 14 and 21 were surveyed independently without parental input. Information was collected by questionnaire that consisted of two types of questions**. Independence questions** included whom the patient would contact in case of worsening disease, medication refills, medical emergencies, missed appointments, and to make an appointment. **Life skills questions** included whether the patient ever had a summer job, a drivers license, current grades, scholastic level achieved, and family income. Data was analyzed to see if there was any correlation between an individual's response to independence questions and his/her response to life skills questions. Significance was determined using Chi-square statistics and Fishers exact test where applicable. Statistically significant or near significant correlations are shown in the table below.

Results:

Life skill question	Independence question	P-value
Higher scores in school	Take meds without a reminder from parents	P = 0.01
Take meds which require laboratory monitoring	Parents give the meds	P = 0.07
Male gender	Likely to call doctor, not parent, if feel sick	P = 0.02
Take meds daily	Parent (not adolescent) phones doctor for emergency	P = 0.07
Increased household income	Parent makes doctor appointment	P = 0.09
Increased household income	Parent calls doctor for disease flare	P = 0.03
Increased household income	Parent cancels doctor appointment	P = 0.02
College level	Cancel own doctor appointment	P = 0.02
Have summer job	Give self meds	P = 0.04
Have summer job	Call doctor (not parent) if disease flares	P = 0.01
Have a drivers license	Call doctor (not parent) if run out of meds	P = 0.001
Have drivers license	Make own doctor appointment	P = 0.01
Have drivers license	Give self meds	P = 0.09

Conclusions: Higher scores in school, college enrollment, having a summer job, and a drivers license all contributed to independence in medical care. Higher family income, taking medications which require lab monitoring, and taking medications daily were associated with less independence. Physicians could assess this information to determine which patients may need more preparation for transition to adult rheumatology versus those ready to transition.

Disclosure: S. E. Banks: None; **C. A. Bingham:** None; **B. P. Groh:** None.

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Assessment of Activity in Children with Enthesitis Related Arthritis Using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Marìa M. Katsicas[2] and Ricardo A. G. Russo[1]. [1]Hospital de Pediatrìa Prof Dr JP Garrahan, Buenos Aires, Argentina, [2]Hospital de Pediatrìa Prof Dr JP Garrahan

Background: Enthesitis related Arthritis (ERA), as defined by ILAR criteria, is characterized by involvement of entheses and pheripheral joints; axial skeleton is affected in some patients The clinical spectrum of ERA overlaps with that of spondyloarthropathy. Bath Ankylosing Spondyliyis Disease Activity Index (BASDAI) is a score designed to determine the degree of activity in patients with Ankylosing Spondylitis. Its value as an outcome measure in children with ERA has not been tested.

Purpose: To assess disease activity using BASDAI in children with ERA. To correlate BASDAI score with disease activity markers.

Methods: Cross Sectional observational-descriptive study.Consecutive patients with ERA were included. Variables recorded were: presence of axial involvement [AI] (spinal pain and reduced spinal mobility or chest expansion), enthesitis, HLA-B27, number of active joints, number of joints with reduced mobility, duration of stiffness, ESR, physician'sglobal evaluation of activity (phy) [0–3], patient's assessment of well-being (p) [0–3] and pain [0–3] meassured on a 10 cm visual analogue scale (VAS), BASDAI, Bath Ankylosing Spondylitis Functional Index (BASFI) and CHAQ scores. BASDAI score was administered by a pediatric rheumatologist (MK) and answered by children (> 8 y) or parents (3–8 y). Association between disease activity markers (ESR, number of active joints, phyVAS, pVAS, painVAS) and BASDAI score was analysed (Spearman's correlation). Patients with AI were compared with those with peripheral involvement.

Results: 57 patients were enrolled (50 M,7 F). Age at onset: 9 ± 2.9 (3–15) years. Age at evaluation: 10 ± 2.9 (6–17) years. AI: 47 %. Enthesitis: 57%. Presence of HLA-B27: 42 %; # active joints: 2 (0–14) [median, range]; # joints with reduced mobility: 2 (0–12); duration of stiffness: 15 (0–180) minutes; Schöber test: 4,5 (2–7) cm; ESR= 2 (15–110) mm/h; phy VAS: 0.35 (0–1.9); pVAS: 0.48 (0–2.62); pain VAS: 0.41 (0–2.43). BASDAI >0 was recorded in 43 (86%) patients. Median BASDAI score: 1.90 (0–7.50). BASDAI correlated with: pVAS (r: 0.67; p=0,003), duration of stiffness (r: 0.65; p=0,004), phyVAS (r: 0.63; p=0,005) and ESR (r: 0.56; p=0,01). Patients with AI showed higher BASDAI score than patients with peripheral involvement. (median BASDAI score: 2.6 vs 1.7). BASDAI score corresponding to patients with AI strongly correlated with: duration of stiffness (r: 86%; p=0,006); ESR (r: 86%; p=0,01); phy VAS (r: 82%; p=0,01). Individual BASDAI score items correlations were: fatigue with pVAS (r: 59%; p=0,01) and phy VAS (r: 50%; p=0,03); spinal pain with painVAS (r: 63%; p=0,007); joint pain with pVAS (r: 64%; p=0,006) and phyVAS (r: 53%; p=0,03); areas of localized tenderness with pVAS (r: 64%; p:0,006); morning stiffness with duration of morning stiffness (r: 60%; p=0,01); ESR (r: 58%; p=0,01) and phy VAS (r: 51%; p=0,03).

Conclusion: BASDAI showed correlation with certain activity disease markers, especially in patients with AI. BASDAI score ranged in the low-medium spectrum of the scale. BASDAI should be included as a useful outcome measure in the asssessment of activity in children with ERA.

Disclosure: M. M. Katsicas: None; **R. A. G. Russo:** None.

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Benefit of Intra-Articular Corticosteroid Injections by Oral and Maxillofacial Surgery Treating Temporomandibular Joint Arthritis in Children with Juvenile Idiopathic Arthritis. Tyler Sharpe[2], Jennifer Good[2], Timothy Beukelman[3], Peter Waite[2] and Randy Q. Cron[1]. [1]Children's Hospital of Alabama, Birmingham, AL, [2]Univ of Alabama-Birmingham, [3]University of Alabama-Birmingham, Birmingham, AL

Background: Temporomandibular joint (TMJ) arthritis in juvenile idiopathic arthritis (JIA) is often asymptomatic and leads to joint destruction and micrognathia. MRI is the most sensitive tool at detecting TMJ arthritis in JIA patients, with prevalence rates ranging from 63–81%. Intra-articular corticosteroid injections (IACSi) of the TMJ under CT or ultrasound guidance are reported to reduce effusion and increase maximal-incisal opening (MIO) in JIA. Herein, MRI was used to determine the prevalence of TMJ arthritis among all subtypes of a large cohort of JIA patients. The efficacy and safety of delivering TMJ IACSi under anesthesia by an oral and maxillofacial (OMF) surgeon without the need for prolonged sedation and image guidance was evaluated.

Methods: A retrospective chart review of 192 patients diagnosed with JIA (ILAR revised criteria) seen at a single children's hospital between January 2008 and June 2010 was executed. MRI with contrast using a TMJ surface coil was performed and read by experienced pediatric radiologists. Sixty-three patients diagnosed by MRI underwent IACSi (0.5 ml of Aristospan per TMJ) by OMF surgery. Data collected included age, JIA subtype, age at diagnosis, immunosuppressive therapy, prior, MIO pre- and post-IACSi, changes on MRI, post-IACSi complications, and TMJ arthritis symptoms.

Results: MRI evidence of acute and/or chronic TMJ arthritis was noted in 46%. Of those with TMJ arthritis, 85% and 79% had received methotrexate and anti-cytokine (TNF or IL-1) therapy, respectively. All 7 JIA subtypes had relatively similar rates of TMJ arthritis (range, 40–57%). Forty-six (48%) of 95 patients with data available had MIO below mean values in age-matched normal subjects, and this was up to 61% (33 of 54 patients) in the subpopulation of patients diagnosed with TMJ arthritis and available data. Forty-two (47%) of 89 patients diagnosed with TMJ arthritis reported TMJ symptoms, particularly among 11–19-year-olds (74%). Sixty-three received TMJ IACSi; 66% showed MIO improvement, 27% decreased, and 7% no change. Post-IACSi MRI completed an average of 6 months post-injection (range 1.5 to 13 months) revealed improvement in 51% of patients (greatest improved opening in the systemic subtype), worsening in 34% of patients, and no change in 15% of patients. 21% reported improvement or symptom relief after IACSi. Only 3 patients (5%) reported post-TMJ IACSi complications, including localized swelling in 2, and 1 injection site hypopigmentation 10 months post-IACSi.

Conclusion: The prevalence of TMJ arthritis (46%) in this large JIA cohort was less than predicted but still substantial. Interestingly, all 7 JIA subtypes were roughly equally involved suggesting screening by MRI for TMJ arthritis in all JIA patients. No subtype had a notably worse response to TMJ IACSi, but the biggest MIO increase was in the oligoarticular subset. When using post-IACSi MRI data, similar outcomes are noted in this large JIA cohort compared to prior studies. Moreover, there is a higher frequency of MIO improvement than prior reports. Thus, TMJ IACSi by OMF surgery is similarly effective and safe as studies using radiographic guidance.

Disclosure: T. Sharpe: None; **J. Good:** None; **T. Beukelman:** None; **P. Waite:** None; **R. Q. Cron:** None.

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Cancer Risk in Juvenile Idiopathic Arthritis. Sasha R. Bernatsky[1], Ann E. Clarke[5], Kiem G. Oen[9], Ciaran M. Duffy[4], Alan M. Rosenberg[8], Jeremy Labrecque[2], Elizabeth M. Turnbull[3], Jennifer L. F. Lee[7] and Rosalind Ramsey-Goldman[6]. [1]McGill UHC/RVH, Montreal, QC, Canada, [2]McGill University, Canada, [3]McGill University Health Ctr, Montreal, QC, Canada, [4]Montreal Childrens Hospital, Montreal, QC, Canada, [5]Montreal General Hospital, Montreal, QC, Canada, [6]Northwestern University, Chicago, IL, [7]RI McGill Univ Health Ctr, Montreal, QC, Canada, [8]Royal Univ Hosp, Saskatoon, SK, Canada, [9]University of Manitoba, Winnipeg, MB, Canada

Purpose: There is considerable interest in the increased risk of malignancy in adult rheumatoid arthritis, particularly for lymphoma and lung cancer. However, to date there are few assessments specifically in juvenile idiopathic arthritis (JIA). Our objectives thus were to assess the observed malignancy incidence in JIA, and compare this to the expected incidence, based on general population cancer data.

Methods: We examined cancer occurrence within JIA registries at three Canadian pediatric rheumatology centers. The subjects in the clinic registries were linked to regional tumor registries to determine the occurrence of invasive cancers over the observational interval (spanning 1974–2006). The total number of cancers expected was determined by multiplying the person-years in the cohort by age, sex, and calendar year-specific cancer rates. The standardized incidence ratio (SIR, ratio of cancers observed to expected) was generated, with 95% confidence intervals(CI).

Results: The study sample was comprised of 1,834 patients. The female proportion was 67.6%; average age at cohort entry was 8.6 years(standard deviation, SD=5.1). The majority of cohort members were Caucasian. Subjects contributed 22,341 patient-years (average 12.2, SD=7.8). Within this observation interval, one invasive cancer occurred, compared to 7.9 expected (SIR 0.12, 95% CI 0.0, 0.70). This was a haematological cancer (Hodgkin lymphoma), representing a SIR for haematological malignancies of 0.76 (95% CI 0.02, 4.21).

Conclusion: Only one invasive cancer was demonstrated in this large sample of individuals with JIA, observed for an average of 12.2 years each. These data suggest that, at least in the initial years following JIA diagnosis, the risk of invasive cancers over-all is not markedly increased. However, the results do not rule out the possibility of a baseline increased risk of haematological malignancies. Potential limitations include the small number of specific minorities (e.g. blacks, Asians, Hispanics, etc.) and the difficulty in identifying risk related to specific JIA subtypes. A larger multi-center, multi-ethnic cohort study is underway, to provide more precise results for specific cancer types, and additional years of long-term follow-up.

Disclosure: S. R. Bernatsky: NIH, 2, The Arthritis Society of Canada, 2; **A. E. Clarke:** NIH, 2, The Arthritis Society of Canada, 2; **K. G. Oen:** None; **C. M. Duffy:** None; **A. M. Rosenberg:** None; **J. Labrecque:** None; **E. M. Turnbull:** None; **J. L. F. Lee:** None; **R. Ramsey-Goldman:** NIH, 2.

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Childhood Idiopathic Chondrolysis: A Form of Monoarthritis? Rafka Chaiban[1] and Robert P. Sundel[2]. [1]Children's Hospital Boston, Boston, MA, [2]Childrens Hosp Medical Center, Boston, MA

Background: Childhood idiopathic chondrolysis of the hip is condition characterized by substantial destruction of the articular cartilage without an identifiable cause. The incidence of this entity is low, and few pediatric cases have been reported in the literature.

Objectives: We sought to identify cases of idiopathic chondrolysis and determine whether modern diagnostic techniques offered a clearer etiopathologic explanation for the condition

Methods: A retrospective review of all children diagnosed and treated for chondrolysis of the hip since 1988 at a single tertiary care children's hospital was conducted. Subjects were identified from a search of clinic and hospital admissions for cartilage abnormalities. Patients with no definite etiology (idiopathic) were picked for further review. Demographic data, clinical presentation and treatment were studied. Diagnostic imaging and procedures were also noted.

Results: A total of 224 patients with chondrolysis of the hip were found. Out of these, seven had no known etiology (idiopathic chondrolysis of the hip). All seven patients had negative serum inflammatory markers and rheumatologic evaluation (including HLA-B27, ANA, RF). Synovial biopsy showed non-specific inflammatory changes with negative cultures for infectious organisms. Three patients were evaluated by rheumatology at the time of hospitalization for synovial biopsy, and were found to have a psoriasiform rash, dactylitis, nail pitting, or other signs of psoriatic arthritis. Two more patients had a positive family history of RA. Patients were treated for presumed inflammatory arthritis with intra-articular steroids, methotrexate, pulsed-dose methylprednisolone, and TNF inhibitors. All patients improved rapidly, and four who have been followed for a range of 4–6 years have remained well, without recurrence or progression of their chondrolysis. No patient has required joint replacement.

Conclusions: In a series of seven children at a single children's hospital diagnosed with idiopathic chondrolysis, clinical features and response to treatment were consistent with psoriatic arthritis or JIA. Aggressive therapy resulted in excellent clinical outcomes. The possibility that idiopathic chondrolysis might represent an unusually aggressive form of seronegative mono-arthritis should be considered in such patients.

Disclosure: R. Chaiban: None; **R. P. Sundel:** None.

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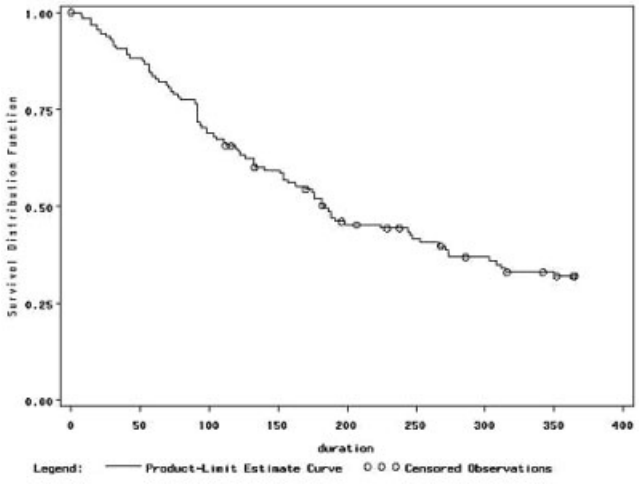
Clinical Outcomes after Withdrawal of Anti-Tumor Necrosis Factor-Alpha Therapy in Juvenile Idiopathic Arthritis: A Twelve-Year Experience. Kevin W. Baszis[2], Dana Toib[2], Richard Brasington[1], Allison King[3], Jingnan Mao[3], Andrew J. White[2], Jane Garbutt[3] and Anthony R. French[2]. [1]Washington Univ Schl of Med, St Louis, MO, [2]Washington University School of Medicine, Department of Pediatrics, St Louis, MO, [3]Washington University School of Medicine, Department of Pediatrics

Objective: To determine length of time to flare and likelihood of clinical remission after discontinuation of tumor necrosis factor-alpha (TNF-α) blockers in patients with juvenile idiopathic arthritis (JIA).

Methods: This is a retrospective cohort review of 241 patients with JIA treated with TNF-α inhibitors at our center between January 1, 1998, and November 1, 2009. Primary outcomes were time to flare after withdrawal of TNF-α inhibitor and proportion of treatment episodes resulting in clinical remission after cessation of anti-TNF-α therapy. Time points of interest were based on preliminary criteria for inactive disease and remission in JIA[1]. Inactive disease (ID) is defined by no active arthritis/uveitis, no systemic symptoms or elevated ESR/CRP attributable to JIA, and physician global assessment indicating no disease activity. Clinical remission on medication (CRM) is defined by ID for 6 months, on medication. Clinical remission (CR) is defined by ID for 12 months while off all anti-arthritis/uveitis medications. For our purposes, patients were not excluded if remaining on anti-rheumatic drugs after stopping anti-TNF-α therapy, but any further use of corticosteroids or biologic agents was cause for exclusion. Descriptive statistics, survival analyses, and hazard ratios were calculated.

Results: One hundred seventy-one patients met inclusion criteria, yielding 255 discrete episodes of anti-TNF-α treatment. Two hundred thirteen (83.5%) episodes resulted in ID; 127 (49.8%) episodes achieved CRM. After cessation of anti-TNF-α therapy in patients with ID, 50% of episodes remained in ID at 6 months, and 32% of episodes achieved CR off of anti-TNF-α therapy.



The median duration of anti-TNF-α therapy after ID was obtained was 6.1 months; there was no correlation between this duration and time to flare (r=0.01, p=0.91). Using hazard ratios and covariance analysis, subtype of JIA, sex, and age at diagnosis did not significantly affect risk of relapse. Median patient observation was 59.7 months.

Conclusion: In 171 patients with JIA achieving inactive disease on TNF-α inhibitors, 50% remained in remission at 6 months and 33% at one year. Results did not significantly vary by JIA subtype, sex, age at diagnosis, or duration of therapy. Although these results support the observation that JIA is a chronic relapsing/remitting disease, they suggest that one-third of patients can be successfully withdrawn from TNF-α antagonists for at least one year and be spared the cost and potential morbidity of treatment. Further studies are needed to identify predictive factors for those patients who successfully obtain clinical remission after anti-TNF-α cessation.

References:

1. Wallace CA, Ruperto N, Giannini EH. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. J Rheumatol. 2004; 31: 2290–4.

Disclosure: K. W. Baszis: None; **D. Toib:** None; **R. Brasington:** None; **A. King:** None; **J. Mao:** None; **A. J. White:** None; **J. Garbutt:** None; **A. R. French:** None.

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Contribution of TNFalpha–308 and T676G TNF-RII Polymorphism on Response to Etanercept and Posibility To Discontinue Treatment. Jelena Vojinovic[1], Gordana Susic[3], Jelena Basic[2], Dragana Lazarevic[1] and Nemanja Damjanov[3]. [1]Dept Ped Rheumatology, University Clinic Center Nis, Nis, Serbia, [2]Institute of Biochemestry Faculty of Medicine Nis, Nis, Serbia, [3]Institute of Rheumatology Belgrade, Belgrade, Serbia

Background: Genetic contribution of TNFα–308 promoter and T676G TNF-RII polymorphism on response to TNF-blocking agents in JIA is not yet well established. Primary endpoint of this study was to evaluate influence of these promoter polymorphisms, as biomarkers, in JIA patients treated with etanercept, on clinical outcome and possibility to discontinue treatment.

Methods: Genomic DNA was extracted and TNFα–308 promoter and T676G TNF-RII polymorphism was evaluated using the PCR-RFLP method in 60 JIA patients treated with etanercept, included in Serbian JIA registry who donated blood samples. Time cut of point for outcome data analysis was 4 years after first drug dose.

Results: At enrolment JIA patients mean age was 14.7±4.22, disease duration 6.59±2.76, average dose of MTX 11.91±6.68 mg/m2/week. Average duration of etanercept therapy was 34.61±12.11 months. Disease subtype distribution was 6.78% systemic, 54.24% polyRF- and extended oligo, 18.64% polyRF+, 16.95% ERA and 3.38 PsA. The distribution of TNFα308 and T676G genotypes was not significantly different among JIA subtypes. TNFα308 genotypes distribution was 6.78% AA, 30.51% GG and 62.71% GA while T676G genotypes were 59.3% TT, 8.3% GG and 26.4% TG. T676G genotype polimorphism did not significantly influenced outcome. ACR Pedi 30,50,70 and 100 improvement was significantly faster and sustained in TNFα308 GG-genotype patients compared to GA genotype.

ACR	30		50		70		100	
%	GG	GA	GG	GA	GG	GA	GG	GA
1 year	5.6	18.9[a]	22.2	35.14[a]	22.2	32.43[a]	50.9	13.51[a]
2 years		14.71[a]	5.6*	17.65**	44.4*	44.12*	50.0	23.52**

Results in table: *significant compared to 1 year; a-significant compared to GG Treatment could stopped (remission) in 35.14%, had to be reintroduces due to disease worsening in 16.22%, disease was in remission under medication in 21.62% or still active in 24.32% GA patients while respectively in 38.9%, 16.7%, 27.8% and 11.1% in GG patients. Patients with systemic or RF+ disease course were mostly treatment resistant in both genotypes.

Conclusion: JIA patients with GG TNFα308 genotype can achieve better outcome and etanercept treatment can be stopped earlier compared to GA genotype patients who need two years of treatment to achieve same results. TNFα308 genotype could be useful clinical predictive biomarker for treatment response in all disease subtypes except systemic and RF positive JIA.

Disclosure: J. Vojinovic: None; **G. Susic:** None; **J. Basic:** None; **D. Lazarevic:** None; **N. Damjanov:** None.

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Effectiveness of Dexamethasone Iontophoresis in Temporomandibular Joint (TMJ)-Arthritis in Juvenile Idiopathic Arthritis (JIA). Rina Mina[3], Paula G. Melson[3], Stephanie Powell[2], Claas H. Hinze[1], Joshua Pendl[2], Thomas B. Graham[5] and Hermine I. Brunner[4]. [1]Children's National Medical Center, Rockville, MD, [2]Cincinnati Children's Hosp Medical Ctr, [3]Cincinnati Children's Hospital Medical Ctr, Cincinnati, OH, [4]Cincinnati Children's Med Ctr, Cincinnati, OH, [5]Vanderbilt Children's Hospital, Nashville, TN

Background: TMJ-arthritis is common in JIA and the best treatment approach is unknown. The effectiveness of dexamethasone iontophoresis, a non-invasive method of transdermal steroid administration, has not been evaluated for TMJ-arthritis in JIA.

Objective: Evaluate the effectiveness of dexamethasone iontophoresis for the treatment of TMJ-arthritis in JIA.

Methods: Medical records of all JIA patients who underwent TMJ iontophoresis at Cincinnati Children's Hospital from 1997–2010 were reviewed. Effectiveness was assessed by comparing primary outcomes (i.e. inter-incisor distance and lateral translation) and secondary outcomes (pain, clicking and crepitus) before and after treatment using two-sided paired t-test.

Results: There were 28 JIA patients (all subtypes; median age ± IQR = 12 ± 8 years) who received TMJ iontophoresis. At baseline (median ± IQR) the number of active joints was 3 ± 4 and ESR was 5 ± 7. Medications included methotrexate (29%), biologics (25%) and NSAIDS (53%), with no clinically relevant medication-change during the treatment period. Iontophoresis was done using a standard dose of dexamethasone (6 mg) per TMJ per session (average number of sessions = 8, 45% bilateral). Statistically significant improvement was observed in the inter-incisor distance and right lateral translation (*see Table*). Improvement in TMJ pain (70%), clicking (80%) and crepitus (40%) were noted in those who initially presented with these findings. Side effects reported were transient and included site erythema (46%) and metallic taste (27%). Imaging with MRI was available only in select number of patients and thus not useful as study endpoint.

TMJ measurements at initial and final iontophoresis visit

	Initial Visit				Final Visit				
TMJ measurements	N	Median	IQR	Range	N	Median	IQR	Range	p-value
Inter-Incisor distance (mm)	24	34.5	14.5	20–55	24	38.5	10	26–55	0.0005
Right lateral deviation (mm)	11	7	6	4–15	14	10	1	5–20	0.04
Left lateral deviation (mm)	11	8	2	2–13	14	10	2	2–17	0.34

Conclusion: Dexamethasone iontophoresis appears to be effective in the management of TMJ-arthritis in JIA. Because of its ease of use and relative lack of side effects, it may be a good initial therapy for TMJ-arthritis and thus warrants prospective evaluation with focus on durability of response, imaging outcomes and optimization of treatment protocol.

Disclosure: R. Mina: NIAMS-NIH, 2; **P. G. Melson:** None; **S. Powell:** None; **C. H. Hinze:** None; **J. Pendl:** None; **T. B. Graham:** None; **H. I. Brunner:** NIAMS-NIH, 2.

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Effectiveness of Etanercept in Juvenile Psoriatic Arthritis and in Children with Enthesitis Related Arthritis. Marieke H. Otten[3], Femke H. M. Prince[4], Marinka Twilt[7], Nico M. Wulffraat[12], Rebecca ten Cate[7], Esther P. A. H. Hoppenreijs[9], Yvonne Koopman-Keemink[6], Simone L. Gorter[10], Wineke Armbrust[11], Koert M. Dolman[8], Joost F. Swart[13], Arnold P. Oranje[4], Flora B. de Waard-van der Spek[2], Marion A. J. van Rossum[1] and Lisette W. A. van Suijlekom-Smit[5]. [1]Academic Medical Centre Emma Children's Hospital and Jan van Breemen Institute Amsterdam, [2]Erasmus MC Rotterdam, [3]Erasmus MC Sophia Children's Hospital Rotterdam, Rotterdam, The Netherlands, [4]Erasmus MC Sophia Children's Hospital Rotterdam, [5]Erasmus MC Sophia Children's Hospital Rotterdam, The Netherlands, [6]Haga Ziekenhuis Juliana Children's Hospital The Hague, [7]Leiden University Medical Centre, [8]St Lucas Andreas Hospital and Jan van Breemen Institute Amsterdam, [9]St Maartenskliniek Nijmegen, [10]University Hospital Maastricht, [11]University Medical Centre Groningen Beatrix Children's Hospital, [12]Utrecht Medical Centre Wilhelmina Children's Hospital, [13]VU Medical Centre and Jan van Breemen Institute Amsterdam

Background: Etanercept (ETN) has proven to be effective in children with systemic and polyarticular Juvenile Idiopathic Arthritis (JIA). Experience with ETN in the treatment of Juvenile Psoriatic Arthritis (JPsA) and Enthesitis Related Arthritis (ERA) subtypes is limited. We therefore explored the effectiveness of ETN in these subtypes.

Methods: This study is embedded in the ABC-register, a since 1999 prospective ongoing multicentre, observational study of all Dutch JIA patients using biological agents. Patient and disease characteristics are collected at baseline. At start of treatment, after 3, 6, 15 months and thereafter yearly variables of the JIA disease activity score; physician's global (VAS), Childhood Health Assessment Questionnaire (CHAQ), including global assessment of wellbeing (VAS), number of active and limited joints and ESR, are retrieved. Response was assessed by the ACR pediatric criteria, and Wallace criteria for inactive disease. We collected additional data regarding the diagnostic ILAR criteria for JPsA and ERA.

Results: Our register includes 17 JPsA and 14 ERA patients treated with ETN.

JPsA patient characteristics: 71% female, median age at onset 11.0 (range 3.3–13.3) years, 47% with psoriatic skin lesions, 41% nail psoriasis, and 24% dactylitis. Median follow-up since start etanercept of 26 (range 3–62) months.

ERA patient characteristics: 79% male, median age at onset 10.4 (range 2.3–17.0) years, presence of enthesitis in 86%, SI-joint tenderness and/or inflammatory lumbosacral pain in 57%, and HLA-B27 positivity in 79%. Median follow-up since start etanercept of 46 (range 6–110) months.

After 3 months of treatment 82% of JPsA and 86% of ERA patients achieved ACRpedi30 response, increasing after 15 months to 100% and 91% resp. Of the JPsA patients reaching 39 months of follow-up (n=6) 67% achieved inactive disease and of the ERA patients (n=4) 50% (Figure 1).

In only 4 of the 8 patients with pre-existing psoriasis the skin lesions improved. Two JPsA patients and 2 additional JIA patients with other subtypes from our register developed *de novo* psoriasis during ETN treatment.

In both subtypes there was no ETN discontinuation because of inefficacy. Six JPsA patients and 1 ERA patient discontinued treatment after good clinical response. However, all except 1 JPsA patient flared again. They all restarted treatment with good clinical response.

Conclusion: We showed that ETN is very effective to treat the arthritis in the JPsA and ERA subtypes, with more than 90% achieving ACRpedi30 response after 15 months of treatment. However the psoriatic skin lesions did not respond very well and *de novo* psoriatic skin lesions occurred in JPsA patients and in patients with other JIA subtypes during ETN treatment. In most patients the arthritis flared after discontinuation of treatment, emphasizing the need to investigate optimal duration of therapy.

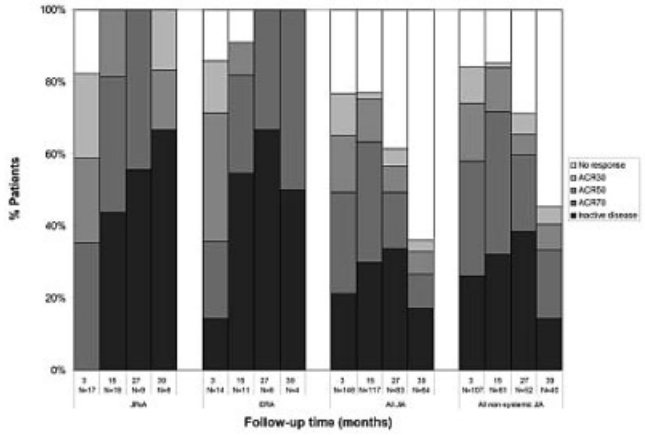

Figure 1. Improvement and inactive disease based on an intention-to-treat modus. Shown are percentages of JPsA and ERA patients that met the criteria for the ACR Pedi 30, 50 and 70 and inactive disease compared to all JIA subtypes and all non-systemic JIA subtypes (i.e. subtypes other than systemic JIA), as published from our register in 2009.

Disclosure: M. H. Otten: None; **F. H. M. Prince:** None; **M. Twilt:** None; **N. M. Wulffraat:** None; **R. ten Cate:** Pfizer Inc, 2; **E. P. A. H. Hoppenreijs:** None; **Y. Koopman-Keemink:** None; **S. L. Gorter:** None; **W. Armbrust:** None; **K. M. Dolman:** None; **J. F. Swart:** None; **A. P. Oranje:** None; **F. B. de Waard-van der Spek:** None; **M. A. J. van Rossum:** None; **L. W. A. van Suijlekom-Smit:** Abbott Immunology Pharmaceuticals, 2, Pfizer Inc, 2.

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Efficacy and Safety of Oral and Parenteral Methotrexate Therapy in Children with Juvenile Idiopathic Arthritis. Gerd Horneff[2], Gerd Ganser, Ivan Foeldvari[1], Andreas Urban and Ariane Klein. [1]Hamburg, Germany, [2]Asklepios Clinic Sankt Augustin, Germany

Background: Methotrexate is widely used as first-line disease-modifying antirheumatic drug in juvenile idiopathic arthritis (JIA). Both, oral and parenteral administrations have been shown to be effective.

Methods: In the German Methotrexate Registry data concerning efficacy and safety of methotrexate treatment are collected since 2005. In a retrospective analysis we compared oral and parenteral methotrexate treatment regarding efficacy, adverse events and rate of and reasons for discontinuation of treatment.

Results: Between 2005 and 2009 1066 JIA patients were documented in whom treatment with methotrexate has been initiated. 612 patients received methotrexate for at least 6 months, 3 patients had to be excluded because of concomitant treatment with biologics and 198 who changed the mode of application. 259 patients (63%) received oral (0.42+/−0.24mg/kg) and 152 patients (37%) parenteral (0.43+/−0.15mg/kg) methotrexate. At start of treatment patients of the two groups did not differ in numbers for active joints, joints with limited range of motion, CHAQ score, duration of disease, MTX dosage and concomitant steroid therapy. At 6 months, comparable numbers of patients treated orally or parenterally showed a PedACR 30, 50 and 70 response (oral 75.6%/68.8%/52.8% and s.c. 76.1% /72.1%/54.4%).

In the evaluated group 151 adverse events (AE) were reported, 76 in the group of 259 patients with oral (0.3/patient) and 75 in 152 patients with parenteral MTX (0.44/patient), gastrointestinal AEs (40 and 25) being the most frequent, followed by infections (10 and 12) and elevated liver enzymes (7 and 8).

10 patients in the oral group and 9 patients in the parenteral group discontinued methotrexate treatment during the first 6 months of treatment. Until last observation, significantly more patients with parenteral application discontinued methotrexate because of adverse events (11 of 152 versus 6 of 259, p = 0.016). However, significantly more patients in the oral group received folic acid (46.7% vs. 31.6%, p-value = 0.001).

	Patients on oral MTX			Patients on parenteral		
Parameter	month 0 Mean (SD)	month 6 Mean (SD)	Mean improvement	month 0 Mean (SD)	month 6 Mean (SD)	Mean improvement
Number of active joints	5.4 (+/−6.4)	1.5 (+/−2.4)	72%	6.1 (+/− 7.9)	1.3 (+/−2.2)	79%
Number of joints with LOM	4.8 (+/−5.6)	1.9 (+/−0.6)	60%	5.5 (+/−7.8)	1.6 (+/−2.5)	71%
Parent's global VAS 0–100	38 (+/−24)	13 (+/−18)	66%	44 (+/−27)	16 (+/−18)	64%
Physician's global VAS 0–100	39 (+/−23)	12 (+/−18)	69%	49 (+/−24)	16 (+/−20)	67%
CHAQ 0–3	0.57 (+/−0.69)	0.21 (+/−0.34)	63%	0.61 (+/−0.63)	0.25 (+/−0.41)	59%
ESR mm/h	21 (+/−18)	10 (+/−10)	52%	28 (+/−25)	13 (+/−14)	54%

Conclusion: In this patient group parenteral administration of methotrexate was not superior to oral administration regarding efficacy and tolerability. JIA patients treated with methotrexate did not show significantly different PedACR responses whether they received oral or parenteral MTX. These results could not argue for a possibly painful and more expensive application mode of methotrexate especially in younger children until controlled, randomised prospective studies have been performed.

Disclosure: G. Horneff: Abbott Laboratories, 5, Bristol-Myers Squibb, 5, Genzyme Corporation, 5, Wyeth Pharmaceuticals, 5; **G. Ganser:** None; **I. Foeldvari:** Abbott Immunology Pharmaceuticals, 5, Actelion Pharmaceuticals US, 5, Wyeth Pharmaceuticals, 5; **A. Urban:** None; **A. Klein:** None.

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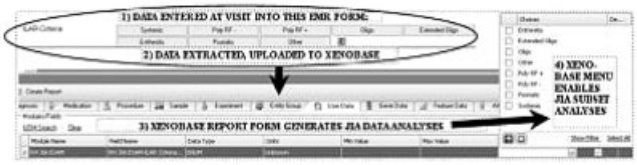
Electronic Medical Record (EMR) Entries Can Provide a Source for Quality Improvement Projects for Juvenile Idiopathic Arthritis (JIA): Results of a Pilot Study. Michael L. Miller[2], Jason Ruprecht[1], George Lales, Sean McKenna and Frank Dupont. [1]Chicago, IL, [2]Childrens Memorial Hospital, Chicago, IL

Although EMRs have facilitated care for children with juvenile idiopathic arthritis, relevant quality improvement projects have required use of paper or manual re-entry of clinical data. To establish continuous, periodic QI activities tracking care of JIA patients, we have started EMR discrete data

entry for joint examination and related clinical parameters. This IRB approved pilot study reports successful data extraction from our EMR to Xenobase™, an application permitting cohort analysis of a clinic JIA population, stratified by disease subtype and disease severity.

Methods: During clinic visits, starting March, 2010, data were entered into flow sheet rows in EpicCare™ (Epic Systems, Verona, WI), extracted every 2 weeks, using Clarity Reports, as de-identified data. Data were de-identified and uploaded to Xenobase™. Parameters included detailed joint examination, ILAR diagnosis, MD disease activity assessment (10 = very active), Patient/Parent global assessment (10 = very good), Pain Score (10 = most severe).



Results: Data on 175 patients with JIA seen from March-May, 2010 were extracted from EMR records and analyzed in Xenobase™. Number, age, and gender distribution were: oligo (64; 52 females; 10.3±4.6yrs); extended oligo (6; 5 females; 15.5±3.8 yrs); poly rf- (50; 41 females; 11.8±4.2yrs); poly rf+ (15;14 females; 14.3±3.6yrs); systemic (18; 7 females; 11.1±3.9yrs); enthesitis (19; 10 females; 16.1±8yrs); psoriatic (3; 2 females; 13.0±4.5yrs). Patient Global assessment showed weak correlation with joint counts in active polyarticular JIA, RF positive and negative (r=0.409), but in no other group.

Conclusion: Data extraction from the EMR is feasible and useful to track JIA patients for QI projects. In this pilot study, we found data accurately reflected distribution of age, gender, and numbers typically seen in pediatric rheumatology clinics. Further data extraction and analyses (IRB approved) will compare longitudinal response to treatment. This approach may be helpful in contributing data to national disease registries.

Disclosure: M. L. Miller: None; **J. Ruprecht:** None; **G. Lales:** None; **S. McKenna:** None; **F. Dupont:** XB TransMed. Inc., 3.

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Evaluation of the Role of Bone Mass Determinants in the Prediction of Bone Strength in Patients with Juvenile Idiopathic Arthritis (JIA): Bone Status Assessment Using pQCT, DXA and QUS. Fernanda Falcini[1], Loredana Cavalli[2], Laura Masi[2], Serena Capannini[1], Giovanni D'Elia[4], Valentina Denaro[1], Marco Matucci Cerinic[1], Stefano Stagi[3] and Maria Luisa Brandi[2]. [1]Department of BioMedicine, Section of Rheumatology, Transition Clinic, Florence, Italy, [2]Department of Internal Medicine, Endocrinology Unit, University of Florence, Florence, Italy, [3]Pediatric Unit, Villamarina Hospital, Piombino, Livorno, Italy, [4]Radiology Unit, AOC Careggi, Florence, Italy

Background: Despite the current more effective drugs, JIA pts have a low bone mass. The main reasons are disease activity, medications, reduced physical activity, and unbalanced nutrition. Using peripheral Quantitative Computed Tomography (pQCT) emerged that altered bone geometry, reduced muscle cross sectional area and muscle force, are the major responsible of bone loss in JIA.

Aim: To evaluate bone status in a cohort of pts affected with JIA.

Methods: 139 pts with JIA (median age 16.2 years, range 8.9 to 21.1 years: 101 oligoarticular, 29 polyarticular, and 9 systemic onset), after informed consent, entered the study. In all pts, peripheral Quantitative Computed Tomography (pQCT), Dual energy X-ray Absorptiometry (DXA) at lumbar spine 1–4, and phalangeal Quantitative Ultrasound (QUS) were performed. The data obtained were compared with 62 age- and sex- matched healthy subjects.

Results: Patients with JIA showed a reduced spine Bone Mineral Apparent Density (BMAD) SDS in comparison to controls ($p < 0.01$). These results were confirmed when the subjects were divided into JIA subtypes: systemic onset pts showed more impaired parameters than polyarticular and oligoarticular ($p < 0.005$). Spine BMAD SDS significantly correlated with JIA onset type ($p < 0.05$), age at JIA onset ($p < 0.005$), flares ($p < 0.01$), sex ($p < 0.01$), and corticosteroids exposure ($p < 0.01$). Also Amplitude-Dependent Speed of Sound (AD-SoS; $p < 0.005$) obtained by QUS, and volumetric cortical Bone Mineral Density (cBMD; $p < 0.001$), muscle cross-sectional area (mCSA; $p < 0.005$) and Stress-Strain Index (SSI; $p < 0.05$) obtained by pQCT were reduced in comparison to controls. Otherwise, the fat area was increased in JIA patients ($p < 0.001$). These results were confirmed also when the subjects were divided into JIA subtypes; systemic pts showed more impaired parameters than polyarticular and oligoarticular ($p < 0.001$).

Conclusions: JIA pts have decreased skeletal size, muscle mass, cortical bone density, cortical bone geometry, and muscle strength. These pts have also a higher fat mass. Not surprisingly, these bone abnormalities are more pronounced in pts with more severe disease activity. To reduce the risk of impaired bone mass, a close monitoring of BMD, a better control of disease activity, physical activity, and a dietary intake of calcium and vitamin D are advocated.

Disclosure: F. Falcini: None; **L. Cavalli:** None; **L. Masi:** None; **S. Capannini:** None; **G. D'Elia:** None; **V. Denaro:** None; **M. Matucci Cerinic:** None; **S. Stagi:** None; **M. L. Brandi:** None.

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Gut Inflammation in Pediatric Spondyloarthritis. Matthew Stoll[2], Marilynn G. Punaro[3] and Molly Dempsey-Robertson[1]. [1]Texas Scottish Rite Hospital for Children, [2]UT Southwestern Med Ctr, Dallas, TX, [3]UT Southwestern Medical Ctr, Dallas, TX

Purpose: Sub-clinical gut inflammation has been identified in two-thirds of adult spondyloarthritis (SpA) patients[1]. Similar findings were observed in a study of 12 pediatric SpA patients[2]. These studies used colonoscopy, an expensive and invasive test not well-suited for routine use in research studies. Although non-invasive tests have been studied in patients with inflammatory bowel disease (IBD), they have not been used to evaluate for sub-clinical gut inflammation among SpA patients. Our intention in this study is to evaluate whether non-invasive tests can detect gut inflammation in pediatric SpA patients.

Methods: Stool samples were obtained from children with active juvenile idiopathic arthritis (JIA). Calprotectin levels were assayed in a commercial lab (ARUP). Children with elevated calprotectin (calp) levels were offered an MRI of the intestines. Flavored sports drink containing polyethylene glycol 3350 was used as oral contrast. Glucagon was used to arrest peristalsis. Patients were imaged in the prone position on a 1.5-T scanner. Heavily T2-weighted fat-suppressed coronal and axial images using breath-hold technique were obtained, followed by post-gadolinium fat-suppressed T1-weighted gradient echo images.

Results: Results are available on 7 children with enthesitis-related arthritis (ERA) and 5 controls with oligo-articular (n = 3) or poly-articular (n = 2) JIA. 3 of the ERA patients and none of the controls reported mild gastrointestinal (GI) symptoms. Median fecal calp levels were 171 in the ERA patients, compared to 37 in the controls ($p = 0.073$; Figure 1.) The presence of GI symptoms was not associated with calp levels among ERA patients (median levels 210 in those without GI symptoms, versus 125 in those with complaints, $p = 0.480$). Two of the patients with abnormal calp levels underwent MRI of their intestines; one of them had evidence of terminal ileitis (Figure 2). Colonoscopy in this child was consistent with IBD primarily limited to the terminal ileum.

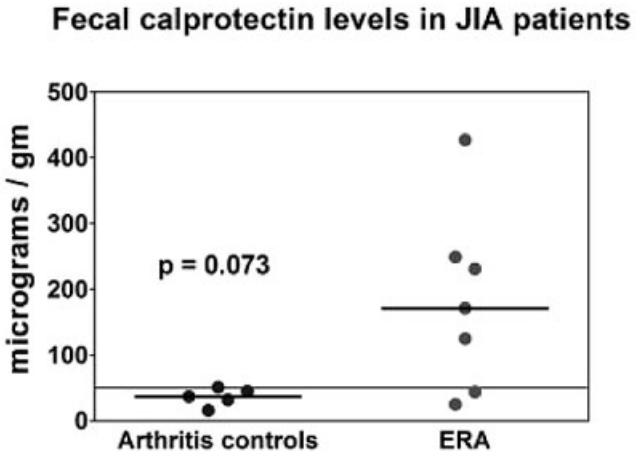

Figure 1. Calprotectin level in patients with ERA compared to patients with oligo-articular or poly-articular JIA.

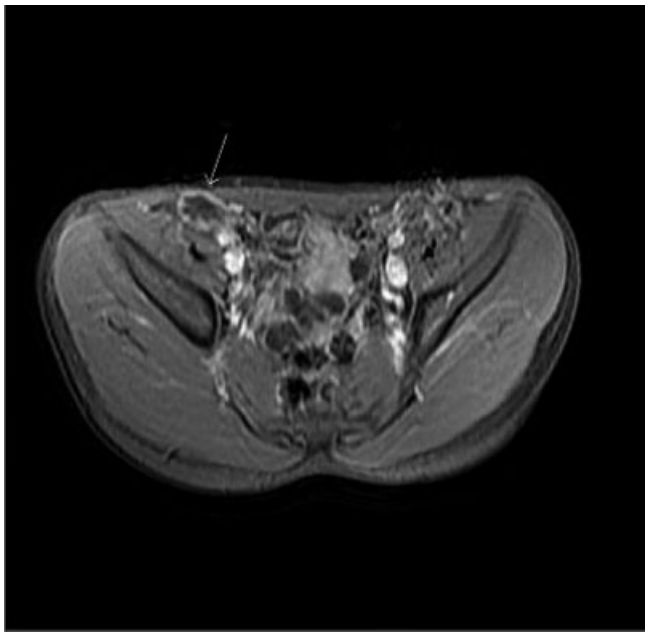

Figure 2. Axial T1 fSPGR with fat saturation post contrast. Arrow indicates site of abnormal enhancement in terminal ileum.

Conclusions: Although preliminary, the data from this study suggest that non-invasive markers can be used to evaluate for sub-clinical gut inflammation in children with SpA. This may have both research and clinical implications.

1. Mielants H, Veys EM, Goemaere S et al. J Rheumatol 1991;18:1542–51.
2. Mielants H, Veys EM, Cuvelier C, et al. J Rheumatol 1993;20:1567–72.

Disclosure: M. Stoll: None; **M. G. Punaro:** None; **M. Dempsey-Robertson:** None.

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Immunogenicity and Short Term Safety of Pandemic Influenza Vaccine (Anti-H1n1) in Patients with Juvenile Idiopathic Arthritis. Nadia E. Aikawa[3], Lucia M. A. Campos[5], Clovis A. Silva[5], Vanessa R. Guissa[5], Adriana M. Sallum[5], Adriana A. Jesus[5], Julio B. Moraes[4], Cleonice Bueno[4], Maria C. S. T. Timenetsky[1], Alex R. Precioso[2] and Claudia Goldenstein-Schainberg[4]. [1]Adolpho Lutz Institute, University of Sao Paulo, [2]Butantan Institute, [3]Division of Rheumatology, Pediatric Reumatology Unit, Universidade de Sao Paulo, [4]Division of Rheumatology, Universidade de Sao Paulo, [5]Pediatric Reumatology Unit, Universidade de Sao Paulo

Purpose: To assess immunogenicity and safety of pandemic influenza vaccine (anti-H1N1) in patients with juvenile idiopathic arthritis (JIA).

Methods: 60 JIA patients and 55 age-matched healthy controls were vaccinated with cepa A/California/7/2009 (NYMC X-179A) anti-H1N1 vaccine. All participants received 1 dose of immunization, and those <9yrs of age received a second dose 3 weeks apart. All subjects were evaluated before and 3 weeks after complete vaccination. Serology against H1N1 virus was performed by hemagglutination inhibition (HI) antibody (Ab) assay. Appropriate endpoints included the percentage of subjects achieving HI Ab titer ≥1:40 (seroprotection) and rates of seroconversion, defined as the percentage of subjects with either a pre-vaccination HI titer <1:10 and a post vaccination HI titer >1:40 or a pre-vaccination HI titer >1:10 and a minimum 4-fold rise in post-vaccination HI Ab titer. Demographic data, JIA onset subtype, disease duration, activity status, patient VAS and CHAQ score were analyzed. Post-vaccination adverse events (AEs) were searched. Fisher's exact and Mann Whitney tests were used for statistical analysis considering $p<0.05$ significant.

Results: Mean age of JIA patients and controls was 13.5±5.3yrs and 12.3±2.6yrs, (p=0.08); median JIA disease duration was 6.7±5.3yrs.

JIA subtypes were 48% polyarticular, 27% oligoarticular, 13% systemic and 12% others. Thirty seven patients (62%) were taking at least one DMARD and 17 (28%) were under biologic therapy (22% anti-TNF; 7% abatacept). Patient VAS, CHAQ score, ESR and CRP levels remained unchanged after immunization (p>0.05). Seroprotection rates against H1N1 influenza virus increased from 23 to 83% in JIA and from 22 to 95% in controls (p=0.08). Seroconversion rates were achieved in 78% JIA and 89% controls (p=0.14). Following vaccination, mean HI Ab titers ranged from 39±103 to 495±634 for patients and from 24±44 to 457±497 for controls (p=0.44). Seroprotection, seroconversion and mean HI Ab titers were not associated to use of DMARDs and/or biologic agents by JIA patients, although, mean HI Ab titer was significantly lower in patients <9yrs of age compared to those between 9–18yrs (217±354 vs. 628±723, p=0.016); notably, frequencies of MTX and DMARDs use were higher in the former group (71% vs. 35%, p=0.03 and 86% vs. 46%, p=0.01, respectively). AEs were reported by 40% patients and 42% controls with rates of 2.4 AE/JIA patient and 1.6 AE/control. Most frequent AEs in patients and controls were local pain (23% vs. 29%, p=0.53), headache (18% vs. 18%, p=1.0), malaise (15% vs. 7%, p=0.24), myalgia (13% vs. 7%, p=0.37), arthralgia (13% vs. 2%, p=0.07) and fever (5% vs 3.6%, p=1.0).

Conclusion: Vaccination of JIA patients against pandemic influenza A (H1N1) generated successful protective antibody production with short term safety profile.

Disclosure: N. E. Aikawa: None; **L. M. A. Campos:** None; **C. A. Silva:** None; **V. R. Guissa:** None; **A. M. Sallum:** None; **A. A. Jesus:** None; **J. B. Moraes:** None; **C. Bueno:** None; **M. C. S. T. Timenetsky:** None; **A. R. Precioso:** None; **C. Goldenstein-Schainberg:** None.

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Intra-rater Reliability of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Bath Ankylosing Spondylitis Functional Index (BASFI) in Children with Spondyloarthritis. Michelle Batthish[2], Alisa Rachlis, Bertha Wong, Samantha Stevens, Michelle Anderson, Brian M. Feldman[1], Ronald M. Laxer[1], Joanne Marcuz, Margaret Reaume, Lynn Spiegel, Kristi Whitney-Mahoney and Shirley M. L. Tse[1]. [1]Toronto, ON, Canada, [2]The Hospital for Sick Children, The University of Toronto, Toronto, ON, Canada

Background: Juvenile spondyloarthritis (JSpA), referred to as enthesitis-related arthritis (ERA) sub-type under the International League of Associations for Rheumatology (ILAR) classification of juvenile idiopathic arthritis (JIA), is characterized by inflammation in the joints and entheses. Axial involvement is uncommon at presentation but may develop in the second decade of life. Several instruments assessing disease activity in ankylosing spondylitis have been validated including the BASDAI and BASFI. At this time, there are no disease activity scores for JSpA or ERA. The objective of this study is to measure the intra-rater reliability of the BASDAI and the BASFI in JSpA/ERA.

Methods: Patients diagnosed with ERA (ILAR criteria) and followed at The Hospital for Sick Children Spondyloarthritis Clinic were included in this study. Patients were excluded if they were unable to understand, speak or write English, if they were less than 6 years of age or greater than 18 years of age. Prospective subjects were consecutively enrolled (June 2009 to June 2010) and, the patient and/or one parent completed the BASDAI and BASFI at baseline and 2 weeks later (a period during which little change is expected). Intra-class correlation coefficient (ICC) was calculated and values greater than 0.6 were considered indicative of good reliability.

Results: Forty-eight patients (39 males, 81.2%) were enrolled. The average age at diagnosis was 12.5 years (range, 7.6 to 16.7 years). 41.7% were HLA-B27 positive, 18.8% had a positive family history for ankylosing spondylitis, 52% had involvement of the hip and 40% had radiographic evidence of sacroiliitis. Eight patients dropped out or were excluded due to protocol violation. 40 patients completed both sets of questionnaires. All subjects reported their overall health as "the same" when compared to their baseline visit. The mean BASDAI at baseline was 1.97 ± 1.90 and at 2 weeks was 1.69 ± 1.80 – the reliability was substantial; ICC = 0.74, Bland-Altman limits of agreement (LOA) = 2.4 to −2.8. The mean BASFI at baseline was 0.99 ± 1.49 and at 2 weeks was 0.75 ± 1.00 – likewise the reliability was excellent; ICC = 0.87, Bland-Altman LOA = 1.1 to −1.4. When examining individual questions from the BASDAI and BASFI, the following had the highest ICCs, respectively: "How long does your morning stiffness last from the time you wake up?" and "Doing a full day's activities, whether it be at home or at work", ICC = 0.88 each. Meanwhile, from the BASDAI, "How would you describe the overall level of AS neck, back or hip pain you have had?" resulted in the lowest reliability; ICC = 0.57.

Conclusions: At this time, there is no validated disease activity score for JSpA/ERA. Both the BASDAI and BASFI showed excellent intra-rater reliability in a cohort of ERA patients. Next steps will include the measurement of the construct validity and responsiveness of these tools in JSpA/ERA in order to determine if pediatric rheumatologists can use these as validated

disease activity/functional impairment measures in the clinic and in clinical research.

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Juvenile Idiopathic Arthritis (JIA) Classification: An Audit of a Tertiary Paediatric Rheumatology Service's Adherence to ILAR (Edmonton 2001) Classification Criteria. Angela J. Cox[2], Sern Chin Lim[1], Roger C. Allen[3], Jonathan D. Akikusa[1] and Jane Munro[1]. [1]Royal Children's Hospital, Melbourne, Victoria, Australia, [2]Royal Children's Hospital, Melbourne, Australia, [3]Royal Childrens Hospital, Melbourne, Australia

Background: The International League of Associations for Rheumatology (ILAR) classification criteria for Juvenile Idiopathic Arthritis are widely used in prospective and retrospective studies of chronic arthritis in childhood. They define seven subtypes of chronic arthritis based on strict inclusion and exclusion criteria involving both clinical and laboratory parameters, some of which may not appear relevant in certain clinical situations and therefore may not be tested for in daily practice. The inaccuracy in patient classification that this may produce could have a significant impact on the results of research conducted using such cohorts.

Aim: To determine whether patients newly diagnosed with JIA within a year at the Royal Children's Hospital (RCH), Melbourne met strictly applied ILAR classification criteria for their assigned JIA subtype.

Methods: All newly diagnosed JIA patients seen in the Rheumatology Department at the RCH in 2009 were identified using the RCH rheumatology database. A retrospective review of the clinical and laboratory data collected for these patients was performed. The JIA subtype entered into the database for each patient was checked against ILAR classification inclusion and exclusion criteria. If they did not meet the designated subtype criteria or could not be classified because of incomplete data, the reason was recorded.

Results: 56 patients were included (35F, 21M). The diagnoses recorded in the database were Oligoarthritis 32(57%), Polyarthritis Rheumatoid Factor negative (RF-ve) 10(17.9%), Systemic arthritis 3(5.4%), Extended Oligoarthritis 2(3.6%), Polyarthritis Rheumatoid Factor positive (RF +ve), 2(3.6%), Psoriatic arthritis 2(3.6%), Enthesitis-related Arthritis (ERA) 1(1.8%) and Undifferentiated arthritis 4(7%). Only 13(23%) had complete clinical and laboratory information allowing classification by ILAR criteria. In 11 patients this matched the diagnosis assigned in the database. Two patients were reassigned to another subtype; one from Oligoarthritis to Undifferentiated arthritis due to the presence of psoriasis in a first degree relative, the other from Polyarthritis RF +ve to Polyarthritis RF-ve due to a negative follow-up RF. 43 patients had insufficient information to allow classification using ILAR criteria. The commonest reason was failure to test for RF, in 34(60%) patients. The majority of these patients, 20(58%), were Oligoarthritis. The second most common reason was an incompletely documented family history in 17(30%) patients, followed by 7(14%) patients who had not had a HLAB27 performed or documented.

Conclusion: The strict application of the ILAR classification criteria for JIA requires information that may not be routinely collected in daily clinical practice. At our centre collection of all data required to classify children with chronic arthritis according to strictly applied ILAR criteria was uncommon, seen in less than 25% of patients. We suggest that for centres wishing to participate in research involving patients with JIA that a minimum dataset be devised and applied to all newly diagnosed JIA patients to enable accurate ILAR classification.

Disclosure: A. J. Cox: None; **S. C. Lim:** None; **R. C. Allen:** None; **J. D. Akikusa:** None; **J. Munro:** None.

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Long-Term Outcome of Patients with Juvenile Idiopathic Arthritis Treated with Etanercept – Results of the Biologic Register JuMBO. Kirsten Minden[3], Martina Niewerth[4], Angela E. Zink[2], Eva Seipelt[6], Ivan Foeldvari[5], Hermann Girschick[7] and Gerd Horneff[1]. [1]Asklepios Kinderklinik St. Augustin GmbH, [2]German Arthritis Res Centre, Berlin, Germany, [3]German Rheumatism Research Center Berlin, a Leibnitz Institute, Berlin, Germany, [4]German Rheumatism Research Center Berlin, a Leibnitz Institute, [5]Hamburger Zentrum für Kinder- und Jugendrheumatologie am Klinikum Eilbek, Hamburg, Germany, [6]Immanuel Krankenhaus Berlin-Buch, Germany, [7]Scientific Advisory Board

Purpose: To assess the outcome of patients with juvenile idiopathic arthritis (JIA) who received Etanercept in childhood.

Methods: JIA patients ≥ 18 years who were formerly included in the nation-wide child Etanercept/Methotrexate register were contacted and asked to participate in the prospective cohort study JuMBO (Juvenile arthritis Methotrexate/Biologics long-term Observation). For those included in JuMBO, clinical status, therapy, and patient-derived data, e.g. functional capacity, quality of life and socioeconomic status, were documented every 6 months. Here, data of the last available visit of patients included and treated with Etanercept at any time were analyzed.

Results: Until April 2010, 486 out of 645 (75%) patients could be relocated and contacted, 398 of them agreed to participate in JuMBO. Baseline or follow-up data were available for 285 patients ever treated with Etanercept. These patients had a mean age of 20 years (SD 2.8) and a mean disease duration of 11 years (SD 5.3). At last documentation more than 80% of the patients still received DMARDs, 58% Etanercept. Twenty four percent of the patients had an inactive disease, 45% reported no functional limitations (HAQ-score = 0). The patients rated their quality of life lower than age-matched controls, but only regarding physical functioning, vitality, bodily pain, general health, and physical role.

Three deaths occurred in this cohort, all patients died of complications connected to their rheumatic disease. Considering the years of observation of all patients contacted (2,320 patient-years), the calculated standardized mortality ratio was 6.2 (95% CI 1.04–20.48) for women and 1.4 (95% CI 0.12–11.6) for men.

Co-morbidities or serious adverse events reported over the observation period of 1,097 patient years included the following: three new-onset inflammatory bowel diseases of which two occurred under Etanercept, seven newly diagnosed uveitis cases (four in patients receiving Etanercept), and 16 medically important infections (1.5/100 patient-years). Only six of the serious infections occurred under Etanercept, one was an infection of an endoprosthesis. No malignancy was recorded.

Conclusion: First data of the JuMBO register point to a better functional long-term outcome of patients with severe JIA treated in the biological era as compared to those treated before the year 2000. There seems to be an acceptable safety profile of Etanercept long-term use, however, more data are needed to confirm this.

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Magnetic Resonance Imaging Findings of Temporomandibular Joint in Patients with Active and Inactive Juvenile Idiopathic Arthritis. Liete Zwir, Soraia Souza, Maria Teresa Terreri, Antônio Sérgio Guimarães, Artur Fernandes and Maria Odete Hilário. UNIFESP

Introduction: The temporomandibular joint (TMJ), like any other synovial joint, may be involved in Juvenile Idiopathic Arthritis (JIA). According to literature, the frequency of TMJ involvement varies from 17 to 87%, depending on the population under study, on the subtype of the disease and on the method of image used.

TMJ involvement is, generally, associated to early onset of the disease, polyarticular subtype JIA, and long-duration of the disease. Condylar damage may be present early in the disease course and progress, even in absence of clinical symptoms or signs.

Gadolinium-enhanced magnetic resonance imaging (MRI) is a well-established technique considered to be the gold standard to detect TMJ arthritis in JIA even in asymptomatic cases.

Materials and Methods: Ninety-three consecutive patients (61 girls and 28 boys) who presented to our outpatient pediatric rheumatology clinic and fulfilled the ILAR criteria of JIA were included in this study. The mean age was 12.7 years (range 5 – 20 years) and the median follow-up time at the examination was 6.2 years (0.6 to 18).

The patients were divided into 3 groups: patients with active disease (40 children), patients with inactive disease on medication (20 children) and patients with inactive disease off medication (29 children). For practical reasons the patients were classified in oligoarticular and polyarticular course type.

All patients underwent Gadolinium Enhanced MRI. The findings were blindly evaluated by two observers. Presence of TMJ synovial enhancement was considered to be pathological.

Results: Forty-eight patients were oligoarticular (16 active, 13 in remission on medication and 19 in remission off medication) and 45 were

polyarticular (26 active, 8 in remission on medication and 11 in remission off medication). The tables below show MRI findings according to JIA activity status and subtype of the disease.

TMJ Synovial Enhancement	Active (n = 40)	Remission on medication (n = 20)	Remission off medication (n = 29)	Total
Yes	32	14	19	65
No	8	6	10	24
Total	40	20	29	89

TMJ Synovial Enhancement	Oligo	Poly	Total
Yes	33	32	65
No	12	12	24
Total	45	44	89

Conclusion: A large number (65%) of patients considered as being in remission off medication presented inflammatory TMJ alterations in RMI. Although synovial enhancement is considered the gold standard in assessing TMJ involvement, we should be cautious in interpreting this finding.

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Methotrexate and Leflunomide Combination Therapy Is a Safe and Effective Alternative to Methotrexate and Etanercept in JIA. Arturo Borzutzky[1], Tamy Lagunas[2], David Zurakowski[2] and Robert P. Sundel[3]. [1]Children's Hospital Boston, Boston, MA, [2]Children's Hospital Boston, [3]Childrens Hosp Medical Center, Boston, MA

Background: Methotrexate combined with TNF-inhibitors is generally regarded as the most effective treatment for recalcitrant juvenile idiopathic arthritis (JIA). Ongoing studies are evaluating the possibility that this should be first-line treatment in some situations. TNF inhibitors, however, are currently available only as parenteral formulations, and they are associated with significant immunosuppression, an increased risk of opportunistic infections, and possibly an increased risk of malignancies. These factors make the combination less than ideal for treating children with JIA. Combination therapy with methotrexate and leflunomide (MTX-LEF) has been shown to be effective in active rheumatoid arthritis as an alternative to the use of biologic agents. However, there is little information on the use of this combination in JIA.

Objectives: To compare the efficacy and safety of MTX-LEF to that of MTX and etanercept (MTX-ETN) in children with polyarticular JIA incompletely responsive to MTX or LEF monotherapy.

Methods: We retrospectively reviewed the clinical data of children with JIA treated at a single tertiary care children's hospital between 1999 and 2009. We compared outcomes and adverse events in patients treated with combination MTX-LEF to those treated with MTX-ETN after failure of methotrexate monotherapy. Inactive disease was defined as absence of active arthritis and normal inflammatory parameters. Remission was defined as 6 months of inactive disease.

Results: 56 patients met inclusion criteria: 25 patients treated with MTX-LEF and 31 patients treated with MTX-ETN were available for evaluation. Groups did not differ significantly for age, sex, race, time from diagnosis to combination therapy, follow-up length, JIA subtype, initial joint count or initial ESR (Table 1). Outcomes and significant adverse events did not differ significantly between the two groups after a mean follow-up of 20.5 ± 13 months. No serious adverse events were identified in any of the treatment groups. Inactive disease was achieved in 52% of the MTX-LEF group and 61.3% of the MTX-ETN group (P = 0.59). Remission was achieved in 28% of the MTX-LEF group and 35.5% of the MTX-ETN group (P = 0.58). Kaplan-Meier survival distributions for time to inactive disease and to remission were comparable between groups (P=0.94 and P=0.86, respectively).

Conclusions: In a retrospective pilot study of 56 children with JIA, MTX-LEF was a safe and effective alternative to MTX-ETN in patients with arthritis refractory to DMARD monotherapy. Lower costs, availability of oral dosing, and an absence of risk of opportunistic infections or malignancies favor the use of combination DMARDs over biologics. Randomized controlled trials are necessary to evaluate this prospectively.

Table 1. Clinical characteristics of patients.

Characteristic	MTX+LEF (n = 25)	MTX+ETN (n = 31)	*P*
Age, mean ± SD	12 ± 5.2	10.55 ± 5.1	0.3
Female sex, %	72	84	0.34
Race (% white)	84%	90.3%	0.56
Diagnosis to combination therapy (months)	56.7 ± 50	47.9 ± 44	0.49
Duration of follow-up (months)	18.5 ± 11.7	22.1 ± 13.9	0.3
ILAR JIA diagnosis			0.81
Polyarthritis (RF+)	16%	16%	
Polyarthritis (RF−)	56%	42%	
Oligoarthritis	4%	10%	
Psoriatic arthritis	16%	19%	
Enthesitis related arthritis	8%	13%	
Initial joint count, mean ± SD	8.5 ± 8.6	6.7 ± 6.9	0.37
Initial ESR, mean ± SD	12.9 ± 9.6	13.9 ± 14.5	0.77

Disclosure: A. Borzutzky: None; **T. Lagunas:** None; **D. Zurakowski:** None; **R. P. Sundel:** None.

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Methotrexate Gives Protection Against the New Onset of Uveitis in Combination with Etanercept. Data from the German Etanercept Registry. Ivan Foeldvari[1], Nina Thome[2] and Gerd Horneff[2]. [1]Hamburger Zentrum Fuer Kinder- und Jugendrheumatologie, Hamburg, Germany, [2]Kinder- und Jugendrheumatologie Asklepios Clinics, Sankt Augustin, Sant Augustin, Germany

Introduction: Uveitis occurs in 10 % of patients with juvenile idiopathic Arthritis (JIA). Methotrexate (MTX) and corticosteroids (ST) appear to be an effective treatment for uveitis, We evaluated the occurrence of uveitis under different treatment combinations in the German Etanercept Registry.

Methods: We evaluated the prevalence of uveitis flares or new onset of uveitis in patients in the different treatment arms of the German Etanercept Registry.

Results: We reviewed the data of 868 patients. We grouped the patients in 8 therapy arms, these were Etanercept(ETA) monotherapy (n=74); ETA + glucocorticoids (ST) (n=34); ETA + Methotrexate (MTX)(n=246); ETA+ MTX+ST(n=290); ETA + other DMADs (n=45); ETA + other DMARDs + ST(n=45); ETA+MTX+ other DMARDs(n=32); ETA+MTX+ other DMARDs +ST(n=102).

Treatment group	Number of patients	AE-Uveitis	Uveitis/ Patient	Patient - Treatment years	Uveitis/100 year of treatment Mean value
Etanercept (Eta)	74	4	0.05	113.75	3.5
Eta + Steroids	34	1	0.03	54.10	1.8
Eta + MTX	246	4	0.02	431.49	0.9
Eta + MTX + Steroids	290	7	0.02	703.65	0.9
Eta + other DMARD	45	2	0.04	79.83	2.5
Eta + other DMARD + Steroids	45	3	0.06	92.66	3.2
Eta + MTX + other DMARD	32	2	0.06	82.80	2.4
Eta + MTX + other DMARD + Steroids	102	6	0.06	267.42	2.2
All patients treated with Steroids	471	17	0.04	1118.00	1.5
All patients treated with MTX	670	19	0.03	1485.00	1.3
All patients treated with other DMARDs	224	13	0.06	523.00	2.5
All Patients	868	29	0.03	1826.00	1.6

We evaluated the rate of uveitis per patient in the different groups. The lowest rate was found in the combination with MTX with ETA with 0.02. We evaluated the mean number of uveitis per 100 patient years and MTX +ETA group showed 0.9 compared to 3.5 for ETA monotherapy. ST in combination with ETA showed a protective effect too. Interestingly the other DMARDs did not had this protective effective of uveitis, the other DMARDs were mostly leflunomide or sulfasalazine.

Discussion: MTX and ST seems to be protective in this group of patients against the new onset of uveitis. Based on this data patients with a history of uveitis should receive a combination therapy of ETA and MTX to prevent flares of uveitis.

Disclosure: I. Foeldvari: Wyeth Pharmaceuticals, 5; **N. Thome:** None; **G. Horneff:** Wyeth Pharmaceuticals, 5.

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Obesity and Disease Activity in Juvenile Idiopathic Arthritis. Christina F. Pelajo[1], Jorge M. Lopez-Benitez[2] and Laurie C. Miller[2]. [1]Floating Hospital for Children at Tufts Medical Center, Boston, MA, [2]Floating Hospital for Children at Tufts Medical Center

Background: Children with physical disabilities may have an increased risk of obesity. In adults, the odds of having arthritis, other than osteoarthritis, are 4.33 higher for the obese population, in comparison to the ideal weight population. Rates of obesity in patients with juvenile idiopathic arthritis (JIA) ranging from 5 to 16.7% have been reported. The aim of this study was to explore the relationship between obesity and disease activity in patients with JIA.

Methods: Body mass index (BMI) and disease activity were determined in 102 consecutive patients with JIA attending a pediatric rheumatology clinic from October 09 to May 10 who were having blood drawn for routine clinical monitoring. Patients who took corticosteroids in the previous 3 months were excluded. Disease activity was determined by physician assessment using a visual analog scale (VAS), along with number of active joints and erythrocyte sedimentation rate (ESR); child well-being was determined by parent completion of a VAS. Children were classified as obese (BMI $\geq$ 95th percentile) or normal BMI (BMI between 5th and 94th percentiles). The results were analyzed using T-tests, ANOVA, Fisher's exact test, and linear regression in the entire patient sample. In addition, the relationship between BMI and active inflammatory joint disease was analyzed on a subset of children with JIA matched by age and gender.

Results: Of the 102 children, the male:female rate was 42:60, and ages ranged from 3–19 years (mean 11.4 years). Twenty-one children were obese (21%) and 81 had normal BMI. 100% of obese and 84% of non-obese children were Caucasian. JIA subtypes were distributed as follows: 40% oligoarticular, 21% RF-negative polyarticular, 21% enthesitis-related arthritis, 11% psoriatic arthritis, 4% systemic, and 3% RF-positive polyarticular. Mean time since disease onset was 48.3 months ($\pm$47.6 SD). BMI ranged from 13.9 to 36.7 (median 19.5); BMI percentiles ranged from 6 to 99 (mean 63.3). Mean BMI percentiles did not differ among JIA subtypes, gender, or age. The mean parent VAS scoring the child's overall well-being was worse for obese than non-obese children [2.9 ($\pm$2.4 SD, range 0–7.5) vs 1.8 ($\pm$1.75, range 0–7.3), ($p=0.015$)]. However, physician assessment of disease activity, joint count, and ESR elevation did not differ between the two groups. In the comparison of 21 age- and gender-matched pairs, there was no difference between obese and normal BMI children, regarding parent or physician VAS, ESR, or number of active joints.

Conclusions: Parent scores for well-being were worse for obese than non-obese children. This might reflect arthralgias due to mechanical overload, qualitative differences in parent perception, or other causes of reduced well-being associated with obesity. There were no differences for other indices of disease activity between subjects with JIA who were obese and those with normal BMI. As obesity confers an additional health risk in children with arthritis, addressing this co-morbidity should be a health priority in patients with JIA.

Disclosure: C. F. Pelajo: None; **J. M. Lopez-Benitez:** None; **L. C. Miller:** None.

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Preliminary Definition of Remission and Minimal Disease Activity Cut-Points for the Juvenile Arthritis Disease Activity Score (JADAS). Alessandro Consolaro[3], Giovanni Filocamo[4], Bianca Lattanzi[3], Giulia C. Varnier[3], Angela Pistorio[3], Nicolino Ruperto[3], Alberto Martini[2] and Angelo Ravelli[1]. [1]IRCCS G. Gaslini and Università di Genova, Genova, Italy, [2]IRCCS G. Gaslini and Università di Genova, Genova, Italy, [3]IRCCS G. Gaslini, Genova, Italy, [4]Policlinico Sant'Orsola, Bologna, Italy

Background: Recent advances in treatment of juvenile idiopathic arthritis (JIA), namely the introduction of biologic agents, have markedly increased the potential for achieving a remission or minimal disease activity (MDA) state. These states have been defined so far using a categorical model, which requires simultaneous fulfilment of multiple criteria. This approach has been followed in the development of the current criteria for remission (Wallace criteria) (Wallace CA, et al. Arthritis Rheum. 2005;52:3554-62) and MDA (Magni-Manzoni S, et al. Arthritis Rheum 2008;59:1120-7). However, definition of remission and MDA through the dimensional model, based on pooling individual measures of disease activity into a composite disease activity score, has never been attempted.

Objective: The identification of the remission and MDA cut-points of the recently developed composite disease activity score for JIA, the JADAS (Consolaro A, et al. Arthritis Rheum. 2009;61:658-66).

Methods: For the purposes of this study, the JADAS-10 version was used. The JADAS-10 is computed as the simple sum of 4 variables, each with a 0–10 range: the physician's global assessment, the parent's global assessment, the normalized ESR and the 10-joint reduced count. At each visit, all main physician- and parent-centered outcome measures were recorded. JADAS-10 was calculated for 432 patients in 914 visits. At each visit, both physicians and parents were asked to rate independently the disease status as remission or active disease. Furthermore, we assessed the presence of remission by Wallace criteria and, after grouping patients in oligoarthritis or polyarthritis, of MDA by the preliminary definition. In the first step, we calculated the JADAS-10 values corresponding to the 75th percentile of score distribution among patients' who were classified as having disease remission by physician's and parent's subjective rating and Wallace criteria, or having MDA. In the second step, we calculated, by means of the receiver operating characteristic (ROC) curve analysis, the JADAS-10 values that showed the best trade-off between sensitivity and specificity (i.e. accuracy) in discriminating between patients who had remission or active disease according to the physician, the parent, or the Wallace criteria, or who had MDA according to the preliminary definition.

Results: The results in the 2-step analysis are shown in table.

	Remission			MDA	
	Physician	Parent	Wallace crit.	Oligoarthr.	Polyarthr.
75th pct.	2.1	2.5	1.0	2.0	1.7
Best accuracy	2.9	2.8	1.0	2.6	4.2

The numbers obtained for each definition using the 75th percentile or ROC curve method were then averaged. The values obtained for remission were further averaged achieving the value of 2.0, The values obtained for MDA are 2.3 for oligoarthritis and 2.9 for polyarthrtritis

Conclusion: The value of 2.0 is the remission cut-point for the JADAS-10 proposed for use in future clinical trials on JIA. The proposed cut-points for MDA in oligoarthrtitis and polyarthritis are 2.3 ad 2.9, respectvely.

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Prevalence of Enthesitis in Pediatric Patients with Enthesitis-Related Arthritis. Pamela Weiss[2], Andrew J. Klink[4], Edward M. Behrens[1], David D. Sherry[5], Terri H. Finkel[3], Mark Ramos[4], Robert Grundmeier[4], Ron Keren[4] and Chris Feudtner[4]. [1]Childrens Hospital of Phil, Philadelphia, PA, [2]The Children's Hosp of Philadelphia, Philadelphia, PA, [3]The Children's Hospital of Philadelphia, Philadelphia, PA, [4]The Children's Hospital of Philadelphia, [5]The Children's Hospital of Philadelphia, Philadelphia, PA

Background: Juvenile idiopathic arthritis (JIA) is the most common rheumatologic chronic condition in childhood, affecting 1 to 4 per 1,000 children. Enthesitis-related arthritis (ERA) is a JIA category that accounts for 10–20% of JIA. Enthesitis is a distinct pathologic feature of ERA. Descriptions of enthesitis in ERA are sparse and little has been published about which entheses are most commonly affected.

Methods: We conducted a retrospective cohort study of children with ERA who were diagnosed and treated at Children's Hospital of Philadelphia between November 2007 and April 2010. The cohort consisted of children with an ICD-9-CM code of 720, indication "ERA" or "ankylosing spondylitis," given at diagnosis or a subsequent follow-up visit.

Results: During the thirty-month study period there were fifty-nine ERA patients and 256 clinic visits. Subjects ranged from 5.5 to 18.5 years and had a mean age of 14 years at date of initial evaluation. Fifty-three percent were male. Eighty-five percent were white, 5% African American, 3% Asian, and 7% other. The mean number of tender entheses at diagnosis was 5 (95% CI: 0,15). There was at least 1 tender enthesis at 47% of visits. The most commonly affected entheses were the patellar ligament insertion on the inferior pole of the patella (6 o'clock position of patella) and the plantar fascial insertions on the calcaneus and metatarsal heads (Table). Enthesitis was most often asymmetric. The mean number of swollen joints at diagnosis was 1 (95% CI: 0, 7). The most commonly affected joints were the knees ($N=16$ patients, 6 unilateral, 5 bilateral), ankles ($N=11$ patients, 5 unilateral, 3 bilateral), and fingers. Of the finger joints the proximal interphalangeal joints were most commonly affected. The arthritis was most often asymmetric.

Table 1. Sites of enthesitis by visit (N = 256)

Tender enthesis	Any N (%)	Unilateral N (%)	Bilateral N (%)
6 o'clock position of patella	88 (34.4)	34 (13.3)	54 (21.1)
Plantar fascial insertion at calcaneus	47 (18.4)	15 (5.9)	32 (12.5)
Plantar fascial insertion at metatarsal heads	43 (16.8)	10 (3.9)	33 (12.9)
Achilles tendon	38 (14.9)	14 (5.5)	24 (9.4)
2 o'clock position of patella	34 (13.3)	21 (8.2)	13 (5.1)
Greater trochanter	33 (12.9)	13 (5.1)	20 (7.8)
10 o'clock position of patella	31 (12.1)	19 (7.4)	12 (4.7)
Tibial tuberosity	16 (6.2)	7 (2.7)	9 (3.5)
Sacroiliac joint	13 (5.1)	4 (1.6)	9 (3.5)
Base of 5th metatarsal	11 (4.3)	5 (2.0)	6 (2.3)

Conclusions: Enthesitis comprises a significant portion of disease activity in ERA. Future studies should address the pattern of enthesitis over time, enthesitis response to therapy, and the impact of enthesitis on quality of life.

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Prospective Study of Infliximab for Treatment of Pediatric Uveitis. Egla C. Rabinovich[4], Janet Wootton[4], Lawrence S. Zemel[3], Lisa F. Imundo[2], Jennifer E. Weiss[5], Leslie S. Abramson[7], Mark F. Hoeltzel[1], Deborah M. Levy[6] and David Wallace[4]. [1]Children's Mercy Hospital, Kansas City, MO, [2]Childrens Hospital of NY, New York, NY, [3]Connecticut Childrens Med Ctr, Hartford, CT, [4]Duke University Medical Center, Durham, NC, [5]Hackensack Univ Med Ctr, Hackensack, NJ, [6]The Hospital for Sick Children, Toronto, ON, Canada, [7]University of Vermont, Morrisville, VT

Background: Uveitis is a persistent disease for which there is little prospective data on treatment. Previous retrospective studies suggest TNF blockade may be efficacious for treatment of uveitis, but do not address time to response or optimal dose.

Methods: Ongoing 9 month multi-center prospective study of infliximab for treatment of persistent pediatric inflammatory uveitis (onset ≤ 16 yrs), randomizing subjects to one of 2 initial doses: 5 mg/kg or 10mg/kg monthly. Scheduled ophthalmologic exams utilized the Standardization of Nomenclature (SUN) criteria. Entry criteria: ≥ 1+ anterior chamber inflammation, failure of at least one DMARD, on stable dose of methotrexate. Primary outcome variable was percent who had improvement per SUN criteria.

Results: 14 subjects (9 female, mean age 11.8 yrs, range 6–19) with persistent inflammatory uveitis (1 sarcoid, 13 idiopathic) from 6 Childhood Arthritis and Rheumatology Research Alliance (CARRA) A sites were randomized to receive 5 mg/kg (N=8) or 10 mg/kg (N=6) initial infliximab dose. At the baseline visit, 5 had unilateral and 7 bilateral inflammation.

Inflammation*	Baseline (n) N = 14	After 1st dose N = 12	After 4th dose N = 12	After 8th dose N = 7
3+ (26–50)	0	0	0	0
2+ (16–25)	4	1	0	0
1+ (6–15)	10	3	0	1
0.5+ (1–5)	0	4	5	3
0 (0)	0	4	7	3

* Inflammation is reported utilizing SUN criteria and on the most active eye. Anterior chamber inflammation is graded as cells per high power field (hpf).

Conclusion: Infliximab works rapidly to decrease inflammation with 57% having 0 to.5+ inflammation after one infusion. Low grade inflammation may persist despite treatment. Improvement persisted 8 months after initiation of infliximab.

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Safety and Efficacy of H1N1 Influenza Vaccination in Children with Chronic Inflammatory Rheumatic Diseases. Catherine F. Cortot[1] and Robert P. Sundel[2]. [1]Children's Hospital Boston, Brookline, MA, [2]Childrens Hosp Medical Center, Boston, MA

Background: Children with chronic inflammatory disease are more susceptible to infections and therefore have been considered a priority target group for immunization with the H1N1 influenza vaccine. However, the safety and efficacy of this vaccination in such patients remain unknown.

Objective: We conducted a prospective study to assess the toxicity profile and effectiveness during actual use of the H1N1 vaccination in children with chronic inflammatory rheumatic diseases.

Methods: Patients with a chronic inflammatory disorder from the rheumatology clinic of a large, tertiary care children's hospital, and who had received at least one dose of the influenza A (H1N1) 2009 monovalent, unadjuvanted, inactivated vaccine, were included. Fifty six (54%) of the subjects received the vaccine in the clinic and were assessed prospectively; the remainder received their vaccinations elsewhere are were administered questionnaires during their clinic visit. Information gathered included vaccination side effects and the incidence of flu in study subjects.

Results: One hundred and five patients (median age 12.8 years, range 1.7–26.6) were included. In order of frequency, rheumatologic diagnoses included juvenile idiopathic arthritis (45.7%), psoriatic arthritis (15.2%), enthesitis-related arthritis (8.6%) SLE (8.6%) and other (21.9%). The vast majority of patients (91.4%) were treated with immunosuppressive therapy (IMT) including at least one of methotrexate (71.9%), leflunomide (18.8%), TNF inhibitor (16.7%), corticosteroids (20%) or other (12.3%). During up to 6 months of followup during the peak of the influenza pandemic, one patient (1%) developed presumed H1N1 flu not confirmed by biological tests. Two cases (1.9%) of mild local symptoms at the injection site were observed. Four cases (3.8%) of systemic side effects of the H1N1 vaccine were reported, including 2 cases (1.9%) of flu-like symptoms, one case (1%) of myalgia and fatigue, and one flare of a patient's spondyloarthritis (1%) requiring the use of steroids for 15 days.

Conclusions: Influenza A (H1N1) 2009 monovalent, unadjuvanted, inactivated vaccine was well tolerated and apparently effective in children with chronic inflammatory rheumatic diseases. One patient developed a flare of his arthritis following the immunization, and one developed a flu-like illness despite the vaccination. No one had persistent sequelae or complications requiring hospitalization. These findings support the recommendation that children with rheumatologic conditions should receive the H1N1 monovalent inactivated vaccine.

Disclosure: C. F. Cortot: None; **R. P. Sundel:** None.

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Status of Vaccination Coverage in Children with Juvenile Idiopathic Arthritis (JIA) Followed at a Pediatric Tertiary-Care Center. Marie-Paule Morin[1], Élise Fortin[3], Caroline Quach[3] and Gaëlle Chédeville[2]. [1]The Montreal Children's Hospital, Montreal, QC, Canada, [2]The Montreal Children's Hospital, Montréal, QC, Canada, [3]The Montreal Children's Hospital

Background: Immunization is recognized as being one of the most efficient ways to prevent mortality, morbidity and complications related to infectious diseases in children. Recent studies reported on the safety and efficacy of single vaccines in patients with juvenile idiopathic arthritis (JIA). However, no data on vaccination coverage rate is available in JIA patients. Factors such as the presence of chronic disease, fear of inducing flare of disease and treatment with immunosuppressive medication may impact on the vaccination schedule of this population.

Objectives: To evaluate the vaccination coverage rate of patients with JIA followed at a pediatric tertiary-care center and to determine the coverage rate for individual vaccine required as per the Quebec Public Health guidelines.

Methods: The Division of Rheumatology at the Montreal Children's Hospital (MCH) follows actively a cohort of 356 patients with JIA. During the period from August 1st 2008 to March 31st 2009, all consecutive JIA patients coming for their scheduled visit were included if they were between 2 and 18 years old and if they had an available written immunization record. Demographic data, ILAR disease subtype, active joint count and medications used since diagnosis were retrospectively collected for each patient. Descriptive statistics were used to evaluate the proportion of children with complete vaccination status according to the Quebec Public Health guidelines at 2.5, 10 years and at the last visit to the clinic.

Results: A total of 200 patients were included, 69% were girls. Mean age of the cohort was 11.4 years, with a median age at diagnosis of 4.8 years (0.5–16.6 years). The diagnosis at onset was oligoarthritis in 51.5% of the children, rheumatoid factor (RF) negative polyarthritis in 20.5%, RF positive polyarthritis in 1.5%, systemic in 6%, psoriatic in 6%, ERA in 7.5%, and undifferentiated in 7%. Over time, NSAIDs were used in 99 % of patients, methotrexate in 51%, steroids in 10.5%, and biologics agents in 7.5%.

Vaccination coverage rates at 2.5, 10 years and at the last clinic visit for each vaccine are shown in the table, as well as the proportion of patients with complete vaccination status.

	At 2,5 years		At 10,5 years		Last visit to clinic	
	N	n (%)	N	n (%)	N	n (%)
Rubella and mumps	198	186 (94)	118	110 (93)	200	194 (97)
Measles	198	114 (58)	118	91 (77)	200	165 (83)
Polio	198	193 (97)	118	116 (98)	200	198 (99)
Diphteria/tetanus	198	197 (99)	118	94 (80)	200	160 (80)
Pertussis	198	197 (99)	118	94 (80)	200	155 (78)
Meningococcus C	47	40 (85)	–	–	49	45 (92)
Hepatitis B	–	–	–	–	98	80 (82)
Hib	198	172 (87)	–	–	–	–
Pneumococcus	31	27 (87)	–	–	–	–
Varicella	12	11 (92)	–	–	14	12 (86)
Complete vaccination status	198	103 (52)	118	80 (68)	200	121 (61)

Conclusion: Despite overall good vaccination coverage rate of single vaccines, only 61% of our cohort has a complete vaccination status at the last clinic visit. Further analysis is required to determine factors that may influence vaccination such as age at diagnosis, activity of the disease and medication use. Further studies need to be done to explore the reasons underlying incomplete vaccination status in the JIA population, both from a parental and a physician perspective. Measures to optimize vaccination coverage, such as catch-up vaccination, should be implanted when possible.

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The Clinical Feature of 2009–2010 Influenza Virus Infection during Tocilizumab Treatment for Systemic Onset Juvenile Idiopathic Arthritis. Toru Uchimura[1], Tomoyuki Imagawa[1], Takuma Hara[1], Masako Kikuchi[1], Ryoki Hara[2], Takako Miyamae[1], Masaaki Mori[1], Akiyoshi Nariai[3], Toshihiro Mitsuda[1] and Shumpei Yokota[1]. [1]Department of Pediatrics Yokohama City University, Yokohama, Japan, [2]Department of Pediatrics Yokohama City University, [3]Department of Pediatrics Yokohama Minami Kyosai Hospital, Yokohama, Japan

Background: We had reported that tocilizumab (a humanized anti-IL-6 receptor antibody, TCZ) had been proved to be highly effective in the clinical management of refractory systemic onset juvenile idiopathic arthritis (sJIA).TCZ inhibits interleukin-6 (IL-6) signal which relates to inflammation in sJIA by binding IL-6 receptor. It also affects the inflammatory reaction in infectious disease, such as pneumonia and gastroenteritis. Influenza virus infection has been known to make the disease activity of sJIA worse.

Objective: We evaluated the impact of influenza virus infection during tocilizumab treatment for sJIA.

Method: A total of 76 patients satisfying the WHO/ILAR criteria for sJIA were treated with TCZ, and received intravenous TCZ 8 mg/kg every 2 weeks. The patients who had the positive result of rapid chromatographic immunoassay for the detection of influenza A and B viral antigens from nasopharyngeal swabs were subject of this study from 2009 September to 2010 December. We examined the clinical manifestations and complications of the influenza virus infection, and the deterioration of sJIA.

Results: Seven patients (4 boys and 3 girls) affected with influenza virus infection. The median age was 13.7 years and the median duration of TCZ treatment was 42 months. The disease activities including fever, arthritis, rheumatoid rash, and inflammatory examinations in all patients were well controlled by TCZ. All of seven patients showed the result of influenza virus A by rapid antigen test. Clinical symptoms at the time of the influenza infection were fever (> 38.0 degrees Celsius) in 6 patients (86%), cough in 7 patients (100%), nasal discharge in 5 patients (71%), vomiting in 1 patients (14%), diarrhea in 1 patients (14%) and fatigue in 3 patients (43%). The mean febrile period was 1.8 days (0 to 5 days). No complications including pneumonia, otitis media and influenza encephalopathy were observed. Six of 7 patients were treated with anti-influenzavirus medications; oseltamivir in 5 patinets, zanamivir in 3 patients. One patient switched from zanamivir to oseltamivir because of prolonged fever. One patient relapsed to sJIA after influenza. One patient presented with fever, arthritis and rheumatoid rash. Serum C-reactive protein and amyloid A were increased in 2 patients. None of patients developed macrophage activation syndrome (MAS).

Conclusion: Neither influenza symptoms nor disease progression to MAS were observed in the patients affected with influenza virus infection during TCZ treatment. However, disease activities of sJIA might be aggravated by influenza in these patients. In addition, TCZ might mask inflammatory symptoms of influenza infection.

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The Financial Burden of Juvenile Idiopathic Arthritis. Andrea Ens[2], Bianca A. Lang[1], Suzanne E. Ramsey[1], Elizabeth Stringer[2] and Adam M. Huber[1]. [1]IWK Health Ctr, Halifax, NS, Canada, [2]IWK Health Ctr

Objectives: Very little is known about the financial burden of Juvenile Idiopathic Arthritis (JIA), particularly the burden borne by families in Canada. There are considerable medical and non-medical costs related to having JIA that families are expected to pay, in order for their children to receive the standard of care. The primary objective of this study was to determine the annual medical and related non-medical out-of-pocket costs associated with having a child who has JIA borne by families in Nova Scotia (NS).

Methods: All families in NS with a child followed by the Pediatric Rheumatology Clinic at the IWK Health Centre in 2008, with JIA as per the International League of Associations for Rheumatology criteria, were mailed a self-report, parental questionnaire. Families were excluded if there was more than 1 child with JIA, or if there were other chronic illnesses. The questionnaires evaluated medical and non-medical related out-of-pocket costs, as well as gross household income. Dilman's method was used to optimize return rates. One hundred and seventy-three questionnaires were mailed out. Of these, 5 were returned unopened due to incorrect addresses, giving a potential total of 168. Fifty-five (32.7%) were returned completed, and another 11 (6.5%) were returned blank or called to decline participation, for a total return rate of 39.3%.

Results: The majority of questionnaires were completed by the child's mother (81.8%). The mean age of the children was 13.1y (range 5, 20) and 60% were female. The mean household income was $78,850 (median $70,000, range $2,500, $175,000). On average, families lived 116km (median 34.5km, range 4.5km, 530km) from the pediatric rheumatology clinic. The financial burden was rated as large by 1.9%, moderate by 35.2%, minimal by 44.4% and nothing by 18.5%. Resources available to help with the costs were rated as either fair or poor by 54.9% of parents. The mean total annual cost per patient was $1,281.71 (median $641.50, range 0, $12,556) which was on average 2.9% (median 0.9%, range 0, 46%) of their household income. The mean annual medication cost was $357.86 (median 0, range 0, $10,000). The annual mean visit costs for appointments with physicians or related allied health care workers was $276.89 (median $45, range 0, $2,286), and the annual mean non-medication cost was $80.64 (median $0, range 0, $1,850). Non-medication costs included the cost of physiotherapy, assistive aids, and home adaptations. The mean loss of paid work per year was $348.36 (median $0, range 0, $2,600). The Pearson correlation for total costs per year and distance was 0.46 ($P=0.0005$) and for annual visit costs for appointments and distance was 0.68 ($P=0.0000$), demonstrating a moderate direct relationship between distance and costs.

Conclusions: The financial burden associated with having a child with JIA in NS is considerable, particularly for some families. The impact of this burden on outcomes is unknown and warrants further evaluation.

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Usage of TNFα Inhibitors for the Treatment of Juvenile Idiopathic Arthritis: Data from a National U.S. Administrative Claims Database. Timothy Beukelman[3], Fenglong Xie[1] and Jeffrey R. Curtis[2]. [1]Univ of Alabama at Birmingham, [2]University of Alabama–Birmingham, Birmingham, AL, [3]University of Alabama-Birmingham, Birmingham, AL

Background: Tumor necrosis factor alpha inhibitors (anti-TNF) have been used for over 10 years in the treatment of juvenile idiopathic arthritis (JIA), but little has been reported regarding their usage in clinical practice. We

analyzed national administrative claims data from a large commercial U.S. health insurer to characterize the usage of anti-TNF in the treatment of JIA.

Methods: Using national administrative claims data for the years 2005 – 2008 inclusive, we identified children less than 16 years old with ≥1 physician diagnosis code consistent with JIA (ICD-9 codes 714, 720, 696.0, or 713.1 with 555 or 556). We identified adults with ≥1 physician diagnosis code for rheumatoid arthritis (RA; ICD-9 code 714.0) for comparison. Pharmacy benefits were determined for each subject. Treatment with anti-TNF, methotrexate (MTX), and leflunomide (LEF) was determined through dispensed pharmacy and infusion claims. New anti-TNF users were defined by no treatment with any anti-TNF in the prior 6 months. Uveitis was defined by ≥1 physician diagnosis code (ICD-9 code 364). We examined anti-TNF usage over time and compared to MTX and LEF. We also performed cross-sectional analyses restricted to claims from 2008. Chi-square test was used for comparisons of proportions.

Results: During the study period, 2442 children with at least 1 JIA diagnosis code and full pharmacy benefits were identified; 55,010 adults with RA were identified. The mean age at first JIA diagnosis code was 10.1 ± 4.3 years. JIA patients were from 48 of the United States; 33% from northeast, 14% from mid-west, 34% from south, and 20% from west census regions. The proportion of JIA patients with full pharmacy benefits who were receiving anti-TNF increased from 7% in 2005 to 19% in 2008, compared to an increase from 15% to 24% for RA.

In cross-sectional analysis restricted to 2008, among all MTX, LEF, or anti-TNF users with JIA, 57% received any anti-TNF compared to 42% for RA. Also in 2008 among JIA patients, there were 1.3 users of any anti-TNF for each 1 user of MTX or LEF without anti-TNF; for RA this ratio was 0.71. From 2005–2008, 45% of all JIA anti-TNF users received concurrent MTX or LEF at any point, compared to 32% for RA. JIA new anti-TNF users with a prior diagnosis of uveitis were much more likely to initiate a monoclonal antibody (infliximab or adalimumab) (74%) compared to those without a prior diagnosis of uveitis (33%; $p < 0.0001$). JIA new anti-TNF users without full pharmacy benefits were much more likely to initiate infliximab (95%) compared those with full pharmacy benefits (13%; $p < 0.0001$).

Conclusions: The prevalence of anti-TNF treatment for JIA more than doubled from 2005 to 2008 and approached the prevalence seen in adult RA. In 2008, there were more JIA current users of anti-TNF than of MTX or LEF without anti-TNF. Less than one-half of JIA anti-TNF users received concurrent MTX or LEF. A prior diagnosis of uveitis and patient's access to prescription drug coverage were strongly associated with the use of specific anti-TNF agents.

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Use of Abatacept for Childhood Refractory Vision-Threatening Uveitis. Gabriele Simonini[2], De Libero Cinzia[1], Roberto Caputo[1], Teresa Giani[2], Laura Pascoli[2], Ilaria Pagnini[2] and Rolando Cimaz[2]. [1]Opthalmology Unit, A Meyer Children's Hospital, Florence, Italy, [2]Rheumatology Unit Dpt of Pediatrics, A.Meyer Children's Hospital-University of Florence, Italy

Background: Improvement of refractory JIA-related uveitis has been reported with Abatacept.

Objective: Aim of our study was to evaluate the efficacy and safety of Abatacept in an open-label prospective, monocenter, study of childhood non-infectious chronic uveitis.

Methods: Four patients with refractory, vision-threatening non-infectious uveitis were enrolled to receive Abatacept 10 mg/kg at weeks 0, 2, 4, and thereafter monthly, for at least 6 months. Absence/recurrence rate of uveitis throughout the study period, according to the SUN Working Group criteria, visual acuity pre- and post-Abatacept treatment, and tapering of steroid medication were recorded. *Improved* visual acuity was defined as a doubling of the visual angle (converted in a LogMAR format) in at least one eye. All children had active uveitis: 6 out of 8 eyes were involved, despite treatment with methotrexate (MTX) (15 mg/m^2/weekly) in association with Infliximab (6 mg/kg every 6–8 weeks) followed by Adalimumab (24 mg/m^2, every other week), then by mycophenolate mofetil in 3 cases; and by Adalimumab in 1 case. Due to active uveitis, along with topical steroids, all children were also receiving oral prednisone (1–2 mg/kg/day), at stable doses for at least 6 weeks (range 45–55 days).

Results: Demographics, clinical characteristics and outcomes on treatment are reported in the Table.

	1	2	3	4
Age, years, months	17 y, 6 m	18 y, 4 m	14 y, 1 m	9 y, 4 m
Gender	F	F	M	F
Age at onset of uveitis, (years, months)	10 y, 10 m	3 y, 5 m	4 y, 10 m	2 y, 11 m
Uveitis duration	7 y, 4 m	14 y, 11 m	10 y, 9 m	7 y, 7 m
Diagnosis:				
Age at onset of disease, (years, months)	Idiopathic uveitis 10 y, 10 m	JIA 1 y, 5 m	Blau syndrome 4 y	JIA 2 y, 7 m
Previous DMARD/anti-TNF-α treatment, duration (months)	Infliximab 28	Infliximab 37	Infliximab 32	–
	Adalimumab 8	Adalimumab 7	Adalimumab 21	Adalimumab 17
	MMF 16	MMF 18	MMF 11	–
N* of previous flares, 6 months before	3	6	5	4
Time to remission (weeks)	8	12	14	12
Time to steroid discontinuation (months)	4	6	–	5
Visual acuity 6 months before → 6 months after	R 20/60 → 20/30	R 20/50 → 20/40	R 20/20 → 20/20	R 20/25 → 20/20
	L 20/20 → 20/20	L 20/60 → 20/40	L 20/30 → 20/20	L 20/20 → 20/20
Concomitant therapy (duration, months)	MTX: 15 mg/m^2	MTX: 15 mg/m^2	MMF: 1 gm/m^2	MTX: 15 mg/m^2
	6	6	4	6
Follow-up duration on treatment	12	14	8	6

JIA = Juvenile Idiopathic Arthritis, MTX = methotrexate, MMF = mycophenolate mofetil
R = right eye, L = left eye

Median time of abatacept treatment was 10 months (range 6–14). During treatment, all children achieved a complete remission over a median period of 12 weeks (range 8–14). Steroid administration was discontinued during the first 6 months (range 4–6) in 3/4 children. The patient with Blau syndrome was able to taper the dose down to 0.3 mg/kg/day. In all children, no relapse of uveitis occurred during treatment, whilst during the 6 month-period before starting Abatacept, the median number of relapses was 4 (range 3–6). At 6 months of treatment, all patients, (5/8 eyes), met the criteria for improved visual acuity. Two children reached a completely normal visual acuity, while the other two improved, eventhough the pre-existing complications, due to chronic uveitis, affected a complete recovery. No major side effects, infusion reactions and/or drug-related adverse events were recorded during the treatment period.

Conclusion: Even if limited to a small group, our results suggest that Abatacept may be effective and safe in chronic refractory childhood uveitis, both in JIA-uveitis and in not JIA-uveitis.

Disclosure: G. Simonini: None; **D. L. Cinzia:** None; **R. Caputo:** None; **T. Giani:** None; **L. Pascoli:** None; **I. Pagnini:** None; **R. Cimaz:** None.

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Use of TNFα Antagonists in the Treatment of Chronic Non-Bacterial Osteomyelitis (CNO). Sara Stern[2], Katherine Marzan[2], Arturo Borzutzky[1], Evan Steinberg[3] and Andreas Reiff[2]. [1]Boston Children's Hospital, Boston, MA, [2]Childrens Hospital Los Angeles, Los Angeles, CA, [3]Kaiser-Permanente Sunset Hospital, Los Angeles, CA

Purpose: CNO is a chronic autoimmune inflammatory osteopathy syndrome that is culture negative and has no demonstrable organism on histopathology. Anti-inflammatory medications are typically used to prevent pathologic fractures, pain, and disease relapse. The objective of this study was to describe the use of TNFα antagonists in the treatment of CNO in 8 patients with treatment refractory disease.

Methods: We retrospectively analyzed 23 patients with CNO seen from 1985–2009 at Childrens Hospital Los Angeles (18) and Kaiser-Permanente Sunset Hospital Los Angeles, CA, USA (5). CNO disease activity was evaluated by clinical, laboratory and radiographic parameters. Response to treatment was assessed by laboratory values (CRP, ESR) and a global response score, which also included clinical and radiographic parameters. A score of 0 indicated lack of response, 1 indicated partial response, and 2 indicated full response. Descriptive statistics were used for analysis.

Results: 23 patients (14 F: 9M) with a mean age of 9.6 ± 2.9 were followed for a median of 1.83 (0.1–13) years. Patients had a mean of 3.3 ± 2.5 lesions which were most commonly seen in the pelvic bone (9), tibia (8), clavicle (6), calcaneus (5), femur (5), humerus (5), vertebrae (5), and mandible (4). Eight patients (34.7%) had unifocal disease. The most common presenting symptoms included bone pain (90.9%), soft tissue swelling

(45.5%), and fever (29.4%). Extra osseous manifestations were observed in 7 patients including enthesitis (2), myositis/fasciitis (4), anterior uveitis (1), oral ulcers (1), discoid rash (1) and Crohn's disease (1). Pathologic fractures were seen in 11 (47.8%) patients. All but one patient received NSAIDS, which was sufficient to control disease activity in 7 (31.8%) of patients. Eight patients were treated with methotrexate of which 7 failed this treatment and 5 were subsequently switched to TNFα antagonists of whom 3 improved. The overall failure rate in the anti TNFα group was 50%.

		Response			
		Global	Clinical	Radiologic Images	Laboratory
NSAIDs n=22	Lack of Response	4 (17.4%)	3 (13.0%)	7 (48.7%)	6 (30.0%)
	Partial Response	12 (52.2%)	11 (47.8%)	6 (40.0%)	6 (30.0%)
	Full Response	7 (30.4%)	9 (39.1%)	2 (13.3%)	8 (40.0%)
Methotrexate n=8	Lack of Response	2 (25.0%)	2 (25.0%)	2 (33.3%)	5 (62.5%)
	Partial Response	5 (62.5%)	5 (62.5%)	3 (50.0%)	2 (25.0%)
	Full Response	1 (12.5%)	1 (12.5%)	1 (16.7%)	1 (12.5%)
TNFα Antagonists n=8	Lack of Response	0 (0%)	0 (0%)	0 (0%)	2 (28.6%)
	Partial Response	4 (50.0%)	5 (62.5%)	3 (60.0%)	4 (67.1%)
	Full Response	4 (50.0%)	3 (37.5%)	2 (40.0%)	1 (14.3%)

Conclusions: CNO is a chronic autoimmune inflammatory syndrome with a high risk for pathologic fractures and systemic morbidity. Treatment of these patients remains challenging since they tend to respond poorly to traditional NSAID and DMARD therapy. TNFα antagonists offer a viable treatment option and appeared to be the most beneficial in our study.

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ACR Poster Session A
Pediatric Rheumatology - Pathogenesis and Genetics: Bench to Bedside - The Science of Pediatric Rheumatology
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A Pilot Study of Gene Expression (GE) Profiles in Juvenile Dermatomyositis (JDM) Responders and Non-Responders: Diagnostic and Follow-Up Muscle Biopsy (MBx) Data. Lauren M. Pachman[1], Yi-Wen Chen[2], Peter Hendrickson[1], Sheela Shrestha[1], Gabrielle Morgan[1] and Simone Sredni[1]. [1]Children's Memorial Research Center, Chicago, IL, [2]Children's National Medical Center

Background: Previous data documented that both the TNF-α-308 A allele and a long duration of untreated disease (DUD) before diagnosis contributed to the lack of response of JDM children to therapy. Studies of untreated juvenile dermatomyositis (JDM) muscle biopsies (MBx) had documented a marked increased in IFN-α induced genes (Tezak, JI, 2000). It is not known if there are differences in the GE profiles in the untreated muscle biopsy of responders (R) vs non-responders (NR) at the diagnosis of JDM, or if this dysregulation persists once the children have been classified as having responded by clinical standards to immunosuppressive therapy. Finally, there is no information about the genetic status after a course of therapy that may have improved the muscle symptoms, despite other evidence of active disease.

Objective: To compare the GE profiles in the diagnostic muscle biopsies in untreated children at diagnosis of JDM and after immunosuppressive therapy.

Materials and Methods: Seven children with definite/probable JDM were recruited for this study, along with four healthy age-, race-, and gender-matched controls undergoing orthopedic surgery. All JDM were initially untreated at the time of the diagnostic MBx, mean age 7.43 $\pm$4.21 yrs, 3/7 female; six Caucasian and one Hispanic. Four of the children responded to therapy and were off all medication at the time of follow-up needle MBx, two of the NR still required medication, and one was non-compliant. RNA was extracted and hybridized to Affymetrix U133A arrays (at diagnostic) and U133Aplus2 arrays (post-treatment). Data was normalized and filtered to exclude the controls and probes with maximum expression less than a log scale of 6 across all samples. The GE of R was compared to the NR using two-sample t-tests. Evaluation of gene functions and networks utilized Ingenuity Pathway Analysis software (Ingenuity Systems, Redwood City, CA).

Results: The NR were older at the time of the diagnostic MBx: mean age of 9.6 $\pm$ 5.7 yrs with a longer DUD of 14.0 $\pm$1.24 mos vs mean age of 5.8 $\pm$2.5 yrs and DUD of 3.3 $\pm$1.4 mos for the R. At needle follow-up biopsy, R were mean age of 10.7 $\pm$1.8 yrs vs 17.7 $\pm$7.4 yrs for NR.

A significant number of genes were found to be differentially expressed in R compared with NR. Skeletal-muscular and cardiovascular system development and function were within the main networks represented. Of importance, at diagnostic MBx several apoptosis related genes were significantly up regulated in R compared with NR, including CASP1 (FC 2.3; p=0.03) and CASP7 (FC 1.8; p=0.02). After treatment, the NOS1 gene that is usually expressed in skeletal muscle and is regulated by IL1B and TNF was over-expressed in non-responders compared with responders (FC 3.7; p=0.02).

Conclusion: The results of this preliminary analysis point to specific genetic mechanisms involved with non-responsiveness to treatment in JDM patients. GE studies involving larger cohorts will clarify these mechanisms and allow the identification at diagnosis of patients that may not respond to treatment and may benefit from more aggressive or alternative therapy.

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A Whole Blood Gene Expression Profile of Untreated Children with Polyarticular JIA Enrolled in the TREAT Trial. Mark Barton Frank[3], Kaiyu Jiang[2], Yanmin Chen[2], Melissa Bebak[3], Carol A. Wallace[4], Susan Thompson[1] and James N. Jarvis[2]. [1]Cincinnati Children's Hospital Medical Center, [2]Dept. of Pediatrics, U of OK College of Medicine, [3]Oklahoma Medical Research Foundation, [4]Seattle Children's Medical Center

Background: The Trial of Early Aggressive Therapy (TREAT) in Juvenile Idiopathic Arthritis is a once-in-a-generation, multi-institutional trial comparing methotrexate with etanercept + methotrexate + prednisone as initial treatments of polyarticular JIA. To maximize the scientific utility of this trial, biological samples have been collected for translational research to answer questions of high relevance to the field of pediatric rheumatology; these samples include whole blood preserved in stabilizers to perform gene expression profiling. We report here the first translational study to emerge from the TREAT trial, which will be completed in late October, 2010.

Methods: We received 45 samples from children with untreated polyarticular JIA at the time of their enrollment within the TREAT trial. All children were rheumatoid factor negative. Of these 45 samples, RNA was degraded in 11 and was insufficient for microarray analysis on another 5. Thus, microarray analysis was performed on 29 children entering the TREAT trial and 19 healthy control children. RNA purification, assessment of RNA purity and integrity, labeling, and hybridization were all undertaken using conventional methods. The Illumina microarray platform was used and conventional biocomputational approaches were taken to identifying differentially expressed genes.

Results: 130 genes distinguished TREAT baseline from control samples with a 5% false discovery rate and a minimum 1.5-fold difference between groups. These genes were largely subsumed into 5 large overlapping networks, demonstrating that pathological systems, like physiologic systems, demonstrate a property referred to by systems biologists as modularity. Gene networks also showed the hub-and-node structure (scale free systems) that we have previously described in the pathologic networks associated with childhood-onset rheumatic diseases. As is typical with gene array experiments, signaling molecules (JNK, Akt) and transcription factors (MYC, HNF4A, NFkB) represented prominent hubs in these networks. Small groups of genes regulated by type 1 and type 2 interferons and TGFB were also seen. A network of IL-12-regulated genes, not previously recognized on our earlier array studies, was down-regulated in untreated JIA patients. Hierarchical cluster analysis of the array data suggested that the JIA subjects could be divided into 2 dichotomous groups. As the TREAT study is still blinded, it is not possible at the present time to determine whether there is a specific phenotype associated with those clusters.

Conclusion: Whole blood gene expression profiling of untreated subjects from the TREAT trial demonstrates multiple gene networks that distinguish children with polyarticular JIA from healthy control children. The complexity of these gene networks demonstrates the challenge still facing us in understanding JIA at the cell and molecular level. At the same time, translational

samples collected from the TREAT trial will allow us to understand how these networks change in response to therapy and provide unprecedented insight into the biology of therapeutic response.

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Angiopoietin-Like 4 Is Expressed in Human Synovial Fibroblasts and Expression Is Increased in Response to TGFβ. Ndate Fall[2], Malinda Frederick[2], Alexei A. Grom[1] and Sherry Thornton[3]. [1]Childrens Hospital Medical Center, Cincinnati, OH, [2]Childrens Hosp Med Ctr, [3]Childrens Hospital Medical Center, Cincinnati, OH

Objective: We previously identified angiopoietin-like 4 (Angptl4) as a novel angiogenic protein that is highly increased in early inflammatory stages of collagen-induced arthritis. The present study determines the expression of Angptl4 mRNA in human synovium and the factor(s) regulating its expression.

Methods: Quantification of Angptl4 mRNA levels in synovial tissues was performed by RNase protection analysis. JIA (juvenile idiopathic arthritis) synovial fibroblast cultures were generated from joint replacement synovial tissues. Synovial fibroblast cultures were treated for 2 hours with systemic JIA (sJIA) synovial fluid (SF) or TGF-β, with or without the addition of recombinant human TGF-βRI kinase inhibitor (TβRI Inhibitor). RNA was isolated and Angptl4, IL-1β and GAPDH mRNA levels quantified by realtime RTPCR.

Results: Angptl4 is expressed at higher levels in rheumatoid arthritis (RA) and JIA than in osteoarthritis (OA) synovial tissues. JIA synovial fibroblasts express Angptl4 mRNA, which increases dramatically in the presence of systemic JIA (sJIA) SF. Treatment of JIA synovial fibroblasts with TGF-β shows a dramatic increase in Angptl4 expression that is nullified in the presence of TβRI Inhibitor. Angptl4 mRNA expression in response to SF is also dramatically diminished in the presence of TβRI Inhibitor.

Conclusion: Angptl4 is expressed in human arthritic synovium, suggesting a role for Angptl4 in human arthritic disease. The expression of Angptl4 is highly increased in JIA synovial fibroblasts in response to systemic JIA SF, and is abrogated by inhibition of TGF-βRI signaling, suggesting that TGF-β is a major mediator of Angptl4 expression in inflammatory arthritis.

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Anti-CCP Antibodies Identify a Subset of RF-Negative Juvenile Idiopathic Arthritis. Anne E. Tebo[2], Troy D. Jaskowski[1], K. Wayne Davis[1], April Vigus[6], Bronte Clifford[4], Andrew S. Zeft[5], Bernadette McNally[5], Harry R. Hill[2], John F. Bohnsack[5] and Sampath Prahalad[3]. [1]ARUP Laboratories, [2]ARUP Laboratories, Univ Utah, [3]Emory Children's Center, Atlanta, GA, [4]Nationwide Children's Hospital, [5]University of Utah, Salt Lake City, UT, [6]University of Utah

Purpose: Juvenile idiopathic arthritis (JIA) is the most common cause of chronic arthritis in children. One subtype of JIA, characterized by rheumatoid factor (RF) positive polyarthritis, phenotypically resembles rheumatoid arthritis (RA) in adults. Recent studies have demonstrated anti-citrullinated protein/peptide antibodies (ACPA), have high specifity for RA. Furthermore most known genetic associations with RA are confined to autoantibody positive RA (ACPA and/or RF). Prior investigations of the prevalence of ACPA in children have mostly been in small cohorts of children with JIA, with very few cases of RF-positive polyarticular JIA included. We sought to investigate the prevalence of ACPA in a large well-characterized cohort of JIA and investigate the relationship between RF and ACPA.

Methods: Cases were 334 children with JIA, 30 of whom had RF+ polyarticular JIA. The mean age of onset in the JIA cohort was 6.7 years. Controls were 50 healthy children with a mean age of 11.5 at the time of blood draw. Sera from all JIA patients and healthy controls were investigated at a single time point for anti-cyclic citrullinated peptide (anti-CCP) IgG by ELISA (INOVA Diagnostics, San Diego, CA), RF IgM, IgA and IgG (Theratest, Lombard, IL), anti-RA33 ELISA (IMTEC, Wiesbaden, Germany), antinuclear antibodies (ANA) screened by ELISA (BioRad, USA) and positives confirmed by IFA on HEp2 cells. Comparisons between cases and controls were made using Chi-square or Fisher exact tests for categorical variable and T-tests for continuous variables.

Results: The prevalence of RF was 8% among controls, and 12% among cases, (not statistically significant). However the mean titer of RF was higher among positive cases. ACPA were detected in one control and 48 cases (2% vs. 14.3 %; OR 8.2, $p < 0.01$). Of particular interest were 23 children (7%) who had a positive ACPA and were negative for RF (IgM, IgG or IgA). These children had a significantly earlier age of onset than those children who had both RF and ACPA (4.6 years vs. 12.1 years, $p < 0.00001$ by T-test), included more males (8/23 vs. 2/30, $p < 0.01$), and included children with polyarticular ($n = 6$) as well as oligoarticular onset ($n = 10$). High resolution HLA-DRB1 genotyping indicated that they had fewer shared epitope alleles compared to those with ACPA and RF, who resembled adults with RA. Twenty-five JIA cases had both RF and ACPA, and generally had higher titers of ACPA than those with only ACPA. Among children classified as having RF+ polyarticular JIA per ILAR criteria, 73% were positive for ACPA. Notably, two children with ACPA and RF had oligoarticular onset and were classified as "undifferentiated JIA" per the ILAR criteria. ANA was positive in 6% of controls and 26% of cases by IFA (OR 5.6, $p < 0.01$). RA-33 antibodies were observed in 6% of controls, and 6% of cases (not significantly different).

Conclusions: Using the largest cohort investigated to date for ACPA, we have demonstrated that anti-CCP antibodies are detectable in 15% of children with JIA. Children with positive ACPA but negative RF are frequent, and may define a distinct subset of children with JIA. If validated in other large JIA cohorts, ACPA testing should be included in the classification of JIA.

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CD4+CD161+ Cells with Th1 or Th17/Th1 Profile Accumulate in the Synovial Fluid of Patients with Juvenile Diopathic Arthritis and Correlate with Inflammation Parameters. Rolando Cimaz[1], L. Cosmi[2], L. Maggi[2], V. Santarlasci[2], M. Capone[2], F. Borriello[3], F. Frosali[2], V. Querci[2], G. Simonini[2], G. Barra[3], F. Liotta[2], R. De Palma[3], E. Maggi[2], S. Romagnani[2] and F. Annunziato[2]. [1]University of Florence, Firenze, Italy, [2]University of Florence, [3]University of Naples

Objective: A recently described subset of CD4+ T helper (Th) cells, named as type 17 Th (Th17) cells, has been suggested to be pathogenic in chronic inflammatory disorders, including rheumatoid arthritis and juvenile idiopathic arthritis. We wanted to investigate the phenotype and function of CD4+ T cells in synovial fluid (SF) of affected joints from children with juvenile idiopathic arthritis (JIA), and to establish a possible link with disease activity.

Methods: CD4+ T cells of peripheral blood (PB) and SF of 37 JIA patients, as well as of PB from 15 healthy children were analyzed for expression of CXCR3, CCR6, CD161 and production of IFN$\gamma$and IL-17A. Intracellular cytokine production assays, cytokine secretion assays, and cell cultures were performed. CD161+IL-17+IFNγ- and CD161+IL-17-IFNγ+ cells derived from PB of one healthy donor and the SF of one JIA patient were also cloned. RORC expression was evaluated by real-time quantitative RT-PCR in FACS sorted populations. Spectratyping and clonotypic analyses on different T cell subsets were performed.

Results: Numbers of CD4+CD161+, showing either the Th1 (IFNγ-producing) or the Th17/Th1 (producing both IFN-g and IL-17A) phenotype, were higher in SF than in PB from JIA children. The few Th17 cells from SF of JIA spontaneously shifted in vitro to Th1 cells, whereas Th17 cells from PB of healthy children did it only in presence of SF, this effect being neutralized by blocking IL-12 activity. Spectratyping and clonotypic analyses showed a similar skewing of the TCR-BV repertoire in both SF-derived CD161+Th17 and CD161+Th1 cells from the same JIA patient. The frequencies of CD4+CD161+ cells, particularly of those showing the Th17/Th1 phenotype, in SF of JIA positively correlated with levels of erythrocyte sedimentation rate and C-reactive protein.

Conclusion: These findings suggest that a shifting of CD4+CD161+Th17 cells into Th17/Th1 or Th1 cells in the SF from affected joints of JIA can occur, and indicate that the accumulation of these latter correlates with parameters of inflammation, thus supporting the hypothesis that these cells play a role in disease activity.

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Characterization of Granulocyte Transcriptome in Polyarticular Juvenile Idiopathic Arthritis (JIA). Mark Barton Frank[3], Kaiyu Jiang[1], Yanmin Chen[1], Jeanette Osban[3], Pascal Gellert[2] and James N. Jarvis[1]. [1]Dept of Pediatrics, U of OK College of Medicine, [2]Max Planck-Institute for Heart and Lung Research, [3]Oklahoma Medical Research Foundation

Background: Previous studies have demonstrated aberrations in granulocyte activation in patients with polyarticular JIA, and gene expression profiles of patients with active disease and in remission support an important role of these cells in pathogenesis. The goal of this study was to extend our previous work to define molecular aspects of gene differences in JIA.

Methods: Children were grouped as having active JIA (AD, n=18), clinical remission on medication (CRM, n=12) or healthy controls (C, n=15) according to the criteria of Wallace et al. AD ad CRM patients were treated with similar medications. RNA was extracted from purified granulocytes, labeled and hybridized to Affymetrix Exon and microRNA (miRNA) arrays. Statistically significant differences with minimum two-fold changes in exon splicing were characterized by Exon Array Analyzer programs, and miRNA differences were defined using BRB-Array Tools.

Results: Exon splicing differences were detected and confirmed in 4 genes when cohorts of AD were compared to CRM. However, exon splicing occurred in a larger number of genes including amyloid P component, when samples from the same patients in AD were compared to those collected later in CRM. Numerous splice variations were found between AD and C samples including genes encoding Ro60, transcriptional regulators, and an IL-6 cytokine family receptor. These differed from those found when CRM was compared to controls. No differences in miRNA expression were detected between AD and CRM, AD and C, or CRM and C samples.

Conclusions: These results support the hypothesis that the transcriptional differences between patients with JIA and healthy children occur not only at the gene expression level as we and others have previously reported, but also in subtle ways in the usage of exons of genes of pathological interest. The absence of differences in miRNA levels in patients and controls suggests the regulatory events in RNA transcription are not controlled by miRNA or altered by treatment protocols used in these patients. The study further clarifies the important role at the molecular level of granulocytes in the pathogenesis of JIA.

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CLARITY: ChiLdhood Arthritis Risk Factor Identification Study. Justine Ellis[1], Jane Munro[2], Anne-Louise Ponsonby[1], Angela Pezic[1], Betty Lim[1], Raul Chavez[1], William Siero[1], Jonathan Akikusa[2] and Roger Allen[2]. [1]Murdoch Childrens Research Institute, Melbourne, Parkville, Victoria, Australia, [2]Royal Children's Hospital, Melbourne, Parkville, Victoria, Australia

Introduction: Juvenile idiopathic arthritis is an autoimmune rheumatologic disease of unknown cause. As a complex disease, it is assumed that an interaction between genetic predisposition and environmental factors determines risk. Research to identify JIA risk factors lags behind that of other childhood autoimmune disorders of similar incidence. Over the last few years, the underlying genetic predisposition has begun to emerge, mainly through candidate gene analyses. However, few studies have examined environmental risk factors for JIA in detail, but past infection is of interest, both as a possible beneficial early life immunomodulator and an adverse trigger of disease (Ellis *et al.* Rheumatology 49:411-25, 2010). In 2008, we established CLARITY, a JIA Biobank that is collecting biospecimens and extensive information about environment from cases presenting to the Royal Children's Hospital (RCH), Melbourne, Victoria, Australia. A control sample of healthy children attending the RCH Day Surgery Unit for specific minor surgical procedures is also been collected. Our goal is to recruit at least 1000 cases and 1000 controls, to allow adequate statistical power to detect not only main effects but also gene-environment interactions. To date we have recruited 260 cases and 400 controls.

Methods: Here we concentrate on a preliminary analysis of a subset of the environmental measures collected in 224 incident and prevalent cases (mean age 9.5 ± 4.5 SD yrs, 69% female) and 272 controls (mean age 7.3 ± 4.1 SD yrs, 39% female) so far entered into a database. We examined the incidence of common childhood illnesses by logistic regression (adjusted for age and sex).

Results: A history of illness such as gastroenteritis (Adjusted odds ratio (AOR) = 0.52; 95% CI: 0.32, 0.83; p = 0.006), colds and flu (AOR = 0.36; 95% CI: 0.22, 0.58; p <0.001), and chest infection (AOR = 0.44; 95% CI: 0.26, 0.74; p = 0.002) were associated with a reduced likelihood of being a JIA case. These associations remained significant when we restricted the dataset to cases diagnosed within 3 years of interview as well as cases and controls born in Victoria with four Caucasian grandparents (case n = 100, control n = 223). The associations between reduced JIA risk and childhood illness remained particularly strong and consistent for colds and flu (AOR = 0.38; 95% CI: 0.21, 0.68, p = 0.001). We then further restricted the dataset to test the association of the incidence of colds and flu prior to school entry (4 years or younger) with diagnosis of JIA at 6 years or greater (case n = 113, control n = 272). The association was observed in this subgroup (AOR = 0.42; 95% CI: 0.15, 0.82; p = 0.016).

Conclusions: To date, these findings are consistent with other work indicating early life microbial exposure that leads to an increased incidence of common childhood illnesses confers protection against autoimmune disease, potentially through more efficient priming of the developing immune system. Further analyses will be undertaken in the larger study to examine whether the indications for control day surgery influenced these findings.

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Costimulation Mediated Rescue of Superantigen Stimulated T Cells in Kawasaki Disease. Aaron Wong[2] and Rae S. M. Yeung[1]. [1]Hospital for Sick Children, Toronto, ON, Canada, [2]The Hospital for Sick Children, Toronto, ON, Canada

Background: Kawasaki Disease (KD) causes coronary arteritis and is the leading cause of acquired heart disease in children of the developed world. Evidence suggests that superantigens (SAgs) are involved in the pathogenesis of KD. Lactobacillus Casei cell wall extract (LCWE), a mouse model of KD, closely mimics human KD and SAg activity in LCWE directly correlates with its ability to induce coronary arteritis. Superantigens are potent T cell mitogens, initiating a tremendous inflammatory response with massive cytokine release characterized by production of tumor necrosis factor-alpha (TNFa). Our work suggests that enhanced costimulation can rescue SAg-stimulated T cells from apoptosis and thus could enable survival of autoreactive T cells which persist in our mouse model.

Objective: To determine the mechanisms involved in costimulation mediated rescue of SAg-stimulated T cells.

Methods: Splenocytes from C57BL/6, TNFR1 −/−, B7.2 −/−, and Cbl-b −/− mice were cultured in media containing various stimuli: Staphylococcal Enterotoxin B (SEB)-a prototypic SAg, recombinant TNFa (rTNFa), anti-CD28 antibody, CTLA4-Ig, and anti-TNFa antibody. Expression of B7.1, B7.2, Bcl-2, and Bcl-xl was determined by staining with fluorescent antibodies in flow cytometry experiments. In costimulatory rescue experiments, splenocytes were stimulated for 5 days and the levels of apoptosis within the SAg-reactive T cell population was determined by staining for TCRVb8 and annexin V. To determine the contribution of costimulatory molecules on T-cells versus antigen presenting cells (APC), cell populations were purified by magnetic bead separation, then mixed and co-cultured as described above.

Results: Stimulation with SEB upregulated B7.2 expression in wildtype mice, but this response was diminished in TNFR1 −/− mice. Addition of rTNFa in the absence of SEB independently upregulated B7.2 expression. Enhancing costimulation with stimulatory anti-CD28 antibody rescued superantigen-reactive T cells from apoptosis in wild type and TNFR1−/−, but not Cbl-B −/− mice. Disrupting costimulation by blocking B7 with CTLA4-ig or neutralizing TNF increased apoptosis of SAg-reactive T cells. Mixing experiments with purified wildtype T cells and B7.2 −/− APCs exhibited no change in SAg-induced apoptosis when compared to cultures completely lacking B7.2. Increased expression of the anti-apoptotic markers Bcl-2 and Bcl-xl was found in cells receiving enhanced costimulation.

Conclusion: TNFa plays an important role in regulating costimulation by regulating the expression of costimulatory ligand, B7.2, on APCs. The resultant B7.2/CD28 interaction is functionally relevant, leading to survival of SAg-reactive T cells. Rescued T cells had increased expression of anti-apoptotic markers Bcl-2 and Bcl-xl. As costimulation enables autoreactive cells to evade apoptosis and persist leading to persistent inflammation and tissue damage, this study lends additional mechanistic support to therapies that target TNF and costimulatory molecules for the treatment of KD. These principles are generalizable to many diseases where superantigens are implicated as triggers of a persistent immune response.

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Detection of Potentially Disease Associated Copy Number Variants in Children with Rheumatoid Arthritis. Sampath Prahalad[1], Jennifer Gladys Mulle[2], Anne Dodd[3], Jennifer Prozonic[3], Milton Brown[3], Andrew S. Zeft[4], John F. Bohnsack[4], Stephen T. Warren[3], M. Katharine Rudd[3] and Christa L. Martin[3]. [1]Emory Children's Center, Atlanta, GA, [2]Emory University, Atlanta, GA, [3]Emory University, [4]University of Utah, Salt Lake City, UT

Purpose: Rheumatoid arthritis (RA) is a common chronic inflammatory arthropathy with a peak age of onset in the fifth decade. About 5% of children with juvenile idiopathic arthritis phenotypically resemble adult RA. We hypothesize that children with the RA phenotype are a genetically enriched early-onset disease cohort which could enable the identification of additional susceptibility factors for RA. Most studies to date have focused on adults with RA and on single nucleotide polymorphisms (SNPs). Copy number variants (CNVs), defined as duplications or deletions of DNA sequences, occur extensively throughout the human genome and have the potential to explain larger phenotypic effects than SNPs. We sought to identify CNVs which may influence susceptibility through disruption of genes in children with early onset RA.

Methods: Subjects were 13 children with very early onset of RA. The mean age of onset was 8 years (range 2 – 12.8 years). All subjects had at least two positive tests for rheumatoid factor and were positive for antibodies to cyclic citrullinated peptide (anti-CCP). We used a custom-designed oligonucleotide microarray (EmArray Cyto 180K, Agilent Technologies, Santa Clara, CA, USA) to detect CNVs. Following the manufacturer's protocol, DNA isolated from peripheral blood was hybridized to an array containing 180K oligonucleotides, including targeted coverage of known clinically relevant regions and a whole genome backbone with a resolution of ~75 kb. We eliminated common benign CNVs in the population using online databases (http://www.genome.ucsc.edu/ and http://projects.tcag.ca/variation/) and our own internal laboratory database.

Results: Three CNVs were identified. The first CNV was a 168-kb loss of chromosome 10, that includes the gene *HPSE2* (heparanase 2) which cleaves heparan-sulfate proteoglycans into heparan-sulfate side chains and proteoglycans. Heparanase-2 is also implicated in the extravasation of leukocytes. Another CNV was a 106-kb gain of chromosome 18 involving *ROCK1* which encodes a protein kinase that phosphorylates a large number of important signaling proteins, and is involved in regulation of lymphocyte migration. Both these CNVs were not observed in ~11,000 normal individuals in the Database of Genomic Variants ($p < 0.001$ by Fisher's exact test). Both CNVs were confirmed by Affymetrix 6.0 Arrays. A third CNV was a 79.8-kb gain of chromosome 6 which involves *HLA-DRB5*, a paralog of *HLA-DRB1* that is strongly associated with RA. This CNV has been reported previously. Common CNVs not associated with any phenotypes were observed in seven children. We also observed small deletions or gains in some children that were in regions with no relevant genes.

Conclusions: We have identified CNVs potentially associated with childhood presentation of RA. The genes identified are plausible candidates for RA. We are typing additional children with RA for CNVs using a higher density array. These preliminary findings support additional searches for CNVs in children with RA.

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Differences in Transcription Profiles in Juvenile Idiopathic Arthritis (JIA) Patients Who Achieved Remission Using Different Therapies. Mark Barton Frank[2], Kaiyu Jiang[1], Yanmin Chen[1] and James N. Jarvis[1]. [1]Dept of Pediatrics, U of OK College of Med, [2]Oklahoma Medical Research Foundation

Background: We have previously shown that remission in JIA represents a distinct biological "state" that can be recognized clinically and at the molecular level. However, remission can be achieved with different medications. While ~30% of children with polyarticular JIA achieve remission on methotrexate (MTX) in combination with an NSAID, most achieve remission only when MTX and NSAIDs are used in conjunction with a TNF inhibitor (TNFi). We undertook this study to determine whether remission in a cohort of children with RF-negative, polyarticular onset JIA induced by MTX differs at the molecular level from remission achieved in the presence of a MTX plus a TNFi.

Methods: RNA was prepared from 29 patients' peripheral blood mononuclear cells (PBMC) and granulocytes to identify differentially expressed (DE) genes using whole genome microarrays between the two patient groups and 15 healthy childhood controls. Statistical analysis and in silico modeling using Ingenuity software were undertaken as described in our previous work.

Results: Only 6 DE genes were found in PBMC from patients who achieved remission using MTX+TNFi v MTX alone. Additional differences became apparent when each treatment group was compared to healthy controls. It is interesting to note that a number of the DE genes in both cell types are known to be regulated by the transcription factors NFkB and HNF4A.

There were 33 DE genes in granulocytes from patients treated with the two regimens, including many whose patterns were previously reported to be modulated in arthritis. As with PBMC, a number of these genes are also regulated by NFkB and HNF4A. Subsequent work from our group (see related abstract) has demonstrated unequivocally that that HNF4A is present in PBMC and granulocytes.

Both cell types from both groups of patients revealed hundreds of DE genes when compared to healthy controls. In granulocytes, these genes were subsumed into 9 large, overlapping networks that included the TGFB, TNFA, and IFNG hubs we have previously described. In PBMC, DE genes were subsumed into 2 networks that included the IFNG, TGFB, and IL1 hubs that have appeared on other JIA transcriptional profiles, including our own.

Conclusions: There appear to be strong similarities in the molecular "signatures" of remission in PBMC of children with JIA, regardless of whether remission was induced by MTX or MTX plus TNFi. The larger number of identified genes in granulocytes suggests important distinctions in innate immunity occur while achieving clinical remission. However, remission is not a return to "normal," but, rather, a homeostatic state in which pro- and anti-inflammatory gene networks are held in balance.

Disclosure: M. B. Frank: None; **K. Jiang:** None; **Y. Chen:** None; **J. N. Jarvis:** None.

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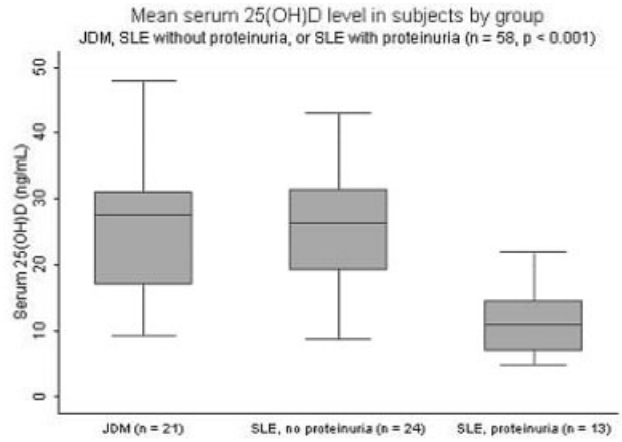
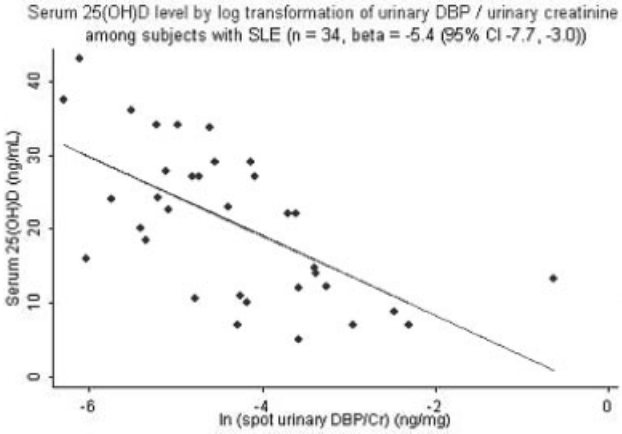
Disease Activity, Proteinuria, and Vitamin D Status in Children with Systemic Lupus Erythematosus and Juvenile Dermatomyositis. Angela B. Robinson[1], Myrtle Thierry-Palmer[2], Keisha L. Gibson[3] and Egla C. Rabinovich[1]. [1]Duke University Medical Center, Durham, NC, [2]Morehouse School of Medicine, [3]University of North Carolina at Chapel Hill

Background: Recent studies have implicated low vitamin D levels with greater disease activity in pediatric systemic lupus erythematosus (pSLE); there is no data on children with dermatomyositis. The objective of this study was to determine whether low levels of 25-hydroxyvitamin D [25(OH)D] are associated with proteinuria and assess the relationship between vitamin D deficiency and disease activity in two photosensitive autoimmune conditions [systemic lupus erythematosus (SLE) and juvenile dermatomyositis (JDM)].

Methods: Subjects diagnosed with JDM or SLE prior to the age of 18 were recruited and given a questionnaire regarding demographics, sunscreen use, and dietary habits to assess conventional risk factors for vitamin D deficiency. Serum 25(OH)D and albumin levels were determined. Disease activity was rated using a 10-cm visual analogue scale (VAS) in all subjects and a SLE disease activity index (SLEDAI) in subjects with SLE. Linear regression was used to examine the association of race, sunscreen use, vitamin D intake, and disease activity with serum 25(OH)D levels. Urine was analyzed for vitamin D binding protein (DBP) and protein to creatinine (UP/C) ratio.

Results: There were 58 subjects; 21 with JDM and 37 with SLE (13 with UP/C values ≥ 0.5). Serum 25(OH)D levels in subjects with SLE were inversely associated with urinary DBP ($r = -0.63$, $p < 0.001$) and urine protein to creatinine ratio ($r = -0.67$, $p < 0.001$), and directly associated with serum albumin ($r = 0.56$, $p < 0.001$). In a multivariate linear regression model adjusting for known risk factors including race and vitamin D supplement intake, serum 25(OH)D levels were inversely associated with disease activity (VAS), SLEDAI, and proteinuria in subjects with SLE. Prednisone dosage was not associated with 25(OH)D levels. UP/C ratios $\geq$ 0.5 were associated with an adjusted mean 10.9 ng/mL (95% CI 5.1 to 16.8 ng/mL) decrease in 25(OH)D level. Excluding subjects with proteinuria from analysis, serum 25(OH)D levels were inversely associated with disease activity in subjects with JDM, but not in subjects with SLE.





Conclusions: Low levels of serum 25(OH)D in systemic lupus erythematosus may result, in part, from urinary loss of DBP-25(OH)D in those patients with SLE-related glomerulonephritis. Serum 25(OH)D levels inversely correlate with disease activity in both JDM and SLE patients, but the relationship between disease activity and serum 25(OH)D levels in SLE patients may be confounded by the presence of proteinuria. Further studies should prospectively assess the effect of vitamin D supplementation on disease activity and outcomes in SLE and JDM.

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Effect of Methotrexate and Genotype on RBC Folate Concentrations and Polyglutamate Distribution in JIA. Mara L. Becker[1], Leon van Haandel[5], Roger Gaedigk[3], Bradley Thomas[3], Mark F. Hoeltzel[2], Andrew Lasky[4], John Stobaugh[5] and J. Steven Leeder[3]. [1]Children's Mercy Hospital, Kansas City, MO, [2]Children's Mercy Hospitals and Clinics, Kansas City, MO, [3]Children's Mercy Hospitals and Clinics, [4]Childrens Mercy Hospitals and Clinics, Kansas City, MO, [5]University of Kansas

Purpose: The mechanism of action of methotrexate (MTX) remains incompletely understood. As a potent anti-folate drug, MTX has several enzymatic targets in the folate pathway. We measured intracellular folate redox states and polyglutamates to better understand the effect of drug and genotype upon intracellular folate pools in JIA.

Methods: This single center cross-sectional study evaluated 101 JIA patients on stable doses of MTX, and 94 JIA patients who were not currently on MTX. After obtaining informed consent, blood was obtained during routine lab monitoring. Genotyping for 34 SNPs in 19 genes within the MTX metabolic pathway was performed. Folates were extracted from RBCs and analyzed in a semi-quantitative relative fashion (i.e. without standards) using a similar method as for MTX polyglutamates, involving an ion-pairing chromatographic procedure with mass spectrometric detection.

Results: Measured intracellular folate isoforms included: 5,10 methenyl tetrahydrofolate **(5,10-MTHF)** which included the isoforms 5 formyl THF, 10 formyl THF and 5,10 methenyl THF; 5 methyl tetrahydrofolate (**5-MTHF**); and 5-MTHF polyglutamates **(5-MTHF-PG%$_{3–10}$)**. Subjects on MTX had expectedly lower folate isoform concentrations than those not on MTX including 5-MTHF (678.6 ± 281.2 nmol/L vs. 1022.2 ± 489.3 nmol/L, $p<0.0001$) and 5,10-MTHF (68.4 ± 77.0 nmol/L vs. 91.7 ± 106.3 nmol/L, $p=0.04$). 5-MTHF-PG% distribution revealed higher proportions of long chain polyglutamates in patients receiving MTX.

Table 1. 5-MTHF-PG% Distribution: Means (± SD)

	PG3%	PG4%	PG5%	PG6%	PG7%	PG8%	PG9%	PG10%
No MTX	2.1 (1.6)	6.3 (1.5)	47.7 (5.1)	30.3 (3.6)	8.4 (2.0)	3.5 (0.8)	1.4 (0.4)	0.29 (0.2)
MTX	1.5 (1.4)	7.1 (1.8)	43.9 (3.9)	31.1 (4.0)	9.8 (1.9)	4.2 (2.2)	2.0 (1.6)	0.43 (0.2)
p value	0.0007	0.0006	<0.0001	0.1	<0.0001	<0.0001	<0.0001	<0.0001

Of all clinical variables tested (including the use of folate supplementation) only MTX dose (in mg/kg) was inversely related to 5-MTHF concentrations ($p=0.0009$). Study participants with active arthritis had higher concentrations of summed RBC folates than those without active arthritis ($p=0.01$).

Variations in folate pathway genes were further investigated in the individuals on MTX. Homozygote variant (var/var) subjects in *MTHFD1* (rs2236225) had significantly higher concentrations of 5-MTHF than heterozygotes (wt/var, $p=0.009$) and wild type patients (wt/wt, $p=0.016$). *MTHFR* (rs1801133) var/var subjects had significantly lower concentrations of 5-MTHF than wt/var individuals ($p=0.017$). On the contrary, *MTHFR* (rs1801133) var/var subjects had significantly higher concentrations of 5,10-MTHF than both wt/var and wt/wt patients ($p<0.0001$). Two distinct SNPs in the *ATIC* gene had opposite effects upon 5,10-MTHF concentrations. *ATIC* (rs12995526) var/var subjects had significantly higher concentrations of 5,10-MTHF than wt/wt subjects ($p=0.01$), and *ATIC* (rs4673990) wt/var subjects had significantly lower concentrations than wt/wt subjects ($p=0.015$).

Conclusions: Variation in intracellular folate isoforms may be predictive of drug response in JIA. Genotypic differences beyond *MTHFR* may explain differential intracellular folate concentrations.

Disclosure: M. L. Becker: PhRMA Foundation Faculty Development, 2; **L. van Haandel:** None; **R. Gaedigk:** None; **B. Thomas:** None; **M. F. Hoeltzel:** None; **A. Lasky:** None; **J. Stobaugh:** None; **J. S. Leeder:** None.

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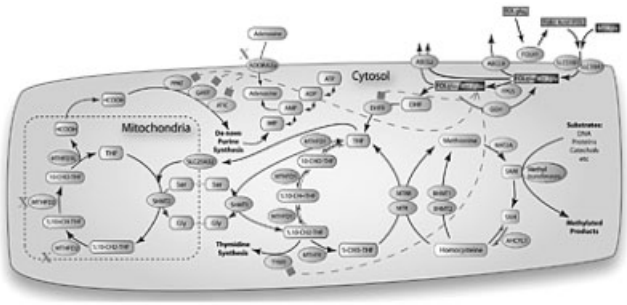
Genetic Variation Associated with Methotrexate Response in Juvenile Idiopathic Arthritis: Role of the Mitochondrial and Purine Synthesis Pathways. Mara L. Becker[1], Roger Gaedigk[3], Bradley Thomas[3], Andrew Lasky[4], Mark F. Hoeltzel[2], Hongying Dai[3] and J. Steven Leeder[3]. [1]Children's Mercy Hospital, Kansas City, MO, [2]Children's Mercy Hospitals and Clinics, Kansas City, MO, [3]Children's Mercy Hospitals and Clinics, [4]Childrens Mercy Hospitals and Clinics, Kansas City, MO

Purpose: Response and toxicity to Methotrexate (MTX) is unpredictably variable in Juvenile Idiopathic Arthritis (JIA). A known folate antagonist, there are several identified folate pathway gene targets for MTX and, therefore, there is a large potential for variation in genotype which may affect drug response. We investigated the combination of folate pathway polymorphisms and MTX response in JIA.

Methods: This is a single center cross-sectional study evaluating JIA patients on stable doses of MTX at a tertiary care children's hospital. After obtaining informed consent, blood was obtained from 104 JIA patients during routine MTX screening labs. Clinical data were collected by chart review. Genotyping for 34 SNPs in 19 genes within the MTX metabolic pathway was performed. Chi square analysis and Multifactor Dimensionality Reduction (MDR) methods were employed to investigate gene to gene interactions associated with the presence of active arthritis.

Results: All genes included in the analysis were in Hardy Weinberg equilibrium. Initial chi square analyses revealed a statistically significant association with the following genes and the presence of active arthritis (active disease): *ATIC* (rs4673990; $P=0.019$), *MTHFD2* (rs12196, and a 5nt ins/16nt del in the promoter; $P=0.005$, and $P=0.015$, respectively), and *ITPA* (rs2295553; $P=0.014$). The MDR method was applied to the outcome of presence/absence of active joints. The most pronounced combination of genes differentiating patients with active arthritis and those without included *ATIC* (rs4673990) and *MTHFD2* (rs56168672).



In fact, subjects who carried the combination of these two SNPs were 9.7 times more likely to have active arthritis [OR 9.66 (95%CI: 3.9, 24; $P<0.0001$)]. Sensitivity was 74%, specificity was 86.7% and overall accuracy was 76%.

Table 1. MDR analysis evaluating gene-gene interactions differentiating subjects with active arthritis from those without

Model	Training Accuracy	Testing Accuracy	CVC	Odds Ratio (95% CI)
One locus		Not significant		
ATIC (rs1673990)	76%	69.4%	9/10	9.66 (3.0, 24)
MTHFD2 (rs56168672)		(P = 0.0145)	(P = 0.0810)	($p < 0.0001$)
Three loci		Not significant		

Conclusions: MTX has a known inhibitory effect on several target enzymes, resulting in disruption of the folate cycle and a subsequent decrease in production of DNA precursors, disruption of methyl-dependent reactions, and accumulation of adenosine, which has anti-inflammatory properties. Due to the importance of the folate pathway it is unlikely that altered drug response is a consequence of variation in a single gene, rather a network or pathway of genes may be of interest. We have identified SNPs in the mitochondrial *(MTHFD2)* and purine synthesis *(ATIC)* pathways which may, in combination, play a role in MTX response in JIA.

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Hierarchy of Risk Conferred by the HLA-DR Shared Epitope in Childhood Onset Rheumatoid Arthritis. Sampath Prahalad[3], Susan D. Thompson[2], Karen Conneely[6], Yunxuan Jiang[6], Jennifer Prozonic[6], Milton Brown[6], Sheila Angeles-Han[5], Larry B. Vogler[7], Christine W. Kennedy[4], Carol A. Wallace[14], Carol Wise[12], Marilynn G. Punaro[11], Ann M. Reed[8], Jane L. Park[10], Elizabeth D. Mellins[9], Andrew S. Zeft[13], John F. Bohnsack[13] and David N. Glass[1]. [1]Childrens Hospital Med Ctr, Cincinnati, OH, [2]Cincinnati Childrens Hospital Med Ctr, Cincinnati, OH, [3]Emory Children's Center, Atlanta, GA, [4]Emory Children's Center, Decatur, GA, [5]Emory University, Atlanta, GA, [6]Emory University, [7]Emory University School of Medicine, Atlanta, GA, [8]Mayo Clinic, Rochester, MN, [9]Stanford University Med Ctr, Stanford, CA, [10]Stanford University Med Ctr, San Jose, CA, [11]Texas Scottish Rite Hospital for Children, Dallas, TX, [12]Texas Scottish Rite Hospital for Children, [13]University of Utah, Salt Lake City, UT, [14]University of Washington and Seattle Childerns's Hospital, Seattle, WA

Purpose: Rheumatoid arthritis (RA) is an inflammatory arthritis with a peak age of onset ~50, although childhood cases occur. There is a strong association between certain HLA-DR alleles and RA. RA associated alleles encode DRβ1 chains with conserved amino acid sequence in positions 70–74. The molecular structure encoding the susceptibility residues is termed the shared epitope (SE). While associations between SE and risk of RA is well established, some alleles (e.g. *0401) seem to confer a greater degree of risk than others (*0101). Tezenas Du Montcel et al proposed a classification in which some SE alleles conferred more susceptibility than others. While SE alleles have been evaluated in childhood cases of RA, most cohorts were small ($n < 50$), and used low resolution DNA typing. We sought to investigate possible hierarchy of SE alleles in the largest cohort assembled to date of RA in children.

Methods: Cases were 189 children with JIA who had one or more positive tests for rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (CCP) antibodies. Controls were 100 healthy Non-Hispanic White (NHW) adults. High resolution sequence based HLA-DRB1 genotypes were determined on cases and controls. In addition DRB1 genotypes were available on 273 healthy NHW controls. Per Tezenas Du Montcel et al, SE alleles were classified as follows: S2: (KRAA at amino acid positions 71–74) *0401, *1303; S3P: (QRAA) *0101, *0102, *0404, *0405, *0408, *1001, *1402. All other alleles were designated as low-risk (L) alleles. Logistic regression was performed using NHW cases and controls to calculate the odds ratio of various combinations of SE alleles (L/L, S3P/L, S2/L, S3P/S3P, S2/S2, S3P/S2).

Results: The mean age of onset of RA was 10.7 years. Of 87 children tested for anti-CCP antibodies, 72% were positive. Of 21 African-American (AA) cases 48% carried 1 or 2 SE alleles. Of 25 Hispanic children 76% carried 1 or 2 SE alleles. Of the 134 NHW cases, 76% carried 1 or 2 SE alleles compared to 54% of controls (OR = 2.73, $p < 0.00001$). A significantly greater proportion of cases carried 2 copies of SE alleles compared to controls (31.3% vs. 5.4%, OR 8.1, $p < 1 \times 10^{-7}$). The effect of the number of risk alleles (SE) was very significant (OR = 2.5 (95% C.I.: 1.5–4.2) for each additional risk allele, p = 0.0003). There was a greater risk for S3P/S2 individuals beyond that expected based on the number of risk alleles alone (OR = 2.9 (95% C.I.: 1.1–7.4), p = 0.025). Genotype-specific risk estimates with L/L as reference group suggested a hierarchy of risk, with highest risk among those who had a S2 and a S3P allele (Table).

Genotype	Number (%) of controls (N = 373)	Number (%) of RA patients (N = 134)	Comparison to L/L genotype OR (95% CI)	P
S_2/S_{3P}	9 (2.4)	28 (20.9)	19.5 (8.4–45.2)	<0.0001
S_2/S_2	3 (0.8)	4 (2.9)	8.4 (1.8–39.2)	0.0069
S_{3P}/S_{3P}	8 (2.1)	10 (7.5)	7.8 (2.9–21.4)	<0.0001
S_2/L	60 (16.1)	22 (16.4)	2.3 (1.2–4.3)	0.0078
S_{3P}/L	92 (24.7)	38 (28.4)	2.6 (1.5–4.4)	0.0004
L/L	201 (53.9)	32 (23.9)	1.0 (referent)	

Conclusions: This is the largest described cohort of children with RA. We confirm the association between SE alleles and susceptibility to RA in children. The excess risk conferred by individuals who carry the combination of S2/S3P risk alleles suggests that children with DRβ1 chains containing KRAA/QRAA might be especially prone to RA.

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HLA Associations in Oligo- and Polyarticular RF (-) Juvenile Idiopathic Arthritis-Associated Uveitis. Sheila Angeles-Han[5], Andrew S. Zeft[8], John F. Bohnsack[8], Bronte Clifford[7], Lori Ponder[1], Jennifer Prozonic[3], Milton Brown[3], Christine W. Kennedy[4], Larry B. Vogler[6] and Sampath Prahalad[2]. [1]Children's Healthcare of Atlanta, [2]Emory Children's Center, Atlanta, GA, [3]Emory Children's Center, [4]Emory Children's Center, Decatur, GA, [5]Emory University, Atlanta, GA, [6]Emory University School of Medicine, Atlanta, GA, [7]Nationwide Children's Hospital Research Institute, [8]University of Utah, Salt Lake City, UT

Purpose: Juvenile idiopathic arthritis-associated uveitis (JIA-U) can lead to complications such as cataracts, glaucoma, and synechiae, and increase risk for vision loss and blindness. Retrospective studies show an association between polymorphisms of HLA class II genes and JIA-U, especially in females with the oligoarticular subtype and early disease. While HLA-DR11 and HLA-DR13 alleles increase susceptibility to disease, HLA-DR1 is protective. Most studies have not included children who have poly RF (-) JIA-U. We sought to validate previously reported HLA associations and investigate the association between HLA-DRB1 in oligo- and polyarticular RF (-) JIA-U. Most prior studies also have not examined the effect of carriage of two risk alleles, which we sought to do.

Methods: Thirty children of Northern European ancestry with oligo- or polyarticular JIA-U were followed in pediatric rheumatology and ophthalmology clinics. Chart reviews confirmed the diagnoses of JIA and uveitis. Controls were 100 healthy adults screened for several common autoimmune disorders. Cases and controls were matched for ethnicity. High resolution sequence based typing was performed to determine HLA-DRB1 genotypes. Statistical analysis was performed using chi-square or fisher's exact test for odds ratio (OR).

Results: Of 30 subjects, 43.3% were females, 76.7% were ANA positive, 83.3% had oligo JIA and 16.7% had RF (-) poly JIA. Mean age of JIA

diagnosis was 3.0 years (SD 2.4). Of 10 subjects, mean age of JIA-U diagnosis was 3.4 years (SD 2.5) with a mean of 20 months (SD 28.5) of arthritis before uveitis onset. In our cohort, we found the following DR13 alleles – *0101 (n=9), *1302 (n=2), and *1303 (n=2), and the following DR11 alleles- *1101 (n=7), and *1103 (n=3). There was evidence for an association between JIA-U and DRB1*13 (OR 2.18, p=0.08), and DRB1*11 (OR 6.71, p=0.0003). There was also an association between carriage of either DRB1*11 or DRB1*13 (OR 3.25, P=0.005). There was a very strong association between JIA-U and carrying two copies of risk alleles (DRB1*11 and 13) (OR 30, p=0.0000007). There was a decreased frequency of DRB1*01 among cases with JIA-U compared to controls, although this was not statistically significant, reflecting the modest sample size.

Conclusions: We have validated the reported associations between DRB1*13 and DRB1*11 in JIA-U. We have also demonstrated the strong association between JIA-U and the presence of two risk alleles. These HLA risk genotypes should be further investigated in a large prospective group of children with JIA-U to determine the risk for uveitis severity and associated complications.

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Hyaluronidase Mutation (HYAL1) Presenting as JIA, a Description of an Extended Family Provides New Information and Characterizes This Genetic Disorder That Causes Widespread Synovitis. Lisa F. Imundo[2] and Wendy Chung[1]. [1]Columbia University, NY, NY, [2]Columbia University, New York, NY

Background: More than 10 years ago Natowitcz described a single case of Mucopolysaccharidoses IX [1], characterized by a lack of hyaluronidase activity coupled with continued biosynthesis of the substrate. The affected case was 14 years old with painful synovitis and hip erosions that eventually required hip replacements. Only this index case has been characterized

Report: We report a consanguineous Saudi Arabian Family with familial arthropathy in three siblings. Onset ranged from 4yrs-18 yrs. The arthropathy is clinically apparent in large joints primarily hips and knees. Radiographic studies- indicate fulminant inflammatory synovitis with septated cysts and early marginal erosive disease. Synovial biopsy indicated synovial hypertrophy with a prominent histiocytic infiltrate, paillary hyperplasia and focal sclerosis. Notable there is no inflammatory infiltrate. The mononuclear cells contained vacuolated granular cytoplasm. The cytoplasm contained glcosaminoglycans. Genetic testing indicated three of the five siblings were homzygous for MPS IX. The mutation in HYAL 1 (c.44delT) causes premature termination and is predictive of no functional HYAL1 production. The parents and two siblings are heterozygotes. They do not have symptoms of synovitis.

Results: On further radiologic survey of symptomatic and non symptomatic joints by MRI and joint ultrasound indicated that homozygous children have demonstrated abnormalities and synovitis in every synovial joints, including small joints of the hands and feet. In addition the heterozygote asymptomatic siblings may have a mild phenotype. The only homozygous female has an earlier onset of symptoms and more severe radiographic changes similiar to the described index case.

Summary MPS IX is characterized by clinical symptoms isolated to synovial joints and likely represents an important etiology of familial arthritis.We add important information to further characterize this disease and to define features that can differentiate MPS IX from JIA. Treatments for JIA will not be effective for this genetic disorder characterized by a lack of hyaluronidase, however directed treatments may include making use of commercially available hyaluronidase enzyme.

1. Natowitcz MR, et. al. NEJM 1996, 335: 1029–33.

Disclosure: L. F. Imundo: None; **W. Chung:** None.

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Leukocyte Expression of Transcription Factor HNF4a, a Regulator of Gene Expression in Polyarticular Juvenile Idiopathic Arthritis. Kaiyu Jiang[1], Yanmin Chen[1], Mark Barton Frank[2] and James N. Jarvis[1]. [1]Dept of Pediatrics, U of OK College of Medicine, [2]Oklahoma Medical Research Foundation

Objective: Our previous work has shown that there are distinct gene expression profiles in peripheral blood mononuclear cells (PBMC) and in granulocytes derived from patients with polyarticular juvenile idiopathic arthritis (JIA) compared with healthy control children of the same age and sex. Network analysis of these differentially expressed genes demonstrates that many of those genes are under the control of a single transcription factor, hepatocyte nuclear factor alpha (HNF4A). Furthermore, HNF4a appears to determine both response to therapy and achievement of remission. However, HNF4a has not previously been known to be expressed in leukocytes. To understand the role of HNF4a in JIA, we examined its expression in PBMC subsets and granulocytes.

Method: PBMC, CD4+ T cells, CD8+ T cells, CD14+ monocytes, CD19+ B cells and granulocytes were isolated using conventional methods. RNA was separately extracted and reverse transcription- polymerase chain reaction was used to detect the expression of HNF4a mRNA. Immunofluorescence staining and confocal microscopy were used to observe the expression of HNF4a protein. The DECODE database (SABiosciences Company) was used to search HNF4A binding sites within the differentially expressed genes.

Results: Polymerase chain reaction (PCR) analyses revealed that expression of HNF4a mRNA is leukocyte subset-dependent. PBMC, T cells and granulocytes, but not not CD14+ monocytes or CD19+ B cells, express HNF4a mRNA. Immunofluorescence staining for HNF4a was used to detect HNF4a in leukocyte subsets. HNF4a is expressed in granulocytes in a distinct pattern demonstrating two cell subsets. The first population observed on on confocal microscopy consisted of CD66b bright/HNF4a dim cells, and the second consisted of HNF4a bright/CD66b dim cells. In T cells, the HNF4a signal was significantly brighter in CD8+ cells than in CD4+ cells. All of these findings were observed in healthy children, healthy adults, and children with JIA. Thus, expression of HNF4a is not in itself pathological, and HNF4a may an important and previously unrecognized regulatory protein. Bioinformatics analysis of the promotor regions of ZNF281, IER5 and OAZ2, genes shown in Ingenuity analysis of PBMC array data from children with JIA to be under HNF4a transcriptional control, demonstrated sequence motifs typically associated with HNF4a binding.

Conclusion: HNF4A is an important systems hub that emerges from microarray analysis of JIA leukocytes. This transcription factor, which has not previously been demonstrated in leukocytes, may play a role in both disease pathogenesis and response to therapy. Expression of HNF4a was found in CD4+ and CD8+ T cells and neutrophils and was seen in both healthy children and children with JIA. Given the potential importance of HNF4a is regulating response to therapy in JIA, we believe that these studies may shed light on potential new targets of therapy in this challenging disease.

Disclosure: K. Jiang: None; **Y. Chen:** None; **M. B. Frank:** None; **J. N. Jarvis:** None.

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Low Serum Levels of NT-proCNP in Children with Poly-Articular Onset Juvenile Rheumatoid Arthritis. Fozia Khan[1], Ann Pokelsek[2], Lori Galla[2], Mary Toth[2] and Hulya Bukulmez[3]. [1]Akron Children's Hospital, NEOUCOM, Akron, OH and MetroHealth Medical Center, CWRU, Cleveland, OH, [2]Akron Children's Hospital, NEOUCOM, OH, [3]MetroHealth Medical Center, CWRU, Cleveland, OH

Children with juvenile rheumatoid arthritis (JRA) develop longitudinal growth delay. Increased levels of proinflammatory cytokines (IL-6, TNF-α) in serum and in synovial fluid have been blamed for suppressing the local and/or systemic growth factors that regulate endochondral bone growth. Aside from growth hormone signaling pathway, it is unknown whether other growth factors that regulate the endochondral bone growth are affected in JRA.

C-type natriuretic peptide (CNP) has been recently described as an essential paracrine factor for normal endochondral bone growth. Serum level of N-terminal pro-peptide of CNP (NT-proCNP) has been suggested to be a marker for endochondral bone growth. In this study, we aimed to investigate whether CNP signaling is affected during active juvenile inflammatory arthritis in children by measuring the serum NT-proCNP levels during active disease and investigated whether serum NT-proCNP levels correlated with the serum IL-6 and TNF-alpha levels.

We collected clinical and laboratory data and serum from children diagnosed with juvenile rheumatoid arthritis (JRA) according to ACR criteria (n=18, 9 pauci-articular, 8 poly-articular, and 1 systemic onset JRA). Concurrent clinical and laboratory data were collected from patients during their enrollment in the study as a part of their routine care. Pro-inflammatory cytokine levels and the NT-proCNP levels were measured using ELISA.

Z-scores of NT-proCNP levels for each patient were calculated using NT-proCNP levels of age matched healthy children. Statistical analysis software was used (SAS 9.2) to calculate the correlations between the z-scores, cytokines and laboratory data.

All patients with JRA had low NT-proCNP z-scores compared to age matched controls. Poly- and systemic JRA patient's z-scores were significantly lower. IL-6 levels showed negative correlation with the z-scores in children with poly-JRA ($r=-0.67$, $p=0.06$). When stratified for gender, correlation of z-scores with IL-6 level became significant ($r=-0.99$, $p=0.034$). Sedimentation levels correlated with TNF-α levels in poly-JRA patients ($r=0.91$, $p=0.003$), but TNF-α levels correlation with NT-proCNP z-scores did not reach statistical significance. Seven of eight poly-JRA patients were under treatment with Methotrexate (20mg/m^2) and five were also treated with oral prednisone (>0.5mg/kg/d). The mean z-scores of NT-proCNP in patients who used prednisone ($n=5$) were not different than those who did not use prednisone ($n=3$).

Serum NT-proCNP levels of children with JRA are lower than age matched controls. In poly-articular onset JRA patients, the serum levels of IL-6 show negative correlation with z-scores of NT-proCNP. In addition to ongoing systemic inflammation, patients with poly-JRA were also being treated with medications such as methotrexate and prednisone which might lower the NT-proCNP levels. Further studies with larger JRA patient population are necessary to further delineate the disruption of CNP signaling during JRA. Serum NT-proCNP levels could be a biomarker for endochondral bone growth in children with JRA.

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Novel Founder Mutation in *IL1RN* Accounts for Deficiency of the IL-1 Receptor (DIRA) in Brazil. Adriana Almeida Jesus[4], Clovis Artur Almeida Silva[4], Peter W. Kim[2], Tuyet H. Pham[2], Débora Romeo Bertola[4], Magda Carneiro-Sampaio[4], Barbara Yang[2], Deborah Stone[2], Dawn Chapelle[2], Nicole Plass[2], Massimo Gadina[2], John Sims[1], Hatem El-Shanti[3] and Raphaela Goldbach-Mansky[2]. [1]Amgen Inc, Thousand Oaks, CA, [2]NIAMS/NIH, Bethesda, MD, [3]Shafallah Medical Genetics Center, Doha, Qatar, [4]Universidade de São Paulo, Sao Paulo, Brazil

Objective: To describe the clinical, immunological and genetic phenotype of 2 unrelated patients from Brazil presenting with pustular skin disease, osteolytic bone lesions and systemic inflammation and incoplete responses to multiple DMARDs.

Patients and Evaluation: Two Brazilian patients with perinatal onset skin pustulosis and osteolytic bone lesions and systemic inflammation, consistent with the clinical diagnosis of DIRA were evaluated and genetic analysis of the *IL1RN* gene locus was performed. Multi-disciplinary clinical evaluation including a total body MRI, and immunological and laboratory characterization of the structure and function of the mutated gene and encoded protein were performed to characterize the inflammatory phenotype of these patients.

Results: Both patients had classical pustular skin lesions with a neutrophilic infiltrate in the dermis and epidermis. One patient presented with clinically concerning spine lesions, she has non-fusion of the os odontoid with the body of the dens (C2) and an incomplete posterior arch of C1 leading to an over 7 mm atlantoaxial subluxation between head flexion and extension. Post-inflammatory fusion of several lower cervical and thoracic spine lesions led to the formation of a gibbus. Genetic analysis of *IL1RN* (isoform 1) showed a homozygous inframe 15 base pair deletion (c.213–228delAGATGTGGTACCCAT; p.72–77del DVVPI) in both girls leading to 5 amino acid deletion. Expression levels of messenger RNA were reduced on RT PCR and the mutated protein was expressed at low levels compared to healthy controls and heterozygous parents. Modeling of the mutated protein predicted a severe defect in the secondary structre and functional analysis confirmed no binding of the protein to the IL-1 receptor. Both patients had an immediate response to treatment with the rcombinant Il-1 receptor antagonist, anakinra, with complete resolution of skin lesions and normalization of systemic and organ specific inflammation. The patient's parents were carriers for the mutation but clinically asymptomatic.

Conclusions: A novel founder mutation in *IL1RN* accounts for 2 cases of DIRA from 2 unrelated Brazilian families. The clinical signs and symptoms in these patients are similar to those previously reported. In contrast to the previously reported cases of DIRA, in whom the mutated protein is not secreted, patients with the Brazilian mutation express low levels of the mutated protein. The severity of the 5 AA deletion was predicted based on modeling data and the response to the recombinat IL-1 receptor antagonist, anakinra, was immediate with complete resolution of inflammatory disease manifestations.

Determination of the frequency of the mutation in Brazil and establishing neonatal screening in areas with a high prevalence of the disease may be indicated.

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Novel Mutations of Camptodactyly Arthropathy Coxa Vara Pericarditis (CACP) Syndrome: A Study on Ten Cases. Sara Ciullini Mannurita[7], Marina Vignoli[7], Lucia Bianchi[7], Chiara Azzari[7], Maurizio de Martino[7], Angelo Ravelli[4], Anuela Kondi[6], Valeria Gerloni[5], Rebecca ten Kate[2], Luciana Breda[3], Eleonora Gambineri[7] and Fernanda Falcini[1]. [1]Department of BioMedicine, Section of Rheumatology, Transition Clinic, University of Florence, [2]Department of Pediatrics, Leiden University Medical Centre, The Netherlands, [3]Department of Pediatrics, University of Chieti, Chieti, Italy, [4]Istituto di Ricovero e Cura a Carattere Scientifico G. Gaslini and Università degli Studi di Genoa, [5]Istituto G. Pini, Milan, Italy, [6]Pediatric Department, University Hospital Centre, Tirana, Albania, [7]University of Florence, Department of Sciences for Woman and Child's Health

Background: The Camptodactyly Arthropathy Coxa vara Pericarditis (CACP) syndrome is an autosomal recessive disease characterised by congenital camptodactyly, no inflammatory arthropathy, joint failure, synovial hyperplasia, coxa vara, and thickening of the pericardium. The causative gene for CACP is *PRG4 that* is located on chromosome band 1q25–31 and consists of 12 exons. It encodes for a mucin-like glycoprotein named "proteoglycan-4" (PRG-4) which acts as the major surface lubricant for joints and tendons.

Objectives: 1.To investigate possible genomic alteration in patients with clinical manifestations of CACP. 2.To perform a comprehensive analysis of the *PRG-4* gene.

Patients and Methods: Six unrelated patients and two pairs of siblings (2 sisters, 1 sister,1 brother) with a phenotype resembling CACP syndrome were referred to us for mutational analysis of *PRG-4* gene. The age of onset was mainly at birth (median age at diagnosis 5.5 years). Genomic DNA was extracted by peripheral blood and polymerase chain reaction was performed to amplify *PRG-4* exon sequences including intro-exon boundaries using specific primers. The coding regions were sequenced, with the exception of 800bp, within exon 6 due to highly repetitive motifs.

Results: Six novel homozygous mutations within *CACP* gene were identified in seven patients. The 2 sisters harboured the same nonsense alteration (Y1216X) that cause a frame-shift that creates a premature stop signal leading to the production of a truncated protein. Four mutations were small deletions of 1bp, 2bp and 5bp, three of which located within exon 6. These deletions cause frame-shift mutations and create a premature stop codon. In the remaining patients, we detected one substitution affecting the donor splice site (IVS8+3A>G); the bioinformatics analysis of this alteration predicts a decrease of the strength of the new splice site sequence that could be responsible for an aberrant splicing of the premature transcript. The analysis of CACP protein would be necessary to test the predicted effect of the mutations.

Conclusions: CACP syndrome is a rare disorder often misdiagnosed with other paediatric connective tissue diseases. This is the first study analysing the largest *PRG-4* coding region, and it allowed identifying a new set of molecular aberrations associated with the occurrence of CACP syndrome.

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Plasma Osteopontin as a Marker for Damage in Pediatric Systemic Lupus Erythematosus. Ornella J. Rullo[2], Jennifer M. P. Woo[2], Alice D. C. Hoftman[1], Timothy B. Niewold[5], Angela Presson[4], Deborah K. McCurdy[2] and Betty P. Tsao[3]. [1]CHOC-Children's, Orange, CA, [2]Mattel Children's UCLA, Los Angeles, CA, [3]UCLA School of Medicine, Los Angeles, CA, [4]UCLA School of Public Health, [5]University of Chicago, Chicago, IL

Introduction: Osteopontin (OPN; aka SPP1 and Eta-1) is a secreted phosphoprotein that functions in macrophage and T cell adhesion, migration,

and signaling, and plays an important role in tissue and wound repair. OPN has been implicated in IFN-α production, and participates in monocyte/macrophage recruitment to kidneys in SLE, where it may functionally contribute to dysregulated tissue repair and fibrosis associated with chronic inflammation. We investigated the relationship of OPN protein levels and genetic variants with disease manifestations in pediatric SLE (pSLE), a subset with an increased proportion of lupus nephritis compared with SLE of adult onset.

Methods: DNA and plasma were collected from 72 (52 female; 20 male) pSLE patients (age of SLE onset < 18 years), and 51 healthy controls (32 female; 19 male) consisting of 35 unaffected siblings and 16 unrelated young people. All subjects were ≤ 22 years at time of blood draw. 49 pSLE patients had adequate clinical data to complete SLICC/ACR damage index (SDI) scores; disease activity was scored on all patients using the SELENA-SLEDAI index. Circulating plasma OPN (cOPN) was measured by ELISA. SNP genotyping was performed by Taqman assays. Serum IFN activity was measured by WISH-cell assay in 49 pSLE samples. Immunohistochemistry by standard fluorescence techniques was performed on anonymous WHO class IV lupus nephritis tissue obtained from our tissue core lab. Statistical analysis was performed using Student's t test, Pearson's correlation, Fisher's exact test, and multivariate linear and logistical regression modeling.

Results: pSLE patients with active disease (SLEDAI > 4) had high IFN activity ($p = 0.0009$), as in previous research, but disease activity did not correlate with cOPN in this cross-sectional analysis. Overall, cOPN was significantly higher in pSLE versus healthy unrelated controls ($p < 0.001$) with increasing cOPN correlating with SDI ($R = 0.5$; $p = 0.0003$). High IFN activity was more likely in pSLE patients with cOPN levels in the top quartile compared with those in the lowest ($p = 0.03$); similarly, pSLE patients with an SDI > 0 were more likely to have high IFN activity than those with SDI = 0 ($p = 0.02$). Considering disease status, 5 *OPN* variants previously associated with SLE, and gender as covariates in a multivariate regression analysis, the 3' untranslated region (UTR) single nucleotide polymorphisms (SNPs) of *OPN* (rs1126772 and rs9138) were associated with increased cOPN ($p = 0.004$ and 0.02, respectively). Interestingly, both 3' UTR SNPs as well as a promoter variant, rs2857094, were associated with SDI > 0 (ORs of 1.5–2.2; $p < 0.01$ for each SNP); we also observed rs2857094 allelic association with increased percentage of glomerulonephritis in pSLE (87% vs. 60%; $p < 0.0001$). In 3/3 renal biopsies from patients with diffuse proliferative glomerulonephritis, we noted the co-localization of OPN with macrophage marker CD68.

Conclusion: Genetic variants regulate OPN levels, which may contribute to the progression of tissue injury in pSLE, possibly by tissue-infiltrating monocytes/macrophages. The potential of OPN as a predictor of global and/or renal damage in pSLE requires further study in a longitudinal cohort.

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Predominance of Complement Components C1q and C4 Bound to Circulating Immune Complexes (CICs) in Juvenile Idiopathic Arthritis (JIA): Support for Classical Pathway Activation. Brooke E. Gilliam[1], Melinda R. Reed[2], Anil K. Chauhan[1], Amanda Dehlendorf[2] and Terry L. Moore[2]. [1]Saint Louis University, St. Louis, MO, [2]Saint Louis University, St Louis, MO

Purpose: CICs from JIA sera show increased complement activation; however, the scope of involvement from the classical versus alternative pathway remains undefined. To delineate the role of these pathways, we measured activated complement products bound to CICs in sera from JIA patients.

Methods: Sera from 100 JIA patients (87 female, 13 male) were collected, including 68 polyarthritis (41 rheumatoid factor (RF)-negative and 27 RF-positive) and 32 oligoarthritis patients. The mean age was 11.0 years and mean disease duration was 4.1 years. Sera from 17 healthy individuals were also analyzed. C1q, C3, C3d, C4, and membrane attack complex (MAC) bound to CICs were measured by enzyme-linked immunosorbent assays (ELISA). Cut-off values were established as the mean +2 standard deviations of the healthy control results. IgA and IgM RF and IgG anti-cyclic citrullinated peptide (anti-CCP) antibodies were measured by ELISA. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and disease activity were obtained from patient records.

Results: Forty-eight patients were positive for C1q CICs, 45 for C4 CICs, 36 for C3 CICs, 29 for MAC CICs, and 25 for C3d CICs. C1q, C3, C4, MAC CICs were significantly elevated in JIA patients compared to healthy controls ($p<0.05$). MAC CICs demonstrated significant correlation with C1q CIC ($r=0.65$), C4 CICs ($r=0.61$), C3d CICs ($r=0.33$), and C3 CICs ($r=0.27$) ($p<0.05$). C1q CICs also correlated significantly with C4 CICs ($r=0.72$), C3d CICs ($r=0.27$), and C3 CICs ($r=0.22$) ($p<0.05$). C3 and C3d CICs demonstrated significant correlation with each other ($r=0.32$, $p=0.002$). IgA RF correlated significantly with C1q CICs ($r=0.20$, $p=0.049$). IgM RF demonstrated a negative correlation with C3 ($r=-0.24$, $p=0.02$), but correlated positively with C4 CICs ($r=0.22$, $p=0.027$). Of the JIA patients positive for MAC CICs (n=29), 21 (72%) were positive for both C1q CICs and C4 CICs and 13 (45%) were positive for C3. In both polyarticular and oligoarticular JIA, the classical complement pathway (C1q: 46–53% and C4: 44–47%) was more prevalent than the alternative complement pathway (C3: 35–38%).

Conclusions: The assay used in this study is able to capture CICs bound to complement, which reflects physiologically active complement. The classical complement pathway can be triggered by IgM and IgG-containing CICs in systemic circulation. Our results show that IgM RF correlated significantly with C4 CICs and MAC correlated significantly with C1q and C4 CICs, suggesting a dominant contribution of classical complement activation. Elevated IgA RF and IgM RF have both been associated with destructive disease in JIA. C1q and C4 CICs both correlated significantly with these RF isotypes, indicating a link between classical pathway activation and aggressive disease.

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Rheumatoid Arthritis Susceptibility Loci; *PTPRC*, *PTPN2*, *IKZF3*, *c5orf30*, *BLK* and *CD247* Are Also Associated with Juvenile Idiopathic Arthritis. Anne Hinks[1], Steve Eyre[2], Paul Martin[2], Edward Flynn[2], Jon Packham[3], Anne Barton[2], Jane Worthington[2] and Wendy Thomson[2]. [1]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom, [2]Arthritis Research UK Epidemiology Unit, University of Manchester, [3]Haywood Hospital, University of North Staffordshire

Background: Rheumatoid arthritis (RA) shares similar clinical and pathological features with juvenile idiopathic arthritis (JIA); indeed the strategy of investigating whether RA susceptibility loci also confer susceptibility to JIA has already proved highly successful in identifying novel JIA loci, such as *PTPN22*, *IL2RA* and *TRAF1/C5*. There has been a plethora of newly validated RA loci reported in the last year. Therefore the aim of this study was to test SNPs robustly associated with RA in a large cohort of JIA cases and controls to investigate the overlap between these diseases and identify novel JIA loci.

Methods: 29 SNPs that showed validated association with RA and had not been investigated previously in JIA were genotyped in JIA cases (n=1337) and healthy controls (n=2781) using Sequenom MassArray technology. Genotype and allele frequencies were compared between cases with JIA and controls using the Cochrane-Armitage trend test implemented in PLINK and allelic odds ratios (ORs) and their 95% confidence intervals (CIs) calculated.

Results: Strong evidence for association with JIA was seen for eight SNPs. These include a SNP, rs10919563, in *PTPRC* (ptrend $=2.5 \times 10^{-6}$ OR 0.68 95% CI 0.58–0.8) rs7234029, in *PTPN2* (ptrend =0.0003 OR 1.26 95% CI 1.11–1.43), rs2872507 in *IKZF3* (ptrend =0.0004 OR 1.21 95% CI 1.09–1.34), rs26232 in *c5orf30* (ptrend =0.002 OR 0.84 95% CI 0.75–0.94), rs2736340, in *BLK* (ptrend =0.003 OR 1.19 95% CI 1.06–1.34) and rs1773560 in *CD247* (ptrend =0.005 OR 0.87 95% CI 0.79–0.96). There was additional evidence for association of two novel SNPs in genes previously associated with JIA, rs13119723, in the *IL2/IL21* region (ptrend $=7.5 \times 10^{-6}$ OR 0.71 95% CI 0.61–0.83) and rs706778 in the *IL2RA* gene (ptrend =0.0002 OR 1.22 95% CI 1.1–1.35).

Conclusions: The association of *PTPN2* with JIA in the current study validates the findings of a previous US study, confirming it as a JIA locus. The other loci identified are novel and will require validation in independent JIA datasets. To date we have investigated 44 RA loci in JIA and of those 27 are associated with both diseases. The overlap is remarkable for two diseases which, although sharing some phenotypic features, are clinically distinct entities.

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Role of IL-1b in the Development of Human TH17 Cells: Lesson from Patients Carrying NLPR3 Gene Mutations. Denise Lasigliè, Elisabetta Traggiai, Federica Penco, Silvia Federici, Andrea Accogli, Antonella Buoncompagni, Alberto Martini and Marco Gattorno. G. Gaslini Institute, Genoa, Italy

Purpose: Interleukin 17 (IL-17)-producing CD4+ helper T cells (T_h-17) represents a lineage of effectors CD4 T cells abundant at mucosal interfaces, where they contain infection with pathogenic bacteria and fungi. Beyond this function TH-17 cells have been linked to the pathogenesis of several inflammatory and autoimmune diseases. At present, understanding of Th-17 differentiation is limited to the mouse system and in humans remains still a puzzled issue. Recently it has been proposed IL-1b as a pivotal cytokine in driving Th-17 differentiation. *Cryopyrin-associated periodic syndromes* (CAPS) are a group of inflammatory diseases associated to mutations of *NLRP3* gene encoding the inflammasome component *cryopyrin*. These mutations determine an exaggerated IL-1β secretion by monocytes upon Toll like receptors (TLRs) stimulation. We have investigated whether the altered IL-1β secretion, secondary to *NLPR3* mutations, could affect the IL-23/IL-17 axis in CAPS patients.

Methods: IL-17 serum level has been evaluated by ELISA assay. Expression of CCR6 and CD161, two TH-17 specific markers, has been analyzed on CD4+ memory T cells by flow cytometry Frequency of T_H-17+ cells has been quantified upon stimulation with staphylococcus entherotoxin B (SEB). Production of IL-1β and IL-23 by monocyte derived dendritic cells (MoDCs), in response to TLRs ligands, has been quantified by ELISA. CAPS patients have been analysed before and after anti-IL1β treatment.

Results: Untreated CAPS patients display significant increased level of serum IL-17 as well as of Th-17+ T cells respect to age matched controls. Both IL-7 serum levels as well as Th-17 frequency decrease after IL-1β treatment. Also production of IL-1b and IL-23 by MoDCs is increased in CAPS patients, and after anti IL-1β treatment production of both cytokines is significantly reduced.

Conclusions: These findings further support a central role of IL-1b in the differentiation of T_H 17 in human inflammatory conditions.

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Subtype Specific Genetic Associations for Juvenile Idiopathic Arthritis (JIA): *ERAP1* with the Enthesitis Related Arthritis Subtype and *IL23R* with Juvenile Psoriatic Arthritis. Anne Hinks[1], Paul Martin[2], Edward Flynn[2], Steve Eyre[2], Jon Packham[3], Anne Barton[2], Jane Worthington[2] and Wendy Thomson[2]. [1]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom, [2]Arthritis Research UK Epidemiology Unit, University of Manchester, [3]Haywood Hospital, University Hospital of North Staffordshire

Background: There is now strong evidence supporting the hypothesis of common autoimmune susceptibility loci. There is also evidence to support clustering of loci in diseases that share similar clinical phenotypes e.g. Ankylosing spondylitis (AS), psoriasis (Ps), psoriatic arthritis (PsA) and they appear to have some overlapping susceptibility loci such as *IL23R* and *ERAP1*.

Juvenile idiopathic arthritis (JIA) is an umbrella term for all chronic childhood arthropathies and can be classified into 7 subtypes on the basis of features present in the first 6 months of disease. It includes the enthesitis related arthritis (ERA) subtype which displays symptoms similar to AS and juvenile onset psoriatic arthritis which has similarities to psoriatic arthritis and psoriasis. We therefore hypothesized that the two well-established susceptibility loci *IL23R* and *ERAP1* could also confer susceptibility to these JIA subtypes, to this end the most associated SNP within each of these genes have been selected for genotyping across all JIA and also analysed stratified for each subtype.

Methods: SNPs in *IL23R* (rs1129026) and *ERAP1* (rs30187) were genotyped in JIA cases (n=1054) and healthy controls (n=5200). The numbers genotyped per ILAR subgroup were: Systemic onset (n=164), persistent oligoarthritis (n=297), extended oligoarthritis (n=147), Rheumatoid factor (RF) negative polyarticular JIA (n=215), RF positive polyarticular JIA (n=68), enthesitis related JIA (n=63), psoriatic JIA (n=76) and unclassified (n=24).Genotype and allele frequencies were compared between all JIA cases and controls using the Cochrane-Armitage trend test implemented in PLINK and allelic odds ratios (ORs) and their 95% confidence intervals (CIs) calculated. Stratified analysis by subtype was performed.

Results: Neither the SNP in the *IL23R* gene, rs1129026, nor the SNP in the *ERAP1* gene, rs30187, were significantly associated ($p<0.05$) with the total JIA dataset. Stratification by subtype found that the *IL23R* SNP showed significant association in the psoriatic arthritis subtype (ptrend=0.04 OR 0.4 95% CI 0.16–0.98) and a trend towards association in the enthesitis related subtype (ptrend=0.15 OR 0.52 95% CI 0.21–1.28). The enthesitis related arthritis (ERA) subtype showed strong association with *ERAP1* SNP (ptrend=0.004 OR 1.69 95% CI 1.18–2.44). For both SNPs the association is in the same direction as in the original study.

Conclusions: We present evidence for subtype specific association of the *IL23R* gene with juvenile psoriatic arthritis and *ERAP1* gene with ERA. The findings will require validation in independent JIA datasets. These results suggest distinct pathogenic pathways in these subtypes.

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The Role of Platelets and CD40L in the Pathogenesis of Kawasaki Disease. Parnian Arjmand[2] and Rae S. M. Yeung[1]. [1]Hospital for Sick Children, Toronto, ON, Canada, [2]University of Toronto, The Hospital for Sick Children, Toronto, ON, Canada

Background: Kawasaki Disease (KD) is a disease of childhood characterized by systemic inflammation leading to coronary artery damage. Although its etiology remains unknown, superantigens are among the triggers of disease. Lactobacillus Casei Cell Wall Extract (LCWE) induces a disease in mice which mimics KD closely in time-course, histological changes and susceptibility in the young. LCWE contains both a superantigen and a TLR-2 ligand. KD is characterized by marked elevation in platelet numbers. Recent studies have found CD40L expression on platelets and CD4+ T cells to be associated with coronary artery aneurysms in children with KD. CD40L is a member of the TNF family of proteins which is expressed on T-cells. Interestingly, it is also stored in platelet granules and binds to an integrin receptor, gpIIIaIIb, on platelets. Platelets also store and release Matrix Metalleoprotease 9 (MMP-9) upon activation – an enzyme essential for coronary artery break-down and anuerysm formation in KD. Here, we aim to elucidate the role of platelets in the pathogenesis of KD: specifically, the effect of LCWE stimulation on platelet activation, CD40L and MMP-9 expression and release, and its role in coronary artery disease.

Methods: In vivo and in vitro platelet activation (α-granular release, microparticle formation, aggregation, integrin receptor activation) is assayed using flow-cytometry. In vivo, blood is obtained from C57/BL6 mice injected with LCWE or PBS; in vitro, platelets are stimulated with LCWE and assayed. Platelet MMP-9 release is studied by determining protein and enzymatic activity using Western blots and zymography respectively. To differentiate between superantigenic versus TLR-2 agonistic activity of LCWE in stimulating platelets, blood is also drawn from TLR-2 knock-out mice or treated with a TLR-2 blocking mAb prior to analysis.

Results: Stimulation of platelets with collagen and ADP agonists achieves maximal platelet CD40L and P-selectin upregulation in vitro.TLR2 ligand PAM3CSK4, LCWE and SEB are also able to induce CD40L and P-selectin upregulation, gpIIIaIIb activation, leukocyte aggregation and microparticle formation. Upregulation of these platelet activation markers were also observed in vivo after stimulation with the classic superantigen, SEB. Interestingly, LCWE induced platelet activation is unaffected in the absence of TLR-2 signaling, evidenced in assays using TLR2 deficient mice and also with addition of TLR-2 blocking antibody pointing superantigenic and not TLR2 activity as the trigger of platelet activation.

Conclusions: Our results suggest that superantigenic stimulation with LCWE activates mouse platelets α-granular release, CD40L upregulation and integrin receptor gpIIIaIIb. Moreover, we show that TLR-2 signaling does not contribute to platelet activation. Establishing a role for platelets and CD40L in the pathogenesis of KD may have important implications in design of new therapeutic agents in KD.

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Urinary Biomarkers To Distinguish Class IV vs Class V Lupus Nephritis. Hermine Brunner[1], Michael Bennett[2], Lindsey Romick-Rosendale[5], Michiko Suzuki[3], Shannen L. Nelson[2], Joshua Pendl[3], Adnan Kiani[4], Lena Das[3], Michelle Petri[4], Kenneth Greis[6], Pavel Shiyanov[7], Michael Kennedy[5] and Prasad Devarajan[3]. [1]Cincinnati Child Hosp Med Ctr, Cincinnati, OH, [2]Cincinnati Children's Med Ctr, Cincinnati, OH, [3]Cincinnati Children's Med Ctr, [4]John Hopkins Med Ctr, [5]Miami University, Oxford, [6]University of Cincinnati, [7]WPAFB, Dayton

Background: Up to 80% of children with systemic lupus erythematosus have lupus nephritis (LN). The ISN/RPS Morphologic Classification of LN reports on histological features that differentiate between various forms of LN, such as Diffuse Proliferative Class IV and Membranous Class V lesions. Kidney biopsies are the choice for diagnosis of LN, but are impractical to accurately assess the course of LN in clinical practice.

Objective: Discover non-invasive urinary biomarkers that can discriminate LN subtypes using proteomics, peptidomics and metabonomics.

Methods: We used 2-dimensional gel electrophoresis (2-DGE), NMR-based metabonomics, surface-enhanced laser desorption/ionization time of flight MS (SELDI), and iTRAQ liquid chromatography tandem mass spectrometry (LC MS/MS2) to investigate novel biomarkers that could distinguish Class IV vs. Class V LN. Urine samples from children with Class IV LN (n=6) and (pure) Class V LN (n=7) collected within 60 days of a kidney biopsy and those of controls with focal segmental glomerulosclerosis (n=4) were tested. Samples were normalized for total protein (2-DGE and LC-MS/MS2) or urine creatinine (NMR and SELDI).

Results: Using 2-DGE and MALDI-TOF-MS/MS, we found serum albumin fragments (25kDa) and alpha1-B glycoprotein (A1BG, 60kDa) significantly over-expressed in class IV vs. class V LN. Using SELDI, we identified Alpha-1 Antitrypsin (A1AT). This protein was significantly ($p < 0.01$; AUC 0.90) over-expressed in Class V vs Class IV LN and FSGS controls. Principal component analysis of NMR metabonomics spectra suggests decreased levels of citrate and increased levels of taurine in Class V when compared to Class IV patients, while iTRAQ -LC-MS/MS2 uncovered the most differences between the groups. Among proteins upregulated in Class V LN were apolipoprotein D, lipocalin-like prostaglandin D synthetase, inter-alpha-trypsin inhibitor heavy chain 4, Caspase 10, uromodulin and CD14. Those most upregulated in Class IV LN were vitamin D binding protein, ceruloplasmin, hemopexin, A1BG and orosomucoid. A1AT has been linked to SLE flares and hemopexin is associated with glomerular disease.

Conclusions: The discovery of non-invasive biomarkers that can distinguish LN subtypes would greatly aid in diagnosing and monitoring treatment in LN.

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ACR Poster Session A
Rheumatoid Arthritis - Animal Models: Cytokines, Novel Therapeutics and Mechanisms of Action
Monday, November 8, 2010, 9:00 AM–6:00 PM

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AC430, a Potent JAK2 Inhibitor, Provides Protection in Multiple Inflammatory and Autoimmune Disease Models. Barbara Belli[1], Daniel Brigham[2], Alan Dao[2], Ron Nepomuceno[2], Eduardo Setti[2], Gary Liu[2], Michael Hadd[2], Shripad Bhagwat[2], Wendell Wierenga[2], Mark W. Holladay[2] and Robert C. Armstrong[2]. [1]Ambit Biosciences, San Diego, CA, [2]Ambit Biosciences

Rheumatoid arthritis is a multi-factorial disease, and a sub-population of patients who are refractory to current therapy continues to exist. Recent clinical trials have demonstrated the safety and efficacy of small molecule inhibitors of the JAK kinase pathway in alleviating RA symptoms.

We have developed a potent JAK2 inhibitor, AC430, which demonstrates *in vitro* and *in vivo* activities comparable or superior to the activities of current clinical stage JAK inhibitors. In *in vitro* binding assays, AC430 binds potently to JAK2 and TYK2 with sub-nanomolar Kd values. In a TF-1 cell-based GM-CSF/JAK2/STAT5 driven transcriptional reporter system, AC430 inhibited reporter activity with an IC_{50} of 63 nM. BaF3 cell lines were generated that harbor an individual JAK family member gene fused to the activating TEL dimerization moiety. In these TELJAK cell lines AC430 inhibited JAK1, JAK2, JAK3 and TYK2 mediated STAT5 phosphorylation with IC_{50} values of 5500, 68, 7500 and 1300 nM, respectively. Each of the four TELJAK cell lines is leukemogenic following IV inoculation into SCID mice. The efficacy of AC430, and the clinical stage compound INCB18424, were tested in each leukemia disease model. Both compounds, when dosed at 60 mg/kg BID, demonstrated significant efficacy in the TELJAK2 driven model, providing an increase in life span (ILS) of 250% and 140% for AC430 and INCB18424, respectively. Marginal to no activity was observed in the other TELJAK driven leukemic models with either compound.

AC430 was tested in a classic delayed type hypersensitivity reaction model. Balb/C mice sensitized and challenged with ovalbumin in the ear pinna develop inflammation quantifiable by caliper measurement and increase in ear weight. AC430 dosed at 100 mg/kg QD led to a 60% reduction in inflammation. In an established mouse CIA model, therapeutic dosing of AC430 at 60 mg/kg BID led to a reduction in disease severity comparable to dexamethasone. AC430 was tested in two models of rat CIA. In the first model, therapeutic dosing initiated on day 1 of arthritis at 60 mg/kg QD or BID led to a significant reduction in disease severity comparable to the effect induced by dexamethasone, but with less toxicity than seen with dexamethasone. In the second model, therapeutic dosing initiated on day 3 of arthritis at 60 mg/kg BID led to a reduction of disease severity comparable to dexamethasone. In both models, clinical score correlated with histological score. In the standard disease model, 60 mg/kg BID resulted in no inflammation, cartilage damage, or pannus formation. AC430 was also tested in a mouse model of Experimental Autoimmune Encephalitis using a prophylactic dosing regimen. All doses greater than 5 mg/kg completed prevented the onset of disease, both clinically and histologically.

These data support the further development of AC430 as a treatment option for autoimmune or inflammatory disease.

Disclosure: B. Belli: Ambit Biosciences, 1, 3; **D. Brigham:** Ambit Biosciences, 1, 3; **A. Dao:** Ambit Biosciences, 1, 3; **R. Nepomuceno:** Ambit Biosciences, 1, 3; **E. Setti:** Ambit Biosciences, 1; **G. Liu:** Ambit Biosciences, 1, 3; **M. Hadd:** Ambit Biosciences, 1, 3; **S. Bhagwat:** Ambit Biosciences, 1; **W. Wierenga:** Ambit Biosciences, 1, 3; **M. W. Holladay:** Ambit Biosciences, 1, 3; **R. C. Armstrong:** Ambit Biosciences, 1, 3.

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Anti-CXCL5 Therapy Ameliorates IL-17 Induced Arthritis. Sarah R. Pickens[4], Michael V. Volin[1], Arthur M. Mandelin[2] and Shiva Shahrara[3]. [1]Midwestern University, [2]Northwester University, Chicago, IL, [3]Northwestern Univ Feinberg, Chicago, IL, [4]Northwestern University

Introduction: Since CXCL1 and 5 are important downstream targets of IL-17, experiments were performed to determine whether CXCL1 and/or CXCL5 play a role in arthritis mediated by local IL-17 expression in mice ankle joints.

Methods: Mice were treated intraperitoneally with IgG, anti-CXCL1, anti-CXCL5 or both anti-CXCL1 and anti-CXCL5 antibodies on days −4, −2, 0, 3, 5, 7 and 9 post-adenovirus (Ad) injection and arthritis was induced by injecting Ad-IL-17 intra-articularly on day 0. The disease activity was determined by measuring ankle circumference and performing histological studies. Since the expression of proinflammatory mediators is characteristic of joint inflammation, the effect of therapy on joint TNF-α, IL-6, IL-1β, CCL2, CCL3, CCL5, CCL20 and CXCL2 was examined by ELISA. Additionally, neutrophil infiltration was measured by staining ankles harvested from different treatment groups with an antibody for neutrophil marker GR1.

Results: The disease activity determined by articular index score and ankle circumference was significantly lower in mice receiving anti-CXCL1 on days 3 and 5 compared to the control group. However, as the arthritis progressed there was no difference noted at later time points (days 7 and 9). In contrast, mice receiving anti-CXCL5 demonstrated significantly reduced clinical signs of arthritis compared to the mice treated with IgG control. The combination of anti-CXCL1 and 5 did not ameliorate IL-17 induced joint inflammation beyond the effect observed using anti-CXCL5 alone. Hence, the clinical efficacy is due to neutralization of joint CXCL5. Consistently, while inflammation, synovial lining thickening, and bone erosion were markedly reduced in the anti-CXCL5 and anti-CXCL1+5 treatment groups, mice receiving anti-CXCL1 antibody had similar clinical scores compared to the control group. The effect of therapy on joint TNF-α, IL-6, IL-1β, CCL2, CCL3, CCL5, CCL20 and CXCL2 was examined. Our results demonstrate that mice receiving anti-CXCL5 or anti-CXCL1 and 5 had significantly lower levels of joint TNF-α and RANTES compared to the control group. Reduction in joint TNF-α levels in the anti-CXCL5 and combination therapy

may be due to the fact that IL-17 induced joint pathology is abrogated in TNF-$\alpha-/-$ mice indicating that in this model TNF-α is required, and therefore suppression in the inflammatory response modulates levels of this cytokine. Additionally, since both TNF-α and IL-17 synergize in inducing the expression of CXCL5 from RA ST fibroblasts, neutralization of CXCL5 may negatively regulate joint TNF-α concentration. GR1 staining demonstrated that the mice receiving anti-CXCL5 or anti-CXCL1 and 5 had significantly reduced neutrophil migration compared to anti-CXCL1 and IgG therapy.

Conclusion: Our results suggest that expression of CXCR2 ligand, CXCL5, and not CXCL1 plays an important role in IL-17 mediated arthritis potentially through modulating TNF-α levels.

Disclosure: S. R. Pickens: None; **M. V. Volin:** None; **A. M. Mandelin:** None; **S. Shahrara:** None.

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Beneficial Effects of Systemic IFNβ Are Mediated by IL-1Ra: Implications for Rheumatoid Arthritis. Mary Corr[4], David L. Boyle[3], Lisa Ronacher[4], Brian R. Lew[4], Lisa G. M. van Baarsen[2], Paul P. Tak[1] and Gary S. Firestein[4]. [1]Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, [2]Academic Medical Center, Amsterdam, The Netherlands, [3]UCSD Schl of Medicine, La Jolla, CA, [4]UCSD School of Medicine, La Jolla, CA

Objectives: Systemic IFNβ treatment provides only minimal improvement in rheumatoid arthritis (RA), yet is effective in multiple sclerosis and murine models of arthritis. To explain this paradox, we evaluated the mechanism of IFN-β benefit in passive K/BxN arthritis and the effect of IFNβ treatment on RA synovium.

Methods: Il10 null, Il1rn (which encodes IL-1Ra) null, Il1rn transgenic and wild type mice were administered K/BxN serum and in some cases treated with mouse IFNβ (1000 IU/d) or vehicle. Clinical response and histologic scores were assessed. Gene expression was measured by quantitative PCR. Serum IL-1Ra and IL-6 were measured by ELISA. Pre- and post IFNβ treatment (purified natural fibroblast IFNβ (Frone) s.c. 3 times weekly 6 million IU, 12 million IU, or 18 million IU) synovial biopsy specimens from RA patients were immunostained for IL-1Ra and IL-10.

Results: Il1rn transgenic mice had an attenuated course of arthritis (area under the curve [AUC] for paw swelling=1.0 vs. 4.9 for wild type controls, $P<0.001$). In contrast Il1rn$-/-$ mice (AUC 11.6 vs. 5.7, $P<0.01$) and Il10$-/-$ mice (AUC 7.3 vs. 4.2 $P<0.05$) had more severe serum transfer arthritis than wild type mice. Daily IFNβ treatment in Il1rn$-/-$ mice with serum transfer arthritis had no benefit (AUC 11.6 vs. 13, NS), but significantly decreased clinical arthritis severity in Il10$-/-$ mice (AUC 7.3 vs. 4.4, $P<0.05$). IFNβ treatment also did not reduce the histologic scores in the Il1rn$-/-$ mice or gene expression of articular cytokines and chemokines. Paired synovial biopsy specimens from RA patients treated with IFN-β demonstrated increased IL-1Ra expression ($P=0.05$) and reduced IL-10 expression ($P=0.04$) on Day 85 levels compared with pretreatment specimens.

Conclusions: The anti-inflammatory effects of IFNβ in passive K/BxN arthritis are dependent on IL-1Ra and are mediated by increased IL-1Ra production in this model. However, the benefit of IFNβ is not dependent on IL-10. IFNβ treatment in RA also increases synovial IL-1Ra. Passive K/BxN arthritis is IL-1 dependent, whereas IL-1-directed therapy in RA is only modestly effective. The lack of benefit for systemic IFNβ therapy in RA compared with mouse models is likely in part due the fact that IL-1 inhibition has only modest effect in RA.

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Combined Depletion of Interleukin-1 and Interleukin-6 Does Not Exceed Single Depletion of Interleukin-1 in TNF-Mediated Arthritis. Silvia Hayer, Birgit Niederreiter, Josef Smolen and Kurt Redlich. Medical University of Vienna, Department of Internal Medicine III, Division of Rheumatology, Vienna, Austria

Background: Previous studies demonstrated a regulatory role of interleukin 1 (IL-1) in inflammatory cartilage damage and bone destruction in human tumor necrosis factor transgenic (hTNFtg) mice, an animal model for Rheumatoid Arthritis (RA). Moreover, blocking of IL-6 has been shown to reduce local bone erosions in this model. Therefore we wanted to investigate the effect of a combined depletion of IL-1 and IL-6 on the development and severity of inflammatory, erosive arthritis.

Methods: We first crossed IL1α and β deficient (IL1$^{-/-}$) mice with IL6$^{-/-}$ mice to generate IL1$^{-/-}$IL6$^{-/-}$ double knockout mice. We next intercrossed these animals with arthritogenic hTNFtg mice to receive IL1$^{-/-}$IL6$^{-/-}$hTNFtg mice. We weekly assessed clinical signs of arthritis in hTNFtg, IL1$^{-/-}$hTNFtg mice, IL6$^{-/-}$hTNFtg mice and IL1$^{-/-}$IL6$^{-/-}$hTNFtg mice starting from week 4 after birth until week 16. We stained decalcified paw sections from all 4 genotypes with hematoxylin&eosin to determine the amount of inflammatory synovial pannus formation, with tartrate-resistant acid phosphatase (TRAP) to evaluate the number of synovial osteoclasts and the occurrence of subchondral bone erosions, with toluidine-blue to assess articular cartilage damage. Quantitative analysis of histopathological changes were performed using the Osteomeasure Software System.

Results: We found a significant reduction in the clinical signs of arthritis, indicated by an increase of paw swelling and a decrease in grip strength, in IL1$^{-/-}$IL6$^{-/-}$hTNFtg mice when compared to their hTNFtg littermates. In line with these findings we observed a significant decrease in synovial inflammation in IL1$^{-/-}$IL6$^{-/-}$hTNFtg mice when compared to hTNFtg animals. Moreover, the number of synovial TRAP+ osteoclasts was markedly diminished in IL1$^{-/-}$IL6$^{-/-}$hTNFtg mice and reduced osteoclast formation, was accompanied by significantly less subchondral bone erosions. Additionally, we found a conserved articular cartilage structure showing almost no cartilage degradation in IL1$^{-/-}$IL6$^{-/-}$hTNFtg mice compared to their hTNFtg littermates. In IL1$^{-/-}$IL6$^{-/-}$hTNFtg mice clinical, as well as, histological signs of disease, including joint inflammation, bone destruction and cartilage damage were also significantly diminished when compared to IL6$^{-/-}$hTNFtg mice. However, by comparing IL1$^{-/-}$IL6$^{-/-}$hTNFtg mice with IL1$^{-/-}$ hTNFtg mice we found a similar reduction on synovial inflammation, as well as subchondral bone erosions and articular cartilage destruction.

Conclusion: The phenotype of IL1$^{-/-}$IL6$^{-/-}$hTNFtg mice does not differ from IL1$^{-/-}$hTNFtg animals indicating no synergistic effects when IL-1 and IL-6 is simultaneously blocked in TNF-mediated arthritis.

Disclosure: S. Hayer: None; **B. Niederreiter:** None; **J. Smolen:** None; **K. Redlich:** None.

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Efficacy of the Selective CSF1R (Fms) Inhibitor PLX5622 in Mouse Models of Rheumatoid Arthritis. Gaston Habets, Jiazhong Zhang, Betsy Burton, Chao Zhang, Prabha Ibrahim, Bernice Wong, Marika Nespi, Wayne Spevak, Ben Powell, Brian West, Paul Lin, Gideon Bollag and Peter Hirth. Plexxikon

Purpose: PLX5622 is a potent inhibitor of the Fms receptor tyrosine kinase activity (K_I = 5.9 nM) with at least 50-fold selectivity over 4 related kinases, and over 100-fold selectivity against a panel of 230 kinases. Fms is the receptor for CSF1 and a key regulator of macrophages, dendritic cells, and osteoclasts. The target cells of this receptor control autoimmune processes involved in many diseases, including rheumatoid arthritis (RA). Therefore, PLX5622 is a valuable compound to test the role of Fms target cells in autoimmune diseases.

Methods and Results: In cell based assays PLX5622 is a potent and selective inhibitor of Fms dependent processes. CSF1 stimulated autophosphorylation of Fms is inhibited in THP1 cells (IC50 20 nM) and CSF1 + RANKL dependent differentiation of human osteoclasts is also inhibited *in vitro* (IC50 52 nM). The attractive pharmaceutical properties of PLX5622 allow once a day oral dosing. Based on these data, the efficacy of PLX5622 was examined in an aggressive, collagen-induced arthritis model of RA. DBA/1 mice were immunized with bovine collagen II in CFA on day 0 and given a collagen boost ip on day 21. By day 19, disease had progressed to a mean paw inflammation score of 2.4 (out of 16), and PLX5622 daily oral dosing was initiated. Within the first week all treatment groups (10, 20 and 50 mg/kg qd po) of PLX5622 experienced significant suppression of disease that continued through the course of treatment. Following three weeks of treatment, the mean disease score of the PLX5622-treated animals was 6.9, 5.5 and 5.0 for the 10, 20 and 50 mg/kg dose groups, respectively, while progressive disease in the vehicle-treated animals reached a mean score of 12.9. The histopathological disease scores for inflammation, pannus formation, cartilage damage and bone resorption in the wrist, paw, and ankle joints

were all significantly lower in the PLX5622 treated animals compared to vehicle-treated animals. The counts of the direct target cell population of macrophages, osteoclasts, and T-cells were lower in the joints of the PLX5622 treatment group. The benefit on joint function of these clinical, histopathological and cellular readouts was also reflected in an increased range of motion in the knee joint of PLX5622 treated animals, compared to the vehicle controls.

Conclusion: Inhibition of Fms kinase activity by the potent and highly selective inhibitor PLX5622 results in substantial efficacy in an aggressive model of RA and warrants further development in clinical studies.

Disclosure: G. Habets: Plexxikon, 1, 3; **J. Zhang:** Plexxikon, 1, 3; **B. Burton:** Plexxikon, 1, 3; **C. Zhang:** Plexxikon, 1, 3; **P. Ibrahim:** Plexxikon, 1, 3; **B. Wong:** Plexxikon, 1, 3; **M. Nespi:** Plexxikon, 1, 3; **W. Spevak:** Plexxikon, 1, 3; **B. Powell:** Plexxikon, 1, 3; **B. West:** Plexxikon, 1, 3; **P. Lin:** Plexxikon, 1, 3; **G. Bollag:** Plexxikon, 1, 3; **P. Hirth:** Plexxikon, 1, 3, 4.

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HMPL-011, a Small Molecule Compound, Modulates Pro-Inflammatory Cytokine Production, in Part, Via Potentiating IL-10 Production. Weihua Gu[2], Weigang He[2], Yan Qiu[2], Zhenhao Zhou[2], Xiaomin Dai[2], Wuzhong Shen[2], Xiaoning Yang[2], Linfang Wang[2], Yuan Zhou[2], Yu Cai[2], Edwin Lee[2], Wei Deng[2], Weiguo Su[1] and Haoran Zhao[1]. [1]Hutchison MediPharma Ltd, Shanghai, China, [2]Hutchison MediPharma Ltd

Purpose: HMPL-011, a small molecular compound, was shown to be effective in reducing clinical arthritis score and joint swelling in collagen induced arthritis (CIA) in mouse (ACR 2010 Abstract). An inhibition on pro-inflammatory cytokines, such as IL-1β, MCP-1 and IL-6, and an increase in anti-inflammatory cytokine IL-10 was found in the arthritic joints. In this study, the mechanism of action of HMPL-011 was investigated.

Methods: Cytokine mRNA was analyzed by RT-PCR and protein by ELISA or CBA (Cytometric Bead Array). Phosphorylated MKK3/6 and p38 in RAW264.7 was analyzed by WB. For LPS induced inflammation in vivo, female Balb/C mouse was p.o. treated with HMPL-011 followed by LPS stimulation 30 minutes post HMPL-011 administration. Protein and mRNA levels were assessed 2hr and 8hr after LPS dosing. In IL-10 neutralization assay, IL-10 neutralizing antibody (JES5-2A5) was dosed i.v. and concurrently p.o. treated with HMPL-011 for 30min, followed by LPS treatment. Plasma cytokines were analyzed as indicated above.

Results: HMPL-011 was screened at 10 μM against 48 inflammation related targets, include cytokine release, cytokine, chemokine and glucocorticoid receptor binding, caspases, MMPs, phosphatase and kinase activity, T, B cell proliferation, and NF-κB, NF-AT transcription activity. No significant activity of HMPL-011 was identified, except for the inhibition of IL-1β and IFNγ release (IC50=11.0 μM and 9.7 μM, respectively). Furthermore, in a screen against 60 enzymes consisting of receptor tyrosine kinases and other inflammation- related kinases at 10 μM, no significant inhibition was observed. T, B cell activation, macrophage phagocytosis, NK cell cytotoxicity was also not affected by HMPL-011. However, IL-10 expression was found to be elevated by HMPL-011 in LPS stimulated mouse macrophage cells, RAW264.7, and this induction was shown to be inhibited by the p38 inhibitor, SB203580. Moreover, LPS induced MKK3/6 and p38α phosphorylation was shown to be enhanced by HMPL-011 in RAW264.7. In LPS treated mouse, HMPL-011 increased IL-10 at 2hr post LPS treatment, followed by a significant, potent inhibition on IL-6, MCP-1 and IFNγ at 8hr post LPS treatment. In IL-10 neutralized mouse, HMPL-011 anti-inflammatory effect was found to be partially reversed, indicating the anti-inflammatory effect of HMPL-011 is only partially mediated by IL-10.

Conclusion: HMPL-011's anti-inflammatory effect was mediated at least in part through enhancement of IL-10. HMPL-011 may represent a novel class of small molecular drug in arthritis treatment.

Disclosure: W. Gu: Hutchison MediPharma Ltd, 3; **W. He:** Hutchison MediPharma Ltd, 3; **Y. Qiu:** Hutchison MediPharma Ltd, 3; **Z. Zhou:** Hutchison MediPharma Ltd, 3; **X. Dai:** Hutchison MediPharma Ltd, 3; **W. Shen:** Hutchison MediPharma Ltd, 3; **X. Yang:** Hutchison MediPharma Ltd, 3; **L. Wang:** Hutchison MediPharma Ltd, 3; **Y. Zhou:** Hutchison MediPharma Ltd, 3; **Y. Cai:** Hutchison MediPharma Ltd, 3; **E. Lee:** Hutchison MediPharma Ltd, 3; **W. Deng:** Hutchison MediPharma Ltd, 3; **W. Su:** Hutchison MediPharma Ltd, 3; **H. Zhao:** Hutchison MediPharma Ltd, 3.

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IL-1 Driven IL-22 Expression by TH17 Cells Aggravates Experimental Arthritis. Renoud J. Marijnissen[3], Marije I. Koenders[3], Mark H. T. Stappers[4], Leo A. B. Joosten[1], Ruben L. Smeets[2], Cheryl Nickerson-Nutter[5], Annemieke M. H. Boots[2] and Wim B. van den Berg[3]. [1]Department of Internal Medicine, RUNMC, Nijmegen, The Netherlands, [2]Department of Pharmacology, MSD, Oss, The Netherlands, [3]Department of Rheumatology, RUNMC, Nijmegen, The Netherlands, [4]Department of Rheumatology, RUNMC, The Netherlands, [5]Inflammation, Pfizer, Cambridge, MA

Purpose: Our previous studies in IL-1Ra-deficient mice and various other arthritis models have shown an important role for IL-17, not only in the initiation, but also the further progression of experimental arthritis. Although recent papers demonstrate that also mast cells and neutrophils can produce this proinflammatory cytokine, activated CD4+ T cells are considered as the main source of IL-17.

Recently, these IL-17 producing T helper cells (Th17) have been shown to produce other inflammatory cytokines like IL-21 and IL-22 which might contribute to the disease severity as well. In this study, we investigated how the expression of IL-22 is regulated during the induction of TH17 cells from naïve T cells. Furthermore, the therapeutic effects of blocking IL-22 in IL-1Ra-deficient mice, a spontaneous IL-1-driven experimental arthritis model, was investigated.

Methods: For our in vitro experiments, naive murine T cells were cultured under Th17 polarizing conditions using TGFβ, IL-6 and anti-IL-2. During different stages of the differentiation, IL-1 and IL-23 were supplied to influence the IL-17 and IL-22 production. Beadplex technology was used to measure cytokines in the supernatants, and the cells were analyzed for intracellular cytokine production by flowcytometry. From the inflamed ankles of the IL-1Ra-deficient mice, the synovia were isolated and mRNA expression of IL-22 and its receptor were quantified using QPCR. Finally, IL-1Ra-deficient mice were treated after clinical onset of arthritis with neutralizing anti-IL-22 antibodies and isotype controls for four weeks.

Results: Our in vitro Th17 culture experiments demonstrated that differentiated naïve CD4+ T cells could only produce high levels of IL-22 in the presence of IL-1. Accordingly, addition of IL-23 to the culture significantly increased this IL-22 induction. However, following restimulation of the differentiated T cells, IL-1 alone lost its effect on the IL-22 production, while IL-23 alone was sufficient to maintain the IL-22 production.

In addition, the expression of Th17 effector genes was investigated in our arthritis models, and IL-17, IL-22 and IL-22R mRNA levels were found to be significantly and specifically upregulated in the synovium of IL-1ra−/− mice with established arthritis. Moreover, IL-17 and IL-22 protein production by the draining lymph node cells was detected only after anti-CD3/anti-CD28 challenge. Most importantly, anti-IL-22 treatment significantly reduced bone erosion, suggesting an important role of IL-22 in IL-1-driven joint destruction.

Conclusions: Our combined data suggest that not only the IL-1 – IL-17 axis, but also the IL-1 – IL-22 axis plays an important role in experimental arthritis.

Disclosure: R. J. Marijnissen: None; **M. I. Koenders:** None; **M. H. T. Stappers:** None; **L. A. B. Joosten:** None; **R. L. Smeets:** None; **C. Nickerson-Nutter:** None; **A. M. H. Boots:** None; **W. B. van den Berg:** None.

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IL-27 Is Increased by IL-17 from Synovial Macrophage and Bone Marrow-Derived Dendritic Cells in Collagen-Induced Arthritis. Seunghoon Baek[5], Juin Kim[4], Huashu Jin[4], Seonghu Park[5], Youngeun Park[5], Joungwook Lee[1], MIRA Cho[6], Geuntae Kim[3], Junhee Lee[2] and Sungil Kim[5]. [1]Busan St Mary Hospital, Korea, Republic of, [2]Choonhae Hospital, Korea, Republic of, [3]Kosin University Medical School, Korea, Republic of, [4]Pusan National University Hospital Research Institutes, Korea, Republic of, [5]Pusan National University Medical School, Korea, Republic of, [6]Pusan National University Medical Shool, Korea, Republic of

Background: IL-17 plays important roles in synovial inflammation and bone destruction in CIA. IL-27, produced by activated macrophages and dendritic cells, stimulates Th1 cell-mediated immune response and suppress Th17 cell-mediated immune response. Therefore, IL-27 aggravates inflammation in predominant Th1 immune-mediated disease such as proteoglycan-induced arthritis, and suppress inflammation in predominant Th17 immune-mediated disease such as Experimental Autoimmune Encephalomyelitis, Experimental Autoimmune Uveitis and CIA.

Objectives: To investigate IL-27 expression during CIA, and the effect of IL-17 on IL-27 expression in CIA.

Methods: CIA was induced by type II collagen in DBA1 mice. During CIA, mice were sacrificed at day 0, 28, 35, 39, 47, 56, 63 and 68, and knee joint synovial IL-27 expressions were measured by real-time RT-PCR and western blot. In CIA, phosphate-buffered saline (PBS group) or IL-17 (IL-17 group) was injected into knee joints at day 28 and 32, sacrificed at day 35, and synovial IL-27 expressions were determined by real-time RT-PCR, western blot, and immunohistochemistry. Bone marrow-derived dendritic cells (BMDCs), isolated from femur of CIA mice at day 35, were cultured with IL-17, and IL-27 expressions were determined by ELISA.

Results: Knee joint synovial IL-27 expressions were gradually increased during CIA (fig 1). Synovial IL-27 expressions of IL-17 group were significantly high compared to PBS group (fig 2 and 3), and synovial anti-IL-27p28 antibody positive cells were double-stained with anti-CD68 antibody (fig 3). IL-27 expressions of BMDCs were significantly increased by IL-17 (fig 4).

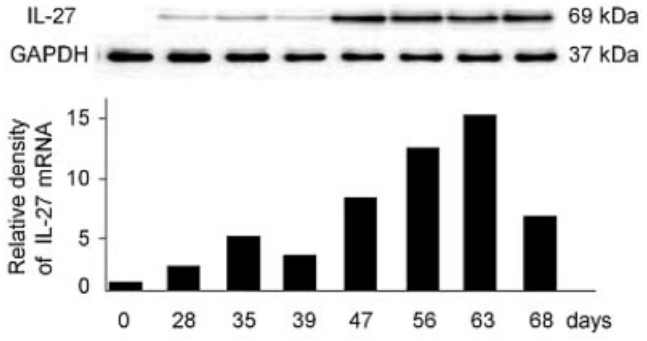

Figure 1. IL-27 expressions were gradually increased during CIA determined by western blot and real-time RT-PCR.

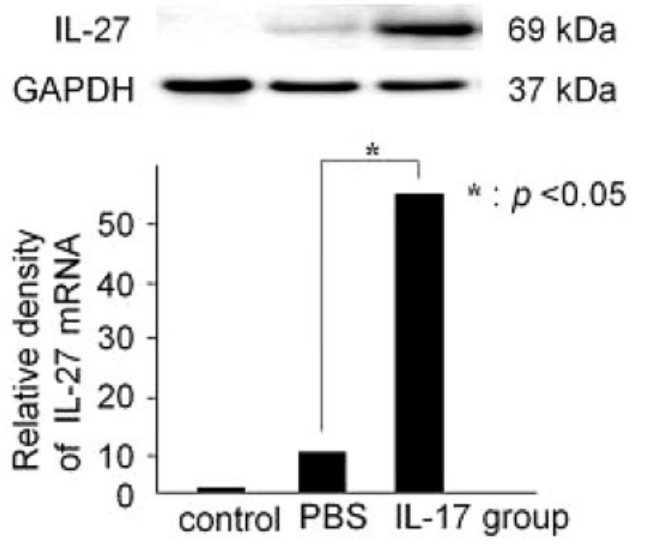

Figure 2. IL-27 expression of IL-17 group was significantly high compared to PBS group determined by western blot and real-time RT-PCR.

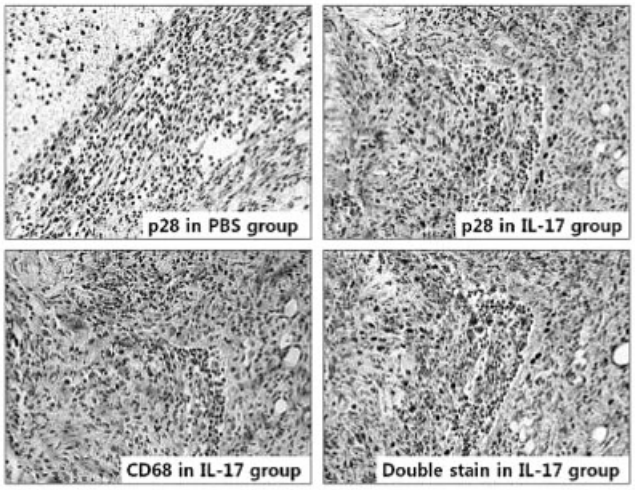

Figure 3. Synovial anti-IL27p28 antibody positive cells were increased in IL-17 group compared to PBS, and double stained with anti-CD68 antibody.

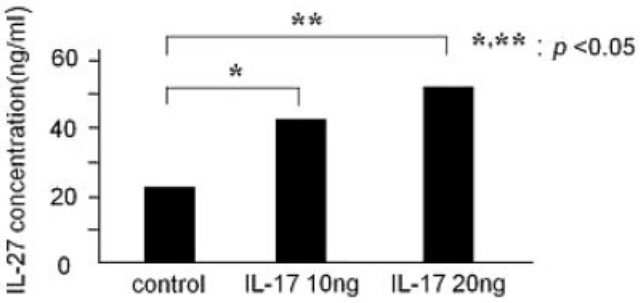

Figure 4. IL-27 expressions were increased by IL-17 in cultured BMDCs of CIA mice determined by ELISA.

Conclusions: Synovial IL-27 expression was gradually increased during CIA. IL-17 increased IL-27 expressions of synovial macrophages and BMDCs in CIA. These results suggest that IL-17 induced increase of IL-27 expressions from synovial macrophages and BMDCs might be involved in immunopathogenesis of CIA, and IL-17/IL-27 networks may play role as an autoregulatory mechanism.

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IL-32 Aggravated Synovial Inflammation and Bone Destruction, and Increased Synovial NK Cells in Experimental Arthritis Models.

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Purpose: IL-32 is a novel cytokine that is formally known as natural killer cell transcript 4, and appears to play a role in inflammatory processes and diseases including rheumatoid arthritis. NK cells are known as a regulator in infection, tumor and autoimmunity. But the underlying relationship between them and their effects on inflammatory diseases remain largely unclear. Here, we investigated in mouse model of collagen-induced arthritis (CIA), the role of IL-32 in inflammatory process and the effect of IL-32 on NK cells.

Methods: CIA was induced by type II collagen in DBA1 mice, and PBS (PBS group) or IL-32 (IL-32 group) were injected into both knee joints at day 28 and 32, then mice were sacrificed at day 35. Severity of knee joint arthritis was scored by macroscopy, and synovial inflammation and bone erosion were determined by histology. Synovial expressions of proinflammatory cytokines (IL-1β, TNF-α, IL-17, IL-18, IL-21, IL-23, IFN-γ), chemokines (CCL2, CCL3, CC5, and CCL9), chemokine receptors (CCR2, CCR5, CXCR3, and CX3CR1), were measured by real-time RT-PCR and western blot. Expression

of NK cells was determined by real-time RT-PCR, western blot, and immunohistochemistry using NKp46, a surface marker of NK cell.

Results: Scores of knee arthritis, synovial inflammation and bone erosion were significantly high in IL-32 group compared to PBS group. Synovial expression of proinflammatory cytokines (IL-1β, TNF-α, IFN-γ and IL-18), chemokines (CCL2 and CXCL9) and chemokine receptors (CCR2 and CCR5) that are associated with NK cells migration were significantly increased in IL-32 group compared to PBS group ($p<0.05$). Expression of synovial NK cells, comfirmed by real-time RT-PCR, western blot, and immunohistochemisty, were significant increased in IL-32 group compared to PBS group.

Conclusion: IL-32 increased synovial expressions of proinflammatory cytokines, and aggravated synovial inflammation and bone destruction. IL-32 also increased synovial NK cells and expressions of chemokines and chemokine receptor that are associated with NK cells migration. These results suggest that IL-32 induced increase of synovial NK cells might play roles in IL-32 induced aggravation of synovial inflammation and bone destruction in CIA.

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IL-7 Correlates with Severity of Proteoglycan-Induced Arthritis, and Arthritis Severity Is Diminished by IL-7 Neutralization. Sarita A. Y. Hartgring[3], Cynthia R. Willis[1], Kim M. G. van der Wurff-Jacobs[3], Femke Broere[2], Johannes W. J. Bijlsma[3], Floris P. J. G. Lafeber[3] and Joel A. G. van Roon[3]. [1]Inflammation Dept. Amgen Inc, Seattle WA, [2]Inst. Infectious Diseases & Immunology, UU, Utrecht, The Netherlands, [3]Rheumatology & Clinical Immunology, University Medical Center Utrecht, The Netherlands

Background: Serum levels of IL-7 are increased in arthritic individuals, including patients with rheumatoid arthritis (RA) compared to healthy controls and serum IL-7 levels correlate with markers of disease activity. IL-7 effects are mediated by heterodimers of the high affinity IL-7 receptor-α chain (IL-7Rα) and the common gamma (γc) chain. IL-7 can activate IL-7Rα^{bright} arthritogenic T cells, overriding suppressive effects of IL-7R$\alpha^{dim/-}$ T cells. CD4 T-cell activation achieved by IL-7Rα-mediated immune activation can be inhibited by soluble huIL-7Rα. IL-7 induces T cell-dependent activation of monocytes, B cells, and osteoclasts. Previously we have shown that administration of IL-7 or TSLP enhanced severity of inflammation and joint destruction in collagen induced arthritis. In this study we analyzed IL-7 expression in experimental proteoglycan-induced arthritis (PGIA). Furthermore, we assessed the effects of IL-7 neutralization on arthritis and inflammatory activity in PGIA.

Methods: Levels of IL-7 were assessed in serum and paw protein lysates of arthritic mice. Splenocytes were cultured in presence of IL-7, PG, or a combination of PG and an anti-IL-7 neutralizing antibody. PGIA was initiated by immunizing aged female BALB/c mice with human proteoglycan (day 0 and 21). Mice were given 200 or 500 μg anti-IL-7 antibody, and PBS or isotype antibody as a control treatment in a prophylactic manner (on day -2, 3, 10, 19, and 24). Clinical arthritis severity was determined by visual examination of the paws. Total cellularity of thymus and spleen, and numbers of T-cell subsets were assessed.

Results: Increased IL-7 concentrations were found in serum of arthritic mice ($p<0.05$) compared to mice that were naive or mice that did not develop arthritis. Moreover, levels or IL-7 in pawlysates correlated with arthritis severity. Blockade of IL-7 significantly reduced PG-induced proliferation of splenocytes (mean inhibition of 70 $\pm$ 8%, $p=0.015$). Most importantly, the low dose of anti-IL-7 mAb (200μg) was more effective than the 500μg dose in reducing arthritis severity and resulted in a mean arthritis inhibition of 37 $\pm$ 5% (mean of day 28–52) as compared to the control-treated mice ($p<0.05$ on day 28, 33, and 35). Treatment with 500μg anti-IL-7 reduced arthritis as compared with control mice with a mean arthritis inhibition of 24 $\pm$ 4 % (mean inhibition day 28–52) although not statistically significant. Total numbers of thymus or spleen, and thymic subsets or splenic subsets were not significantly affected by either dosage of anti-IL-7.

Conclusion: This study for the first time shows that IL-7 is increased in serum and joints of arthritic mice, and that local IL-7 levels correlate with disease severity. *In vitro*, splenocytes from arthritic mice were activated by IL-7 and PG, and PG-induced proliferation of these splenocytes was inhibited by IL-7 neutralization. Blocking IL-7 in PGIA diminished clinical arthritis severity. Together this study demonstrates an important role of IL-7-driven immunity in proteoglycan-induced arthritis in mice and suggests a therapeutic potential of IL-7 neutralization in RA.

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Immunomodulatory Properties of Novel CRAC Channel Inhibitors Exhibit Promising Potential in Rheumatoid Arthritis. Kanthikiran V. S. Varanasi, Meyyappan Muthuppalaniappan, Gayatriswaroop Merikapudi, Sridhar Veeraraghavan, Kasi V. Routhu, Srikant Viswanadha and Swaroop Vakkalanka. Incozen Therapeutics Pvt. Ltd.

Background: Calcium release activated calcium channels are the major pathway for calcium influx in developing and mature T- cells and contribute to several aspects of lymphocyte development and function. CRAC channel inhibitors have potent role in treatment of autoimmune disorders, asthma and rheumatoid arthritis. Herein, we describe the immunomodulatory properties of a series of novel and potent CRAC channel inhibitors with scope to be further developed as clinical candidates for rheumatoid arthritis.

Methods: Reductions in pro-inflammatory cytokines such as IL-2, TNFα, and IFNγ in Human Whole Blood and freshly isolated PBMC were estimated by ELISA. *In vivo* efficacy of the compounds in mice and rats was determined in an experimental model of rheumatoid arthritis. Briefly, DBA/1 mice were treated with the test compounds (10mg/kg/po/qd) from day 1 to day 35 and clinical arthritis scores were recorded. In a similar experiment male wistar rats were treated with compounds (10mg/kg/po/qd) for 28 days and paw volumes were measured.

Results: Among the compounds evaluated, RP3120 and 3163 demonstrated marked potency against IL-2 (<100 nM), TNFα (<300 nM), and IFNγ (<100 nM) in both HWB and PBMC. Animals treated with RP3120 displayed much slower onset of CIA and significantly lowered the severity (64% in mice and 46% in rats compared to vehicle control, $P < 0.05$) and much lower incidence (50% in mice and 40% in rats) of arthritis with no effect on body weight. Histopathology analysis revealed reduced cartilage and joint destruction following treatment with compound ($P < 0.005$) in both rat and mice.

Conclusion: Results demonstrate the immense potential of our compounds as immunomodulatory and anti-inflammatory agents as evidenced by cytokine reductions obtained *in vitro*. Delay in arthritic onset and progression upon administration of our compounds indicate their effectiveness as disease modifying anti-rheumatic drugs. Further *in vivo* and *in vitro* studies are in progress to evaluate the efficacy of the compound in other immune- disorders prior to the initiation of clinical trials.

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Inhibition of c-Fos/AP-1 Suppresses Passive Anti-Collagen Antibody-Induced Arthritis in Mice. Masaaki Mikami[4], Yukihiko Aikawa[5], Akira Hashiramoto[3], Mari Yamamoto[5], Hidetoshi Murao[5], Hisaaki Chaki[5], Hirokazu Narita[5], Shuichi Hirono[1] and Shunichi Shiozawa[2]. [1]Department of Pharmaceutical Sciences, School of Pharmacy, Kitasato University, Tokyo, Japan, [2]Division of Rheumatology, Kobe University Graduate School of Health Sciences and Medicine/ The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan, [3]Division of Rheumatology, Kobe University Graduate School of Health Sciences and Medicine/ The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan, [4]Research Laboratories, Toyama Chemical Co., Ltd., Toyama, Japan, [5]Research Laboratories, Toyama Chemical Co., Ltd., Toyama, Japan

Purpose: Activator protein-1 (AP-1) directly regulates the genes that participate in rheumatoid arthritis (RA), including inflammatory cytokines and matrix metalloproteinases (MMPs). Anti-collagen antibody (Ab)-induced arthritis (CAIA) in mice is beneficial to study the inflammatory phase of arthritis without involving the priming phase of the immune response. Therefore, to elucidate the involvement of c-Fos/AP-1 in the development of arthritis, the levels of c-Fos/AP-1 in the hind paws were determined, and the effect of a novel c-Fos/AP-1 inhibitor T-5224 on CAIA was investigated.

Methods: CAIA was induced in BALB/c mice by *i.p.* injection of the mixture of anti-type II collagen (CII) Abs on day 0 and LPS on day 3. The levels of c-Fos/AP-1 in extracts from hind paws were determined using TransAM™ kit on day 0, 3, 4, 7, and 15. T-5224 was orally administered once daily. The effect was assessed by arthritis score, pathological examination, and serum biological analysis of IL-1β and MMP-3. Furthermore, effects of methotrexate (MTX) and leflunomide were also evaluated in the same procedure for the comparison.

Results: c-Fos/AP-1 activity increased in the hind paws of mice after day

4 in coincidence with onset of the arthritis. The administration of T-5224 from day 5 efficiently suppressed the development of arthritis at 1 to 30 mg/kg, and the arthritis score on day 14 was inhibited by 81% at 30 mg/kg (ED_{50}: 6.0 mg/kg). Histological changes such as cartilage degradation in the joints of hind paws of mice with T-5224 were also suppressed on day 14. In addition, the increases of IL-1β and MMP-3 levels in sera were reduced by T-5224, and the inhibition rates at 30 mg/kg were 97% and 89%, respectively. On the other hand, either MTX at 3 mg/kg or leflunomide at 30 mg/kg had no effects on passive CAIA.

Conclusions: The activation of c-Fos/AP-1 was observed in the arthritic lesion of mouse CAIA in which the priming phase of the immune response is skipped. Inhibition of c-Fos/AP-1 by T-5224 attenuated the arthritis through suppressing the inflammatory cytokine and matrix degrading MMP. On the other hand, immunosuppressive treatment with MTX and leflunomide did not show the inhibitory effects on CAIA. These data support a key role of c-Fos/AP-1 in the development of arthritis and joint destruction, and suggest that T-5224 with the novel mechanism of action is expected to exert anti-arthritic effects in the therapy of RA.

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Innovative Treatment of Experimental Arthritis and Inhibition of Human Osteoclasts Differentiation by Dendrimers. Myriam Hayder[2], Mary Poupot[1], Jean-Pierre Majoral[4], Cédric Olivier Turrin[4], Anne-Marie Caminade[4], Alain Cantagrel[3], Jean-Jacques Fournié[1], Rémy Poupot[1] and Jean-Luc Davignon[3]. [1]INSERM U563, CPTP, IFR150, Toulouse, France, [2]JE2510, IFR150, Paul Sabatier University, Toulouse, France, [3]JE2510, IFR150, Paul Sabatier University, University Hospital Purpan, Toulouse, France, [4]Laboratoire de Chimie de Coordination, CNRS, Toulouse, France

Background: Current treatments of RA depend largely on biotherapies based on monoclonal antibodies directed against pro-inflammatory cytokines. The development of new drugs is needed in order to obtain sustained clinical remission and target multiple factors involved in the pathogenesis and / or inflammation in RA.

Phosphorus-containing dendrimers harbor activating properties towards the human immune system. Among these dendrimers, a particular one, capped with azabisphosphonate groups, activates human monocytes in an anti-inflammatory and immuno-suppressive pathway. These biological properties rely in part on the multivalency of this category of molecules.

Objectives: The goals of this study were:

To use dendrimers to test for their inhibition of osteoclast (OC) differentiation from human monocytes in vitro.

To assess the anti-inflammatory properties of dendrimers in IL-1 ra−/− mice which develop spontaneous arthritis.

To investigate the mechanism of action of dendrimers on the inhibition of inflammation and osteoclastogenesis.

Methods: Dendrimers were synthesized from a core which is derivatized by branches and finally capped with surface groups.

Purified monocytes were differentiated into osteoclasts in the presence of M-CSF and RANKL. OCs were identified using a TRAP assay. Bone resorption was measured in a CTX assay.

IL-1 ra −/− mice which spontaneously develop arthritis were injected intravenously weekly with dendrimers (1mg/kg and 10 mg/kg). Paw swelling was measured and clinical score evaluated. Joint tissues were examined for histopathology. Pro-inflammatory cytokines were quantified in sera by Elisa.

Results: Dendrimers inhibited in a dose dependent manner the in vitro differentiation of human monocytes into OCs and inhibited bone resorption. In vivo, weekly injections of dendrimers in IL-1ra −/− mice, starting at the age of 8 weeks, stopped the development of arthritis and reversed paw swelling, clinical scores and bone erosion. Pro-inflammatory cytokines (IL-1, IL- 6, IL-17, TNF-a) were significantly diminished and returned to normal levels after 8 weeks of treatment while IL-4 and IL-10 were increased.

M-CSF inhibition was identified as a mechanism of inhibition of inflammation and bone erosion.

Conclusion: Our data describe the properties of a novel molecule capable of both anti-inflammatory and anti-OCs activities with great potential in the treatment of RA and other inflammatory diseases.

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IRF-1 Reduces TNFα-Induced-IL-18 Bioactivity in Rheumatoid Arthritis Synovial Fibroblasts by Induction of IL-18BPa. Hubert Marotte[1], Adam J. Pinney[2], Tatiana Fedorora[2], Nalin Lalwani[2], Pei-Suen Tsou[2], Bradley J. Rabquer[2] and Alisa E. Koch[3]. [1]University of Michigan Medical School, Ann Arbor, MI, [2]University of Michigan Medical School, [3]Veteran's Administration and University of Michigan

Purpose: The development of alternative therapies remains critical, as one quarter of all rheumatoid arthritis patients fail to respond to current biologic therapies. Interleukin (IL)-18 is an important cytokine in RA, because it induces T helper-1 immune response as well as angiogenesis. IL-18 bioactivity is regulated by its natural inhibitor IL-18 binding protein (IL-18BPa). Interferon regulatory factor-1 (IRF-1) was originally identified as a transcriptional activator of interferon-gamma. We have previously shown that TNF-α induces IL-18 and IL-18BPa in RA synovial fibroblasts. Others have shown that IRF-1 binds to the IL-18BP promoter. Here, we investigate the role of IRF-1 on IL-18BPa expression and IL-18 bioactivity in RA synovial fibroblasts.

Methods: IRF-1 synthesis in RA synovial fibroblasts treated with TNF-α was assessed by qRT-PCR and Western blot. Then, the effect of TNF-α on IRF-1 nuclear translocation in a time dependent manner (2 hr, 4 hr, and 8 hr) was examined using nuclear extracts and Western blots. The critical pathways for TNF-α-induced IRF-1 expression and nuclear translocation were determined by using chemical inhibitors: pyrrolidine dithiocarbamate (PDTC; a nuclear factor kappa-light-chain-enhancer of activated B cells [NFκB] inhibitor; 200μM) or MAPK inhibitors (ERK1/2, PD98059; p38, SB202190; or JNK2, SP600125; 10μM) followed by TNF-α stimulation. IRF-1 antisense or sense oligodeoxynucleotides (ODNs) were used to knockdown IRF-1 in RA synovial fibroblasts. Fibroblasts were then stimulated with TNF-α and examined for IL-18BPa expression by qRT-PCR, Western blot and IL-18 bioactivity assay. IL-18 bioactivity was determined using KG-1 cells.

Results: TNF-α induced RA synovial fibroblast IRF-1 expression at the mRNA and protein levels with a maximal effect at 2 hours ($P < 0.05$; $n \geq 3$ patients). Furthermore, TNF-α induced nuclear translocation of IRF-1 with maximal translocation at 2 hours (~6 fold-induction; $P < 0.05$; $n = 4$). This effect persisted for 8 hours (~6 fold-induction; $P < 0.05$). However, blocking NFκB or JNK2 pathways reduced TNF-α-induced-IRF-1 nuclear translocation by approximately 35% and 50%, respectively ($P < 0.05$; $n \geq 4$). Blocking ERK1/2 or p38 pathways had no effect on TNF-α-induced-IRF-1 nuclear translocation. Finally, using ODN to knockdown IRF-1, we observed a reduction of IL-18BPa expression by qRT-PCR and ELISA. IL-18 bioactivity was higher in the case of knockdown of IRF-1 than in its presence.

Conclusions: These results show that IRF-1 is a key regulator of IL-18BPa expression in RA synovial fibroblasts and can thus regulate IL-18 bioactivity. Hence strategies to augment IRF-1 activity may be beneficial in RA.

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Liposomal Targeting of Glucocorticoids to the Synovial Lining during Experimental Arthritis Inhibits M1 Macrophage Activation in Favour of M2 Differentiation. Wouter Hofkens[2], Gert Storm[3], Wim B. Van Den Berg[1] and Peter van Lent[2]. [1]Radboud Univ Nijmegen Med Cntr, Nijmegen, The Netherlands, [2]Radboud University Nijmegen Medical Center, [3]Utrecht University

Background and Objective: Recently we found that systemic delivery of liposomes containing glucocorticoids strongly suppresses joint inflammation during experimental antigen-induced arthritis (AIA). During the course of AIA, macrophages in the synovial lining layer are activated towards a pro-inflammatory ('M1') and in later phases towards an anti-inflammatory ('M2') activation state. M1 macrophages are characterized mainly by an up-regulation of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6 and IL-12p40 whereas M2 macrophages show an increase in IL-10 expression and expression of membrane markers IL-1 receptor type II (IL-1RII) and CD163. We now explored whether liposomal targeting of synovial lining macrophages with glucocorticoids exerts its effect through M1/M2 macrophage skewing.

Materials and Methods: Mice with established antigen-induced arthritis (AIA) were treated with a single intravenous injection of 10 mg/kg liposomal prednisolone phosphate (Lip-PLP) or PBS. Naïve mice were injected intra-

articularly with IFNg/LPS to induce M1 phenotype and 24 hours thereafter with Lip-PLP or PBS. Mice were sacrificed at day 1 after Lip-PLP treatment and whole knee joints were isolated for histology and synovial biopsies were isolated for RNA analysis. In vitro, murine bone marrow macrophages were differentiated towards M1 phenotype with LPS and IFNγ, treated with Lip-PLP and M1/M2 markers characterized by quantitative RT-PCR, LUMINEX and FACS.

Results: A single intravenous injection with Lip-PLP in mice with established AIA significantly reduced synovial infiltration from control treatment (PBS) within 1 day. At this time point, synovial gene expression was strongly down-regulated by Lip-PLP for the M1 cytokines TNF-α (3.3 fold), IL-1β (10.6 fold), IL-6 (5.6 fold) and IL-12p40 (6.3 fold) compared to PBS treated mice, whereas expression of M2 markers was only slightly down-regulated (IL-10: 2.1 fold and IL-1RII: 1.2 fold) or even up-regulated (CD163: 1.9 fold). Liposomes entered the synovium by blood vessels lying just beneath the lining layer and were directly engulfed by macrophages as detected by gold containing liposomes. To evaluate whether Lip-PLP had a direct effect on M1 macrophages, these cells were induced in vitro by IFNγ and LPS and subsequently incubated with Lip-PLP for 24 hours. Lip-PLP suppressed expression of TNF-α, IL-1β, IL-6 and IL-12p40 and induced expression of IL-10, IL-1RII and CD163 in M1 macrophages *in vitro* suggesting a selective skewing of M1 macrophages towards an M2 phenotype. Local M1 activation and subsequent treatment with Lip-PLP led to a similar gene expression pattern as in the AIA providing cogent evidence for selective skewing of M1 macrophages in favour of the M2 phenotype.

Conclusion: Systemic delivery of liposomal glucocorticoids during experimental arthritis inhibit M1 macrophages in favour of M2 phenotype in the lining layer and may drive their strong suppressive effect.

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Nanoparticles of LDE: A Potential Delivery Route for MTX in Sinovial Tissue of Antigen-Induced Arthritis. Suzana B. V. Mello[2], Eloisa D. O. Bonfá[3], Claudete J. Valduga[1], Adriana Bugaralli[1], Elaine R. Tavarez[1] and Raul Maranhão[1]. [1]Heart Institute (InCor), Faculdade de Medicina da Uiversidade de São Paulo, [2]Reumatology Division, Faculdade de Medicina da Unversidade de São Paulo, São Paulo, Brazil, [3]Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo

Objective: Methotrexate (MTX) remains the first choice in the management of rheumatoid arthritis (RA). Resistance to this drug is largely associated to MTX entry into the cell. Uptake of lipidic nanoemulsion has emerged as a new strategy for cancer chemotherapy since it carries drugs directed to affected tissue increasing its concentration with a reduced toxicity. The aim of the present study was therefore to evaluate the anti-inflammatory efficacy of a novel cholesterol-rich nanoemulsion coupled MTX (MTX-LDE) in antigen induced arthritis (AIA) in rabbits.

Methods: Toxicity, pharmacokinetics and biodistribution assays were performed. The dose-effect curve of the complex was also determined (0.05 – 0.4 mg/Kg of MTX-LDE). Arthritis (AIA) was induced in the knee joint of methylated serum albumin sensitized NZW rabbits. Twenty four hours after AIA induction animals were intravenously (IV) or intraarticularly (IA) injected with a single dose of commercial MTX (0.25 mg/Kg), LDE or saline. To give an equivalent dose of MTX-LDE, the amount of drug associated to the nanoemulsion was evaluated by HPLC prior the injection. Animals were sacrificed 48h after AIA induction when synovial fluid (SF) and membrane (SM) were collected. The inflammatory parameters analyzed were: total and differential leukocyte count, protein leakage in the SF and histopathological evaluation of SM.

Results: MTX-LDE did not promote any hematological toxicity. The uptake of this complex was preferentially to liver, spleen and inflamed SM. MTX-LDE intravenously injected promoted a reduction of 65% of leukocyte infiltrate in the joint, and 41% in protein leakage and a significant reduction in the SM cell infiltrate. Likewise, the treatment with MTX-LDE by intraarticular route significantly reduced inflammatory parameters (table). In contrast, a single dose of commercial MTX, a DMARDs that requires several weeks to have a clinical effect, did not alter any evaluated parameter. LDE alone or saline were also ineffective (table).

Treatments	n	Leukocyte/mm^3 of SF	Protein leakage μg/ml of SF
AIA control	15	13514 ± 1254	5.31 ± 0.52
MTX-LDE (IV)	9	4714 ± 415 (p = 0.000)	3.17 ± 0.36 (p = 0.008)
MTX (IV)	6	19450 ± 3896	6.87 ± 2.15
LDE (IV)	6	17375 ± 1504	5.50 ± 1.28
MTX-LDE(IA)	9	8416 ± 997 (p = 0.010)	3.37 ± 0.63 (p = 0.029)
MTX (IA)	4	18750 ± 2125	4.24 ± 0.34

Results are expressed as mean ± SE, p by comparison with control values

Discussion: Our study suggests that MTX-LDE is effective, well tolerated and exhibit a rapid effect, probably as a result of their good uptake by the synovial tissue. This novel therapeutic strategy represents a treatment option for RA.

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Novel Small Molecule Aminopyridizines Inhibit Rat Collagen-Induced Arthritis and Suppress Proinflammatory Cytokine Pathways. Soo-In Choi[2], Lori D. Klaman[3], Bruce Connop[3], Aleksandra Pastrak[3] and Ernest Brahn[1]. [1]Division of Rheumatology, UCLA School of Medicine, Los Angeles, CA, [2]Division of Rheumatology, UCLA School of Medicine and VA Greater Los Angeles Healthcare System, Los Angeles, CA, [3]Transition Therapeutics

Introduction: Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by aggressive synovial hyperplasia and inflammation. Activated macrophages and synoviocytes produce many key cytokines and mediators that contribute to the inflammation and joint destruction. Blocking proinflammatory cytokines such as TNFα, IL-1, and IL-6 has led to clinical and radiographic benefits in patients with RA. TT301 and TT302 are novel, orally available, small molecule aminopyridizines that can suppress proinflammatory cytokines and reduce inflammation in rodent models of multiple sclerosis and Alzheimer's disease. Here we report the effects of these compounds on inflammatory pathways, *in vitro*, and rat collagen-induced arthritis (CIA), *in vivo*.

Methods: The *in vitro* effects of TT301 and TT302 on cytokine production were examined in stimulated primary human synovial fibroblasts and human RAW264.7 macrophages. Cells were preincubated with compound or vehicle in serum-free media and stimulated with LPS (5μg/mL), IL-1β (5ng/mL) or TNFα (30ng/mL). Supernatants were collected and analyzed by cytokine specific ELISA. *In vivo* studies used Lewis rats immunized with porcine type II collagen on day 0 to induce CIA. A total of 79 rats were randomized to vehicle controls or 4 treatment arms (TT301 at 1mg/kg and 7 mg/kg; TT302 at 1mg/kg and 7 mg/kg). Based on the degree of joint involvement and soft tissue swelling, each limb was scored from 0–4, with a maximum total score of 16. At the end of the study (day 28) serum was harvested for subsequent cytokine profiles, the left hind limbs were fixed for immunohistochemistry, and the right hind limbs were microdissected to obtain pure synovium for gene expression profiles, gene hub, module, and network analysis. All hind limbs were also evaluated by high resolution digital radiographic imaging.

Results: In stimulated human RAW264.7 macrophages and synovial fibroblasts, increasing concentrations of TT301 and TT302 dose-dependently inhibited the induction of key cytokines relevant to the pathology of RA including TNFα, IL-6, RANTES and MCP-1/CCL-2. In Lewis rats, virtually all controls developed CIA on day 11 but TT302 and TT301 recipients had a delayed arthritis onset ($p<0.03$ and $p<0.002$, respectively). The clinical severity was significantly lower than vehicle controls for both agents (at all doses) within 24 hours of disease onset and this was sustained throughout the study. By day 28, TT301 and TT302 (at both doses) markedly inhibited clinical disease ($p< 1 \times 10^{-10}$ vs. controls). Radiographic damage was also suppressed (TT301 at 1mg/kg and 7mg/kg, $p< 2 \times 10^{-6}$ & $p < 2 \times 10^{-7}$, respectively; TT302 at 1mg/kg and 7mg/kg, $p< 2 \times 10^{-5}$ & $p< 2 \times 10^{-8}$, respectively). The analysis of serum cytokines, joint immunohistochemistry, and synovial gene expression profiles is ongoing.

Conclusions: TT301 and TT302 inhibited inflammatory cytokine pathways and suppressed CIA. These studies indicate that these novel small molecules might have therapeutic benefits in RA.

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PCI-45292, a Novel Btk Inhibitor with Optimized Pharmaceutical Properties, Demonstrates Potent Activities in Mouse Models of Arthritis. Betty Y. Chang[2], Patricia Thiemann[1], Nadia Moore[3], Michelle Francesco[3], Min Mei Huang[3], Chitra Mani[3], Purvi Jejurkar[3], Danielle Tonev[3], Wei Chen[3], Joseph J. Buggy[3] and David J. Loury[3]. [1]Pharmacyclics, [2]Pharmacyclics, Research, Sunnyvale, CA, [3]Pharmacylics

Purpose: Btk is an essential element of BCR signaling in B cells and FcγR signaling in monocytes/macrophages, and is considered an ideal molecular target for the treatment of autoimmune diseases such as rheumatoid arthritis. PCI-45292, was derived from the chemical scaffold of PCI-32765, a first-in-man Btk inhibitor currently in Phase I/Ib clinical trials in patients with NHL/CLL*. Both PCI-32765 and PCI-45292 are irreversible inhibitors of Btk, forming a covalent bond with the sulfhydryl group of Cys-481 at the ATP-binding site. The two compounds were evaluated in vitro for their effects on human lymphocytes, monocytes, and basophils, and in vivo for therapeutic effects in multiple models of arthritis.

Methods and Results: In Btk biochemical assays, PCI-32765 and PCI-45292 have an IC_{50} of 0.5 nM and 1–2 nM, respectively. PCI-45292 was a more selective inhibitor of Btk than either PCI-32765 or dasatinib, with no significant inhibition of VEGFR2, EGFR, JAK, or Abl. Both compounds were potent inhibitors of human B cell activation following BCR stimulation by anti-IgM with an EC_{50} of 2 nM while failing to inhibit T cell activation at concentrations up to 2 μM. Both inhibited anti-IgE mediated upregulation of CD63 in human whole blood basophils with an EC_{50} of 20–100 nM. In addition, PCI-45292 inhibited cytokine release from human monocytes at 20–100 nM but did not inhibit IgG-mediated phagocytosis up to 10 μM. In vivo, both Btk inhibitors dose-dependently inhibited inflammatory synovitis, synovial fluid cytokines, cartilage damage, and bone erosion in both preventive and established murine CIA models. PCI-32765 and PCI-45292 inhibited overt manifestations of arthritis in mice with EC_{50} values of 2.23 and 0.61 mg/kg/day, respectively. In a murine CAIA model, PCI-32765 and PCI-45292 completely suppressed the development of arthritis at doses of 6.25 and 0.8 mg/kg/day, respectively. In glutathione binding assays, the rate of glutathione conjugation was 20 fold lower for PCI-45292 than for PCI-32765. In human liver microsomes, the half-life of PCI-32765 was 2.5 min compared to 19.2 min for PCI-45292. PK studies in rats showed that the bioavailability of PCI-32765 and PCI-45292 was 22.8% and 24.7%, respectively. Hepatic extraction ratio, a measurement of first-pass metabolism, was 0.690 and 0.289 for PCI-32765 and PCI-45292, respectively. Based on PK/efficacy relationships in mice and interspecies scaling of clearance, the daily efficacious dosage of PCI-45292 was estimated to be ≤10 mg/patient/day.

Conclusions: Both PCI-32765 and PCI-45292 are potent irreversible inhibitors of Btk that suppress B cell activation following BCR stimulation and inhibit monocytes/macrophage release of pro-inflammatory cytokines following FcγR activation. PCI-45292 was shown to have increased selectivity for Btk inhibition over other tyrosine kinases, a reduced potential for off-target protein binding, and improved metabolic stability. Also, PCI-45292 had a more potent effect in ameliorating inflammation and tissue damage in CIA and CAIA models when compared to PCI-32765. PCI-45292 is currently undergoing preclinical development for autoimmune applications.

*ASCO 2010 presentation

Disclosure: B. Y. Chang: Pharmacylics, 3; **P. Thiemann:** Pharmacylics, 3; **N. Moore:** Pharmacylics, 3; **M. Francesco:** Pharmacylics, 3; **M. M. Huang:** Pharmacylics, 3; **C. Mani:** Pharmacylics, 3; **P. Jejurkar:** Pharmacylics, 3; **D. Tonev:** Pharmacylics, 3; **W. Chen:** Pharmacylics, 3; **J. J. Buggy:** Pharmacylics, 3; **D. J. Loury:** Pharmacylics, 3.

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Recognition of IL-23 Dependent and Independent Stages during Autoimmune Collagen-Induced Arthritis. Ferry Cornelissen[2], Patrick Asmawidjaja[2], Anne-Marie Mus[2], Odilia Corneth[2], Kristine Kikly[1] and Erik Lubberts[2]. [1]Eli Lilly, [2]Erasmus MC, University Medical Center

Background: IL-23 is a heterodimeric cytokine composed of an IL-12/23-p40 subunit together with an IL-23-specific p19 subunit. The critical role of IL-23 in the development of autoimmune collagen-induced arthritis (CIA) has been shown using IL-23p19 knockout mice. However, it is unknown what the role of IL-23 is at later stages of CIA and during T cell memory mediated flare-up arthritis.

Materials and Methods: In one set of experiments, an anti-IL-23p19-specific antibody (anti-IL-23) was injected starting 15 days after the first immunization with type II collagen (CII) but before the booster injection of CIA. In another set of experiments, anti-IL-23 was injected starting after the first signs of CIA. Splenocytes, popliteal lymph-node cells (PLNs) and cells isolated from ankles were assessed for intracellular cytokine production by flow cytometry. Serum IgG and IL-6 levels were measured. To test the role of anti-IL-23 in a memory T cell driven arthritis model we utilized the flare-up induced mBSA arthritis model.

Results: Neutralizing IL-23 starting 15 days after the first CII-immunization significantly delayed and suppressed the onset of CIA. In these anti-IL-23 treated mice, serum IL-6 was lower compared to control mice. In addition, the mean fluorescent intensity (MFI) of splenic CD4+ TNF expressing cells was significantly lower in the anti-IL-23p19 treated group compared to the isotype control group. In the sera of anti-IL-23 treated mice, significantly lower CII-specific IgG1 levels were found compared to the control group as well as a trend to lower IgG2a levels. However, anti-IL-23 treatment did not reduce the proportion of Th1 and Th17 cells analyzed at days 15, 24, and 35. In contrast to the marked suppressive effect of anti-IL-23 given during the onset of CIA, neutralizing IL-23 directly after the first signs of arthritis did not ameliorate the arthritis score. No effect on CII-specific IgG's was noted, indicating that the effector phase of CIA is IL-23-independent. Since CIA is both T cell and immune complex-mediated the IL-23-dependency was further investigated during memory T cell-mediated flare-up arthritis. The mBSA-mediated flare-up arthritis was induced after the primary mBSA-induced arthritis has declined to normal background levels. In mice treated with anti-IL-23, a significant lower disease score was observed compared to mice treated with the control antibody, which was accompanied with lower IL-17 and IL-22 expression in the knee joints of these mice.

Conclusion: These data recognized IL-23 dependent and independent stages during autoimmune CIA. Furthermore, the flare-up reaction of arthritis is IL-23-mediated. These data suggest the importance of early intervention using blocking IL-23 therapy in autoimmune arthritis and beneficial effects of neutralizing IL-23 during arthritis relapses.

Disclosure: F. Cornelissen: None; **P. Asmawidjaja:** None; **A.-M. Mus:** None; **O. Corneth:** None; **K. Kikly:** None; **E. Lubberts:** None.

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RO2492, a Phosphoinositide-3-Kinase d Inhibitor, Shows Inhibitory Effects in a Variety of Human Cell Types and Suppresses Collagen-Induced Arthritis in Mice. Cheng Liao[4], Pei-Yuan Hsu[4], Shu Jin[2], Vaishali Patel[2], Mattew C. Lucas[3], Yong Nam Kim[3], Joe Dalpoto[3], Karim Dabbagh[3], Emma Masteller[3], Brian R. Wong[1], Satwant K. Narula[2] and Julie A. Demartino[3]. [1]Hoffma-La Roche Inc., San Francisco, CA, [2]Hoffma-La Roche Inc., Nutley, NJ, [3]Hoffma-La Roche Inc., [4]Hoffmann-La Roche Inc., Nutley, NJ

Background: Phosphoinositide 3-kinase (PI3K) family controls an array of intracellular signaling pathways and regulates many biological functions in a variety of cell types, including T cells, B cells, macrophages and osteoclasts. In this study, we evaluated the effects of a potent and selective PI3Kd inhibitor, RO2492, in multiple human immune cells as well as in mouse collagen-induced arthritis model.

Methods: Anti-IgM-mediated intracellular calcium fluxes in the Ramos cell were measured by FLIPR. Anti-IgM mediated B cell activation in human whole blood as determined by CD69 upregulation was assessed by FACS analysis. Mixed lymphocytes reactions (MLR) were measured by [^{3}H] thymidine incorporation in response to stimulation by mitomycin C-treated allogeneic lymphocytes. T cell proliferation was induced by anti-CD3/CD28 antibodies. Memory T cell recall responses were measured by intracellular staining of TNF^+ or IFN^+ cells in $CD45RA^-$ memory T cell population. Human monocytes were isolated by plate adherence and TNFa production was quantified after stimulation with human IgG-coated beads. Osteoclasts differentiation from monocytes was induced by RANK ligand for 14 days then counted as TRAP positive multinuclear cells. Murine collagen-induced arthritis was induced by intradermal tail base injection with collagen at day 0 followed by a boost at day 21.

Results: RO2492 is a potent, selective small molecule PI3Kd inhibitor. Inhibition of PI3Kd by RO2492 blocked the anti-IgM mediated B cell receptor signaling in both Ramos cells (IC_{50}=2 nM) and human whole blood

(IC_{50}=24 nM) as demonstrated, respectively, by reduced calcium flux and CD69 up-regulation. In addition, RO2492 blocked Fcg receptor-mediated TNFa production in human monocytes with similar potency (IC_{50}=9 nM). With respect to T cells, PI3Kd blockade inhibited proliferation in MLR assay (IC_{50}=10 nM). Moreover, proliferation of purified CD4 T cells stimulated by plate-bound anti-CD3 antibody was also potently inhibited by RO2492 (IC_{50}=6 nM), although there was an apparent decrease in compound potency in cells co-treated with anti-CD3 plus anti-CD28 antibody (IC_{50}=134 nM, 505 nM with 1 mg/ml, 5 mg/ml anti-CD28 antibody costimulation, respectively). In a memory T cell recall response, anti-CD3/CD28-mediated increases of TNF^+ (IC_{50}=35 nM) or IFN^+ (IC_{50}=40 nM) memory T cells were also blocked by RO2492. RO2492 also inhibited osteoclast differentiation in a dose-dependent manner. Finally, oral administration of RO2492 ameliorated disease severity in mouse collagen-induced arthritis model. Histopathological examination demonstrated diminished inflammation and cartilage destruction in RO2492 treated group compared to vehicle group.

Conclusion: In summary, our data showed that inhibition of PI3Kd blocks several key pathways in B cells, T cells, macrophages and osteoclasts, which are related to inflammation and bone destruction in the pathology of rheumatoid arthritis. Furthermore, RO2492 is efficacious in mouse collagen induced arthritis model. The beneficial effects of RO2492 suggest the therapeutic potential of blocking PI3Kd isoform for treatment of rheumatoid arthritis.

Disclosure: C. Liao: Hoffmann-La Roche, Inc., 3; **P.-Y. Hsu:** Hoffmann-La Roche, Inc., 3; **S. Jin:** Hoffmann-La Roche, Inc., 3; **V. Patel:** Hoffmann-La Roche, Inc., 3; **M. C. Lucas:** Hoffmann-La Roche, Inc., 3; **Y. N. Kim:** Hoffmann-La Roche, Inc., 3; **J. Dalpoto:** Hoffmann-La Roche, Inc., 3; **K. Dabbagh:** Hoffmann-La Roche, Inc., 3; **E. Masteller:** Hoffmann-La Roche, Inc., 3; **B. R. Wong:** Hoffmann-La Roche, Inc., 3; **S. K. Narula:** Hoffmann-La Roche, Inc., 3; **J. A. Demartino:** Hoffmann-La Roche, Inc., 3.

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Selective Switch Pocket Kinase Inhibitors Suppress Autoimmune Inflammatory Models of Rheumatoid Arthritis. Soo-In Choi[3], Scott C. Wise[1], Daniel L. Flynn[1], Zejin Zhu[3] and Ernest Brahn[2]. [1]Deciphera Pharmaceuticals, [2]Division of Rheumatology, UCLA School of Medicine, Los Angeles, CA, [3]Division of Rheumatology, UCLA School of Medicine and VA Greater Los Angeles Healthcare System, Los Angeles, CA

Introduction: Kinase activation is controlled by phosphorylation and dephosphorylation of key residues on the activation loop which subsequently binds to an internal region on the kinase domain, known as the switch pocket, resulting in a conformational change to allow substrate binding and phospho-transfer. Certain kinases, including cFMS, cKit, and PDGFR, have recently been identified as targets for treatment of autoimmune disorders including rheumatoid arthritis. We have developed a novel class of compounds which were designed to engage critical switch pocket residues and prevent adoption of an activated conformation, resulting in potent and highly selective inhibitors of these kinases. Switch pocket inhibitors targeting these kinases were tested in collagen antibody-induced arthritis (CAIA) and collagen-induced arthritis (CIA), animal models of chronic autoimmune inflammatory synovitis.

Methods: Initial prevention protocols studied kinase inhibitors DP-3556, DP-4178, and DP-4610 in murine CAIA starting on day 0. In a pilot protocol, Lewis rats were immunized with type II collagen on day 0 with clinically evident CIA on day 11. The rats were allowed to develop established disease (day 22) and then administered DP-4610 for 3 days. Synovium was micro-dissected and on-target kinases, such as pFMS, were assayed. In a subsequent study of established rat CIA (days 11–28), DP-4178 (50mg bid or 100mg qd) was compared to vehicle controls. Recipients were scored for clinical severity and structural damage (based on blinded digital radiographs).

Results: Prevention protocols in murine CAIA demonstrated marked reduction in footpad swelling ($p< 1 \times 10^{-3}$) and clinical scores ($p< 1 \times 10^{-3}$) with DP-3556, DP-4178, and DP-4610. Ankle histology/immunohistochemistry revealed significant suppression of inflammation, pannus, cartilage damage, osteoclast activity, bone resorption, and periosteal reaction. Synovium harvested from established rat CIA treated with 3 days of DP-4610 indicated a 75% inhibition of on-target pFMS. Chronic administration of DP-4178 beginning at day 11 arthritis onset (50mg bid or 100mg qd) significantly suppressed clinical disease ($p< 1 \times 10^{-8}$ and $p< 1 \times 10^{-7}$, respectively) and radiographic damage ($p< 1 \times 10^{-6}$ and $p< 1 \times 10^{-3}$, respectively) compared to controls. On-target kinase suppression with chronic DP-4178, administered for 17 days of clinical disease, was also demonstrated in the synovium by the end of the study on day 28.

Conclusions: Small molecules, generated by structure-based design, had selective kinase inhibitory profiles. They could suppress synovial on-target phospho-kinases in the murine CAIA model and involute established arthritis in the rat CIA model. These studies suggest that specific kinase pathways, including cFMS, may be critical in the induction and propagation of autoimmune inflammatory arthritis and that inactivation by allosteric inhibitors, which bind at the kinase switch control pocket, are a potent and effective intervention.

Disclosure: S.-I. Choi: None; **S. C. Wise:** Deciphera, 3; **D. L. Flynn:** Deciphera, 3; **Z. Zhu:** None; **E. Brahn:** Deciphera, 2.

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The Effects of Low Dose Etanercept on Disease Control and Radiographic Progression in Moderate to Severe Rheumatoid Arthritis. Bernd Raffeiner[1], Costantino Botsios[2], Paolo Sfriso[2], Francesca Ometto[2], Livio Bernardi[2], Silvano Todesco[2] and Leonardo Punzi[2]. [1]University Hospital of Padova - Rheumatology Unit, Padova, Italy, [2]University Hospital of Padova - Rheumatology Unit (Italy)

Background: Rheumatoid arthritis (RA) remains a socio-economic emergency: 100 billions of Euros were spent in 2006 for the disease in the USA and Europe. RA leads to disability, work loss and premature death. Biologics changed history of disease and patients' outcome. To justify elevated treatment costs biologics have been proved for cost-effectiveness. Some attempts are reported to reduce treatment costs. Etanercept (ETA) neutralizes TNFα with 20-fold higher potency than do other inhibitors at low concentrations of TNFα as for disease in remission. ETA appears suitable for dose reduction once patients gained remission.

Objectives of the Study: To elucidate efficacy of low dose ETA to maintain remission. To compare radiological progression and safety of low with standard dose. To estimate cost savings of low dose ETA strategy.

Material and Methods: Prospective observational study was performed on consecutive RA patients in DAS28 remission since 12 months by standard dose ETA from January 2004 to December 2009. Patients continued low (25 mg weekly) or standard dose ETA as follows: 56 with severe and 53 with moderate disease activity prior biologic continued with low dose ETA, 54 patients with severe and 54 with moderate activity standard dose. Patients were monitored every three months. Patients who failed dose reduction returned to full dose once remission was lost. Kaplan Meier survival curve was calculated for low dose patients. Modified Sharp score/van der Heijde (TSS) was performed on x-rays at baseline and after one year. Progression was reported as absolute $\Delta TSS > 0$ and as real progression $\Delta TSS \geq 5$ according to the smallest detectable difference of the method. Progression prior to biologic was estimated for each patient using preceding X-rays. Incidence of infections was calculated by Mid-P exact test modified by Miettinen. Cost savings of low dose strategy were calculated based on national pricing including tax. All comparisons were controlled for statistical significance by Mann-Withney or exact Fisher test.

Results: Between low and standard dose patients for both severe and moderate disease no differences for age, sex, disease duration, positivity for auto-antibodies, concomitant and past therapy, HAQ and ΔTSS/year were found. Severe groups resulted more aggressive from x-rays than moderate groups and were treated more likely with concomitant DMARDs. Up to now 89 patients (81,6%) maintained remission with low dose for a mean of 2.59 years. Patients failing dose reduction regained remission with full dose except one. Success was higher in younger patients taking less symptomatic, but was not different between severe and moderate groups. Radiological progression occurred only in a minority of patients in low dose ETA: $\Delta TSS > 0$ in 13.6% and $\Delta TSS \geq 5$ in 0.8% of cases. Capability to arrest radiological progression was identical in low and standard dose and in patients who failed dose reduction. Low dose patients had fewer infections. Low dose ETA strategy produced costs savings of €1,583,273 since its introduction, and continues to save €562,071 per year.

Conclusion: Low dose ETA sustains clinical and radiological remission. Low dose strategy is safe and produces notable cost savings.

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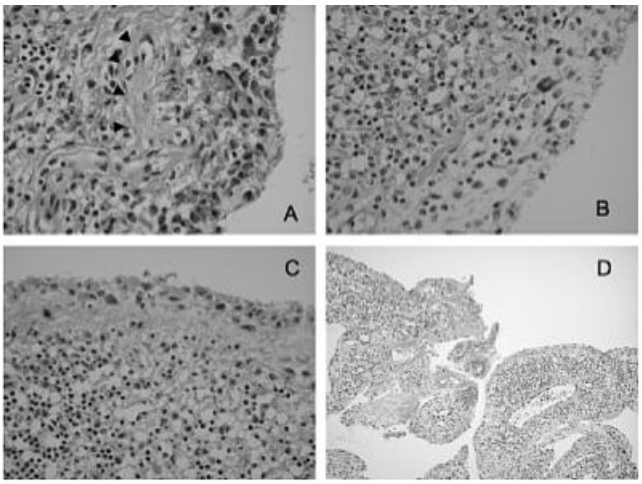
TNF Inhibitors Induce the Fibrosis in Deep Lining Layers of the Synovium with Degeneration of Synoviocytes in Rheumatoid Arthritis. Shunsei Hirohata[1], Tetsuya Tomita[2], Hideki Yoshikawa[3] and Masahisa Kyogoku[4]. [1]Kitasato Univ School of Med, Kanagawa, Japan, [2]Osaka Univ Med School, Suita Osaka, Japan, [3]Osaka Univ Med School, [4]Tohoku Univ School of Med

Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by hyperplasia of synovial tissues, leading to the destruction of joint structures. TNF inhibitors, including anti-TNF-α antibodies and soluble TNF receptors, have been demonstrated to have prominent therapeutic efficacy in RA. However, detailed mechanism actions of TNF inhibitors have not been fully understood.

Objective: The current studies were therefore designed to determine the characteristic features of synovial tissues of RA patients treated by TNF inhibitors in order to delineate their mechanism of action.

Methods: Synovial tissues were obtained from 12 RA patients who had been treated with TNF inhibitors in addition to disease modifying antirheumatic drugs (DMARDs) for at least 5 months (5–25months) during the joint surgical operations. As a control, synovial tissues were similarly obtained from 12 RA patients who had been treated with only DMARDs, but not with TNF inhibitors. Synovial tissues were fixed in formaldehyde and embedded in paraffin. The sections were evaluated by hematoxylin and eosin staining and Masson trichrome staining.

Results: There were no significant differences in serum CRP levels and treatment regimen except for TNF inhibitors between RA patients with TNF inhibitors and those with DMARDs alone. The most prominent changes in the synovium from RA patients with TNF inhibitors were hyalinization and fibrosis in deep lining layers of the synovium with degeneration of synoviocytes (mostly type B synoviocytes) and formation of multinucleated small giant cells, accompanying with marked decrease in vasculature. Figure 1 shows A. degeneration of synoviocytes with giant cells and obliterating vessels in the sublining layer (arrow heads), B. disappearance of synoviocytes with residual giant cell, C.decreased synoviocyte stratification and appearance of fibrosis in the lining layer with edematous changes in the sublining, D. extended fibrosis in the deep lining layers of the synovium.



There was no significant difference in the synovial changes between RA patients with infliximab and those with etanercept. Interestingly, appearance of foreign-body giant cells was observed more frequently in RA patients with TNF inhibitors (3 out of 12 patients) than in those without TNF inhibitors (1 out of 12 patients), suggesting the activation of healing process.

Conclusions: These results indicate that not only infliximab, but etanercept might have direct actions on synovial cells, presumably type B synoviocytes in the deep lining layers of the synovium, leading to the fibrosis and hyalinization thereof. Moreover, the data confirm that deep lining layers of the synovium are the most important portion that steer the disease process of RA synovitis.

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TNFα-Induced Adipose-Related Protein (TIARP) Regulates Autoimmune Arthritis Via the Suppression of IL-6. Asuka Inoue[1], Isao Matsumoto[2], Yoko Tanaka-Watanabe[2], Kayo Yamamoto[2], Naoto Umeda[2], Yuki Tanaka[2] and Takayuki Sumida[3]. [1]Division of Clinical Immunology, Doctoral Program in Clinical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba/ JSPS Research Fellow, Tsukuba City, Ibaraki, Japan, [2]University of Tsukuba, [3]University of Tsukuba/ Inst Clin Med, Tsukuba City, Japan

Background and Objective: Recently, we found that TNFα-induced adipose-related protein (TIARP) is dominantly expressed in spleens and joints in TNFα-dependent model such as glucose-6-phosphate isomerase (GPI)-induced arthritis. TIARP is a six-transmembrane protein induced by TNFα, interleukin-6 (IL-6) and IL-1β in adipose tissue, although mechanisms in the pathogenesis of arthritis remains unclear. To elucidate the role of TIARP in the development and pathogenesis of autoimmune arthritis, we have generated TIARP-deficient (TIARP$-/-$) mice.

Methods: (1) Collagen induced arthritis (CIA) was induced by immunization with 200μg of chicken typeII collagen (CII) emulsified in complete freund's adjuvant (CFA) to C57BL/6(B6) mice, followed by boost immunization after 21 days of primary immunization. The TIARP mRNA in spleens and joints was evaluated in CIA mice on day 14, 23, 28, by quantitative RT-PCR.

(2) We generated TIARP$-/-$ in B6 background. TIARP$-/-$ and wild type (WT) mice were immunized with CII as described methods above. The severity of arthritis was monitored by clinical score and evaluated histologically on day 60.

(3) The level of anti-CII antibodies (Abs) in serum were assessed by enzyme-linked immunosorbent assay (ELISA).

(4) Draining lymph nodes and splenocytes on day10 were cultured for 96hr with CII in vitro. IFNγ, IL-17 and IL-4 in their culture supernatant were measured by ELISA.

(5) The level of IL-6 and TNFα in serum on day60 after CII immunization were measured by ELISA.

Results: (1) In CIA model, the expression of TIARP mRNA in splenocytes was the highest in the early phase of arthritis (on day23). On the other hand, the expression in joints was accompanied with the joint swelling (on day28).

(2) The arthritis score in TIARP$-/-$ mice was higher than that in WT mice. Histological analyses showed that a lot of neutrophil infiltration, synovial proliferation, and cartilage destruction.

(3) The level of anti-CII Abs in serum were not significantly different between TIARP$-/-$ and WT mice.

(4) The amount of IFNγ, IL-17 and IL-4 was not significantly different between TIARP$-/-$ and WT mice.

(5) The serum IL-6 was significantly increased in TIARP$-/-$ mice, whereas serum TNFα was not detected.

Conclusion: These findings suggest that TIARP might be a negative regulator against autoimmune arthritis via the suppression of IL-6. TIARP might be a future target for the treatment of rheumatoid arthritis.

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Tyrosin Kinases Are Essential Mediators in the Development of Antigen Induced Arthritis Regulating Formation of Dendritic Cells and Antigen Presentation. Mats I. Dehlin[1], Sofia Andersson[2], Malin Erlandsson[2] and Maria Bokarewa[2]. [1]Department of Rheumatology and Inflammation Research, Sahlgrenska University Hospital, University of Göteborg, Gothenburg, Sweden, [2]Department of Rheumatology and Inflammation Research, Sahlgrenska University Hospital, University of Göteborg, Sweden

Background: Tyrosine kinases (TKs) are a family of intracellular signaling molecules participating in cell proliferation, development and apoptosis. Inhibition of TKs is effective in the treatment of various malignancies as well as diabetes mellitus. Several families of TKs are implicated in the pathogenesis of rheumatoid arthritis regulating processes in disease onset as well as progression. In previous work we demonstrated that a ligand to TK Flt3 is accumulated in the joints of RA patients and has proarthritic and erosive properties. Here we evaluate the role of TKs and Flt3-signaling in the antigen-induced model of arthritis.

Methods: Mice (n=75) were immunized with mBSA followed by an i.a.

injection of mBSA on day 21. Treatment with TK inhibitor sunitinib (10 an 40 mg/kg/day) was started on day 7 (n=30) and on day 21 (n=30) and continued until day 28. Controls (n=15) received citrate buffer. The mBSA-injected joints were evaluated morphologically and compared to circulating levels of bone (CTX-I) and cartilage (CTX-II) degradation marker and to anti-mBSA antibodies measured by ELISA. The effect of sunitinib on the levels of TK ligands Flt3-L, RANKL and VEGF were measured by ELISA. Expression of Flt3 and development of dendritic cells (DC) was evaluated in the bone marrow and spleen by flow cytometry.

Results: Sunitinib treatment alleviated mBSA-induced arthritis, reducing intensity of synovitis and frequency of bone erosions. This was accompanied by a reduction of mBSA antibodies and marker for bone degradation, CTX-I.

Sunitinib induced a pronounced increase in Flt3-ligand levels, while levels of VEGF and RANKL were changed only slightly, indicating relative specificity on Flt3-signaling. Following sunitinib treatment, the expression of Flt3 was selectively decreased on CD3+ population in bone marrow.

In spleen, sunitinib induced a significant decrease of pDCs as well as cDCs affecting all cDC subsets. However, sunitinib increased CD8+ population in spleen while the populations of B-cells and CD4+ T-cells were unchanged.

Conclusion: Sunitinib blocks TKs through Flt3 pathway alleviating synovial inflammation and bone resorption in antigen induced arthritis. This effect is potentially mediated through downregulation of DCs and decreased antigen presentation.

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ACR Poster Session A
Rheumatoid Arthritis - Clinical Aspects:Drug Studies, Drug Safety, Disease Activity and Remission, Infections I
Monday, November 8, 2010, 9:00 AM–6:00 PM

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A Decrease in Neutrophil Counts Following a Single Infusion of Tocilizumab Is Predictive of Low Disease Activity and Remission after 24 Weeks. Jasemine Saech[2], Kathrin Kuhr[1], Matthias Laudes[1], Olaf Schultz[1], Thomas Rath[1], Tobias Roehrs[1] and Andrea Rubbert-Roth[1] [1]University Clinic Cologne, [2]University Clinic of Cologne, Cologne

Background: Tocilizumab, a humanised monoclonal antibody targeting the IL-6 receptor, represents a potent new therapeutic principle for patients with active RA and intolerance or inadequate response to conventional DMARDs and/or TNF-blockers. Given the broad therapeutic armentarium of biologics that is available for RA patients today, predictive parameters before or during the early treatment period are urgently needed to optimize therapeutic strategies.

Method: In our center, 40 patients with active RA were started on tocilizumab 8 mg/kg iv q4w and followed prospectively for 24 weeks. DAS 28 and routine laboratory parameters were obtained at baseline and every 4 weeks subsequently.

Results: 40 patients (25% male, 75% female, mean baseline DAS28 6.09) were treated with tocilizumab 8mg/kg. 15/40 (42%) patients received tocilizumab as monotherapy and 25/40 (58%) with concomitant DMARD treatment. In 26/40 (64%) patients, tocilizumab was used as the first biological.

After 24 weeks, 20 patients achieved low disease activity LDA (DAS 28≤3.2) and 12 were in remission (DAS28≤2,6). CRP, neutrophils or other clinical or laboratory parameters at baseline did not correlate to outcome at week 24.

Patients with a DAS decrease of ≥ 1.2 at week 4 (early responders = ER) were compared to patients with a DAS difference of < 1.2 at week 4 (early non-responders = NR). 64 % of the ER, but only 31% of NR achieved LDA in week 24 (n.s.). More impressively, 52% of the ER, but 11% of the NR achieved remission in week 24 (p=0.02).

CRP levels normalized in all patients at week 4 and did not differ bet-ween ER and NR. Neutrophil counts at week 4 remained within normal limits in all patients. Of note, a decrease in neutrophil counts of ≥25% from baseline to week 4 was observed more frequently in ER (20/31) than in NR (2/9) (p = 0.05). More interestingly, a neutrophil decrease of ≥25% from baseline to week 4 was significantly associated with LDA and remission at week 24 (p=0,03).

Conclusion: Patients who responded to tocilizumab with a DAS 28 decrease of ≥1.2 in week 4 (ER) achieved remission significantly more often in week 24 than patients who do not respond ar week 4. Baseline CRP or normalization of CRP at week 4 did not correlate to ER/NR at week 4 or to LDA/re-mission at week 24. Of note, a decrease in neutrophil counts of ≥25% after a single infusion of tocilizumab (baseline to week 4) was highly predictive for achieving LDA/ remission in week 24.

Disclosure: J. Saech: None; **K. Kuhr:** None; **M. Laudes:** Roche, 2; **O. Schultz:** Roche, 2; **T. Rath:** None; **T. Roehrs:** None; **A. Rubbert-Roth:** Abbott Immunology Pharmaceuticals, 5, Actelion Pharmaceuticals US, 5, Amgen Inc., 5, Bristol-Myers Squibb, 5, Chugai, 5, Pfizer Inc, 5, Roche, 5, Schering-Plough, 5, UCB, Inc., 5.

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A Simplified Disease Activity Score (DAS): Validation in the BeSt Trial. Rosanne Koevoets[6], Yvonne Goekoop-Ruyterman[2], Desiree M. Van Der Heijde[5], K. H. Han[7], H. K. Ronday[1], T. W. J. Huizinga[6], P. J. S. M Kerstens[3], B. A. C. Dijkmans[8] and Cornelia F. Allaart[4]. [1]Haga Hospital, Den Hague, [2]Haga Hospital, Den Hague, The Netherlands, [3]JBI, Amsterdam, [4]Leiden Univ Med Ctr, Leiden, The Netherlands, [5]Leiden University Medical Center, Meerssen, The Netherlands, [6]Leiden University Medical Centre, Leiden, The Netherlands, [7]Maasstad Hospital, Rotterdam, [8]VU Medical Centre, Amsterdam, The Netherlands

Background: Implementation of DAS steered treatment is challenging current daily practice. Some feel that using the Ritchie Articular Index for pain in the original DAS is impractical.

Objective: To assess the validity of a simplified version of the original DAS with different versions of the pain component.

Methods: Within the first year of the BeSt trial, a 4 strategies trial in recent RA patients aiming at a DAS≤2.4, the percentage agreement and kappa statistics were calculated for 3 different versions of a simplified DAS compared to the original DAS: DAS with the Ritchie score reduced to a 0–1 score ('DAS 0–1'), DAS with a 53 joint 0–1 count for pain (DAS-TJC53), and a DAS with a 44 joint 0–1 count for pain (DAS-TJC44). At the same time for all alternative DAS versions and the DAS28 the DAS was calculated with the VAS general health (GH) and the VAS for patient's global assessment of disease activity (PGA). To display the difference for the continuous scores Bland-Altman plots were created with the mean versus the mean difference. Percentages agreement and kappa statistics were calculated for classification into remission, low disease activity (LDA) or moderate (MDA) or high (HDA) disease activity for all indices both with PGA and GH.

Results: DAS scores with a separate joint count are in general higher since there are no single counting joint groups created. As by definition the 'DAS 0-1' was lower in few cases; in the majority of the patients the DAS scores were equal (see figure1).

Mean difference between DAS and 'DAS 0–1' was −0.03; (limits of agreement (-0.24;0.18) between DAS and 'DAS-TJC53' 0.18 (-0.33;0.66) and between DAS and 'DAS-TJC44' 0.11 (-0.42–0.64) (figure 1). Compared with the original DAS, the 'DAS 0–1', 'DAS TJC53' and the 'DAS TJC44' agreed on the classification of patients in LDA, MDA or HDA in 99% (κ=0.98), 86% (κ=0.81) and 86% (κ=0.80), which would have resulted in the same treatment decisions in this trial. Although separate VAS scores are not highly correlated (r=0.5–0.8) all indices with PGA showed high chance corrected agreement (κ=0.87–0.94) compared to the corresponding GH score.

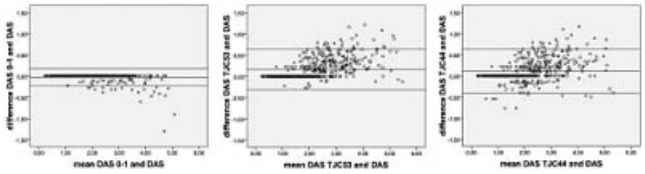

Figure 1. Bland-Altman plots representing the mean of the original DAS and alternative DAS in relation to the difference between both.

Conclusion: There are no important differences between all alternative DAS versions, both with the VAS GH and PGA, and all can therefore be used reliably as alternatives to the original DAS.

Disclosure: R. Koevoets: Centocor, Inc., 2, Dutch College of Health Insurances, 2, Schering-Plough, 2; **Y. Goekoop-Ruyterman:** None; **D. M. Van Der Heijde:** None; **K. H. Han:** None; **H. K. Ronday:** None; **T. W. J. Huizinga:** None; **P. J. S. M. Kerstens:** None; **B. A. C. Dijkmans:** None; **C. F. Allaart:** None.

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Aiming To Reach Remission—Is It Worthwhile? Helga Radner[3], Josef S. Smolen[1] and Daniel Aletaha[2]. [1]Krankenhaus Lainz, Vienna, Austria, [2]Medical University of Vienna, Vienna, Austria, [3]Medical University Vienna, Vienna, Austria

Background: Rheumatoid arthritis (RA) is a prevalent chronic inflammatory disease causing disability and a considerable burden for the single patient and society. Remission (REM) is one of the major goals of RA treatment. In this study, we investigated whether in patients with low disease activity aiming for remission is also effective from a socio-economic point of view.

Patients and Methods: In 356 patients with established RA we obtained information about quality of life (Short Form 36, SF-36), utility (Short Form 6D, SF-6D; Euro-Quol 5D, EQ-5D), physical disability (Health Assessment Questionnaire, HAQ), productivity (Work productivity and activity impairment Questionnaire, WPAI), as well as disease activity (Clinical Disease Activity Index, CDAI). In cross-sectional analyses we compared data obtained of patients in REM (n=89) to those in LDA (n=152) using Students T-Test. We also compared patients who stayed in REM (n=34) for a whole year and compared their values with those of patients in LDA (n=66) for the same period.

Results: In the cross-sectional analyses we found statistically significant differences of utilities when comparing patients in REM with those in LDA (SF-6D 0.75 vs. 0.66; EQ-5D 0.89 vs. 0.78), physical disability (HAQ 0.38 vs. 0.75) and productivity (WPAI % overall impairment: 18.1% vs. 33.8%; WPAI % impairment while working: 11.3% vs. 27.2%) (all comparisons: $p<0.05$?). Regarding quality of life we found significant differences in all domains except role emotional and MCS in favor of REM. Though, compared to healthy populations there are still significant differences in all domains except mental health (figure).

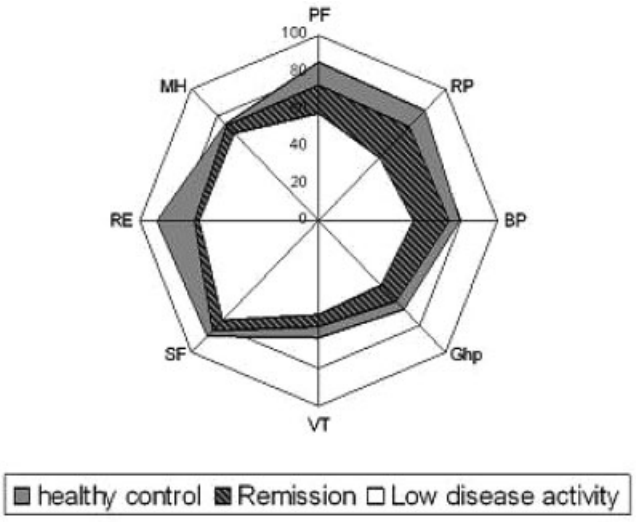

Figure 1. Domains of Short Form 36 in patients within REM compared to LDA and healthy control.
Abbreviations: BP bodily pain; PF physical function; RP role physical, GHP general health perception; SF social function; MH mental health; RE role emotional, VT vitality.

Preliminary longitudinal analyses showed significant differences of outcomes over one year between patients in REM and those in LDA: QALY (SF-6D 0.89 vs. 0.80; EQ-5D 0.80 vs. 0.66), Quality of life over one year (PCS 48.7 vs. 38.0), physical disability over one year (HAQ 0.22 vs. 0.69), and percent of overall activity impairment per year (12.2% vs. 31.0%). No significant difference of percent of activity impairment while working was found.

Conclusion: From a socio-economic perspective including quality of life, disability, and productivity, REM seems to be still superior to any other state of disease, even LDA. Therefore aiming for REM seems worthwhile and should be the major target when treating RA.

Disclosure: H. Radner: UCB, Inc., 2; **J. S. Smolen:** UCB, Inc., 2; **D. Aletaha:** UCB, Inc., 2.

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Body Weight and Response to Biologics in RA and Spondyloarthritides. Obesity Reduces the Rate of Remission-Response. The GISEA Registry. Gianfranco Ferraccioli[2], Francesco Trotta[5], Leonardo Punzi[11], Clodoveo Ferri[10], Piercarlo Sarzi-Puttini[6], Lisa Maria Bambara[4], Giovanni Triolo[3], Roberto Giacomelli[1], Roberto Gerli[12], Roberto Gorla[7], Angelo Marchesoni[13], Walter Grassi[9] and G. Lapadula[8]. [1]Department of Internal Medicine, University of L'Aquila, L'Aquila, Italy, [2]Division of Rheumatology, UCSC, Rome, Italy, [3]Rheumatology Department, University of Palermo, Palermo, Italy, [4]Rheumatology Department, University of Verona, Verona, Italy, [5]Rheumatology Division, University of Ferrara, Ferrara, Italy, [6]Rheumatology Unit, L Sacco University, Milano, Italy, [7]Rheumatology Unit, Spedali Civili of Brescia, Brescia, Italy, [8]Rheumatology Unit, University of Bari, Bari, Italy, [9]Rheumatology Unit, University of Marche, Jesi, Italy, [10]Rheumatology Unit, University of Modena, Modena, Italy, [11]Rheumatology Unit, University of Padova, Padova, Italy, [12]Rheumatology Unit, University of Perugia, Perugia, Italy, [13]UOC DH of Rheumatology, G. Pini Orthopaedic Institute, Milano, Italy

Background: It is well known that obesity produces inflammation and there are conflicting evidences that obesity determines higher disease activity status in rheumatoid arthritis (RA). Even underweight seems to lead to increased disease activity (cachexia). These possibly related changes between weight and disease activity could affect different responses to therapy. In this study we sought to define whether body weight could lead to different remission/response rate to anti-TNF in rheumatoid arthritis (RA) as well as in seronegative Spondyloarthropathies (SNeSpA).

Materials and Methods: The GISEA registry collect data on all RA and SNeSpA receiving Biologics from 14 Centres in Italy. The data we analyzed regards 580 RA and 392 SNeSpA receiving biologic treatments for at least 12 months. RA patients were 81.4% female, the mean age 56.75 yrs, had a mean DAS28 of 5.36, and ESR of 34.6, an HAQ of 1.31 at entry and a mean disease duration of 13 yrs; SNeSpA were 50 % male, the mean age was 49.5 yrs, the mean BASDAI was 5.48, HAQ 0.98 and dis.dur. 9.95 yrs. In RA 39.9 % were in normal weight, in SNeSpA 39.5 % were in normal weight. In RA 73% received anti TNFa, 27 % others (Rituxan, Abatacept). In SNeSpA 100 % were receiving TNFa blockers.

Results: In RA, DAS28 remission was seen in 18.9 % and in 16.2 % of all patients at the 6° month and 12° month of follow-up respectively. The respective percentages in normal weight RA were 20.3 and 19.4 % at the 6° and 12° month of follow up versus 16.9 % and 6.8% in obese patients ($p=0.018$). In SNeSpA a BASDAI < 3 was seen in 13.5 % and in 9.7 % of all patients at the 6° and 12° month of follow-up. The respective percentages in normal weight SNeSpA were 15.5 and 14.1% at the 6° and 12° month of follow-up versus 7.2 and 3.6% in obese patients ($p=0.03$). The numbers of underweight patients were too low to draw any conclusion.

Conclusions: Data suggest that obesity associates with a lower percentage of success in obtaining DAS28 remission in long standing RA. There is a 2.85 fold lower chance of obtaining remission in obese. In SNeSpA there is a 3 fold lower chance of obtaining a BASDAI of < 3 in obese versus normal weight patients. Two conclusions come along, the need to increase the dose of biologics in obese patients, the need to better control inflammation in obese in order to get control of comorbidities such as cardiovascular complications.

Disclosure: G. Ferraccioli: None; **F. Trotta:** None; **L. Punzi:** None; **C. Ferri:** None; **P. Sarzi-Puttini:** None; **L. M. Bambara:** None; **G. Triolo:** None; **R. Giacomelli:** None; **R. Gerli:** None; **R. Gorla:** None; **A. Marchesoni:** None; **W. Grassi:** None; **G. Lapadula:** None.

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Celecoxib, a Selective COX-2 Inhibitor Improved Upper Gastrointestinal (GI) Adverse Lesions in Patients with Rheumatoid Arthritis on Long-Term NSAID Therapy with Endoscopic Evaluation. Shigeyoshi Tsuji[1], Hirofumi Miyoshi[2], Tetsuya Tomita[3], Takanobu Nakase[2], Masayuki Hamada[2], Takahiro Oomae[2], Chikako Tsumoto[2], Yoshimasa Hirata[2], Muneteka Iguchi[2], Shoko Edogawa[2], Hideo Kawai[2] and Hideki Yoshikawa[4]. [1]Hoshigaoka Kosei-Nenkin Hospital, Hirakata City, Osaka, Japan, [2]Hoshigaoka Kosei-Nenkin Hospital, [3]Osaka Univ Med School, Suita Osaka, Japan, [4]Osaka Univ Med School

Purpose: Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for pain relief in patients with rheumatoid arthritis (RA); however, gastrointestinal (GI) adverse events are one of the serious problems of NSAIDs. Selective cyclooxygenase (COX)-2 inhibitors have been proven to be less associated with GI complications than traditional NSAIDs. However,

their effects on the GI tract have not been well studied in patients with preexisting NSAIDs-induced GI complications. Here, we prospectively investigated the effects of celecoxib (CEL) after switching from NSAIDs on the GI tract in RA patients with endoscopically identified GI mucosal injury.

Methods: We conducted upper GI endoscopy to examine GI tract injury in RA patients who had been treated with NSAIDs for 3 or more months with informed consent. GI mucosal injury was evaluated according to the modified LANZA score. Patients with mucosal injury without ulcers were switched from NSAIDs to CEL, while those with ulcers were switched to CEL with famotidine (FAM) on complete ulcer healing with therapy. At 16 week, the extent of GI mucosal injury was endoscopically reevaluated. Disease activity score (DAS28), joint symptoms, and visual analogue scale (VAS; global improvement and pain) were evaluated before and at 8 and 16 weeks after switching to CEL. Wilcoxon signed rank test was used and significance level was set at 0.05.

Results: Eighty-two patients were eligible for the study (69 females), and the average age and affected period were 62.2 (30–83) and 17.5 (1–50) years, respectively. The most prevalently-used NSAID was loxoprofen sodium (49.4%), followed by diclofenac sodium (25.9%), meloxicam (13.6%), and etodolac (11.1%). Endoscopic analysis revealed GI mucosal injury, including 6 ulcers, in 45 of 82 patients (54.9%). LANZA scores were 1, 2, 3, and 4, for 11, 12, 16, and 6 patients, respectively, and the mean score was 2.4 ± 1.0. The incidence ratio of GI mucosal injury was significantly higher in patients using diclofenac sodium ($p<0.05$) compared with those using other NSAIDs. At 16 week, LANZA score and the total number of GI erosions/redness were significantly reduced to 1.6 ± 1.3 and 6.5 ± 6.1, from respective pre-treatment values of 2.1 ± 0.8 and 10.6 ± 8.6, respectively ($p<0.01$). Of the 6 patients achieving complete remission of GI ulcers, 1 exhibited recurrent ulcers at week 16, and was diagnosed as having an *H. pylori* infection. At 16 week, DAS28 (ESR4) and DAS28 (CRP4) were significantly improved to 3.6 ± 1.3 ($p<0.05$) and 3.0 ± 1.1 ($p<0.01$), compared with each pre-treatment value of 3.9 ± 1.3 and 3.3 ± 1.1, and the number of tender and swollen joints were significantly reduced to 2.4 ± 3.7 ($p<0.05$) and 0.8 ± 1.2 ($p<0.01$), compared with each pre-treatment value of 3.1 ± 3.2 and 1.8 ± 2.2, respectively. VAS score was not changed after switching to CEL, suggesting its comparable analgesic effects to other NSAIDs.

Conclusion: In RA patients receiving long-term NSAIDs therapy, we demonstrated for the first time that preexisting NSAID-induced upper GI injury is improved after switching to CEL. Further, Its GI safety profile was accompanied by analgesic effects, suggesting the usefulness of switching to CEL for these patients.

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Changes in Lipoproteins Associated with MTX, MTX + Etanercept, and Triple DMARD Therapy among Early RA Patients in the TEAR Trial. Jeffrey R. Curtis[6], Christina Charles-Schoeman[2], Shuo Yang[4], Lang Chen[4], Stacey Cofield[4], George Howard[4], Theresa M. McVie[4], Larry W. Moreland[5], James R. O'Dell[7], Harold E. Paulus[1], Monika Safford[4] and S. Louis Bridges[3]. [1]Encino, CA, [2]UCLA, Santa Monica, CA, [3]Univ of Alabama-Birmingham, Birmingham, AL, [4]Univ of Alabama-Birmingham, [5]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [6]University of Alabama - Brimingham, Birmingham, AL, [7]University of Nebraska Medical Center, Omaha, NE

Background: DMARDs and anti-TNF agents may affect lipid profiles, but past studies in RA patients have generally been small and lacked comparator groups to quantify and compare changes in traditional lipoproteins. We studied early RA patients participating in the Treatment of Early Rheumatoid Arthritis (TEAR) trial randomized to initiate aggressively-titrated methotrexate (MTX) with step-up at 24 weeks to etanercept or triple therapy for patients not in low disease activity; methotrexate + etanercept (MTX+ETA); or triple therapy (TT) [MTX + sulfasalazine (SSZ) + hydroxychloroquine (HCQ)].

Methods: TEAR is a 2-year investigator-initiated, randomized, placebo-controlled trial of 755 DMARD-naïve early RA patients. In this analysis, participants had total serum cholesterol (TC), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) measured at 0, 48, and 102 weeks. LDL was measured quantitatively since samples were collected non-fasting. Changes in lipoproteins at weeks 48 and 102 were compared to baseline and across treatment arms. Change in LDL was correlated with change in CRP at the corresponding time points. Partial results are available based upon samples run to-date; the remaining samples are currently being analyzed.

Results: Characteristics of TEAR participants with lipid lab data (mean ± standard deviation): age 50.7 ± 13.4 yrs; 74% women; body mass index 30 ± 7; RA disease duration 3.5 ± 6.5 months; 87% RF+; 41% glucocorticoid users (mean dose 2.6 ± 4.1 mg/day); 34% current smokers; DAS28 5.8 ± 1.0. At baseline, mean values for total cholesterol were 233 ± 55 mg/dL, LDL 126 ± 39 mg/dL, HDL 54 ± 18 mg/dL. There were no significant baseline differences between treatment groups.

At 48 weeks, there were statistically significant increases in total cholesterol, LDL, and HDL compared to baseline ($p < 0.001$ for all) (see Table). These increases were greater in the MTX + ETA group than in the other treatment groups; only the increase in LDL was significant compared to MTX step-up group ($p = 0.04$). Changes at week 102 were generally similar but quantitatively lower than changes at 48 weeks. There was a low correlation between increase in quantitative LDL and decrease in CRP between 0 and 48 and also between 0 and 102 weeks ($R^2 \leq 0.03$, $p > 0.05$ across all treatment arms at both timepoints).

Changes in lipid profiles at 48 weeks, by randomization to each TEAR treatment arm

		MTX + Etanercept Group		MTX + HCQ + SSZ Group	
Change between 0 and 48 weeks (mg/dL)	Step-Up MTX Group (all pts)		p value versus MTX alone		p value versus MTX alone
Total Cholesterol	35.9 ± 61.1 (n = 137)	49.4 ± 56.2 (n = 89)	0.19	20.1 ± 61.0 (n = 44)	0.23
LDL (Quantitative)	16.2 ± 32.4 (n = 137)	27.3 ± 32.5 (n = 83)	0.04	9.1 ± 39.8 (n = 44)	0.39
HDL	13.1 ± 21.1 (n = 138)	14.6 ± 15.0 (n = 83)	0.62	8.7 ± 22.0 (n = 44)	0.34

Conclusion: Based upon preliminary results available to-date, substantial increases in cholesterol were observed among early RA patients starting MTX, MTX + ETA, and triple therapy. Physicians should be cognizant of optimizing CV risk factors such as lipoproteins in RA patients, particularly in relation to initiation of RA medications.

Disclosure: J. R. Curtis: Amgen Inc., 2, Centocor, Inc., 2, 5, Corrona, 2, 5, Roche, 5, 8, UCB, Inc., 2, 5, 8; **C. Charles-Schoeman:** Amgen Inc., 2; **S. Yang:** None; **L. Chen:** None; **S. Cofield:** American Shoulder and Elbow Society, 5, GlaxoSmithKline, 5; **G. Howard:** None; **T. M. McVie:** None; **L. W. Moreland:** None; **J. R. O'Dell:** None; **H. E. Paulus:** None; **M. Safford:** None; **S. L. Bridges:** None.

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DAS28 Level at Baseline Best Predicts Which Patients with New Onset Inflammatory Arthritis Will Ultimately Require Biologic Therapy. Vivian P. Bykerk[9], Gilles Boire[6], Boulos Haraoui[3], Carol Hitchon[7], Diane Ferland[2], Carter Thorne[4], Ed C. Keystone[8], Janet E. Pope[5] and CATCH Investogators[1]. [1]Canada, [2]Hopital Maisonneuve Rosement, Montreal, PQ, Canada, [3]Institut de Rhumatologie de Montreal, Montreal, PQ, Canada, [4]South Lake Regional Health Center, Newmarket, Newmarket, ON, Canada, [5]St Joseph Health Care London, London, ON, Canada, [6]Universite de Sherbrooke, Sherbrooke, PQ, Canada, [7]University of Manitoba, Winnipeg, MB, Canada, [8]University of Toronto, Toronto, ON, Canada, [9]University of Toronto, Boston, MA

Background: Use of rapidly escalated higher dose MTX in combination with other DMARDs followed, if needed with biologic therapies, with a goal of reaching remission by 6 months is the current standard of care for patients with new onset rheumatoid arthritis. Whether or not patients with very active new onset inflammatory arthritis should be treated with initial biologic therapies remains controversial amongst most health care providers.

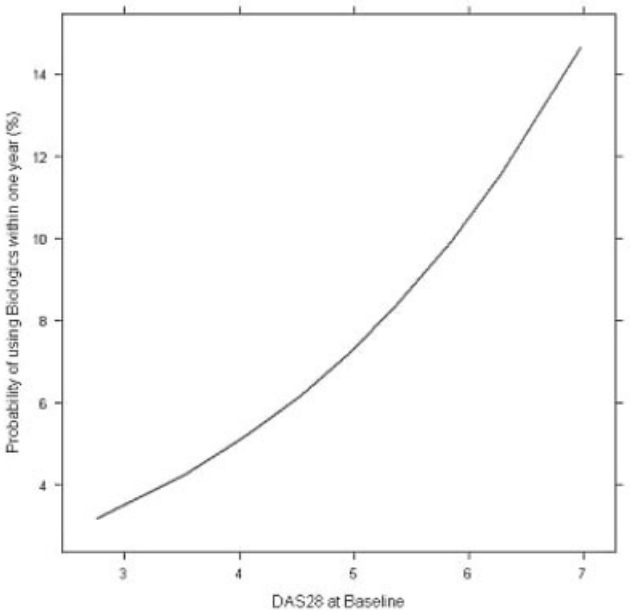
Objectives: To determine what factors at baseline or in the first three months of follow-up of patients with new onset arthritis correctly predict which patients need biologic therapies at one year.

Methods: Data from patients (n=1146) enrolled since July 2007 were collected from the Canadian Early Arthritis Cohort (CATCH) study, a multi-centre observational prospective "real world" cohort of patients with EIA. Inclusion Criteria: age >16, symptom duration 6–52 weeks of persistent synovitis, ≥2 effused joints or 1 swollen MCP/PIP + ≥1 of: +RF, +CCP, AM stiffness >45 minutes, response to NSAIDs, or a painful MTP squeeze test. A regression analysis was performed to determine factors best predict which patients will require biologic therapies at one year. Factors considered for this analysis included age, sex, DAS28 at baseline (BL), DAS28 at 3 months, use of methotrexate at doses of ≥ 20 mg by 3 months, baseline

erosions, socioeconomic status, active smoking status, CCP, RF, higher than normal CRP/ESR, swollen joint count (0–28), tender joint count (0–28), symptom duration. Patients needing and not needing biologics were matched for length of follow up. Patients were treated with ≥ 2 DMARDs prior to being eligible for biologic therapy.

Results: Baseline characteristics: mean age 52±16 years, 73% female, median symptom duration 5.5 months, mean DAS28 ESR 4.9±1.6, 25% already had erosions at baseline. 73% of patients met 1987 criteria for RA.27% treated with oral glucocorticoids, 50% with MTX, 35% with combination DMARDs, 8% with Biologics within 1 year. Patients had a median follow up of 0.75 years with follow up as long as 8 years. Of the variables analyzed the only independent factor predicting the use of biologics at one year was the DAS28 at baseline (OR=1.48, p<0.000001).

Conclusions: Of all the classical baseline factors used to determine prognosis in RA in previous studies, baseline DAS28 was the only independent factor significantly predicting use of biologics at one year.



Disclosure: V. P. Bykerk: Amgen Inc., 2, Pfizer Inc, 2, Wyeth Pharmaceuticals, 2; **G. Boire:** None; **B. Haraoui:** None; **C. Hitchon:** None; **D. Ferland:** None; **C. Thorne:** None; **E. C. Keystone:** None; **J. E. Pope:** None; **CATCH Investogators:** Amgen Inc., 2, Pfizer Inc, 2, Wyeth Pharmaceuticals, 2.

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Decreased Rate of Remission at 1 Year in Menopaused Women with Early Inflammatory Arthritis: The ESPOIR Cohort Study. Cédric Lukas[2], Ihsane Hmamouchi[2], Xavier Le Loet[3], Bruno Fautrel[1] and Bernard Combe[2]. [1]Department of Rheumatology, La Pitie Salpetriere Hospital, Paris, France, [2]Department of Rheumatology, Lapeyronie Hospital, Montpellier, France, [3]Department of Rheumatology, Rouen Hospital, Rouen, France

Background: Remission has become the current aim in the management of rheumatoid arthritis (RA), especially since the advent of biologic antirheumatic agents.

Objectives: To evaluate factors potentially influencing achievement of remission in women with early inflammatory arthritis.

Methods: The ESPOIR cohort study collects data on patients presenting with early arthritis. Remission, defined by a disease activity score (DAS 28) of <2.6, was used as the outcome measure after 1 year of follow-up and standard care. Baseline clinical, laboratory, genetic, and radiographic data were assessed. Logistic regression analysis was performed to determine baseline predictive factors of remission at 1 year, adjusting for patient-, disease- and physician characteristics.

Results: Of the 624 analysed patients, 318 (51%) fulfilled the American College of Rheumatology 1987 revised criteria for the classification of RA after 24 months of follow-up. The mean age was 47±13 years, and the mean symptom duration was 3 months. In the total population, 207 patients (33.2%) were in remission at one year, versus 112 (35.2%) in the RA group. In both populations and after adjustment for age and classical prognostic factors (disease activity at baseline, presence of raised acute phase reactants (CRP >10mg/l), presence of rheumatoid factor or anti-CCP antibodies and functional status), logistic regression analysis showed that the menopausal status had a significant independent pejorative value in achieving a remission status after 1 year of follow-up and usual care: OR=0.47 [95%CI 0.27–0.84], p=0.01 in the total sample, OR=0.54 [95%CI 0.24–1.19], p=0.13 in the patients diagnosed RA after 24 months of follow-up.

Conclusion: In the ESPOIR cohort, about one third of patients achieved remission after 1 year of usual care. Multivariate analysis revealed that beside usual prognostic factors, menopausal status had an independent negative influence on the outcome, with an approximately 50% decreased chance of achieving this favorable status in menopaused women.

Disclosure: C. Lukas: None; **I. Hmamouchi:** None; **X. Le Loet:** None; **B. Fautrel:** None; **B. Combe:** None.

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Demographic, Disease and Treatment Characteristics of the Rheumatoid Arthritis Population Enrolled in the AMORA Study (Applications for Methotrexate Optimization in Rheumatoid Arthritis) in Evaluating the Avise PG^{SM} Test. Prashanth R. Sunkureddi[1], Judith F. Gendreau[2], Rong Zablocki[3] and Dawn Navis[3]. [1]Clear Lake Rheumatology, Nassau Bay, TX, [2]Cypress Bioscience, Inc, San Diego, CA, [3]Cypress Bioscience, Inc

The study evaluated an assay for RBC methotrexate polyglutamates (MTXPG) in terms of its clinical utility and impact on treatment plans in RA patients experiencing inadequate clinical responses. The study also provided the opportunity to assess the relationships between demographic, treatment and disease characteristics and corresponding MTXPG levels.

Methods: 20 rheumatologists enrolled 146 adult RA patients. Patients were to have been taking MTX for a minimum of 3 months and experiencing an insufficient response to current therapies. Demographic, treatment and disease-related information was collected and the physician completed assessments of the patient's global health status and MTX efficacy. The physicians reported proposed treatment plans before and after MTXPG testing. After receiving the MTXPG result, physicians were surveyed regarding their opinion of the clinical utility of the assay.

Results: Presented in Table 1, 67% of patients were receiving 15 mg MTX or more per week at the time of testing. Almost 77% of patients were on MTX monotherapy; 14% were on biologics in addition to MTX; and 9% were on other non-biologics.

10% of patients had a MTXPG level above 60 nmol/L (the threshold above which previous studies showed an odds ratio of a good clinical response 5-fold higher than levels < 60 nmol/L). 64% exhibited intermediate MTXPG levels (20 – 60 nmol/L) and 27% of patients exhibited subtherapeutic MTXPG levels (< 20 nmol/L, the level below which the odds ratio of a poor response was found to be 3-fold higher than levels > 20 nmol/L). For the population as a whole, increasing MTXPG levels were associated with increases in the mean duration of MTX therapy.

Patients' tender+swollen joint counts tended to decrease as MTXPG levels rose. A similar relationship was seen with the physician's Global Health Assessment, which correlated well (rho = −.5) with patients' combined tender+swollen joint counts.

In 97% of the cases, physicians' rated the overall clinical utility of the MTXPG test as very usefulor somewhat useful. Physicians modified the prospective treatment plans for 45% of their patients after reviewing MTXPG results.

Table 1	MTXPG Results								
	<20 nmol/L N = 39			20-60 nmol/L N = 93			> 60 nmol/L N = 14		
Demographic, Disease and Treatment Variables	Median	Mean	Standard Deviation	Median	Mean	Standard Deviation	Median	Mean	Standard Deviation
Age (years)	53.0	53.6	12.65	62.0	61.4	13.13	71.0	72.9	8.45
MTXPG Result (nmol/L)	12.0	11.9	5.38	37.3	38.6	11.26	67.8	73.3	15.09
Current MTX Dose (mg/week)	15.0	14.2	4.66	15.0	16.0	4.09	15.0	15.3	4.61
Duration of Current MTX Dose (months)	6.0	20.2	40.93	8.0	18.7	24.16	13.0	18.0	18.94
RA Duration (months)	20.0	56.2	85.84	32.0	76.6	101.87	54.5	120.1	121.94
Initial MTX Dose (mg)	8.8	9.3	3.06	10.0	10.4	3.61	10.0	10.6	3.84
Total Duration of MTX Therapy since Initiation (months)	16.0	29.4	41.67	19.0	39.7	53.28	32.0	90.8	106.53
Swollen Joint Count	4.0	8.2	8.39	6.0	7.7	6.39	4.0	5.0	3.21
Tender Joint Count	6.0	8.9	8.16	6.0	7.0	5.68	4.0	4.8	4.12
Physician Assessment of MTX Efficacy (VAS: 0-10)	4.9	4.9	2.34	5.9	5.7	2.15	6.5	6.3	1.96
Physician Assessment of Patient's Global Health (VAS: 0-10)	6.0	5.7	2.21	5.6	5.7	2.04	6.6	6.6	1.27

Conclusion: In the AMORA study, higher MTXPG levels were associated with increasing MTX dose, duration of MTX therapy, and age. Clinical markers of disease activity also trended toward improvement as MTXPG levels increased. Physicians' expressed positive opinions regarding the test's overall clinical utility, and treatment plans were frequently modified after receipt of the MTXPG results (in 45% of cases).

Disclosure: P. R. Sunkureddi: Bristol-Myers Squibb, 8, Cypress Biosciences, Inc., 2, 8, Novartis Pharmaceuticals Corporation, 2, 8, Pfizer Inc, 2, 8, UCB, Inc., 8; **J. F. Gendreau:** Cypress Biosciences, Inc., 1, 3; **R. Zablocki:** Cypress Biosciences, Inc., 1, 3; **D. Navis:** Cypress Biosciences, Inc., 1, 3.

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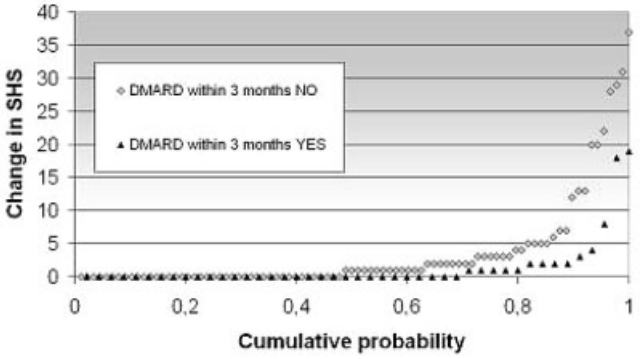
Demonstration of the Structural Efficacy of Very Early DMARD Initiation in Early Inflammatory Arthritis in Clinical Practice: Results of a Propensity Analysis in the ESPOIR. Cédric Lukas[3], Bernard G. Combe[4], Philippe Ravaud[1], Jean Sibilia[2], Robert Landewe[6] and Desiree M. Van Der Heijde[5]. [1]Department of Epidemiology and Biostatistics, Bichat Hospital, Paris, France, [2]Department of Rheumatology, Hautepierre Hospital, Strasbourg, France, [3]Department of Rheumatology, Lapeyronie Hospital, Montpellier, France, [4]Department of Rheumatology, Lapeyronie Hospital, Montpellier, France, [5]Leiden University Medical Center, Meerssen, The Netherlands, [6]Univ Hosp Maastricht, Maastricht, The Netherlands

Background: Despite the consensus recommending early treatment start in patients with early inflammatory arthritis with DMARDs of proven structural efficiency, demonstration of decreased radiographic progression with earlier therapy is scarce.

Objective: To compare radiographic progression in patients treated with a DMARD very early in the course of their disease (within 3 months after the onset of symptoms) and those who were started later on.

Methods: Patients included in the French observational ESPOIR cohort, treated independently of the data collection and without fixed protocol, were followed-up and radiographic progression after 12 months was assessed by Sharp-van der Heijde score (SHS). Propensity score (PS) was obtained by modelling the start of DMARD by logistic regression analysis using baseline disease specific and demographic variables. The influence of a very early DMARD start was evaluated by generalized linear regression, adjusting for PS as continuous covariate.

Results: 661 patients were analysed. Expectedly, patients treated within 6 months (ie with worst prognosis) showed a higher radiographic progression at 12 months ($p=0.026$). After adjustment for PS, the estimated marginal mean was significantly decreased in the early treatment group: 1.11 [0.95;1.27] SHS unit, versus 1.59 [1.48;1.69] ($p<0.001$). Additional analyses showed that this difference was especially pronounced in the groups of patients with a worse prognosis (figure).



Observed radiographic progression in patients with early inflammatory arthritis treated within 3 months after symptoms onset versus later, in the last quintile of propensity score.

Conclusion: Our results confirm for the first time that in a daily clinical practice standard of care of patients with very early arthritis, time to DMARD start clearly influences short-term radiographic outcome. These results strengthen the current recommendations claiming for a very early initiation of specific therapy in patients with early inflammatory arthritis.

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Derivation of a Preliminary Administrative Claims-Based Algorithm To Identify Lack of Effectiveness of Rheumatoid Arthritis Medications. Jeffrey R. Curtis[7], Shuo Yang[4], John Baddley[1], Grant W. Cannon[9], Lang Chen[5], Elizabeth Delzell[5], Nivedita M. Patkar[2], Kenneth G. Saag[8], Monika Safford[3], Jasvinder Singh[1] and Ted R. Mikuls[6]. [1]Birmingham VAMC/UAB, [2]Univ of AL at Birmingham, Birmingham, AL, [3]Univ of AL at Birmingham, [4]Univ of Alabama at Birmingham, [5]Univ of Alabama at Birmingham, Birmingham, [6]Univ of Nebraska Med Ctr, Omaha, NE, [7]University of Alabama–Birmingham, Birmingham, AL, [8]University of Alabama-Birmingham, Birmingham, AL, [9]University of Utah, Salt Lake City, UT

Background: Administrative claims data are commonly used to evaluate medication safety. Use of this type of data to study the clinical effectiveness of medications for rheumatoid arthritis (RA) has been limited by lack of a validated effectiveness algorithm. We created and tested a claims-based algorithm to serve as a proxy for a lack of clinical effectiveness of biologics for RA patients (pts).

Methods: Using national administrative claims data from the Veterans Health Administration (VA), we identified all U.S. veterans with RA using ICD9 code 714.X. We linked medical, pharmacy, and laboratory results to the nested subcohort of rheumatologist-confirmed RA patients participating in the longitudinal VA RA registry (VARA). VARA contains clinical and RA-specific information including DAS28 and CDAI. Among VARA enrollees, we identified the date individuals initiated a new biologics (the 'index date'; no use in prior 6 months) who remained under observation $\geq$ 1 year. The gold standard outcome was low disease activity (LDA, DAS28 $\leq$ 3.2) at one year ($\pm$ 2 months), + persistence with therapy. Alternate LDA criteria was CDAI $<= 10$.

The claims-based effectiveness rule defined lack of effectiveness as non-persistence with biologic therapy or increase in biologic dose. Further, treatment was considered not effective for pts not on steroids at baseline if they initiated chronic steroids, and for those on baseline steroids, if their cumulative steroid use 6 months after treatment exceeded the cumulative dose 6 months prior to treatment. Finally, therapy was considered ineffective if pts received $>$ 1 intra-articular or parenteral joint injection after the index date + 90 days. We calculated the performance characteristics of the effectiveness algorithm, with particular interest in the negative predictive value (NPV) as a proxy for lack of clinical effectiveness.

Results: Among 1397 enrolled VARA participants who were linkable to VA administrative claims data, 292 unique patients were eligible for analysis and initiated biologics for 386 treatment episodes. Characteristics of VARA patients in the analysis were mean $\pm$ SD age 64.7 $\pm$ 11.1 years, 91% male, 64% rheumatoid factor positive. At one year, 84% of treatment episodes did not achieve LDA criteria with persistence by DAS28 criterion. The NPV of the effectiveness rule was 82% (77% – 87%) using DAS28 criteria and 65% (58 –72%) using CDAI criteria. Ongoing work is underway to refine the algorithm and maximize its performance characteristics.

Conclusion: Administrative claims data may be useful in identifying lack of effectiveness of medications for RA. Validation in an external dataset will be useful to assess the generalizability and performance of this algorithm in other RA populations.

		Gold Standard: Low Disease Activity (DAS28 $\leq$ 3.2) and Persistent at 1 year		
		+	−	
Claims-Based	+	17 (4.4%)	112 (29.0%)	129 (33.4%)
Effectiveness Rule	−	46 (11.9%)	211 (54.7%)	257 (66.5%)
		63 (16.3%)	323 (83.7%)	386 (100%)

Disclosure: J. R. Curtis: Amgen Inc., 5, Centocor, Inc., 2, 5, Corrona, 2, 5, Roche, 2, 5, 8, UCB, Inc., 2, 8; **S. Yang:** None; **J. Baddley:** None; **G. W. Cannon:** None; **L. Chen:** None; **E. Delzell:** Amgen Inc., 2; **N. M. Patkar:** None; **K. G. Saag:** Amgen Inc., 2, 8, AstraZeneca, 5, Aventis Pharmaceuticals, 5, Eli Lilly and Company, 2, 5, Genentech and Biogen IDEC Inc, 5, GlaxoSmithKline, 2, 5, Merck Pharmaceuticals, 2, 5, NicOx, 5, Nitec, 5, Novartis Pharmaceuticals Corpora; **M. Safford:** None; **J. Singh:** None; **T. R. Mikuls:** None.

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Differences in Disease Severity and Response to Biologic Agents in a Racially Diverse US-Based Cohort of Patients with Rheumatoid Arthritis (RA). George A. Karpouzas[2], Rosalinda Moran[2], Soha Dolatabadi[1] and Michael Weisman[1]. [1]Cedars Sinai, [2]Harbor-UCLA

Background: Descriptions of RA behavior and response to therapy originate largely from studies in Caucasians. Additionaly, most subjects in clinical practice do not fulfill inclusion criteria for most RA trials. These observations may question the generalizability of the results of such trials to racially diverse populations. We describe RA clinical, serologic parameters, conventional and biologic DMARD utilization and therapeutic outcomes in a large, minority-enriched cohort from a single academic Center in the US.

Methods: We report on 433 pts fullfiling 1987 ACR criteria for RA and with regular follow-up. Patients were assessed quarterly, and Disease Activity Score (DAS28-3v-ESR) and functional outcomes (HAQ-DI, patient assessment of pain) were recorded. Good EULAR response (DAS28<3.2 and DAS28 change>1.2) was the only acceptable outcome and therapeutic adjustments were aimed at that goal. Continuous variables in unmatched and matched groups were analyzed with ANOVA and Wilcoxon's matched pairs test respectively. Categorical variables were analysed with Chi-square tests.

Results: Hispanics (H) comprised 81%, African Americans (AA) 12%, Caucasians (C) 5.1%, and others 3.8%. H and AA were significantly more female, and H were younger. There was no difference in disease duration, ESR, CRP, Rheumatoid Factor (RF) status and titer, or erosions in any group. ACPA (a-cyclic citrullinated peptide Ab) prevailed in AA (p=0.049). H and AA overall showed higher cross-sectional disease severity compared to C (table-p=0.04). Fewer H and AA achieved DAS28<3.2 than C (p=0.02); to accomplish this, H had higher frequency of biologic utilization than both AA and C (p=0.003). H or AA allocated biologics did not have higher disease severity at biologic onset, nor were they prescribed biologics more frequently than C. Despite a robust and similar change in DAS28 from baseline compared to C, significantly less of biologic treated H and AA achieved DAS28<3.2 (p=0.003).

Conclusion: US-based H and AA with RA have higher cross-sectional disease severity than C. In spite of similar disease activity at biologic onset, this likely reflects inferior response to biologic therapy; significantly fewer biologic-treated H and AA subjects achieved good disease control compared to C. The reasons for these disparities are under investigation.

Table. Patient Characteristics

N (%)	Hispanic = 349 (80.6)	AA = 50 (11.5)	C = 22 (5.1)	*p*-all groups
F/M (%)	88/12	92/8	64/36	<0.0001
Age (±SD yrs)	52.4 ± 11.2	56.4 ± 10.6	57.9 ± 8.9	0.01
DAS28-3v (M ± SEM)	3.2 ± 0.06	3.4 ± 0.17	2.7 ± 0.2	0.04
≥1 DMARD (%)	93.6	93.6	100	ns
Biologics (%)	60.3	50	59	ns
DAS28 ≤3.2 (%)	53	48	81.8	0.02
% with DAS28 ≤3.2 on biologics	64.3	41.6	55.6	0.003
DAS28 (M ± SEM) @ biologic onset	4.8 ± 0.09	4.9 ± 0.2	4.5 ± 0.5	ns
Biologic prescribed @ start (%)	70.1	60	59	ns
Δ DAS28 (M ± SEM)	1.48 ± 0.1	1.23 ± 0.27	1.41 ± 0.48	ns
% of biologic Rx with DAS28 ≤3.2	56.9	41.7	76.9	0.003

Disclosure: G. A. Karpouzas: None; **R. Moran:** None; **S. Dolatabadi:** None; **M. Weisman:** None.

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Disease Activity in Patients with Early Rheumatoid Arthritis Receiving Stable Conventional DMARDs Significantly Influences the Timing of Achieving a Low Disease State and Remission at 3 Versus 6 Months. Pooneh Akhavan[3], Vivian P. Bykerk[3], Ye Sun[4], J. Hochman[7], Janet E. Pope[10], Janet E. Pope[10], Carol A. Hitchon[11], Gilles Boire[8], Boulos Haraoui[2], Diane S. Ferland[6], J. Carter Thorne[9], Deborah A. Weber[5], Ed C. Keystone[12] and All CATCH Investigators[1]. [1]Canada, [2]Institut de Rhumatologie, Montreal, QC, Canada, [3]Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [4]Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [5]Mt Sinai Hosp, Toronto, ON, Canada, [6]Rheumatology, Hopital Maisonneuve, LaSalle, QC, Canada, [7]Rheumatology, University of Toronto, [8]Sherbrooke University, Sherbrooke, QC, Canada, [9]Southlake Regional Health Care, Newmarket, ON, Canada, [10]St Joseph Health Care London, London, ON, Canada, [11]University of Manitoba, Winnipeg, MB, Canada, [12]University of Toronto, Toronto, ON, Canada

Purpose: To date timing of treatment outcomes and responses have been evaluated mainly in retrospective studies of clinical trials in patients with high disease activity. Studies in real world patient populations with more moderate disease are sparse. We were interested in evaluating these outcomes in such a setting. The primary objective of this study was to evaluate the influence of disease activity on the timing to achieve Low Disease Activity State (LDAS) and remission (REM) in early rheumatoid arthritis (ERA) patients receiving stable treatment. We also explored the effect of baseline disease activity on response to treatment.

Methods: Patients with early RA in the Canadian Early Arthritis Cohort (CATCH), were evaluated. Patients who were receiving stable DMARDS for 6 months (with no dose adjustments after one month of initiating therapy and not receiving oral or parenteral steroids) were included. The majority of patients were receiving methotrexate ± sulphasalazine ± hydroxychloroquine. Patients with baseline moderate disease activity (MDA) (DAS28 >= 3.2 –5.1) (n= 38) versus high disease activity (HDA) (DAS 28 > 5.1) (n= 61) who had not achieved LDAS or REM at 3 months were evaluated for the proportion achieving LDAS or REM at 6 months. DAS 28 responses for these patients was compared at these two time points. We defined a poor therapeutic response by a ΔDAS 28 < 0.6 and good response by a ΔDAS < 1.2.

Results: 108 patients were evaluated with mean age of 50 years and mean disease duration of 6.3 ± 3.0 (mead ± sd) months at baseline. Rheumatoid factor was positive in 60% of patients. The majority of MDA patients achieved LDAS or REM by 3 months with a slightly greater proportion requiring 6 mo to achieve adequate clinical response. At 3 mo 58% of MDA patients achieved LDAS versus 63% at 6 months. Of 16 patients not in LDAS, 31% achieved it by 6 months. At 3 months 47% of MDA patients achieved REM versus 50% at 6 months. Of 20 patients not in REM at 3months 25% achieved it by 6 months.In patients with HDA a substantial number of patients required 6 months to achieve LDAS or REM. In these HDA patients 34% achieved LDAS at 3 months versus 62% at 6 months. Of 40 patients not achieving LDAS at 3 months 48% achieved it by 6 months while of 51 patients not achieving REM at 3 months 43% achieved it by 6 months. Of interest, almost all HDA patients achieved a ΔDAS > 0.6 (93%) or ΔDAS > 1.2 (84%) at 3 months. In contrast 37% of MDA patients failed to achieve a Δ DAS of 0.6 and 53% a change of 1.2 at 3 months. Of MDA patients with a Δ DAS of < 0.6 at 3 months, 36% achieved LDAS and 29% achieved REM at 6 months. Similar results were observed with a Δ DAS < 1.2 at 3months.

Conclusion: Baseline disease activity has a significant effect on timing to achieve an adequate clinical response. In HDA patients particularly consideration should be given to continuing therapy for at least 6 months if LDAS or REM is not achieved at 3 months.

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Does Sequence Matter When Switching from One Anti–Tumor Necrosis Factor Agent to Another? O. Baser[3], S. Roy[1], C. Akin[2] and M. A. Cifaldi[1]. [1]Abbott Laboratories, Abbott Park, IL, [2]Brigham and Women's Hospital, Boston, MA, [3]University of Michigan, Ann Arbor, MI

Background: A significant proportion of patients with rheumatoid arthritis (RA) switch from one anti–tumor necrosis factor (anti-TNF) agent to another. This study examines patient characteristics, costs, and outcomes of switching from one anti-TNF to another. Predictors of switching between anti-TNFs are also examined.

Methods: Continuously eligible adult patients in a large commercial administrative claims database with confirmed diagnoses of RA between January 2002 and December 2008 were included if they had initiated new anti-TNF treatment after a 12-month biologic-free period. Disease severity was estimated using a composite Severity Index for Rheumatoid Arthritis (SIFRA), a measure validated for administrative databases. Costs and outcomes were compared between groups 12 months after the switch, after adjusting for baseline differences in patient, disease, and prescriber characteristics through a propensity score-matching technique. Cox regression was used to determine the predictors of time to switch of biologic treatment.

Results: There were 1,567 patients in the study who switched to a second anti-TNF. Of these patients, 48% (n=751) switched to ADA, 19% (n=294) to IFX, and 33% (n=522) to ETN. Patients who were younger (HR=0.40), used methotrexate (HR=0.76), or other DMARDs (e.g. SSZ, HCQ and Gold) at baseline (HR=0.73), and had a low SIFRA severity index (HR=0.85) experienced a shorter time to switching to a second anti-TNF. Patients who started with IFX or ETN switched to a second anti-TNF sooner than those

who started on ADA (HR=0.86 for ETN and 0.85 for IFX vs. ADA). Patients switching from ETN to IFX instead of to ADA had more severe disease (p=0.002), had a greater comorbidity burden (p=0.002), were more likely to use MTX (p=0.0259), and were more likely to have had dose escalation prior to switch. Patients switching from ADA to IFX had a greater comorbidity burden compared with those who switched to ETN. Among switchers from IFX, slightly older patients with higher rates of respiratory infections were switched to ADA, compared with ETN. After adjusting for baseline differences, RA-related total annual health care costs were significantly lower for switches between the subcutaneously injected anti-TNFs (ETN-ADA, p<0.0001 both ways) compared with switches to their infusion counterpart (IFX). Among all possible anti-TNF sequences, RA-related total costs, as well as disease severity were lowest one year after a switch to ADA irrespective of which anti-TNF patients were switched from (table).

Adjusted RA-Related Costs and Disease Severity Outcomes 1 Year After Switch

	ETN to IFX	ETN to ADA	P-Value	IFX to ETN	IFX to ADA	P-Value	ADA to ETN	ADA to IFX	P-Value
Total RA-related cost	$19,523	$15,632	<0.0001	$15,324	$14,986	0.574	$18,652	$24,867	<0.0001
SIFRA	5.15	4.65	<0.0001	5.01	4.71	0.0001	4.74	4.76	0.805

Conclusions: The timing and outcomes of switching were observed to be different based on sequence of anti-TNFs used. Relative to ADA, patients switched sooner to a second anti-TNF if they had started on IFX or ETN. Both cost and disease severity outcomes appear to be better for switches to ADA compared with switches to IFX or to ETN.

Disclosure: O. Baser: STATinMED Research, 3, University of Michigan, 3; **S. Roy:** Abbott Laboratories, 1, 3; **C. Akin:** Brigham and Women's Hospital, 3, STATinMED Research, 3; **M. A. Cifaldi:** Abbott Laboratories, 1, 3.

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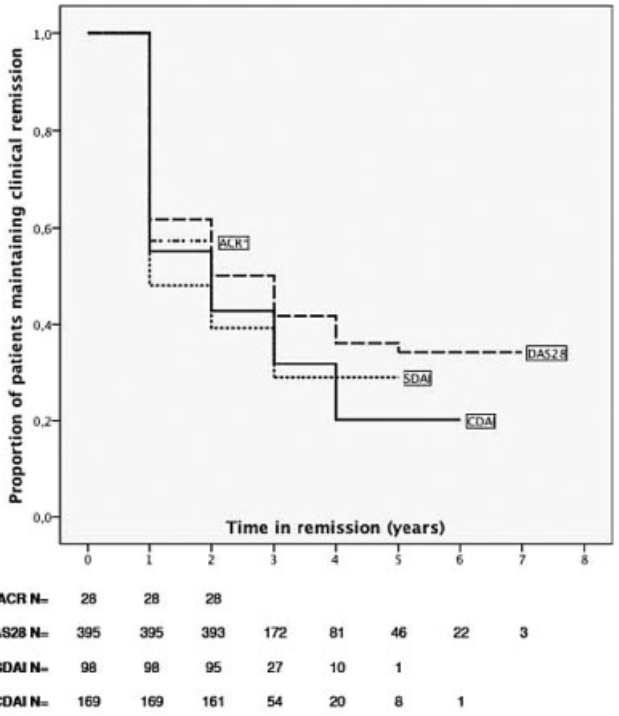
Durability of Clinical Remission in Rheumatoid Arthritis Based on Various Criteria. Femke H. M. Prince[2], Vivian P. Bykerk[2], Nancy A. Shadick[1], Jing Cui[2], Michele Frits[2], Christine K. Iannaccone[2], Michael E. Weinblatt[3] and Daniel Hal Solomon[3]. [1]Brigham & Womens Hospital, Boston, MA, [2]Brigham and Women's Hospital, Division of Rheumatology, Immunology and Allergy, BRASS, Boston, MA, [3]Brigham and Womens Hospital, Boston, MA

Background: The treatment target of Rheumatoid Arthritis (RA) is remission. Clinical remission can be defined by several criteria, but only one incorporates time as a variable. There are few data about the duration of remission by any criteria. The study aim was to describe the duration of remission periods in RA patients enrolled in a cohort from a single academic center, using different remission criteria.

Methods: Data were collected from a prospective, observational, single-center cohort of RA patients. Patients are prospectively followed, and their RA is managed according to the preference of the treating rheumatologist. Disease activity of patients was evaluated annually and remission was defined by: Disease Activity Score 28 (DAS28<2.6), ACR, Clinical Disease Activity Index (CDAI<2.8) and Simplified Disease Activity Index (SDAI<3.3). For the analyses we only included patients with: 1) at least two years follow-up; and 2) at least one remission time-point with subsequently 12 months or more follow-up. First remission time point for each patient was considered baseline. Analyses were performed using Kaplan-Meier survival curves and differences were analyzed using the log-rank-test.

Results: Of the 1095 RA patients in our study cohort, 846 had at least two years follow-up. When we considered the different remission criteria for all 846 patients, 408 were in remission at at least one time-point (with 12 months follow-up) according to the DAS28 (n=395), ACR (n=28), CDAI (n=169), or SDAI (n=98). At entrance of the cohort, median age of the 408 patients was 56 years, 83% were female, 64% were anti-cyclic citrullinated peptide or rheumatoid factor status positive, and median disease duration was eight years. Overall median survival time of remission was two years. Time in remission according to the different remission criteria is shown in the **Figure** (Kaplan-Meier curve). Probability of maintaining remission at the subsequent examination was significantly higher for the DAS28 criteria compared with the CDAI (p=0.029) and SDAI (p=0.030). The difference between duration of remission for DAS28 and ACR criteria was non-significant (p=0.57), however only few patients met the ACR criteria and no data were available for more than two years.



*ACR curve stops at 2 years

Figure. Duration of RA remission based on various remission criteria.

Conclusion: This study shows that approximately 50% of the RA patients who reached clinical remission maintained this state after one year. Even after multiple years in remission, patients can still drop out of remission. Whether patients are considered to be in clinical remission depends on the criteria used.

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Disclosure: F. H. M. Prince: Abbott Immunology Pharmaceuticals, 9, Bristol-Myers Squibb, 5, 9, Niels Stensen Foundation, 2, Novartis Pharmaceuticals Corporation, 9, Teva Pharmaceuticals, 9, Wyeth Pharmaceuticals, 9; **V. P. Bykerk:** None; **N. A. Shadick:** Amgen Inc., 2, Biogen Idec, 2, Crescendo Biosciences, 2; **J. Cui:** None; **M. Frits:** None; **C. K. Iannaccone:** None; **M. E. Weinblatt:** Biogen Idec, 2, 5, Crescendo Bioscience, 2, 5; **D. H. Solomon:** Abbott Immunology Pharmaceuticals, 2, Amgen Inc., 2, Bristol-Myers Squibb, 9.

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Effect of Anti-Tumor Necrosis Factor Alpha Therapy on Cardiovascular Events in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. Cheryl C. M. Barnabe[2], Billie-Jean Martin[1] and William A. Ghali[2]. [1]Libin Cardiovascular Institute, [2]University of Calgary, Calgary, AB, Canada

Background: Rheumatoid arthritis (RA) patients have an increased risk of cardiovascular (CV) events, attributed to both traditional CV risk factors and the inflammatory milieu of inadequately treated RA. Anti-tumor necrosis factor alpha (anti-TNF) therapy has an important role in treating patients with RA resistant to disease modifying therapies, and has been shown to have a positive impact on surrogate biomarkers of CV disease. Our objective was to systematically assess the association of anti-TNF therapy in RA on CV event rates reported in observational cohorts and randomized controlled trials (RCTs).

Methods: A search of PubMed (1950 to November 2009) and EMBASE (1980 to November 2009) was supplemented by manual searches of reference lists and conference abstracts. Observational cohorts and RCTs reporting on CV events (all events, myocardial infarction (MI), congestive heart failure (CHF), and cerebrovascular accident (CVA)) in RA patients treated with anti-TNF therapy were identified to determine the relative risk compared to those patients treated with traditional disease modifying drugs. The systematic review and meta-analysis includes 16 and 13 publications respectively.

Results: In cohort studies (total of 106,202 patients), anti-TNF therapy was associated with a reduced risk for all CV events (pooled adjusted RR 0.46; 95%CI 0.28–0.77), MI (pooled adjusted RR 0.81; 95%CI 0.68–0.96), and CVA (pooled adjusted RR 0.69; 95%CI 0.53–0.89). Cohort study results

for CHF outcomes were not suitable for meta-analysis. Meta-analysis of RCTs (total of 2,126 patients) also produced a point estimate indicating lower risk of CV events but this was not statistically significant (pooled relative risk of 0.85; 95%CI 0.28–2.59).

Conclusions: Anti-TNF therapy is associated with a reduced risk of all CV events, MI and CVA in observational cohorts. The point estimate of effect from RCTs is underpowered with wide confidence intervals, but also demonstrates a trend towards decreased risk. Limitations include heterogeneity among cohort studies and possible publication bias. For the RCT analysis, CV events were secondary outcomes and statistical power was limited.

Disclosure: C. C. M. Barnabe: Abbott Laboratories, 5; **B.-J. Martin:** None; **W. A. Ghali:** None.

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Effect of Intensive Repletion and Maintenance Vitamin D Therapy in Rheumatoid Arthritis Patients. Uzma J. Haque[1], Kevin Fontaine[2] and Susan J. Bartlett[3]. [1]Johns Hopkins School of Medicine, Lutherville, MD, [2]Johns Hopkins School of Medicine, [3]McGill University, Montreal, QC, Canada

Background: We have previously shown that 60% of rheumatoid arthritis (RA) patients attending an academic rheumatology clinic in Baltimore Maryland were vitamin D deficient. We are not aware of any studies that have evaluated the effectiveness of intensive vitamin D supplementation and maintenance therapy in this population.

Objective: To estimate the effectiveness of intensive vitamin D supplementation and maintenance therapy on 25(OH)D levels in a cohort of RA patients.

Participants: 25(OH)D levels were obtained in 111 persons who met ACR criteria for RA and who were receiving treatment at the Johns Hopkins Arthritis Center between January 2009 and June 2010.

Methods: Patients were consecutively approached during routine clinic visits. 25(OH)D levels were ascertained using the DiaSorin radioimmunoassay. Vitamin D deficiency was defined as 25(OH)D $<$ 30 ng/mL. Patients who were deficient were randomly assigned to 8 weeks of standard intensive repletion therapy (INT= ergocalciferol 50,000 IU /week) followed by up to 16 weeks of maintenance therapy (MT= ergocalciferol 50,000 IU/month) or placebo for 16 weeks (followed by the above vitamin D treatment). Hyperparathyroidism was excluded before initiating vitamin D therapy.

Results: Participants were mostly female (83%) and white (83%) with a mean ($\pm$ SD) age of 53.8 $\pm$ 12.1 yrs. At baseline, mean 25(OH)D was 21.5 $\pm$ 5.9; 70/111 (63.1%) were classified as vitamin D deficient. Patients seen from Oct – June had 7.0 times the odds of being deficient (95% CI 1.4–35.6) as those seen July – Sept. Of 46 patients completing INT, mean increase in 25(OH)D was 18.4 $\pm$ 13.5 ng/mL; 89% were classified as vitamin D sufficient. In summer, INT therapy was associated with significantly higher increases in 25(OH)D levels than those seen in the fall and winter (20.5 $\pm$ 4.5 and 12.3 $\pm$ 3.9 mg/dL, respectively.) However, adequate levels were not maintained with maintenance therapy; in 41 patients who completed 8 weeks of MT, 25(OH)D levels decreased by -9.8 ± 10.7 ng/ml; only 61% were now classified as sufficient. Of 36 persons completing a total of 16 weeks of MT, 25(OH)D decreased an additional -3.7 ± 5.9 ng/mL overall; only 31% were classified as sufficient.

Conclusions: Despite increasing awareness of the importance of vitamin D, deficiency remains common in RA patients. Intensive supplementation therapy with ergocalciferol appears to be effective in significantly increasing vitamin D levels in most RA patients. However, maintenance therapy, as currently used in clinical practice, may not be sufficient to maintain adequate vitamin D levels in these patients over time. Given the importance of optimal vitamin D levels, routine monitoring of may be required to ensure that sufficient levels are maintained. Our data suggest that RA patients may require higher maintenance doses to sustain vitamin D sufficiency.

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Effectiveness of Initial Treatment Allocation Based on Expert Opinion for Prevention of Rapid Radiological Progression in a Daily Practice Early RA Cohort. Anne Durnez[2], Geert Vanderschueren[1], Luc Lateur[1], Rene Westhovens[2] and Patrick Verschueren[2]. [1]University Hospital Leuven Radiology, Leuven, Belgium, [2]University Hospital Leuven Rheumatology, Leuven, Belgium

Background: Until now in daily practice initial treatment decisions are essentially based on expert opinion and only informally on prognostic factors. Recently a prediction model for rapid radiographic progression (RRP) was developed using a RA study population(1).

Objective: To evaluate the effectiveness of expert centered treatment selection for early RA and investigate the additional value of a prediction model for RRP in daily practice.

Methods: Consecutive early RA patients were allocated to initial combination therapy with steroids (ICTS) or DMARD monotherapy (IMT), based on informal evaluation of prognostic parameters: joint counts, ESR, CRP, RF, anti-CCP and radiographic damage(2). Subsequently a tight control strategy was applied. Baseline and year 1 radiographs were scored according to Sharp/van der Heijde (SvdH). Changes in SvdH score of more than 5 units at year 1 (=RRP) were documented. Mean change in SvdH scores and proportion of patients with RRP were compared between the ICTS and IMT group. Based on 28-SJC, RF titer and CRP/ESR, each patient was placed in the ASPIRE prediction matrix yielding a theoretical RRP risk for intensive or less intensive initial treatment. The mean risk of the selected treatment was compared between different subpopulations. The numbers needed to treat (NNT) intensively to avoid one RRP after 1 year were calculated based on the matrix model. By roc curve analysis the optimal NNT cut off for RRP prevention was determined.

Results: Patients prescribed ICTS (n=37) had a higher baseline disease activity and more were anti-CCP positive than in the IMT group (n=43). Nevertheless the mean [SD] change in total SvdH score after 1 year was lower in the ICTS group versus the IMT group (-0,95 [2,84] vs. 1,16 [4,11]; NS). There was also less RRP in the ICTS (1/37) compared to the IMT group (4/43). The mean [SD] risk associated with the expert's initial treatment choice was higher in patients with RRP (17,4% [7,7] vs. 12,21% [8,68]). The mean NNT intensively to prevent RRP was lower in the ICTS compared to the IMT group, but also in patients with compared to without rapid progression. The PPV of the NNT for RRP prevention was 12,6%, but the NPV reached 100% (sensitivity 100%, specificity 53,3%) with 9,17 as a cut off in our population.

Conclusion: Also in daily practice ICTS seems more effective for the prevention of RRP than IMT. Treatment allocation based on informal evaluation of risk factors keeps the theoretical risk for RRP under control in most patients with early RA, avoiding over- and under-treatment at group level. After a theoretically more risk full treatment choice only a minority develops RRP at 1 year, probably also thanks to subsequent treatment adaptations. The predictive matrix model would be most helpful for preventing over-treatment in daily practice.

(1)Vastesaeger N, et al. Rheumatology 2009;48(9):1114–21
(2)Verschueren P, et al. Rheumatology 2008;47(1):59–64

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ESR, CRP, or RF Status at Presentation Is Only Marginally Predictive of Future Treatments with Methotrexate or Biologic Agents over 25 Years in Two Settings in the United States and in Finland. Tuulikki Sokka[1], Hannu Kautiainen[2] and Theodore Pincus[3]. [1]Jyvaskyla Central Hospital, Jyvaskyla, Finland, [2]Medcare Oy, Annekoski, Finland, [3]New York University Hospital for Joint Disease, Hastings-on-Hudson, NY

Purpose: To analyze the likelihood of initiation of methotrexate (MTX) or anti-tumor necrosis factor alpha (anti-TNFα) biological agents in treatment of 1,892 RA patients in Jyvaskyla, Finland and 478 in Nashville, TN, USA between 1980 and 2004, according to whether rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), or C-reactive protein (CRP) was in normal or abnormal range at presentation.

Methods: Databases maintained from 1980–2004 on all patients with RA seen at Jyvaskyla Central Hospital, Jyvaskyla, Finland and all patients seen by one rheumatologist at Vanderbilt University in Nashville, TN, USA were analyzed. The first recorded ESR and CRP was available for 1,892 RA patients in Jyvaskyla and 478 in Nashville. The proportion of patients in whom MTX or an anti-TNF agent was initiated over the 25 years was analyzed according to baseline values for ESR $<$28 vs. $\geq$28 mm/h, CRP $<$10 vs. $\geq$10 mg/L, and a positive RF test at any time over disease course.

Results: Findings were quite similar at the 2 sites: at baseline, normal ESR $<$28 mm/h was seen in 45% and 47% of patients and normal CRP $<$10 mg/L in 44% and 58%, in Jyvaskyla and Nashville, respectively. RF was negative throughout disease course in 38% and 37%. The only significant

difference in future therapy was seen for RF and MTX treatment in Jyvaskyla, where 69% of patients with positive RF tests were treated with MTX versus 54% of patients with negative tests (p <0.001). MTX treatment was begun in only 5% more patients in Nashville who were RF-positive vs negative (67 vs 62%, NS). Patients with abnormal values at baseline for ESR and CRP were only marginally (<5%) more likely to be treated with MTX than patients with normal values (Table). No differences were seen in likelihood of future treatment with biological agents according to baseline ESR, CRP, or RF status at any time, in either locale (Table).

Percentage of patients with RA treated with MTX or anti-TNF agent during follow-up, according to high or low baseline values for ESR, CRP, and life-time RF in Jyvaskyla, Finland and Nashville, TN.

		Jyvaskyla, Finland					Nashville, TN				
Measure	**Treatment**	**n**	**Total**	**Normal**	**High**	**p**	**n**	**Total**	**Normal**	**High**	**p**
ESR				**<28mm/h**	**≥28mm/h**				**<28mm/h**	**≥28mm/h**	
	MTX	1892	63%	62%	64%	0.41	478	64%	64%	65%	0.76
	Anti-TNF	1892	4.3%	5.2%	3.6%	0.10	478	8.4%	8.4%	8.3%	0.98
CRP				**<10 mg/L**	**≥10 mg/L**				**<10 mg/L**	**≥10 mg/L**	
	MTX	1744	62%	61%	63%	0.41	175	85%	83%	88%	0.43
	Anti-TNF	1744	4.2%	4.7%	3.9%	0.41	175	20%	19%	22%	0.59
RF				**Neg**	**Pos**				**Neg**	**Pos**	
	MTX	1874	63%	54%	69%	<0.001	292	65%	62%	67%	0.36
	Anti-TNF	1874	4.4%	4.4%	4.4%	0.99	292	14%	15%	14%	0.83

Conclusion: Baseline laboratory values for ESR, CRP, and RF have only marginal impact on the likelihood of treatment with MTX or biological agents. At least 30% of patients with RA have a normal ESR or CRP, or negative RF test. A traditional view that an abnormal laboratory test generally is associated with more severe clinical status and higher likelihood of aggressive treatment has not been studied extensively with an evidence-based approach, although insufficient data are available for ACPA (anti-CCP) in this study. Additional data from usual care at other sites could provide further information toward possible reassessment of laboratory tests in usual care of patients with RA.

Disclosure: T. Sokka: None; **H. Kautiainen:** None; **T. Pincus:** None.

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Invasive Fungal Infections in Seniors with Rheumatoid Arthritis: A Population-Based Study from the Ontario Biologics Research Initiative. Jessica Widdifield[7], Sasha R. Bernatsky[3], J. Michael Paterson[1], Nadia Gunraj[2], Janet E. Pope[6], J. Carter Thorne[5], Alfred A. Cividino[4] and Claire Bombardier[7]. [1]Institute for Clinical Evaluative Science, Canada, [2]Institute for Clinical Evaluative Science, [3]McGill UHC/RVH, Montreal, QC, Canada, [4]McMaster University, Hamilton, ON, Canada, [5]Southlake Regional Health Care, Newmarket, ON, Canada, [6]St Joseph Health Care London, London, ON, Canada, [7]University of Toronto

Purpose: An increased risk of invasive fungal infections has been suggested in rheumatoid arthritis (RA). The Ontario Biologics Research Initiative (OBRI) is an innovative undertaking to promote real-world rheumatic drug surveillance, based in part on Ontario's comprehensive administrative healthcare databases. Our objective was to assess the risk of serious fungal infections in seniors with RA.

Methods: An RA cohort was assembled from Ontario billing and hospitalization data, 1992–2009. Analyses were limited to subjects aged > 65 who filled ≥ 1 prescription for an oral glucocorticoid, disease-modifying agent (DMARD) or biologic. We studied cases of invasive fungal infections (Aspergillosis, Coccidioidomycosis, Histoplasmosis, Blastomycosis, Paracoccidioidomycosis, systemic Candidiasis) identified from the diagnoses most responsible for hospitalizations and/or emergency room visits over 1998–2009. Cases of infection were matched (on age, sex, and date of cohort entry) to up to 5 controls from the same RA cohort. Multivariate conditional logistic regression analyses assessed the independent effects of demographics, comorbidity, medications, and markers of RA severity (number of rheumatology visits, extra-articular RA features, joint replacement).

Results: In 85,458 seniors with RA (contributing 614,915.5 person-years), 57 invasive fungal infections occurred (9.3 events per 100,000 person-years). Cases were more likely than controls (n=285) to be rural (42.1% of cases vs. 19.6% of controls) and to have more co-morbidities especially lung (43.9% vs 24.6%) and renal disease (12.3% vs 4.2%). Cases also had more extra-articular RA features (33.3% vs 21.4%) and more rheumatology visits. Biologic exposures were rare in our cohort, and at the time of infection, no cases were exposed to a biologic agent. In both cases and controls, the most common DMARDs were methotrexate (11.7%) and hydroxychloroquine (6.7%). In contrast, prednisone exposure > 10mg/d occurred in 17.5% of cases, versus 7.0% of controls. Multivariable models demonstrated that risk of invasive fungal infections was higher among rural-versus-urban residents (HR 14.47, 95% CI 4.46, 46.98) and in subjects with more co-morbidities (as assessed by number of distinct drugs used in the year prior, HR 1.24 95% CI 1.12, 1.37). There was a notable trend for greater risk of invasive fungal infection with prednisone doses > 20 mg/d (adjusted HR 6.10 95% CI 0.96, 38.83 (p=0.0556).

Conclusions: Rural residence and greater co-morbidity were associated with increased risk for invasive fungal infections in seniors with RA. Steroids were suggested as an independent risk factor in this population-based sample. Potential limitations of our study include relatively low drug exposure rates, the possibility of incomplete ascertainment of biologic exposures (for individuals receiving drugs through private insurance) and channelling bias (where persons at highest risk for infections may not be prescribed biologics).

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Is DAS28 Remission Good Enough? Disease Activity and Functionality in Rheumatoid Arthritis, Results of the DREAM Remission Induction Cohort. Marloes Vermeer[3], Ina H. Kuper[3], Monique Hoekstra[1], Hein J. Bernelot Moens[4], Piet L. C. M. van Riel[2] and Mart A. F. J. van de Laar[3]. [1]Isala Klinieken, Zwolle, The Netherlands, [2]Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, [3]University of Twente and Medisch Spectrum Twente, Enschede, The Netherlands, [4]Ziekenhuisgroep Twente, Almelo/Hengelo, The Netherlands

Background: Remission is the goal of treatment in rheumatoid arthritis (RA). In general, remission is associated with improved functionality. However, it is unclear whether remission according to the Disease Activity Score in 28 joints (DAS28) criteria is good enough to prevent functional disability. The objective of this study was to assess the relation between DAS28 and functionality after 1 year follow-up in very early RA.

Methods: Data of the Dutch Rheumatoid Arthritis Monitoring (DREAM) remission induction cohort were used (1). Disease activity was indexed as remission (DAS28 < 2.6), low (2.6 ≥ DAS28 ≤ 3.2), moderate (3.2 < DAS28 ≤ 5.1) and high (DAS28 > 5.1). Functionality was measured with the Health Assessment Questionnaire Disability Index (HAQ; scale 0 (best) to 3 (worst)) as well as with the SF-36 Physical Functioning Scale (PF-10; scale 0 (worst) to 100 (best)). HAQ ≤ 0.5 was regarded as HAQ remission (2). Primary outcomes after one year were: median HAQ and PF-10 values and percentages of patients reaching a HAQ ≤ 0.5 stratified by DAS28 level and the association between DAS28 and functionality (HAQ, PF-10).

Results: One year data were available for 239 patients. After one year, mean (SD) DAS28 was 2.59 (1.05) and observed DAS28 levels were 56.9% (136/239) remission, 16.3% (39/239) low, 24.3% (58/239) moderate and 2.5% (6/239) high. One year median (IQR) values of HAQ and PF-10 were 0.38 (0.00–0.86) and 75.0 (55.0–90.0) respectively. Median HAQ increased as median PF-10 decreased in parallel to increasing DAS28 levels (Kruskal-Wallis Test, both p<0.001) (Table 1). Higher percentages of HAQ ≤ 0.5 were found in the lowest disease activity groups (Table 1). Percentages of HAQ ≤ 0.5 were similar for age groups (< 55 yrs and ≥ 55 yrs) and gender. Overall, DAS28 correlated with HAQ (Spearman's rho 0.41, p<0.001) and PF-10 (rho −0.32, p<0.001). In patients who were in remission after one year (n=136), DAS28 still correlated with HAQ (rho 0.22, p=0.010) and PF-10 (rho −0.19, p=0.027).

Table 1. DAS28 levels and functionality scores after one year.

DAS28 level	Median (IQR) HAQ	HAQ ≤0.5, n (%)	Median (IQR) PF-10
Remission (n = 136)	0.25 (0.00–0.50)	104 (76.5)	80.0 (65.0–95.0)
Low (n = 39)	0.38 (0.00–0.75)	25 (64.1)	75.0 (55.0–90.0)
Moderate (n = 58)	0.69 (0.25–1.16)	23 (39.7)	65.0 (40.0–80.0)
High (n = 6)	1.33 (0.94–1.91)	1 (16.7)	40.0 (22.5–60.0)

Conclusion: A lower disease activity is related to better functionality in patients with very early RA. Below the DAS28 remission threshold (DAS28 < 2.6), a lower DAS28 is still associated with better functionality scores. The DAS28 is a composite score and the HAQ and PF-10 are patient reported outcomes. Our results emphasize that aiming for remission is

important but aiming at the lowest possible DAS28 is even better as it results in improved functionality, which is relevant for patients.

References:
1. Kuper et al. Ann Rheum Dis 2008;67(Suppl II):48.
2. Aletaha et al. Rheumatology (Oxford) 2006;45(9):1133–9.

Disclosure: M. Vermeer: None; **I. H. Kuper:** None; **M. Hoekstra:** None; **H. J. Bernelot Moens:** None; **P. L. C. M. van Riel:** None; **M. A. F. J. van de Laar:** None.

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Low Rate of Rheumatoid Arthritis Remission in Real Life: Might Predictive Factors Explain? Elodie Loppin[2], Ronan Garlantezec[1] and Elisabeth Solau-Gervais[2]. [1]Public Heatlh Department, University Hospital Brest, France, [2]Rheumatology Department University Hospital Poitiers, France

Objective: Remission constitutes the best achievable state in patients with rheumatoid arthritis (RA). Remission rates in usual clinical care are much more lower than the one in randomized clinical trials (1). The objective of the study was to define remission factors in "real life".

Methods: Remission has been assessed retrospectively for records of 364 patients with rheumatoid arthritis receiving usual care. These patients were out and in patients followed in an university hospital with at least one visit in year 2008. Disease activity was evaluated on records according to DAS 28 criteria. Remission was defined by a DAS28 < 2.6.Statistical analysis used Chi-2 and multivariate analysis with the software SAS9.

Results: The evaluation of disease activity was available for 328 patients (90 %). Mean age of the patients was 63 years (+/−13,7) and mean duration of the disease was 13,6 (+/−10,7). Rheumatoid factor and anti-CCP was positive respectively in 79.3% and 73.8 %. Eighty five percent had an erosive disease. The rate of global remission was 28 %. Factors associated statistically with remission in multivariate analyse were (Ors 95% confidence intervals): male sex (0,2-0,8), younger age (0,2-0,9), rheumatoid factor-positive (1,2–6,5) and the absence of concomitant prednisolone treatment (0,3-0,9). Younger age and rheumatoid factor-positive represents more a population with a "higher therapeutic objective" and female sex and older age patients have more a difference in the evaluation of the disease, rather than true differences in RA activity. Moreover, the remission rate was significantly different according to the treatment: 15% without DMARDs or biotherapy, 24% with DMARDs and 47% with anti-TNF alpha treatment. As regards to the three anti-TNF alpha, the remission rate was the lowest for infliximab (18%), than etanercept (43%). Patients treated with adalimumab had the highest rate of remission with 64%. The difference was significant between infliximab and adalimumab (OR: 1.2–101) and between infliximab and etanercept (OR: 1,1–30,15) but not between etanercept and adalimumab.

Conclusion: Male sex, younger age, rheumatoid factor-positive and corticoids free are associated with remission. Assessing remission in clinical practice is possible, and etanercept and adalimumab treatments are associated with higher rate of remission.

(1) Sokka T, Hetland ML, Makinen H, Kautiainen H, Horslev-Petersen K, Luukkainen RK, et al. Remission and rheumatoid arthritis: data on patients receiving usual care in twenty-four countries. Arthritis Rheum 2008;58(9):2642–51.

Disclosure: E. Loppin: None; **R. Garlantezec:** None; **E. Solau-Gervais:** None.

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Lymphocytopenia and Infection Risk in Rheumatoid Arthritis: A Population Based Analysis. Deana D. Hoganson[2], Eric L. Matteson[1], Patrick D. Fitz-Gibbon[3] and Cynthia S. Crowson[3]. [1]Mayo Clinic, Rochester, MN, [2]Mayo Clinic Rochester, Rochester, MN, [3]Mayo Clinic Rochester

Background: There is an increased susceptibility for infections in patients with rheumatoid arthritis (RA) which contributes to increased mortality. Lymphocytopenia is prevalent in RA patients and may contribute to increased infection risk. The purpose of this study was to examine the association between lymphocytopenia and infection in RA patients during the pre-biologic era and develop a risk score for infections.

Methods: We utilized a population based cohort of patients with incident RA ascertained between 1955 and 1994 that were followed longitudinally through their complete medical records until 1/1/2000. The outcome measures included all objectively confirmed infections (by microbiology or radiology) and serious infections (requiring hospitalization or IV antibiotics). Data were collected on smoking status, leukopenia, lymphocytopenia, comorbidities (alcoholism, diabetes mellitus (DM), chronic lung disease, cardiovascular disease (CVD)), RA disease characteristics (erosions, extra-articular manifestations (ExRA), rheumatoid factor (RF), nodules, erythrocyte sedimentation rate (ESR)) and medication use. Potential predictors were examined using multivariable Andersen-Gill models (a variation of Cox modeling allowing multiple infections per patient) with time-dependent covariates.

Results: Among the 584 RA patients (mean age 58 years; 72% female; median followup 9.9 years), 277 had ≥1 objectively confirmed infection (706 total infections), and 252 had ≥1 serious infection (646 total infections). Significant predictors of both outcomes included age, male sex, leukopenia, lymphocytopenia, alcoholism, DM, chronic lung disease, CVD, ExRA, RF positivity, nodules, ESR and glucocorticoid use. Lymphocytopenia was significantly associated with objectively confirmed (HR=1.7, 95% CI=1.3–2.2; p<0.001) and serious (HR=1.6, 95% CI=1.2–2.2; p<0.001) infections after adjustment for the other risk factors. Using these models, infection risk scores were developed for each outcome. The score discriminated patients with low (5 year risk 13% ± 4.1%), medium (5 year risk 23% ± 7.4%), and high infection risk (5 year risk 40% ± 8.5%) (figure).

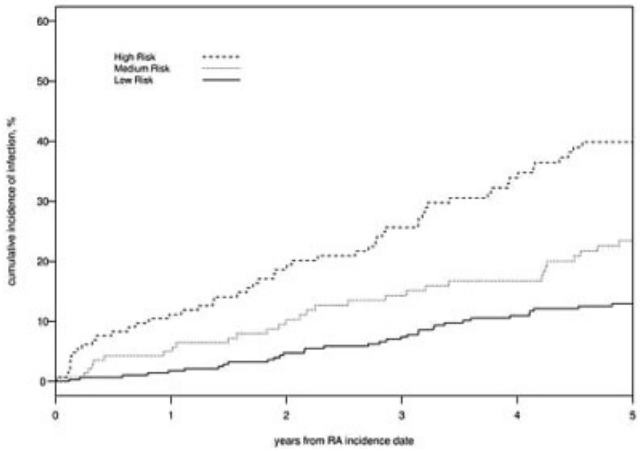

Figure. Cumulative incidence of objectively confirmed infections in RA patients based on risk score.

Conclusions: This study reveals that lymphocytopenia is an independent risk factor for infection in RA patients. A risk score may alert clinicians to the potential occurrence of infection in their RA patients. Further research is needed to examine whether this score accurately estimates the infection risk in patients treated with biologics.

Disclosure: D. D. Hoganson: Genentech and Biogen IDEC Inc, 2; **E. L. Matteson:** Genentech and Biogen IDEC Inc, 2; **P. D. Fitz-Gibbon:** Genentech and Biogen IDEC Inc, 2; **C. S. Crowson:** Genentech and Biogen IDEC Inc, 2.

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Measures of Disease Activity Provide Various Clinical Decisions in Individual Patients. P. H. P. de Jong[1], J. M. W. Hazes[2], J. J. Luime[2] and A. E. A. M. Weel[3]. [1]Department of Rheumatology, ErasmusMC, Rotterdam, The Netherlands, [2]Department of Rheumatology, ErasmusMC, Rotterdam, [3]Department of Rheumatology, Maasstad Hospital, Rotterdam

Background: Disease Activity Score (DAS) and its modified versions, Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) are indices used to measure disease activity. Provided thresholds for activity states to adjust therapy on were solely based on rheumatologists' decisions. To achieve disease remission, treatment adjustments based on tight controlled indices is recommended in individual patients, but no preferred index is defined. Moreover, data on reflection of disease state with clinical remission are missing.

Purpose: To investigate the interchangeability of measures of disease activity to base treatment decisions on. To compare remission thresholds of indices with predefined clinical remission.

Methods: For this study data are used of a currently ongoing clinical trial in patients 18 years or older with recent-onset arthritis (tREACH). Treatment decisions to step up or step down are performed every 3 months and based upon the DAS thresholds >2.4 and <1.6. For the present study DAS indices are recalculated, namely DAS 3 variables (no patient Global), DAS-CRP, DAS-CRP 3 variables, same combinations for 28 joints and SDAI and CDAI. Thresholds for remission and active disease for DAS28, SDAI and CDAI are respectively <2.6 and >3.2, <3.30 and >11, and <2.80 and >10. Clinical remission is defined as having: (1) less than 2 swollen joints, (2) no swollen

joints and (3) no swollen and no tender joints. Discriminative ability of thresholds were calculated by sensitivity and specificity analyses using DAS as reference.

Results: 753 disease activity scores per index were available from 344 patients using data of all visits available. Active disease states of various indices compared to DAS have a sensitivity range from 78% to 90%. DAS indices with 44 joints have a specificity above 95%, others are below 90% (Table 1). For remission all DAS indices have a sensitivity above 82% whereas CDAI and SDAI have a significant lower sensitivity of respectively 28% and 26%. For specificity the indices varied not statistical significantly (Table 1).

Table 1. Discriminative ability of indices using original DAS as reference

	n=344 providing 753 time points		Rheumatoid Arthritis* (n=92 in 283 time points)	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
DAS (CRP)>2.4	0.84 (0.78–0.88)	0.96 (0.94–0.97)	0.78 (0.67–0.87)	0.96 (0.93–0.98)
DAS (3var)>2.4	0.89 (0.84–0.93)	0.99 (0.97–1.00)	0.89 (0.80–0.95)	0.99 (0.97–1.00)
DAS (CRP/3var)>2.4	0.78 (0.72–0.84)	0.97 (0.95–0.98)	0.76 (0.64–0.85)	0.98 (0.95–0.99)
DAS28 >3.2	0.91 (0.86–0.95)	0.81 (0.77–0.84)	0.97 (0.91–1.00)	0.79 (0.73–0.84)
DAS28 (CRP)>3.2	0.88 (0.83–0.92)	0.84 (0.81–0.87)	0.91 (0.82–0.96)	0.85 (0.79–0.89)
DAS29 (3var)>3.2	0.87 (0.82–0.91)	0.84 (0.81–0.87)	0.95 (0.87–0.99)	0.84 (0.78–0.88)
DAS28 (CRP/3var)>2.4	0.79 (0.73–0.84)	0.88 (0.85–0.91)	0.85 (0.75–0.92)	0.89 (0.84–0.93)
SDAI>11	0.89 (0.84–0.93)	0.73 (0.69–0.76)	0.93 (0.85–0.98)	0.75 (0.68–0.80)
CDAI>10	0.90 (0.85–0.93)	0.74 (0.70–0.78)	0.95 (0.87–0.99)	0.76 (0.70–0.82)
DAS (CRP) <1.6	0.90 (0.86–0.93)	0.94 (0.91–0.96)	0.93 (0.87–0.97)	0.91 (0.86–0.95)
DAS (3var) <1.6	0.95 (0.92–0.97)	0.97 (0.95–0.98)	0.95 (0.90–0.98)	0.96 (0.92–0.99)
DAS (CRP/3var) <1.6	0.90 (0.86–0.93)	0.93 (0.90–0.95)	0.91 (0.86–0.96)	0.87 (0.81–0.92)
DAS28 <2.6	0.84 (0.79–0.88)	0.88 (0.84–0.91)	0.85 (0.77–0.90)	0.90 (0.84–0.94)
DAS28 (CRP)<2.6	0.84 (0.79–0.88)	0.87 (0.84–0.90)	0.86 (0.79–0.92)	0.86 (0.80–0.91)
DAS28 (3var) <2.6	0.82 (0.78–0.86)	0.82 (0.78–0.86)	0.80 (0.72–0.87)	0.86 (0.79–0.91)
DAS28 (CRP/3var)<2.6	0.86 (0.82–0.90)	0.82 (0.78–0.86)	0.86 (0.79–0.92)	0.83 (0.76–0.89)
SDAI <3.30	0.26 (0.21–0.31)	0.99 (0.98–1.00)	0.30 (0.22–0.38)	0.99 (0.97–1.00)
CDAI <2.80	0.28 (0.24–0.34)	0.99 (0.97–1.00)	0.34 (0.26–0.42)	0.99 (0.97–1.00)

*Diagnosis Rheumatoid Arthritis according to the ACR classification criteria-1987

SDAI and CDAI have a significant lower sensitivity and high specificity for clinical remission. All DAS indices however have a higher sensitivity but lower specificity (Table 2).

Conclusion: Various indices of disease activity misclassify disease state when compared to the original DAS, which could imply that patients have still active disease in one while not in another. Moreover remission thresholds are also discordant where SDAI and CDAI under detect clinical remission, where DAS indices might misclassify patients to be in clinical remission.

Table 2. Remission thresholds of indices compared to predefined clinical remission states

	n=344 providing 753 time points			
	SJC≤1		SJC=0	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
DAS <1.6	0.58 (0.54–0.62)	0.79 (0.74–0.83)	0.65 (0.60–0.70)	0.75 (0.71–0.79)
DAS (CRP) <1.6	0.49 (0.45–0.54)	0.83 (0.78–0.87)	0.57 (0.51–0.62)	0.80 (0.76–0.84)
DAS (3var) <1.6	0.58 (0.54–0.62)	0.80 (0.76–0.84)	0.64 (0.59–0.69)	0.75 (0.71–0.79)
DAS (CRP/3var) <1.6	0.51 (0.47–0.55)	0.84 (0.80–0.88)	0.58 (0.53–0.63)	0.80 (0.77–0.84)
DAS28 <2.6	0.58 (0.54–0.62)	0.77 (0.72–0.81)	0.64 (0.59–0.68)	0.72 (0.68–0.76)
DAS28 (CRP) <2.6	0.52 (0.48–0.57)	0.85 (0.81–0.89)	0.61 (0.56–0.66)	0.82 (0.79–0.86)
DAS28 (3var) <2.6	0.60 (0.56–0.65)	0.75 (0.70–0.79)	0.67 (0.62–0.72)	0.71 (0.67–0.75)
DAS28 (CRP/3var) <2.6	0.54 (0.50–0.59)	0.80 (0.75–0.84)	0.64 (0.59–0.68)	0.79 (0.75–0.82)
SDAI <3.30	0.16 (0.13–0.20)	0.99 (0.97–1.00)	0.20 (0.16–0.25)	0.98 (0.96–0.99)
CDAI <2.80	0.22 (0.18–0.27)	0.99 (0.97–1.00)	0.26 (0.22–0.31)	0.97 (0.95–0.99)

Table 2. Remission thresholds of indices compared to predefined clinical remission states (Continued)

	n=344 providing 753 time points			
	TJC=0 & SJC=0		SJC=0 & normal acute phase reactants	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
DAS <1.6	1.00 (0.97–1.00)	0.73 (0.70–0.77)	0.67 (0.60–0.72)	0.69 (0.65–0.73)
DAS (CRP) <1.6	0.89 (0.84–0.93)	0.79 (0.75–0.82)	0.65 (0.59–0.71)	0.70 (0.65–0.73)
DAS (3var) <1.6	0.98 (0.95–1.00)	0.73 (0.70–0.77)	0.67 (0.60–0.72)	0.70 (0.65–0.73)
DAS (CRP/3var) <1.6	0.89 (0.84–0.93)	0.78 (0.75–0.81)	0.67 (0.61–0.73)	0.70 (0.66–0.74)
DAS28 <2.6	0.87 (0.81–0.91)	0.68 (0.65–0.72)	0.74 (0.68–0.79)	0.72 (0.68–0.76)
DAS28 (CRP) <2.6	0.87 (0.81–0.91)	0.77 (0.74–0.80)	0.73 (0.67–0.79)	0.71 (0.70–0.75)
DAS28 (3var) <2.6	0.86 (0.81–0.91)	0.65 (0.62–0.69)	0.78 (0.72–0.83)	0.70 (0.66–0.74)
DAS28 (CRP/3var) <2.6	0.87 (0.81–0.91)	0.73 (0.69–0.76)	0.67 (0.61–0.73)	0.70 (0.66–0.74)
SDAI <3.30	0.35 (0.28–0.43)	0.97 (0.95–0.98)	0.26 (0.20–0.32)	0.95 (0.93–0.97)
CDAI <2.80	0.45 (0.38–0.52)	0.96 (0.94–0.97)	0.26 (0.21–0.32)	0.94 (0.91–0.96)

Disclosure: P. H. P. de Jong: None; **J. M. W. Hazes:** None; **J. J. Luime:** None; **A. E. A. M. Weel:** None.

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Minocycline and Doxycycline Therapy in Community Patients with Rheumatoid Arthritis (RA): Incidence, Patient-Level Determinants of Use and Side Effects. Christopher J. Smith[2], Harlan R. Sayles[2], Ted R. Mikuls[1] and Kaleb D. Michaud[1]. [1]Univ of Nebraska Med Ctr, Omaha, NE, [2]University of Nebraska Med Ctr, Omaha, NE

Background: Minocycline (MC) and doxycycline (DC) are safe and moderately effective disease-modifying antirheumatic drugs (DMARDs) in the treatment of early, DMARD-naive RA. Little is known about how these medications are used outside the context of clinical trials. We characterize the use of MC and DC in a large community of RA patients by examining associated prescribing patterns, patient-level determinants of use, and the frequency and severity of patient-reported side effects.

Methods: We studied 15,716 patients with RA observed between 1998 and 2009 while participating in a long-term US observational study. Patients were categorized by their use of MC/DC. Patient-reported side effects and their consequences were also evaluated.

Results: MC and/or DC were used 1,407 (9%) patients during their disease course with 480 (3.1%) incident users. Patients were seen by 1,067 rheumatologists, of which 196 (18.4%) prescribed MC/DC with an interquartile range of 1–2 patients per physician. Significant differences between MC/DC users and non-users are shown.

Table. Sociodemographic and disease characteristics of MC/DC users and non-users

	Initiated MC and/or DC (n = 480)	Never Used MC or DC (n = 14,309)	p-value
RA Duration (years)	14.77 (10.92)	13.70 (11.05)	0.036
Age (years)	58.35 (11.60)	59.76 (13.28)	0.021
Caucasian, Non-Hispanic %	93.68	89.72	0.005
Lifetime DMARD	2.90 (1.83)	2.13 (1.54)	<0.001
Lifetime DMARD & Biologics	3.30 (2.10)	2.52 (1.81)	<0.001
Prednisone %	40.08	35.34	0.033
SF-36 PCS (0–100)	35.03 (11.17)	36.39 (11.09)	0.008

In multivariable Cox regression, initiation of MC/DC was significantly associated with an increase in disease activity, comorbidity, previous number of non-biologic DMARDs, and calendar year, and associated with a decrease in previous number of biologic DMARDs and use of MTX, leflunomide or azathioprine. Side effects were reported by 17.8% of MC users and 11.8% of DC users. About 40% of those reporting side effects discontinued the medication. Skin complaints accounted for 54% of MC patient-reported side-effects. The most-commonly effected organ systems for DC were gastrointestinal (35.4%) and skin (33.7%). Dizziness was reported equally by MC (9.5%) and DC (8.2%) users. The majority of side effects were classified as mild or moderate for MC (70.0%) and DC (76.4%).

Conclusion: Rheumatologists have not embraced MC and DC as primary treatment options for RA and reserve their use primarily in patients with long-standing disease refractory to other agents. These drugs are generally well-tolerated with skin complaints, nausea, and dizziness being the most common patient-reported side effects.

Disclosure: C. J. Smith: None; **H. R. Sayles:** None; **T. R. Mikuls:** None; **K. D. Michaud:** None.

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Multi-Centre, Cross-Sectional, Observational Study of the Safety of Methotrexate and Leflunomide in Combination in the Treatment of Patients with Rheumatoid Arthritis *The SMILE Study— Safety of Methotrexate In Combination with Leflunomide.* Paul Bird[2], Hedley Griffiths[1] and The Optimising Patient Outcomes in Australian RheumatoLogy [OPAL] Consortium. [1]Barwon Rheumatology Service, Victoria, Australia, [2]Combined Rheumatology Practice (CRP), University of NSW, Sydney, NSW, Australia

Background: The combination of methotrexate and leflunomide is effective in early RA[1] and commonly utilized in Australia. The frequency of use of this combination in Australia is in part due to Federal government legislation, mandating the combination as pre-requisite treatment prior to eligibility for government funded biological therapy. Hepatotoxicity and neutropenia are two of the most common adverse effects associated with this combination.

The primary objective of this study was to assess the safety of treating patients with rheumatoid arthritis with a combination of methotrexate (MTX) and leflunomide (LEF) in comparison to methotrexate monotherapy (MTX).

Methods: Multi-centre, observational, cross-sectional, retrospective, safety study. The study was conducted by the OPAL QUMI (**O**ptimising **P**atient outcomes in **A**ustralian rheumato**L**ogy – Quality Use of Medicines Initiative). Using a clinical audit program, data was sourced from 12 participating rheumatology practices comprising 24 rheumatologists. All data was de-identified to patient, clinic and clinician prior to collection. Approval for the study was granted by the University of New South Wales Human Research Ethics Committee.

Results: In total, 3362 patients were included in the study; 72% female, 27% male, <1% gender unassigned, mean age 62 years (SD 13.8). Distribution of therapy: MTX monotherapy 49.2%, LEF monotherapy 7.6%, MTX/LEF 14.8%, Neither MTX or LEF 28.4%.

Mean MTX dose in the monotherapy group was 14 mg/week (SD 6.7), mean MTX dose in the MTX/LEF combination group 18 mg (SD 17). Mean LEF dose in the monotherapy group was 16.8 mg/day (SD 4.9), mean LEF dose in the MTX/ LEF combination group was 16.0 (SD 5.3). Co-morbid liver disease was reported in less than 5% of patients.

Liver function abnormalities were reported in 12% of the MTX monotherapy group, 16% of the LEF monotherapy group, 14% of the MTX/LEF combination group and 16% of the group taking neither of the drugs. The majority of the AST/ALT abnormalities were in the range less than 1.5 times the upper limit of normal in all four groups.

Neutropenia was reported in 2% of the MTX monotherapy group, 8% of the LEF monotherapy group, 5% of the MTX/LEF combination group and 3% of the group not taking either drug.

Conclusion: Liver function abnormalities and neutropenia in the MTX/LEF combination group were mild and equivalent to reported levels in either MTX monotherapy or LEF monotherapy. Levels of liver function abnormalities in the combination group were lower than those reported in previously published trials.[2] The combination of MTX and LEF was well tolerated, with adverse events comparable to monotherapy and the other non biologic DMARD treatment group.

[1] Kremer J et al. JRheumatol 2004 Aug 31(8): 1521–31
[2] Lee SS et al ScandJRheum 2009 Jan-Feb;38(1): 11–14

Disclosure: P. Bird: Abbott Laboratories, 5, Roche, 5, Wyeth Pharmaceuticals, 5; **H. Griffiths:** Roche, 5; **The Optimising Patient Outcomes in Australian RheumatoLogy [OPAL] Consortium:** None.

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Multi-Centre, Observational Study Shows High Proportion of Australian Rheumatoid Arthritis Patients Have Inadequate Disease Control. Geoffrey Littlejohn[2] and Kathleen E. Tymms[1]. [1]Canberra Rheumatology, Canberra, ACT, Australia, [2]Monash Medical Centre, Clayton, Victoria, Australia

Background: Contemporary management of rheumatoid arthritis [RA] includes early use of disease modifying drugs with the aim to achieve disease remission. RA management in Australia involves drug algorithms based on disease activity predefined by health care payers. This study used a new methodology in order to evaluate the disease activity and current therapy of RA patients managed in Australia.

Methods: Using a point of care electronic clinical management program, details of RA patients treated in 21 participating Australian clinics were collected at one point in time. This included patient demographics, diagnosis, medications and disease measures. The data was de-identified to patient, clinic and clinician. Analysis of this data was conducted to determine the proportion of RA patients who were in disease remission (DAS28 <2.6), low disease activity (LDA, DAS28 2.6–3.1), moderate disease activity (MDA, DAS28 3.2–5.1) and high disease activity (HDA, DAS28 >5.1), and their respective treatments. Ethics approval was granted by the University of New South Wales Human Research Ethics Committee.

Results: As of the 23rd April 2010, 4766 rheumatoid arthritis patients (73% females; 26% males, <1% gender indeterminate) had been assessed at 21 participating clinics. The mean age was 61.5 (60.5 females, 64.2 males) and mean disease duration was 12.6 years (13.1 females, 11.3 males). DAS28 scores were recorded for 51% of patients with 42% in remission, 20% in LDA, 30% in MDA and 8% in HDA. Of the patients in remission, 20% were being treated with a bDMARD, 77% with methotrexate (MTX), 24% with leflunomide (LEF), and 36% with prednisone. Of the patients in MDA, 23% were being treated with a bDMARD, 80% with MTX, 33% with LEF and 49% with prednisone. Of the patients in HDA, 30% were being treated with a bDMARD, 84% with MTX, 45% with LEF and 65% with prednisone.

Overall, 18% of patients were being treated with a bDMARD and 35% of patients were being treated with prednisone.

Conclusions: Cross-sectional assessment of this large cohort of Australian RA patients, managed in accordance with contemporary practice, shows a large number who have moderate and high disease activity. As disease activity predicts radiological and functional outcomes, this indicates that current RA management practice in Australia will result in significant future health burden in RA patients.

Disclosure: G. Littlejohn: Roche, 5; **K. E. Tymms:** Roche, 5.

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Multiple Courses of Rituximab Produce Sustained Efficacy in Patients with Rheumatoid Arthritis with an Inadequate Response to One or More TNF Inhibitors. Edward C. Keystone[6], Roy M. Fleischmann[5], Paul Emery[2], Maxime Dougados[3], Sarah Williams[4], Matthew D. Linnik[1] and Mark Reynard[4]. [1]Biogen Idec, San Diego, San Diego, CA, [2]Chapel Allerton Hospital, Leeds, United Kingdom, [3]Hospital Cochin, Paris, France, [4]Roche Products Ltd, Welwyn Garden City, UK, [5]University of Texas Southwestern Medical Center, Dallas, Dallas, TX, [6]University of Toronto, Toronto, ON, Canada

Objectives: To assess the efficacy of repeat courses of rituximab (RTX) in patients (pts) with a prior inadequate response to TNF inhibitors (TNF-IR).

Methods: Rheumatoid arthritis (RA) pts recruited into Phase II or III studies with RTX and who previously had an IR to a TNF inhibitor were permitted to receive further courses of RTX in open-label extensions. Eligibility for retreatment included a response to the initial course (at least 20% reduction in swollen and tender joint counts [SJC/TJC]) with subsequent courses given no more frequently than every 16 weeks. Criteria for retreatment included active disease defined as either ≥8 SJC and TJC or DAS28 ≥2.6 (depending on the study). Each course (C) consisted of 2 × 1000mg given as IV infusions 2 weeks (wks) apart. Efficacy was determined 24 wks following each course of RTX with outcomes assessed relative to the pts pre-RTX treatment baseline. Analyses were performed using observed data on all pts, and on all pts with efficacy data at 24 wks following each of their first five courses of RTX (the within pt-within visit [WW] population).

Results: 500 RA TNF-IR pts had been exposed to at least one course of RTX and had efficacy data at Week 24, with 119 evaluable at 24 wks following each course (WW population). Observed efficacy in all pts show higher responses for C2 onwards compared with C1. However, retreatment criteria may cause this population to become enriched for RTX responders, as pts were required to achieve a response to C1. Similar maintained or improved responses were seen in the WW population.

	All patients					Within pt, within visit				
	C1	C2	C3	C4	C5	C1	C2	C3	C4	C5
ACR responses (n)	500	360	289	222	153	119	119	119	119	119
ACR20 (%)	61.0	70.8	70.9	65.8	65.4	68.9	72.3	71.4	67.2	70.6
ACR50 (%)	30.2	41.4	46.4	43.2	42.5	35.3	41.2	45.4	42.9	44.5
ACR70 (%)	12.0	18.9	25.3	22.5	20.3	16.0	18.5	23.5	21.0	22.7
EULAR responses (n)	489	355	288	215	149	112	112	112	112	112
Good response (%)	15.7	25.4	33.3	28.8	28.2	10.7	20.5	25.9	23.2	30.4
DAS28 LDA (%)	16.2	25.6	33.7	28.8	28.2	11.6	20.5	25.9	23.2	30.4
DAS28 remission (%)	8.4	14.4	17.7	17.2	16.1	6.3	8.9	9.8	15.2	15.2
Change in DAS28										
Mean change	−2.15	−2.64	−2.93	−2.88	−2.93	−2.29	−2.63	−2.83	−2.85	−3.08
SD	1.43	1.43	1.46	1.59	1.73	1.32	1.46	1.46	1.67	1.66

LDA = DAS28 ≤3.2; remission = DAS28 <2.6

From C1 to C5, the proportion of pts in the WW population achieving DAS28 low disease activity (LDA) or remission doubled. Safety over repeat courses did not show any unexpected findings, with consistent rates of infection and serious infection.

Conclusion: In TNF-IR pts with an initial response to RTX, repeated courses of RTX were associated with sustained levels of efficacy.

Disclosure: E. C. Keystone: Abbott Laboratories, 2, 5, 8, Amgen Inc., 2, 5, 8, AstraZeneca, 2, Bristol-Myers Squibb, 2, 5, 8, Centocor, Inc., 2, 5, Genentech and Biogen IDEC Inc, 5, Hoffmann-La Roche, Inc., 2, 5, 8, Novartis Pharmaceuticals Corporation; **R. M. Fleischmann:** Abbott Laboratories, 2, 5, Amgen Inc., 2, 5, Bristol-Myers Squibb, 2, 5, Celgene, 2, Centocor, Inc., 2, 5, Genentech and Biogen IDEC Inc, 2, 5, Lexicon, 2, 5, Lilly USA, LLC., 2, Pfizer Inc, 2, 5, Regeneron Pharmaceuticals; **P. Emery:** Abbott Laboratories, 2, Roche, 2, 5; **M. Dougados:** Abbott Laboratories, 2, 5, 8, Bristol-Myers Squibb, 2, 5, 8, Roche, 2, 5, 8, UCB, Inc., 2, 5, 8, Wyeth Pharmaceuticals, 2, 5, 8; **S. Williams:** None; **M. D. Linnik:** Biogen Idec, 3; **M. Reynard:** GlaxoSmithKline, 1, Roche, 1, 3.

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National Trends in Drug Use, Health Status and Costs in Older Americans with Rheumatoid Arthritis. Leslie R. Harrold[3], Becky Briesacher[4], Daniel Peterson[1] and Jerry H. Gurwitz[2]. [1]Meyers Primary Care Institute, [2]Meyers Primary Care Institute/UMass Medical School, [3]UMass Medical Schl, Worcester, MA, [4]UMass Medical School

Introduction: Little is known about the recent adoption of the nonbiologic and biologic disease modifying anti-rheumatic drugs (DMARDs) in older patients with rheumatoid arthritis (RA), or the potential impact of these drugs on health status and costs.

Method: We identified a nationally-representative sample of RA patients in the Medicare Current Beneficiary Survey linked to Medicare claims data (unweighted unique n of 221 to 258 patients annually; initial response rate ~85%) and tracked DMARD use and health status during the years 2000–2006. RA patients were identified using a combination of ICD-9 diagnoses (714.XX); self-reported RA diagnosis, and use of biologic and nonbiologic disease modifying anti-rheumatic drugs (DMARDs). DMARD use was identified based on self-reported use of adalimumab, etanercept, hydroxychloroquine, infliximab, methotrexate, and sulfasalazine as well as procedure codes for infliximab infusions. Health status was assessed using validated, self-reported measures of functional status (the Nagi, activities of daily living, and instrumental activities of daily living) and general health status. Total costs (in 2006 dollars) for all prescription medications and medical care, as well as the proportion of all medical costs attributable to prescription medications, were examined over time. Tests for trends were conducted using weighted regressions.

Results: From 2000 to 2006, the use of any biologic in the Medicare population with RA increased almost 300% (from 4.6% in 2000 to 13.2% in 2006; p=0.01). Use of cytotoxic DMARDs occurred in 28.5% in 2000 as compared to 34.1% in 2006 (p=0.23). Use of noncytotoxic DMARDs remained at a stable rate of 21.3–25.2%. During this period, the proportion of RA patients rating their health as excellent/good increased by 29% (from 43.0% in 2000 to 55.6% in 2006; p=0.007). Significant improvements in functional status occurred in 2 of the 3 measures (ADL and Nagi). Total costs for prescription medications increased by 77% ($2645 in 2000 to $4685 in 2006, p=0.0001). Total medical costs increased but the trend was not significant. In 2000, the mean proportion of medical costs attributable to prescription medications was 30.2% as compared to 37.5% in 2006 (p=0.001).

Table 1. National trends in drug use, health status and costs in older rheumatoid arthritis patients (only even years shown)

	2000	2002	2004	2006	P values
RA patients (N)	225	258	254	247	
Medication use (%)					
Noncytotoxic DMARDs*	25.2	21.4	22.0	23.2	0.900
Cytotoxic DMARDs**	28.5	26.9	32.6	34.1	0.226
Any biologic use***	4.6	6.7	7.7	13.2	0.007
Self-Reported Health Status (%)					
Excellent/good	43.0	44.0	48.7	55.6	0.005
Functional status, mean					
Nagi	3.56 (0.11)	3.51 (0.12)	3.30 (0.10)	3.16 (0.10)	0.045
IADL	1.65 (0.12)	1.83 (0.12)	1.46 (0.11)	1.51 (0.12)	0.142
ADL	1.35 (0.12)	1.63 (0.11)	1.16 (0.12)	1.12 (0.13)	0.017
Costs					
Prescription costs (mean; 2006 dollars)	2645	3270	3726	4685	0.0001
Total medical care costs (mean; 2006 dollars)	16563	18310	17783	19510	0.296
Mean propostion of medical care costs due to prescription drugs (%)	30.2	31.9	36.6	37.5	0.001

* hydroxychloroquine and sulfasalazine
** methotrexate and leflunomide
*** adalimumab, etanercept and infliximab

Conclusions: Between 2000 and 2006, the use of biologic agents for RA substantially increased in older adults with RA. During the same period, there were concurrent improvements in self-reported health status and functional status. However, these gains were offset by an increase in total prescription medication costs.

Disclosure: L. R. Harrold: Corrona, 5; **B. Briesacher:** None; **D. Peterson:** None; **J. H. Gurwitz:** None.

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Pandemic H1N1 Influenza Vaccination Responses in Rheumatid Arthritis and Systemic Lupus Erythematosus Patients: An Association with Serum IL17 and CXCL13 Level. Sung-Hoon Park[1], Hwa-Jeong Lee[2], Hyun-Hee Kwon[2], Seong-Kyu Kim[2] and Jung-Yoon Choe[2]. [1]Catholic University of Daegu, School of Medicine, Arthritis and Autoimmunity Research Center, Daegu, Korea, Republic of, [2]Catholic University of Daegu, School of Medicine, Arthritis and Autoimmunity Research Center

Background: Infections are the main cause of morbidity and hospitalization in immunocompromised host. With the worldwide outbreak of pandemic H1N1 2009 influenza, many patients in rheumatology department comprised a target group for prophylaxis by vaccination. We investigated an efficacy and safety of pandemic H1N1 vaccine in rheumatoid arthritis(RA) and systemic lupus erythematosus(SLE) patients, and evaluate its correlation with serum cytokine level.

Methods: This is a prospective, case-controlled study. The blood samples drawn from selected patients before vaccination and in post-vaccination weeks 4 were assayed in one session to measure titres of antibodies against haemagglutinin specific for influenza virus strains: A/New Caledonia/20/99(H1N1). Serum IL17 and CXCL13 level were measured in the same session by enzyme-linked immunosorbent assay according to the recommendations of the manufacturer's instructions(R&D Systems, Minneapolis, MN, USA). The association of serum cytokine level with anti-influenza antibody titer and mean fold increase(MFI) was investigated. Each specific side effects after vaccination were monitored in both patients and control groups.

Results: A total of 43 RA patients, 31 SLE patients were enrolled in the study and were compared with age, sex-matched 40 helathy controls(HC). The geometric mean antibody titer(GMT) for pre- and post-vaccination week 12 was not significantly different between RA and HC, SLE and HC. The seroconversion rate in HC and RA was not significantly different, while the seroprotection rate is 82.5% in HC, and 55.8% in RA, is significantly higher in HC. MFI in HC was 19.65 and 6.00 in RA, 6.06 in SLE patients, and was significantly higher in HC. The seroprotection/seroconversion rate of SLE patients were not significantly different from HC. Serum IL17 level was 6.28±2.89pg/ml and 7.56±3.34pg/ml in pre-, post-vaccination SLE patients, 33.85±15.62pg/ml and 38.04±18.60pg/ml in RA patients and was significantly lower in SLE patients. Serum CXCL13 level was 518.73±729.29pg/ml and 431.53±601.23pg/ml in pre-, post-vaccination SLE patients, which was significantly higher than HC(149.64±248.81pg/ml and 147.36±213.92pg/ml in each pre-, post-vaccination) and was not significantly different with the level of RA patients. In SLE patients, serum CXCL13 level was positively correlated with post-vaccination antibody titer(Pearson's correlation coefficient 0.44, $p<0.05$). No serious vaccination-related adverse event or disease flare was observed in HC and the patient groups.

Conclusion: The increase in post-vaccination antibody titer is weaker in both RA and SLE patients group than HC. Post-vaccination antibody titer was positively correlated with B lymphocyte chemoattractant, CXCL13 in RA, not in SLE patients.

Disclosure: S.-H. Park: None; **H.-J. Lee:** None; **H.-H. Kwon:** None; **S.-K. Kim:** None; **J.-Y. Choe:** None.

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Patient Preferences for Biologic Agents in Rheumatoid Arthritis: A Discrete Choice Experiment. David A. Navarta[2], Federico Augustovski[3], Andrea Beratarrechea[3], Vilma Irazola[3], Fernando Rubinstein[3], Pablo Tesolin[3], Juan M. Gonzalez[6], Veronica Lencina[4], Marina Scolnik[2], Christian Wainmann[5], Gustavo Citera[4] and Enrique R. Soriano[1]. [1]Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Capital Federal, Argentina, [2]Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, Argentina, [3]Institute for Clinical Effectiveness and Health Policy, Buenos Aires, Argentina, [4]Instituto Rehabilitacion Psicofisica, Buenos Aires, Argentina, [5]Instituto Rehabilitacion Psicofisica, Buenos Aires, Argentina, [6]RTI Health Solutions, NC

Background: Rheumatoid Arthritis (RA) is a chronic condition which requires a substantial degree of adherence to different recommendations. RA patients' preferences among available treatment options have been previously explored using different approaches. Discrete choice experiments (DCEs) allow systematic assessment of preferences by asking respondents to choose between scenarios with different attributes. We conducted a DCE to elicit RA patients' preferences regarding treatment with Biologic Agents (BA).

Methods: We designed a DCE, in which RA patients had to choose between hypothetical drug profiles that could differ in seven treatment attributes (with three to four levels each): effectiveness, route of administration, frequency of admin-

istration, local and systemic adverse effects, severe infections and out-of-pocket costs. We included RA patients older than 18 years who had never received BA from one private and one public hospital in Buenos Aires, Argentina. A Multinomial probit regression model (MNP) was used to analyze the relative importance of treatment attributes, and their willingness to pay (WTP).

Results: 240 RA patients were included. Mean age was 56.2 (SD: 13.5) years, 87% were women, and median disease duration was 9 years. All patients were receiving conventional DMARDs (84.5% Metotrexate); median Clinical Disease Activity Index was 7.5 (interquartile range [IQR]: 3.5–16), and median HAQ was 0.5 (IQR: 0–1.225). Mean family monthly income was 645 US dollars ($). All the attributes showed to be significant factors affecting choice of treatment. Most attributes levels showed coefficients with the expected signs and were statistically significant. Attributes importance ranking was in the following order: cost, systemic adverse events, frequency of administration, efficacy, route of administration, local adverse events and serious infection.

Table. Model main results. Results expressed the mean distance and CI 95% of the most favored level and the least favored level of each attribute.

Attribute	Mean	Lower limit 95% CI	Upper limit 95% CI
Cost	0.8058	0.6884	0.9245
Systemic adverse events	0.6654	0.5696	0.7573
Frequency of administration	0.6145	0.5164	0.7124
Efficacy	0.4174	0.3253	0.5094
Route of administration	0.4129	0.3053	0.5208
Local adverse events	0.3981	0.3068	0.4875
Serious infection	0.2938	0.2190	0.3701

Patients had relatively high monthly WTP for treatments that significantly reduced the risk of systemic adverse events: mean 331 (95% CI: 212–499) US dollars ($) for a reduction from 30% to 10%; of decreasing dose frequency: mean $ 302 (95% CI: 183–461) for going from weekly to monthly administration; increasing treatment efficacy: mean: $ 386 (95% CI:285–532) for 40 vs 20 mm reduction in patient global assessment VAS, and also for switching from an intravenous to an oral therapy: mean $ 262 (95% CI: 262–555).

Conclusion: Different treatment attributes had a significant and different influence in RA patients choice of BA. The results of the DCE indicated that most respondents would be willing to pay for treatments that importantly reduced the risk of systemic adverse effects, dose frequency, with increased treatment efficacy, and with an oral route of administration.

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Patient Risk Perception of Teratogenicity of Disease Modifying Anti-Rheumatic Drugs. Eliza F. Chakravarty[3], Megan E. Clowse[2], Karen H. Costenbader[1], Christina Chambers[4] and Kaleb Michaud[5]. [1]Brigham and Womens Hospital, [2]Duke University, Durham, NC, [3]Stanford University, [4]University of California, San Diego, [5]University of Nebraska

Purpose: Women with chronic diseases often require long term therapy with disease modifying agents. Some of these medications are known or suspected teratogens (methotrexate has an estimated 10% risk of teratogenicity) while others have fewer pregnancy risks (hydroxychloroquine has an estimated risk of teratogenicity similar to the background rate of 3–5%) and can be safely used during pregnancy. Although counseled to avoid pregnancy while taking potentially teratogenic medications, women with chronic disease occasionally become pregnant and antenatal exposure occurs. Little is known about women's perception of teratogenic risks of immunosuppressive medications.

Methods: A comprehensive reproductive history questionnaire was mailed to women diagnosed by a rheumatologist with RA (n=870), SLE (n=237), or fibromyalgia (n=164) participating in a US longitudinal observational study of rheumatic diseases. Women were asked to estimate the risks of birth defects occurring in the general population, in women with their disease taking no medications, and after exposure to a variety of anti-inflammatory and immunosuppressive medications. Regression models were generated to identify disease, demographic, medication, treating physician, or reproductive variables that may be associated with perceived risk of teratogenicity among patients with RA.

Results: 589 (68%) women with RA, 85 (36%) women with SLE and 96 (59%) women with fibromyalgia completed the risk perception portion of the reproductive history questionnaire.

Variable	RA	SLE	Fib
n	589	85	96
Age	58.6 (12)	53.0 (10)	53.3 (10)
Disease Duration	20 (13)	18 (13)	18 (13)
Reported side effect to any drug	49%	49%	50%
Never pregnant	14 (2.4%)	1 (1.2%)	0
No Children	14 (2.4%)	3 (3.5%)	1 (1%)
Number of children	2.5 (1.4)	2.3 (1.1)	2.3 (1.1)
Ever had child with birth defect	77 (13%)	8 (9.4%)	12 (12.5%)
Risk of birth defect			
In healthy women	1.00%	0.86%	0.41%
In women with your disease	1.14%	1.09%	0.49%
With NSAIDs	1.61%	1.74%	1.19%
With prednisone	4.15%	2.25%	2.60%
With plaquenil	2.63%	2.04%	2.15%
With methotrexate	6.51%	7.28%	3.30%
With leflunomide	5.05%	9.75%	6.23%
With TNF inhibitor	4.83%	4.95%	4.05%

Mean age at questionnaire completion was 53–59 years. Almost all women had children and up to 13% reported a child with a birth defect. Only 1.5% of respondents correctly estimated the risk of birth defects in the general population, whereas 96.2% underestimated risks and 2.3 % overestimated risks. Women underestimated teratogenic risks for all categories, but identified methotrexate or leflunomide as the agents with the highest risk of teratogenicity (see table). No variables were found to correlate with level of risk perception, including: age, education, past medication use, smoking, age of disease onset, number of children, child with birth defect, side effects of medication, menopause, physician gender, or recall of discussion about teratogenicity with provider.

Conclusions: Women with RA, SLE, and fibromyalgia tend to underestimate risks of birth defects and teratogenicity in the general population as well as from chronic disease modifying agents. Educational efforts should emphasize discussions of teratogenicity and pregnancy-related risks of medication use.

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Post-Treatment Changes in Serum C-Reactive Protein Levels and Clinical Response in Rheumatoid Arthritis. Paul Emery[8], Eric L. Matteson[6], Mark C. Genovese[7], Sarah Sague[1], Elizabeth C. Hsia[3], Mittie K. Doyle[4], Hongtao Fan[2], Michael Elashoff[5] and Mahboob U. Rahman[4]. [1]Centocor Research and Development, Inc., Malvern, PA, [2]Centocor Research and Development, Inc., [3]Centocor Research and Development, Inc./Univ of Pennsylvania School of Medicine, Malvern, PA, [4]Centocor Research and Development, Inc./Univ. of Pennsylvania School of Medicine, Malvern, PA, [5]Elashoff Consulting, [6]Mayo Clinic, Rochester, MN, [7]Stanford Universit, Sunnyvale, CA, [8]University Leeds, Leeds, United Kingdom

Background: With the availability of many effective therapies for RA, biomarker(s) that can reliably predict response to a treatment (tx) would be useful in clinical practice. Serum CRP levels have been known to be associated with disease activity including radiographic progression. It is however not clear if early changes in serum CRP levels in response to tx can predict sustained clinical response at later time points.

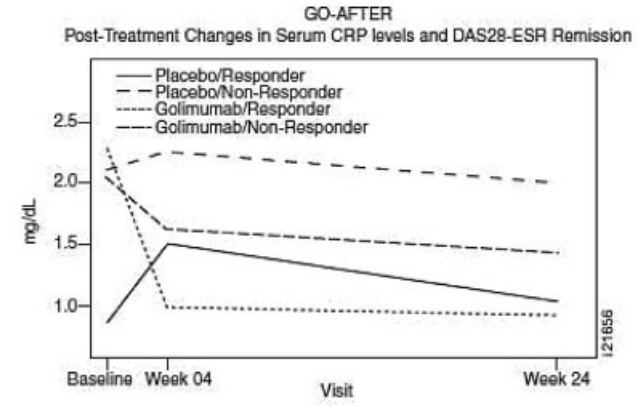
Objectives: To evaluate if early post-tx changes in CRP can reliably predict clinical response, we evaluated the association of early post-tx changes in serum CRP levels with clinical response at a later time point.

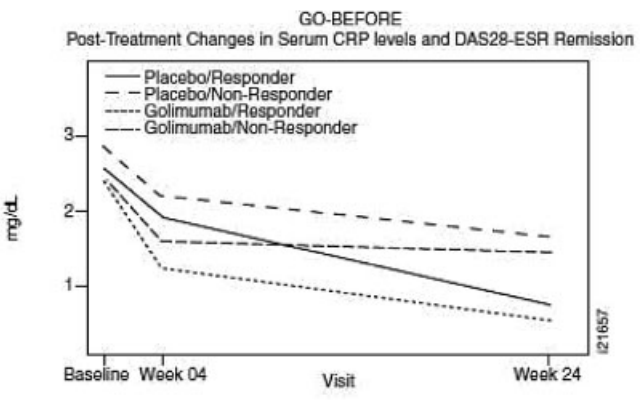
Methods: Sera were collected at wk0, 4 & 24 from GO-BEFORE (MTX naïve RA pts; 477 golimumab[GLM]+/−MTX, 160PBO+MTX), GO-FORWARD (active RA pts despite MTX; 311GLM+/−MTX, 133PBO+MTX) and GO-AFTER (active RA pts previously tx with TNF inhibitors; 304GLM, 155PBO) studies. Samples were tested for CRP levels using Roche Tinaquant assay. CRP levels at baseline (BL), wk4 & 24 in GLM±MTX and PBO+/−MTX pts achieving and not achieving multiple measures of clinical response (ACR & EULAR/DAS response criteria) were evaluated. Logistic regression models were used to test for marker associations with clinical endpts. Positive predictive value (PPV) & Negative predictive value (NPV) were calculated.

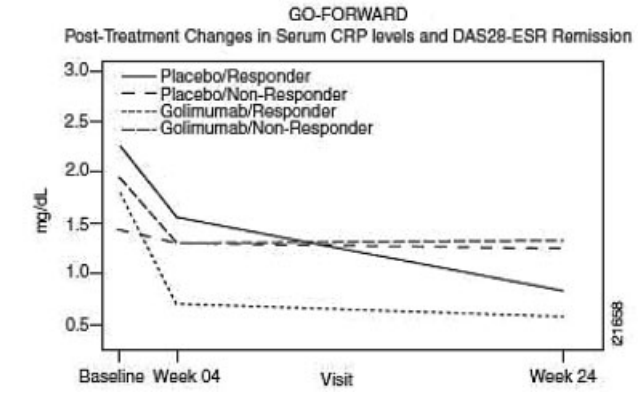
Results: The figure shows CRP levels at wk0, 4&24 among remission (DAS28-ESR<2.6) achievers and non-achievers at wk24 (as a representative data; data for other clinical measures of response were similar but not shown). Pts

achieving remission tend to have lower CRP at BL, wk4&24, compared to pts not achieving remission, & pts treated with GLM had in general lower CRP levels than pts treated with MTX or PBO. Changes from BL in CRP levels were analyzed in 3 RA populations and decreases from BL at wk4 in pts with BL CRP>1 mg/dL were significantly associated with remission at wk24 in GLM±MTX pts from GO-BEFORE (OR=1.4; p<0.002; PPV=67%; NPV=53%), GO-FORWARD (OR=2.1; p<0.000;PPV=70%; NPV=68%) and GO-AFTER (OR=1.3; p=0.06; PPV=51%; NPV=64%). Reductions from BL CRP of >50% at wk4 in these pt subsets were also signif. associated with multiple measures of clinical response including remission (data not shown).

Conclusion: While changes in CRP levels associate with clinical response and may be a good measure of disease activity in RA at any time point, it is not a reliable predictor of clinical response to tx.







Disclosure: P. Emery: Centocor Research and Development, Inc., 2, 9; **E. L. Matteson:** Centocor Research and Development, Inc., 2, 9, Centocor Research and Deveopment, Inc., 2, 9; **M. C. Genovese:** Centocor Research and Development, Inc, 2, 9, Centocor Research and Development, Inc., 2, 9; **S. Sague:** Centocor Research and Development, Inc, 3; **E. C. Hsia:** Centocor Research and Development, Inc, 3; **M. K. Doyle:** Centocor Research and Development, Inc, 3; **H. Fan:** Centocor Research and Development, Inc., 3; **M. Elashoff:** Centocor Research and Development, Inc., 5; **M. U. Rahman:** Centocor Research and Development, Inc., 3.

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Practice Patterns of US Rheumatologists Related to Diagnosis and Assessment of Disease Activity as Well as Switching Biologic Therapies in Rheumatoid Arthritis. Marco DiBonaventura[2], Sanjoy Roy[1], Jochen Ertl[2] and Mary A. Cifaldi[1]. [1]Abbott Laboratories, Abbott Park, IL, [2]Kantar Health, New York, NY

Background and Purpose: This study investigated measures used by US rheumatologists to diagnose RA and assess disease activity. We also describe the treating rheumatologists' practice patterns for switching biologic therapies for patients who discontinued anti–tumor necrosis factor (anti-TNF) agents for any reason.

Methods: A sample of US rheumatologists (N=110) from the All Global physician panel were surveyed online. The All Global physician panel is an opt-in, actively managed, online panel of several hundred thousand physicians in the US and Europe. Respondents were asked for demographic and practice information, as well as, about RA diagnostic and disease severity measures they were aware of and how often they used those measures. Responses for awareness and frequency of use were measured on a 5-point scale, where 1=never use and 5=always use.

Results: Physicians were mostly men (n=81, 74%), fairly equally distributed between urban and suburban practices (suburban: n=58, 53%). The mean number of years in practice (post-residency) was 15.9, and the mean number RA patients seen per month was 143.1. The anti–cyclic citrullinated peptide antibody (anti-CCP) test had the greatest awareness and frequency of use as a diagnostic measure (97% of physicians aware of the test; mean frequency of use score±SD, 4.5±0.9). Regarding awareness and use of assessments of disease activity, swollen joint count was the most common (SJC; 89% of physicians aware; mean use±SD, 4.2±1.4). C-reactive protein (CRP) concentration, erythrocyte sedimentation rate (ESR), and tender joint count (TJC) were among the other measures with high awareness and frequent use. Magnetic resonance imaging (MRI) and Disease Activity Score (DAS), used as measures for diagnosis or assessment, had the largest discordance between high awareness and low use. White blood count (WBC) had the largest discordance between low awareness and high use, both as a diagnostic and an assessment measure. Assessment of their switching behavior showed that rheumatologists switched biologic therapies for 25% of their patients; 67% were switched to a second anti-TNF agent; the remainder were switched to a non-TNF biologic therapy. Approximately 75%, 69%, and 52% of patients were switched to a second anti-TNF agent when the first was etanercept, adalimumab, and infliximab, respectively.

Conclusions: The anti-CCP test and SJC were the most well-known and the most frequently used measures to diagnose RA and assess disease activity. MRI and DAS were well-known but rarely used in routine practice, whereas WBC was used relatively frequently despite low awareness of its value as a diagnostic tool. Rheumatologists switched therapy for a quarter of their patients who received biologic therapy, and the switch to a second anti-TNF was more frequent for subcutaneous anti-TNF agents compared with agents administered by intravenous infusion.

Disclosure: M. DiBonaventura: Kantar Health (contractor for Abbott), 3; **S. Roy:** Abbott Laboratories, 1, 3; **J. Ertl:** Kantar Health (contractor for Abbott), 3; **M. A. Cifaldi:** Abbott Laboratories, 1, 3.

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Predictors of Successful Cessation of TNF Blockers in Patients with RA. M. van den Broek[4], N. B. Klarenbeek[5], L. Dirven[5], A. A. Schouffoer[1], H. M. J. Hulsmans[2], P. J. S. M Kerstens[3], T. W. J. Huizinga[5], B. A. C. Dijkmans[6] and C. F. Allaart[5]. [1]Groene Hart Hospital, Gouda, The Netherlands, [2]Haga Hospital, The Hague, The Netherlands, [3]Jan van Breemen Instituut, Amsterdam, The Netherlands, [4]LUMC, Leiden, The Netherlands, [5]LUMC, Leiden, The Netherlands, [6]VU Medical Centre, Amsterdam, The Netherlands

Objective: To observe disease activity after cessation of infliximab (IFX) and to identify predictors of persistent low disease activity.

Methods: In the BeSt study, 120 patients with recent onset RA were treated with initial methotrexate (MTX)+IFX combination therapy, and 109 other patients started MTX+IFX after failing (DAS>2.4) on 3 previous treatment steps. If DAS remained ≤ 2.4 for at least 6 months, IFX was tapered and finally stopped. In these patients, possible predictors for a rise in DAS > 2.4, resulting in reintroduction of IFX were examined using Cox regression analysis.

Results: IFX was discontinued in 76/120 patients from the initial and

27/109 from the delayed treatment group. Median DAS at time of discontinuation was 1.39 (IQR 0.84–1.70). Over a median period of 81 months (range 16–97) follow up, 54% of patients had a persistent DAS ≤ 2.4. In 47 patients, IFX was reintroduced after a median duration of 14 (IQR 3–44) months. After a median duration of 3 months, 85% of these patients, 25/31 from the initial and 15/16 from the delayed IFX treatment group, again had a DAS ≤ 2.4. Two (4%) patients did not achieve a DAS ≤ 2.4 after reintroduction of IFX, 3 again stopped IFX because of adverse events and 2 at patient's request.

Smoking, IFX treatment duration, physician's assessment of disease activity (VAS) and yearly damage progression were predictors of reintroduction of IFX ($p<0.01$). Shared epitope (SE), erosion score and treatment group showed a trend ($p= 0.01$). Separate analyses for both treatment groups showed similar effect sizes, with the exception of smoking in the delayed treatment group. In the multivariable model, which included treatment group, smoking (Hazard rate 2.17, 95% CI 1.11–4.26), treatment duration ≥18 months (HR 2.28, 95% CI 1.01–5.12) and SE (HR 3.41, 95% CI 1.19–9.81) were independently associated with reintroduction of IFX after cessation.

Conclusion: IFX could be discontinued successfully in more than half of patients. The majority of patients who did have a disease flare quickly regained low disease activity after reintroduction of IFX. Smoking, positive shared epitope status and long IFX treatment duration (≥18 months) were independent predictors of reintroduction of IFX after cessation.

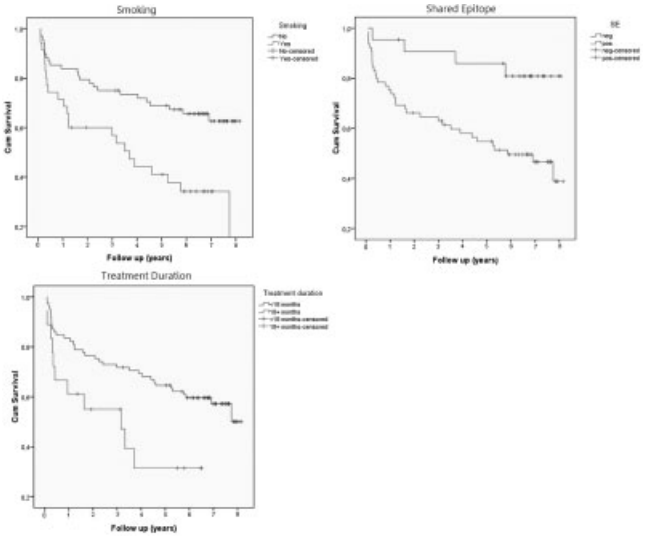

Figure: Kaplan Meier curves depicting reintroduction of IFX over time per risk factor.

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Prevalence of Reactivation of Hepatitis B Virus Replication in Rheumatoid Arthritis Patients. Dai Tanaka[2], Yukitomo Urata[4], Ryoko Uesato[3], Kenji Kowatari[3], Yoshihide Nakamura[1] and Taisuke Nitobe[3]. [1]Department of Orthopaedic Surgery, Hirosaki University Graduate School of Medicine, [2]Department of Orthopaedic Surgery, Seihoku Chuo Hospital, Gosyogawara, Aomori, Japan, [3]Department of Orthopaedic Surgery, Seihoku Chuo Hospital, [4]Departments of Rheumatology, Seihoku Chuo Hospital, Gosyogawara, Japan

Purpose: Reactivation of hepatitis B involves the reappearance of active necroinflammatory liver disease after an inactive hepatitis B surface antigen (HBsAg) carrier state or resolved hepatitis B, occurring during or after immunosuppression therapy or chemotherapy. We prospectively investigated the reactivation rate for hepatitis B virus (HBV)-DNA replication in cases of rheumatoid arthritis (RA) with resolved hepatitis B.

Methods: HBV markers were evaluated in 428 RA patients. Patients with positive findings of HBsAg or HBV-DNA at enrolment were excluded from this study. Subjects comprised 422 RA patients, with resolved hepatitis B diagnosed in 135 patients based on HBsAg-negative and anti-hepatitis B core antibody/anti-hepatitis B surface antibody-positive results. HBV-DNA was measured every 3 months in this group, and if HBV-DNA became positive after enrolment, measurement was repeated every month.

Results: HBV-DNA became positive (≥3.64 log copies/mL) in 7 of 135 patients for 12 months. Use of biologic agents was significantly more frequent in patients who developed reactivation of HBV-DNA replication (85.7%) than in patients who did not (36.0%, $p=0.008$). Hazard ratios for use of biologic agents and etanercept were 10.9 ($p=0.008$) and 6.9 ($p=0.001$), respectively.

Conclusions: RA patients with resolved hepatitis B need careful monitoring when receiving biologic agents, regardless of HBV-DNA levels.

Table 1. Distribution of HBsAb and HBcAb results among HBsAg-negative and -positive patients

	HBsAg-negative		HBsAg-positive	
	HBsAb-positive	HBsAb-negative	HBsAb-positive	HBsAb-negative
HBcAb-positive	85	38	3	3
HBcAb-negative	12	0	0	0

Table 2. Comparison of HBV replication-positive and HBV replication-negative patients for baseline demographic, clinical and laboratory characteristics

Baseline demographic, clinical and laboratory characteristics	HBV replication (+)	HBV replication (−)	*P*
n	7	128	
Age, years (mean)	63.3 ± 12.9 (64.7)	65.8 ± 11.8 (66.8)	0.695
Female, n	5 (71.4%)	105 (82.0%)	0.505
RA duration, years	3.8 ± 2.6 (3.0)	7.8 ± 9.0 (4.6)	0.439
CRP, mg/dL	0.57 ± 0.63 (0.40)	1.03 ± 2.00 (0.19)	0.924
ESR, mm/h	17.6 ± 8.4 (16.0)	25.5 ± 26.3 (15.0)	0.979
IgM RF, IU/mL	56.2 ± 64.8 (28.2)	73.9 ± 117.9 (28.1)	0.835
AST, U/L	23.0 ± 3.8 (23.0)	27.5 ± 17.8 (22.0)	0.103
ALT, U/L	23.1 ± 5.4 (25.0)	25.8 ± 20.1 (20.0)	0.419
IgG, mg/dL	1228 ± 401.5 (1106)	1435 ± 470.7 (1369)	0.361
Neutrophil count	2680 ± 1449 (2094)	4389 ± 2227 (3843)	0.186
Lymphocyte count	1367 ± 483 (1450)	1698 ± 809 (1534)	0.349

Values are given as mean ± standard deviation (median)
RA, rheumatoid arthritis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; RF, rheumatoid factor; AST, aspartate aminotransferase; ALT, alanine aminotransferase

Table 3. Demographic, clinical and laboratory characteristics of patients with HBV replication

Case	Age (years)	RA disease-duration (months)	Biologic agent	MTX (mg/week)	DMARDs	Prednisolone (mg/day)	HBV (log copies/ml)	Entecavir	Final status of HBV-DNA	Time between emergence of HBV DNA and its disappearance (months)	ALT (U/l)
1	77	35	tocilizumab[a]	6	none	none	2.0	none	DNA-negative	1	27
2	65	53	etanercept	none	none	2	5	yes	DNA-negative	5	20
3	46	120	etanercept	8	tacrolimus 1 mg/day	none	3.7	yes	DNA-negative	1	30
4	49	60	etanercept	none	bucillamin 200 mg/day	none	7.4	yes	DNA-negative	18	20
5	60	36	etanercept	none	leflunomide 10 mg/day		2	none	DNA-negative	1	25
6	75	18	etanercept	8	none	6	2.4	yes	DNA-negative	2	26
7	74	19	none	7.5	none	5	3	yes	DNA-negative	2	14

[a]This patient had received 3 biologic agents, infliximab, etanercept and tocilizumab sequentially.
RA, rheumatoid arthritis; ALT, alanine aminotransferase

Table 4: Number of patients using concomitant drugs related to rheumatoid arthritis during the study (comparing HBV replication-positive patients with HBV replication-negative patients)

	Number of patients[a]			
Variables	HBV replication (+)	HBV replication (−)	*P*	HR (95% CI)
Total	7	128		
Biologic agent	6 (85.7%)	46 (36.0%)	0.008	10.9 (1.4–87.7)
Adalimumab	0	7 (5.5%)	0.382	
Etanercept	6 (85.7%)	32 (25.0%)	0.001	6.9 (1.4–33.9)
Infliximab	1 (14.3%)	17 (13.3%)	0.940	1.08 (0.2–8.5)
Tocilizumab	1 (14.3%)	3 (2.3%)	0.175	5.5 (0.8–35.4)
Methotrexate	5 (71.4%)	60 (46.9%)	0.200	2.7 (0.5–13.4)
mean dose	6.3 ± 2.5 mg/week	6.7 ± 1.9 mg/week	0.980	
Corticosteroids	5 (71.4%)	47 (36.7%)	0.070	4.0 (0.8–19.8)
mean dose	3.4 ± 2.1 mg/day	5.2 ± 4.4 mg/day	0.380	
Sulfasalazine	0	28 (21.9%)	0.067	
Bucillamine	2 (28.6%)	25 (19.5%)	0.577	1.6 (0.3–7.8)
Tacrolimus hydrate	1 (14.3%)	8 (6.3%)	0.463	2.3 (0.3–17.3)
Sodium aurothiomalate	0	2 (1.6%)	0.643	
Leflunomide	1 (2.2%)	2 (1.6%)	0.119	7.3 (1.2–43.5)
D-penicillamine	0	2 (1.6%)	0.643	
Actarit	0	1 (0.8%)	0.743	
Auranofin	0	3 (2.3%)	0.570	
Cyclosporine	0	1 (0.8%)	0.744	
Minocycline hydrochloride	0	2 (1.6%)	0.643	
Cyclophosphamide	0	1 (0.8%)	0.743	

[a]Values are given as the number of patients taking a drug; patients can take more than one drug and can switch to another biologic agent
HR, hazard ratio; 95% CI, 95% confidence interval.

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Primary Anti-TNF Failures Experience Better Clinical Responses but Similar Health Care Utilization to a Second Anti-TNF Agent Than Secondary Failures: Analysis of the Alberta Rheumatoid Arthritis Biologics Registry. Walter P. Maksymowych[2], Arto Ohinmaa[1], Liam Martin[3], Anthony S. Russell[2], Susan G. Barr[3], Dale Sholter[2], Chris J. Penney[3], Charles Yan[1] and Philip Jacobs[1]. [1]Institute of Health Economics, Edmonton, AB, Canada, [2]University of Alberta, Edmonton, AB, Canada, [3]University of Calgary, Calgary, AB, Canada

Purpose: Meta-analysis of anti-TNF switching data from observational cohorts has concluded that responses are inferior in those switching due to primary as compared to secondary anti-TNF failures but limitations include small sample size of individual studies, failure to define response, and selection bias. We assessed the impact of switching anti-TNF agents at different time points in the Alberta Biologics Registry, an observational cohort of RA patients starting anti-TNF therapy in 2004, where collection of outcome data on all patients is requested by the Provincial pharmaceutical formulary.

Methods: The Alberta Biologics Registry collects clinical, employment, and health economic data at baseline, 3 months, and every 6 months thereafter. Patients must attain either an ACR20 or EULAR response ($\geq$1.2) plus a HAQ response of $\geq$ 0.22 units by 12 weeks and maintain this at each subsequent visit to continue to receive anti-TNF agent. Health-related quality of life is measured with the EQ-5D and self reported health care utilization is measured for the six months prior to each visit. We analyzed responses according to time of switch (3 month versus subsequent time points) and according to specific anti-TNF agent switches.

Table. Change in health outcomes from baseline to 27 months of anti-TNF therapy.

	HAQ change	DAS change	EQ-5D change
Non-switcher	−0.82 (p<0.001)	−2.84 (p<0.001)	0.30 (p<0.001)
1° failure switcher	−0.70 (p<0.01)	−2.59 (p<0.001)	0.30 (p<0.001)
2° failure switcher	−0.41 (p<0.01)	−1.70 (p<0.001)	0.20 (p<0.01)

Results: From 1,222 patients in the registry, 649 patients had 27 month follow up assessment and 498 (76.7%) of these remained on the first anti-TNF during the study period. There were 28 (4.3%) primary failures and 123 (19%) secondary failures who switched a median of 15 months from baseline. The response rate to the second anti-TNF was somewhat better in the primary versus the secondary failures (p=NS) at 3 months after initiation of the second anti-TNF for HAQ, DAS, EQ-5D. By 27 months, switchers due to primary failures had attained comparable reductions in outcomes to non-switchers while changes in secondary failures were from 50% (HAQ) to 68% (EQ-5D) lower compared to non-switchers (p<0.05). Health care utilization was significantly reduced in four measured parameters over 27 months: number of rheumatologist visits (-0.31 visits, p<0.001), family physician visits (-0.95, p<0.001), % having $\geq$1 outpatient visit (-0.22, p<0.001), and % having day surgery (-0.026, p<0.001). This reduction was comparable between patients switching amongst different anti-TNF agents and non-switchers.

Conclusion: The results from this mandatory registry show that primary failures to anti-TNF show similar responses to patients responding to their first anti-TNF agent. Clinical responses in secondary failures are less optimal. Despite this, there is no significant difference between primary and secondary failures in the significant reduction in the health care utilization while receiving their second anti-TNF agent over the course of the 27 month follow up period.

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Rate of Remission in Clinical RA Patients by ACR/EULAR Criteria. Shadi H. Shahouri[3], James D. Anderson[5], Ruth E. Busch[2], Timothy S. Shaver[4], Shirley Y. Wang[3], David N. Weidensaul[1], Martin J. Bergman[6], Kaleb D. Michaud[8] and Frederick Wolfe[7]. [1]ARCKArthritis & Rheum Clinics KS, Wichita, KS, [2]Arthritis & Rheum Clinic, Wichita, KS, [3]Arthritis & Rheum Clinic of KS, Wichita, KS, [4]Arthritis & Rheum Clinics KS, Wichita, KS, [5]Arthritis & Rheum Clinics KS, Leawood, KS, [6]Arthritis and Rheumatology, Ridley Park, PA, [7]Natil Data Bank for Rheumatic, Wichita, KS, [8]Univ of Nebraska Med Ctr, Omaha, NE

Purpose: Remission is the most desirable outcome of RA treatment, but a multiplicity of definitions has hampered the measured of remission in the community. The ACR/EULAR remission committee has recently made recommendations for RA clinical trials, and also provided possible alternatives for clinical practice. We explored the clinic practice suggestions and determined the rate of remission in a large multicenter RA clinical practice.

Methods: From 1,350 consecutive RA patients seen in clinical practice between January 2007 and March 2010 during 12,801 visits, we studied 1,079 patients with ESR data during 5,289 clinical visits. ESR missing data was primarily a function of patient medical insurance. We calculated a series of remission measures according to the ACR/EULAR recommendations.

Name	Definition
ACR/EULAR-3	SJ28 $\leq$1 & TJ28 $\leq$1 & Pt global $\leq$1
ACR/EULAR-4	SJ28 $\leq$1 & TJ28 $\leq$1 & Pt global $\leq$1 & MD global $\leq$1
ACR/EULAR CDAI	(SJ28 + TJ28 + Pt global + MD global) $\leq$ 2.8
ACR/EULAR-3 + ESR	SJ28 $\leq$1 & TJ28 $\leq$1 & Pt global $\leq$1 & (ESR <30 mm [women] or < 10 mm [men])
ACR/EULAR-3 + Low ESR	SJ28 $\leq$1 & TJ28 $\leq$1 & Pt global $\leq$1 & (ESR <22 mm [women] or <11 mm [men])

Each patient contributed an average of 4.9 observations (range 1–24). We determined the rate of remission by modeling all observation using general estimating equations. We also included ACR/EULAR-3 to define the limit of remission without ESR and we used ACR/EULAR-3 + Low ESR to explore a more restrictive ESR limit based on the distribution of ESR in the community.

Results: Patients' age and RA duration were 58.8 (SD 13.9) years and 10.0 (10.1) years, and 75% of patients were women.

Name	Rate (95% CI)	Biologic effect (On vs. not on)
ACR/EULAR-3	8.4% (7.2, 9.6)	9.3% vs. 7.7%, p = 0.068
ACR/EULAR-4	5.1% (4.2, 6.1)	6.7% vs. 4.0%, p <0.001
ACR/EULAR CDAI	7.5% (6.4, 8.7)	10.3% vs. 5.6%, p <0.001
ACR/EULAR-3 + ESR	6.0% (4.9, 7.0)	6.4% vs. 5.5%, p = 0.229
ACR/EULAR-3 + Low ESR	4.0% (3.2, 4.9)	4.3% vs. 3.8%, p = 0.408

The rate of remission ranged from 5.1% to 7.5% according to the ACR/EULAR recommendation. The rate rose to 8.4% from 6.0% when ESR was eliminated and fell to 4.0% when ESR limits were tightened. In the ACR/EULAR-3 and the ESR criteria, the rate of remission was not higher in biologic treated patients, but was higher in all criteria that included MD global (ACR/EULAR-4 and ACR/EULAR CDAI).

Conclusions: Overall, the rate of remission using contemporary RA treatment in the community is between 5.1% to 7.5%. These rates are substantially lower than reported in clinical trials using DAS-28 criteria. Criteria that include physician global tend to find more benefit with biologic therapy than criteria that do not include physician measures.

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Rituximab Alters the HDL Particle from a Pro-Inflammatory into an Anti-Inflammatory Property in Good Responding Rheumatoid Arthritis Patients. Hennie G. Raterman[2], Han H. M. Levels[1], Alexandre E. Voskuyl[2], Willem F. Lems[2], Ben A. C. Dijkmans[2] and Michael T. Nurmohamed[2]. [1]Academical Medical Center, The Netherlands, [2]VU University Medical Center, Amsterdam, The Netherlands

Background: Rheumatoid arthritis (RA) patients suffer from an increased prevalence and incidence of (non)fatal cardiovascular diseases (CVD). A well known risk factor for CVD is an atherogenic lipid profile and, interestingly, a high inflammatory state is associated with an unfavourable lipid profile in RA patients. Moreover, an inflammatory state alters the HDL into a more proatherogenic composition as the particle loses its anti-inflammatory features. Effective anti-inflammatory treatment with TNF blocking agents improves the lipid profile, but data about effects of novel biological agents like rituximab on lipid profile is limited in RA patients.

Objective: To investigate the changes in HDL protein composition in rituximab treated RA patients.

Methods: In 12 RA patients (6 good responding and 6 non responding patients), who participated in an ongoing observational study of consecutive rituximab treated RA patients, serum and EDTA plasma samples were collected at baseline, 3 months and 6 months and stored at − 80°C. In these

samples lipid levels (including total and HDL cholesterol, triglycerides and apolipoproteins (ApoA-I and ApoB)) were assessed in a single run. After anti apo A-I immunocapture, HDL protein profling was carried out using surface-enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF MS) analysis. GEE analyses were used to determine disease activity marker and lipid changes in time.

Results: At baseline DAS28 was significantly higher in EULAR non responders compared to responders (see table, p = 0.001). Other baseline characteristics did not differ significantly between responders and non responders. As expected, after 6 months treatment significant changes in DAS28 and CRP were observed in responders versus non responders. No other significant changes were observed after 6 months treatment. SELDI-TOF MS analysis revealed a significant decrease in density of the mass charge (m/z) marker 11,743, representing serum amyloid A (SAA)-1, in good responding rituximab patients when compared to non responding patients. Moreover, 7 other markers (i.e. 3,893, 7,065, 8,647, 9,401, 9,764, 15969 and 87,407 m/z ($p<0.05$)) changed significantly in the good responding patients. In these patients no significant changes in HDL, ApoA-1 and ApoB levels were observed, although triglycerides were significant lower in good responding patients during treatment.

Table. Characteristics of rituximab treated RA patients.

	Responders baseline	Non responders baseline	Responders t = 6 months	Non responders t = 6 months
DAS28	5.0 ± 0.7	6.6 ± 0.5*	2.8 ± 0.6#	6.3 ± 0.3*
CRP, mg/l	7.5 (4–14)	16 (10–64)	2.6 (2.5–6.3)	22 (4–60)
total cholesterol, mmol/l	4.72 ± 0.92	5.22 ± 1.2	5.10 ± 1.4	5.05 ± 1.2
HDL cholesterol, mmol/l	1.64 ± 0.4	1.55 ± 0.5	1.68 ± 0.5	1.50 ± 0.3
total: HDL cholesterol	2.97 ± 0.6	3.59 ± 1.1	3.09 ± 0.6	3.38 ± 0.66
Triglycerides, mmol/l	1.03 ± 0.3	1.49 ± 0.4	1.08 ± 0.3	1.68 ± 0.8
LDL, mmol/l	2.62 ± 0.7	3.0 ± 1.0	2.93 ± 1.1	2.79 ± 1.0
ApoA-I, mmol/l	1.62 ± 0.3	1.66 ± 0.4	1.64 ± 0.3	1.64 ± 0.2
ApoB, mmol/l	0.65 ± 0.1	0.77 ± 0.2	0.71 ± 0.2	0.72 ± 0.2
ApoB: ApoA-I ratio	0.42 ± 0.1	0.48 ± 0.1	0.44 ± 0.1	0.44 ± 0.1

*$p < 0.05$ compared with responders. #$p < 0.05$ compared with baseline

Conclusions: In good responding rituximab treated RA patients the qualitative changes in the HDL protein composition reflect the change in disease activity, giving circumstantial evidence that next to quantitative changes in lipid levels during anti-inflammatory therapy the HDL particle seems to alter into a less proinflammatory and anti-atherogenic composition.

Disclosure: H. G. Raterman: None; **H. H. M. Levels:** None; **A. E. Voskuyl:** None; **W. F. Lems:** None; **B. A. C. Dijkmans:** None; **M. T. Nurmohamed:** Abbott Immunology Pharmaceuticals, 2, Bristol-Myers Squibb, 2, Roche, 2, Schering-Plough, 2, Wyeth Pharmaceuticals, 2.

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Rituximab-Reduced Immunoglobulin Free Light Chains in RA Correlate with Disease Suppression: A Novel Mechanism of Action of Rituximab. J. Tekstra[3], T. Groot Kormelink[2], R. Thurlings[1], M. Boumans[1], K. Vos[1], P. P. Tak[1], J. W. J. Bijlsma[3], F. P. J. G. Lafeber[3], F. A. Redegeld[2] and J. A. G. van Roon[3]. [1]Clinical Immunology & Rheumatology, Academic Medical Center/University of Amsterdam, The Netherlands, [2]Pharmacology and Pathophysiology, Utrecht Institute for Pharmaceutical Sciences, Fac. Science, Utrecht, the Netherlands, [3]Rheumatology & Clinical Immunology, University Medical Center Utrecht, The Netherlands

Background: Immunoglobulin kappa and lambda free light chains (FLCs) are produced physiologically and levels are increased in several inflammatory diseases like asthma, inflammatory bowel disease and rheumatoid arthritis (RA). FLCs are short-lived products of B lymphocytes and have been shown to promote inflammation by activation of mast cells.

Objective: To investigate the expression levels of local and systemic levels of FLCs and their correlation with disease activity and to study whether FLC changes upon B cell targeted therapy in RA patients correlate with changes in disease activity.

Methods: FLC expression levels were measured in synovial fluid (SF) and synovial tissue (ST) of RA and OA patients (SF n=68 vs n=24; ST both n=10). 50 RA patients with active disease were treated with rituximab. Clinical response was defined according to the EULAR criteria. FLC kappa and lambda concentrations were measured at baseline and 3 and 6 months after treatment. At these time points, total immunoglobulin concentrations, rheumatic factor (RF) and anti-CCP levels were also measured.

Results: Strongly increased FLC concentrations were found in SF from inflamed joints (mean 24 vs 144 mg/L, $p<0.0001$) that correlated with disease parameters (ESR, both kappa and lambda FLC $p<0.001$). Increased FLC expression was also detected in ST of RA patients. Serum FLC levels also correlated with DAS 28 ($p=0.006$ for kappa and $p=0.04$ for lambda) and ESR and CRP (all $p<0.01$). Over time, kappa and lambda FLC concentrations decreased after rituximab treatment ($p<0.001$ for baseline vs 3 months and $p<0.01$ for baseline vs 6 months after treatment for both kappa and lambda FLC). Patients without clinical response to rituximab showed no significant reduction of FLC concentrations, whereas patients who responded clinically did show a significant decrease in FLCs (both $p<0.001$). Changes in FLC concentrations, 3 and 6 months after treatment, showed a highly significant ($P<0.001$) correlation with the changes in ESR. As described previously, RF levels and, to a lesser extent, anti-CCP antibody levels decreased after rituximab treatment (45% and 26%, resp). In contrast to FLC concentrations, these decreases did not discriminate clinical responders from non-responders. Total IgG, IgA and IgM concentrations remained within normal limits.

Conclusion: Rituximab significantly reduced FLC levels that are increased in RA patients. Changes in FLC concentrations significantly correlate with the clinical response. Our study suggests that inhibition of FLCs may represent a novel anti-inflammatory mechanism of Rituximab treatment.

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Seven Year Results of DAS Steered Treatment in the BeSt Study: Clinical and Radiological Outcomes. L. Dirven[5], M. van den Broek[5], N. B. Klarenbeek[5], M. V. van Krugten[1], P. A. H. M. van der Lubbe[2], P. J. S. M. Kerstens[3], T. W. J. Huizinga[5], B. A. C. Dijkmans[6] and C. F. Allaart[4]. [1]Admiraal de Ruyter Hospital, [2]Haga Hospital, [3]Jan van Breemen Institute, [4]Leiden Univ Med Ctr, Leiden, The Netherlands, [5]Leiden University Medical Center, [6]VU Medical Centre, Amsterdam, The Netherlands

Objective: To compare clinical and radiological outcomes of four treatment strategies after 7 years DAS-steered treatment in recent onset rheumatoid arthritis.

Methods: 508 recent onset RA patients were randomized into four treatment strategies: 1. sequential monotherapy, 2. step up combination therapy, 3. initial combination with prednisone, 4. initial combination with infliximab. Treatment adjustments were made every three months based on DAS measurements (if DAS >2.4: dose increase/switch next treatment step, if DAS ≤ 2.4 during ≥6 months: taper to maintenance dose, next if DAS <1.6 during ≥6 months: stop anti-rheumatic treatment). Functional ability (HAQ) was analyzed with a linear mixed model (LMM) with time, treatment and time*treatment as independent variables. Joint damage progression (Sharp-van der Heijde Score (SHS)) was assessed on X-rays of baseline and year 2, 4, 5, 6, 7 and scored by two independent readers in random order, blinded for patient identity.

Results: After 7-years follow-up, 130 patients (26%) dropped out the study. At t=7 year, 79% had a DAS ≤2.4 and 46% DAS <1.6 (remission), equally distributed among the four groups (table). Sixteen, 16, 17 and 17% of the patients in groups 1–4 were in drug free remission with a median (mean) duration of 36 (31) months. Ten patients lost and six new patients achieved drug free remission in year 7. Four patients with prolonged drug-free remission dropped out. The initial improvement of function, which occurred earlier in groups 3 and 4 than in groups 1 and 2, was maintained without deterioration over 7 years time in all groups. Over time (LMM), patients in group 4 have significantly better functional ability compared to groups 1 and 2 (mean HAQ: 0.70, 0.71 and 0.57 respectively). After initial differences between the 4 groups, yearly radiological damage progression rates were similar between all groups, reflecting the efficacy of DAS-steered therapy. Differences in total damage after 7 years are no longer statistically significant. Mean SHS progression in patients in sustained drug free remission was 0.3 (median (IQR) 0 (0–0.2)) per person year drug-free. Toxicity was comparable between the groups.

Conclusion: With continued DAS steered treatment aiming at DAS ≤2.4, functional improvement was maintained and radiological progression as well as percentages in remission and in drug free remission were stabilized. Over 7 years time, patients treated with initial combination therapy with infliximab had better functioning than patients treated with initial monotherapy.

Table. 7-year results of the BeSt study

	Group 1 n = 126	Group 2 n = 121	Group 3 n = 133	Group 4 n = 128	p-value
completers	n = 83	n = 72	n = 79	n = 97	
DAS ≤2.4, (%)†	82	76	82	76	0.64
DAS <1.6, (%)†	49	39	53	45	0.35
DAS <1.6 drug free, %†	16	18	17	17	0.96
Still on initial treatment step, %‡	21	16	20	55	<0.001
Mean HAQ during 7 years‡	0.70	0.71	0.63	0.57	<0.001*
IFX current use, (%)‡	14	6	11	21	<0.05
Drop outs, n (%)‡	33 (26)	40 (33)	35 (26)	22 (17)	0.04
SHS progression, median (mean)†					
Total, year 0–7	3.8 (15.1)	3.5 (10.7)	2.0 (8.4)	2.0 (5.5)	0.205
year 0–2	1 (6.4)	0.5 (3.2)	0 (1.6)	0.5 (1.7)	0.002
year 2–4	0 (2.6)	0.3 (2.4)	0 (2.1)	0 (1.1)	0.562
year 5	0 (1.2)	0 (1.5)	0 (1.2)	0 (1.1)	0.822
year 6	0 (1.7)	0 (1)	0 (0.9)	0 (0.7)	0.765
year 7	0 (0.9)	0.5 (1.4)	0 (1.1)	0 (0.2)	0.077

*LMM: group 1 and 2 vs 4, $p < 0.05$. †completers analysis, ‡intention to treat.

Disclosure: L. Dirven: Centocor, Inc., 2, Dutch College of Health Insurances, 2, Schering-Plough, 2; **M. van den Broek:** None; **N. B. Klarenbeek:** None; **M. V. van Krugten:** None; **P. A. H. M. van der Lubbe:** None; **P. J. S. M. Kerstens:** None; **T. W. J. Huizinga:** None; **B. A. C. Dijkmans:** None; **C. F. Allaart:** None.

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Surveillance of Surgical Site Infection in Patients with Rheumatoid Arthritis. Kengo Harigane[1], Yuichi Mochida[2], Katsushi Ishii[2], Naoya Taki[2], Naoto Mitsugi[2] and Tomoyuki Saito[3]. [1]Yokohama City University Medical Center, Yokohama, Kanagawa, Japan, [2]Yokohama City University Medical Center, [3]Yokohama City University School of Medicine

Introduction: After introducing the guideline of Centers for Disease Control and Prevention in 1999, clinical concern about SSI has been increasing. Recently, the guideline is widely recognized as the basics for prevention protocols of SSI. Although rheumatoid arthritis (RA) is listed as a risk factor for SSI in the guideline, few studies were reported about the disease specific surveillance with RA.

Objectives: The aims of current study were to examine the incidence and to identify risk factors of SSI in patients with RA.

Methods: The clinical records of 779 patients (female 710 cases and male 69 cases) with RA who underwent orthopaedic surgeries in our hospital between January 1999 and October 2009 were carefully reviewed and the occurrences of SSI were investigated. SSI was strictly determined using the definitions of the guideline of CDC. The associations of SSI with administration of steroids and MTX, and with the presence of diabetes mellitus were also analyzed.

Results: Seventeen cases were recognized as SSI (2.2%); nine cases were superficial and eight cases were deep infections. The incident rate of SSI in arthroplasty cases was 2.9%, which was higher than the rate in non-arthroplasty cases (1.4%), however the p-value did not reach statistical difference ($p=0.2$). Steroids administration showed a statistically significant risk of SSI ($p=0.04$), on the other hand, methotrexate administration was a negative risk factor of SSI ($p=0.047$). The dose of oral steroids at the time of surgery clearly showed a positive dose-dependent correlation with the rate of SSI ($p=0.01$). There was no significant correlation between SSI and the presence of diabetes mellitus.

Conclusion: After introducing the strict guideline of CDC, reported incidences of SSI became higher (approximately 2%). In those reports, more than half cases of SSI occurred in superficial lesions. The results of current study were similar to recent reports. The incident rates of SSI showed no statistical difference between arthroplasty and non-arthroplasty cases. As for risk factors, the administration of steroids was a risk of SSI, in contrast, administration of MTX was a negative risk factor of SSI.

Disclosure: K. Harigane: None; **Y. Mochida:** None; **K. Ishii:** None; **N. Taki:** None; **N. Mitsugi:** None; **T. Saito:** None.

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Sustained Remission in Early RA: Results from SONORA Study. Claire Bombardier[3], Pooneh Akhavan[2], Maggie Chen[1] and Xiuying Li[1]. [1]University Health Network, [2]University of Toronto, University Health Network, [3]University of Toronto, University Health Network, Mount Sinai Hospital, Toronto, ON, Canada

Purpose: Remission constitutes the best achievable state in patients with rheumatoid arthritis (RA). Current measures of Disease Activity - such as the DAS28 - define the patient's remission status at a given point in time. While, for the patient, sustained remission over time is the ultimate goal. The purpose of this study is to assess the frequency and predictors of sustained remission in a large cohort of early RA patients in regular clinical practice.

Methods: A total of 994 patients diagnosed as early RA (symptoms ≥3 and ≤12 months) by a board-certified rheumatologist across North America were recruited in this study. We analyzed remission and sustained remission in 851 patients who had two-year complete follow up information. Remission was defined as less than 2.6 for DAS28 and sustained remission was defined as consecutive remission at year 1 and year 2. Univariate logistic regressions were used to explore the predictors for sustained remission and multivariate logistic regression were used to estimate the remission probabilities controlling for significant factors.

Results: The mean age of patients was 53 years (SD, 14.8), with 72% female and 90% Caucasian. The mean RA symptom duration was 170 days (180), 61% were seropositive for rheumatoid factor and 43% anti-CCP positive (>20 unit/ml) at baseline. Seventy-four percent of patients had received DMARDs at baseline compared to 90% at year 1 and, 87% at 2. Two percent of the subjects were on Biologics at baseline compared to 15%, 23% at year 1 and 2. Remissions at any one of the two visits were seen in 238 (28%) patients. Among them, 68 (8%) patients achieved sustained remission. The univariate logistic regression showed that low baseline DAS28 score, HAQ score, disease duration and CRP are significant predictors for sustained remission. The multivariate logistic regression showed that HAQ is no longer significant when other factors (low baseline DAS28, low CRP and short disease duration) are in the model. The final model therefore excludes HAQ as a predictor.

Table 1.

	Odds ratio	95% CI	P-value
Baseline DAS28	0.660	(0.536, 0.813)	<0.0001
Disease duration (in months)	0.878	(0.796, 0.968)	0.0091
CRP	0.834	(0.723, 0.962)	0.0126

Conclusions: Low sustained remission rates were observed in this early RA cohort recruited before the wide use of biologics. The multivariate model predicts the probability of sustained remission using easily accessible clinical and laboratory variables. These identified factors can help guide rheumatologists in making treatment decisions for early RA patients.

Disclosure: C. Bombardier: None; **P. Akhavan:** None; **M. Chen:** None; **X. Li:** None.

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Sustained Remission, a Realistic Target in Early Rheumatoid Arthritis Patients Treated with Conventional DMARDs. Irazú Contreras-Yáñez, Marina Rull-Gabayet and Virginia Pascual-Ramos. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Ciudad de México, DF, Mexico

Background: A remission-like state has become the treatment goal of patients with early rheumatoid arthritis (≤12 months, ERA).

Objectives: To describe sustained outcomes in an ERA cohort of patients treated with conventional disease modifying anti-rheumatic drugs (DMARDs) in whom long-standing follow-up is performed in a real clinical setting. To identify associated predictors.

Patients and Methods: 101 ERA with at least 2 years of follow-up were included. Standard baseline and consecutive assessments (2 monthly apart for the first 2 years and every 2, 4 or 6 months, thereafter) included swollen and tender joint counts, patient-reported outcomes, acute reactant phase determinations, disease activity score-28 joints evaluated (DAS28),

comorbidity and treatment evaluations. At baseline, socio-demographic data, rheumatoid factor (RF) and antibodies to cyclic citrullinated peptides (a-CCP) were recorded and determined. *Permanent sustained remission* (*PSR*) was defined when patients achieved sustained remission (SR=at least 3 consecutive 2 monthly apart DAS28≤2.4) and maintained it until last follow-up, *lost sustained remission* (*LSR*) when patients achieved SR but within follow-up DAS28 was >2.4 and *persistent disease activity (PDA)* when patients never achieved SR. Cumulative treatment and comorbidity were defined prior to outcomes.

Statistics: X^2, t-Student, ANOVA and Cox regression analysis were used.

Results: At baseline, 88 (87.1%) patients were females, 78 (77.2%) had RF and 71 (71%) a-CCP; their (mean±SD) age was of 38.2±13.5 years, disease duration of 5.2±2.7 months, DAS28 of 6.1±1.3 and health assessment questionnaire (HAQ) of 1.5±0.9. Seventy-one patients (70.3%) received aggressive treatment (≥3 combined DMARDs). At last follow-up (49±13.8 months), 34 patients (33.7%) achieved PSR, 54 (53.5%) achieved LSR and 13 (12.9%) had PDA.

Patients with favorable outcomes (persistent or lost sustained remission) had less frequently baseline RF and a-CCP (p≤0.07) and lower clinical (p=0.07) and serological (p≤0.004) disease activity at baseline than persistently active patients. Patients with PSR achieved sooner their state than patients with LSR (p=0.008). Persistently active patients received more frequently corticosteroids at any time (p≤0.07) and a more aggressive DMARDs treatment at baseline (p=0.02) than both groups of patients who achieved sustained remission.

To identify predictors of favorable outcomes, patients with PSR were compared to LSR patients. Early (within the first year of follow-up) sustained remission was the only predictor of permanent sustained remission (HR: 3.5, 95%CI: 1.6–7.6, 0=0.001) after controlling for baseline RF, aggressive DMARD treatment and disease duration. Similar results were obtained when patients with PDA and LSR were combined and compared to patients with PSR (HR: 4.15, 95%CI: 1.93-0.95, p≤0.001) after controlling for baseline RF and ESR, aggressive DMARD treatment and baseline number of DMARDs/patient.

Conclusions: Sustained remission is achieved by most of the ERA who received DMARDs. Patients who achieve early a sustained remission state show an excellent longstanding outcome.

Disclosure: I. Contreras-Yáñez: None; **M. Rull-Gabayet:** None; **V. Pascual-Ramos:** None.

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Switching Patterns for Biologic Drugs among Patients with Rheumatoid Arthritis Who Have Previously Failed at Least One Biologic Agent. Stephen Johnston[2], Sarika Ogale[1], Nicole Princic[3], Bong-Chul Chu[3] and Tripthi Kamath[1]. [1]Genentech USA, Inc., [2]Thomson Reuters, Washington, DC, [3]Thomson Reuters

Background: There is limited real-world observational data on switching patterns for biologic disease modifying antirheumatic drugs (DMARDs) in patients with rheumatoid arthritis (RA) who have previously failed at least one biologic DMARD.

Methods: Retrospective observational study using healthcare claims from the Thomson Reuters MarketScan® Research Databases.

Selected patients were aged 18 or older and initiated a biologic DMARD (abatacept, adalimumab, etanercept, infliximab, or rituximab) between 3/1/2006–9/30/2008 (initiation date = index) with evidence of at least one different biologic DMARD during the 12 months prior to index. Patients were required to have at least one medical claim with an ICD-9-CM diagnosis code for RA (714.0x) within 12-months prior to index; patients with diagnoses for other conditions in which biologic DMARDs are indicated were excluded.

A 12-month pre-index baseline period was used to measure patient characteristics and a minimum 12-month post-index period was used to measure time-to switch (days from index until the first occurrence of a switch to a different biologic DMARD or censoring at disenrollment). The Kaplan Meier product-limit method of survival analysis and a log-rank test was used to test the statistical significance of differences in time-to switching.

Results: Table 1 displays demographic and clinical characteristics for the 3,049 patients who were selected for study.

Table 1. Baseline demographic and clinical characteristics of RA patients initiating a subsequent biologic DMARD after failing at least one biologic DMARD

	Abatacept N = 620	Adalimumab N = 1,073	Etanercept N = 609	Infliximab N = 424	Rituximab N = 323
Age, mean (SD)	58.4 (12.4)	56.6 (11.8)	55.7 (12.1)	55.6 (12.0)	57.2 (11.9)
Female, %	82.3%	81.7%	78.3%	77.1%	75.2%
Northeast region, %	7.6%	10.2%	11.5%	8.5%	7.7%
North Central region, %	27.7%	27.4%	29.6%	25.0%	32.8%
South region, %	46.6%	40.5%	39.9%	50.0%	44.9%
West region, %	17.6%	21.3%	18.4%	16.3%	14.2%
Deyo-Charlson Comorbidity index, mean (SD)	1.6 (1.1)	1.5 (1.1)	1.6 (1.0)	1.6 (1.0)	1.8 (1.3)
Prior methotrexate, %	56.9%	61.2%	63.7%	70.3%	62.5%
Unique 3-digit ICD-9-CM diagnosis codes, mean (SD)	13.2 (8.0)	11.5 (7.2)	11.9 (7.6)	12.1 (7.2)	13.7 (8.9)
Unique medications, mean (SD)	18.5 (11.2)	18.4 (10.8)	17.5 (9.6)	19.1 (10.1)	19.7 (10.8)

Switch rates per 1,000-person years were: abatacept = 243; adalimumab = 208; etanercept = 170; infliximab = 285; rituximab = 171. Figure 1 displays survival curves for the time-to switch for patients initiating each biologic agent.

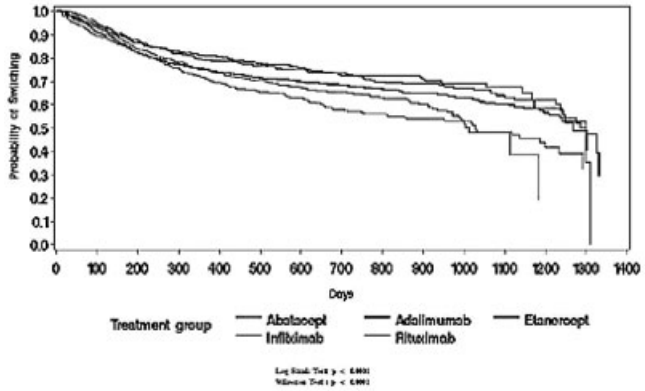

Figure 1. Kaplan Meier survival curve for time-to-switching among RA patients initiating a subsequent biologic DMARD after failing at least one biologic DMARD.

Conclusions: Switching of RA biologics may occur due to inadequate response to the current biologic, burden of side effects, or other variables. In this analysis, switch rates per 1,000 person-years were the lowest among patients initiating rituximab and etanercept and highest among patients initiating infliximab. Time-to switch was significantly different across the groups (p<0.001), and was longest in patients initiating rituximab and etanercept and shortest in patients initiating infliximab.

Disclosure: S. Johnston: None; **S. Ogale:** Genentech and Biogen IDEC Inc, 3, Roche, 1; **N. Princic:** None; **B.-C. Chu:** None; **T. Kamath:** Genentech and Biogen IDEC Inc, 3, Roche, 1.

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Systemic Immunosuppressives and the Risk of Diabetes in Rheumatoid Arthritis (RA) and Psoriatic Arthritis (PsA). Daniel Hal Solomon[3], Elena M. Massarotti[1], Raj Garg[2], Claire Canning[2], Jun Liu[2] and Sebastian Schneeweiss[2]. [1]Brigham & Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital, [3]Brigham and Womens Hospital, Boston, MA

Background: Several inflammatory conditions, including RA and PsA, have been linked with insulin resistance and diabetes mellitus (DM). The underlying inflammation and use of oral glucocorticoids are two possible causes. Prior investigations demonstrate an improvement in insulin resistance with several TNF inhibitors (TNFi), and hydroxychloroquine (HCQ) has been shown to reduce the risk of diabetes in a large observational RA cohort. We compared the risk of incident DM among subjects diagnosed with RA or PsA based on their use of a variety of DMARDs.

Methods: Our study cohort was drawn from two data sources—a population-based cohort from a Canadian province and a large commercial insurance plan. Patients with at least two diagnoses of RA or two diagnoses of PsA who have no evidence of DM (no diagnoses and no diabetes medication use) were eligible for the study cohort at the time they switched or added an immunosuppressive. DMARD regimens were categorized into four mutually exclusive groups: 1) TNFi with or without other DMARDs, 2) methotrexate (MTX) without a TNFi or HCQ, 3) HCQ without MTX or a

TNFi, or 4) other DMARD without a TNFi, MTX or HCQ. The primary outcome was incident DM, defined as a diagnosis and start of a DM-specific medication. Incidence rates for DM were compared across exposure groups. In addition, adjusted hazard ratios were calculated in Cox regression with other DMARD considered the reference exposure. Adjusted analyses included covariates for age, gender, Charlson comorbidity score, oral glucocorticoid use, topical glucocorticoid use, prior DMARDs, calendar year, plus several other health service indicators. Secondary analyses focused on different periods during follow-up and on oral glucocorticoid users.

Results: The study cohort consisted of 22,493 subjects with RA or PsA starting one of the four groups: 4,623 TNFi, 8,195 MTX, 5,682 HCQ, and 3,993 another DMARD. Mean follow-up was 6 months. The four groups' characteristics were similar with respect to age, gender, distribution of underlying rheumatic disease, and health services utilization, but differed by oral steroid use with the TNFi group having more prior steroid use. The incidence rates for DM were as follows: total cohort 24.6 per 1,000 person-years, TNFi 19.7, MTX 23.8, HCQ 22.2, and another DMARD 50.2. Adjusted hazard ratios for DM were 0.62 (95% CI 0.42 – 0.91) for TNFi, 0.77 (95% CI 0.53–1.13) for MTX, and 0.54 (95% CI 0.36–0.80) for HCQ (see Figure). Secondary analyses exhibit consistent findings.

Adjusted Cox Proportional Hazards for Risk of Diabetes Mellitus in RA and PsA

	Non-biologic DMARD	Hydroxy-chloroquine	Methotrexate	TNF inhibitor
Model 1	1.00	0.58 (0.39–0.85)	0.63 (0.45–0.88)	0.72 (0.50–1.03)
Model 2	1.00	0.58 (0.39–0.85)	0.62 (0.44–0.87)	0.76 (0.53–1.09)
Model 3	1.00	0.54 (0.36–0.80)	0.77 (0.53–1.13)	0.62 (0.42–0.91)

Notes: Model 1: Adjusted for diagnosis and data source. Model 2: Adjusted as Model 1 + age and gender. Model 3: Adjusted as Model 2 + Charlson Score, dermatologist visits, dermatology indicator, generics, number of hospital visits, number of MD visits, prior but no current HCQ, prior but no current MTX, prior but no current NBDMARD, prior but no current oral steroids, prior but no current TNFA, prior oral steroids, prior topical steroids, number of rheumatology visits, number of dermatologist visits, and year of index.

Conclusions: Among subjects diagnosed with RA or PsA, the adjusted risk of incident DM appeared reduced for persons starting a TNFi or HCQ compared with another DMARD. This result was robust across secondary analyses and suggests that a treatment trial testing the effects of specific DMARDs on incident DM would be warranted.

Disclosure: D. H. Solomon: Abbott Immunology Pharmaceuticals, 2, Amgen Inc., 2, Bristol-Myers Squibb, 9; **E. M. Massarotti:** Bristol-Myers Squibb, 2, 5, Merck Human Health, 5, Roche, 2, 5, Serono, 2, UCB, Inc., 2, 5, UpToDate, 7; **R. Garg:** None; **C. Canning:** None; **J. Liu:** None; **S. Schneeweiss:** None.

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The Belgian MIRA (MabThera in Rheumatoid Arthritis) Registry: Clues for the Optimization of Rituximab Treatment Strategies. Bert Vander Cruyssen[2], Patrick Durez[1], Rene Westhovens[5], Ilse Hoffman[3], M. J. Kaiser[4] and Filip De Keyser. [1]Cliniques Universitaires Saint-Luc, Brussels, [2]Ghent University Hosptial, [3]GZA St-Augustinus Hospital Antwerp, Belgium, [4]University Hospital Liege, Liege, Belgium, [5]University Hospitals KULeuven, Leuven, Belgium

Background: The Belgian MIRA registry aims to record safety and efficacy data of rituximab treatment. In Belgium, RA patients are eligible for treatment with rituximab if they failed at least 1 anti-TNF and have a baseline DAS28 > 3.7. From week 24 on, patients can be retreated if they have a moderate or good EULAR response at week 16, and a current DAS28 score of at least 3.2.

Methods: All Belgian rheumatologists could participate in the study. Patients entered the registry as from November 2006 and the entry is still open. All patients were treated with 2 infusions per course of rituximab (2 × 1000 mg week 0 and 2) in combination with 100 mg of methylprednisolone and MTX. Baseline patient's characteristics were recorded as well as DAS28-variables every 2 months.

Results: By mid may 2010, 497 patients had entered the registry with a mean follow-up time of 84 weeks. Patients (mean age of 59 years, 77 % female) had a mean disease duration of 12 years.

Rituximab therapy decreased the overall mean disease activity from DAS28-ESR 5.9 (SE = 0.1) at baseline to 4.1 (SE = 0.1) at week 16. 83% of patients fulfilled the EULAR good or moderate response criteria. Further decrease of DAS was observed at the end of year 1 and year 2 with a mean DAS28-ESR of 4.0 (SE = 0.2) and 3.7 (SE = 0.2) at these respective time points.

342 and 188 patients received a 2nd and 3rd course of rituximab respectively. The median time to retreatment was 32 weeks after the first course.

At the start of each treatment course, the DAS28-ESR values were lower compared to values at the start of the previous treatment course. The values reached a minimum at week 16 of each respective treatment course, and then increased slightly, until the start of the following treatment course. Paired analysis of DAS28 scores 6 months after the first and second course suggests that lower DAS scores are obtained after the second course (mean diff = −0.6, SE =0.2, p <0.001).

This further decrease of DAS28 scores between the first and second course was especially seen in those patients who did not flare (increase of DAS28>1.2) between week 24 and their second course (mean diff = −1.1, SE = 0.2 vs. mean diff −0.08, SE = 0.4, p = 0.002).

85 patients discontinued treatment: 62 stopped due to inefficacy and 18 stopped due to safety issues (infusion reactions in 6 patients, infections in 5, other reasons in 7 patients). 2 Patient died. Only 33 patients were lost to follow-up.

Conclusions: The efficacy of rituximab in refractory RA patients is confirmed in this daily practice cohort. DAS28 response was observed in the large majority of our cohort and a sustained DAS 28 decrease was observed during the following course, especially in patients who didn't show an obvious flare. These elements suggest that treatment of RA patients with rituximab could be optimized by earlier retreatment in patients who developed flares.

Disclosure: B. Vander Cruyssen: None; **P. Durez:** None; **R. Westhovens:** None; **I. Hoffman:** None; **M. J. Kaiser:** None; **F. De Keyser:** None.

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The Incidence of Herpes Zoster in Seniors with Rheumatoid Arthritis. Jessica Widdifield[7], Sasha R. Bernatsky[2], J. Michael Paterson[1], Nadia Gunraj[1], Janet E. Pope[5], J. Carter Thorne[4], Alfred A. Cividino[3] and Claire Bombardier[6]. [1]Institute for Clinical Evaluative Science, [2]McGill UHC/RVH, Montreal, QC, Canada, [3]McMaster University, Hamilton, ON, Canada, [4]Southlake Regional Health Care, Newmarket, ON, Canada, [5]St Joseph Health Care London, London, ON, Canada, [6]University of Toronto, Toronto, ON, Canada, [7]University of Toronto

Herpes zoster (HZ) is a painful cutaneous eruption caused by varicella-zoster reactivation. It results in substantial morbidity, particularly in elderly and/or immunocompromised patients. Recent literature suggests that patients with rheumatoid arthritis (RA) are at particular risk for HZ. The Ontario Biologics Research Initiative (OBRI) conducts real-world surveillance through administrative database linkage with primary data collection, based in Canada's largest province (population > 13 million).

Purpose: To study risk and risk factors for HZ, using a case-control sample nested within a cohort of seniors with RA.

Methods: An RA cohort was assembled from Ontario billing, hospitalization and prescription data, 1992–2008. Analyses were limited to subjects aged >65 who filled ≥ 1 prescription for a disease-modifying agent (DMARD), oral corticosteroid, or biologic. We studied cases of HZ identified from physician billing and hospitalization diagnoses over 1998–2009. RA controls (age, sex and time matched) were randomly selected by risk-set sampling. Multivariate conditional logistic regression assessed the independent effects of concomitant drug treatments on HZ, adjusted for demographics, comorbidity, and markers of RA severity (rheumatology visits, extra-articular RA features, joint replacement).

Results: A total of 3,999 cases of HZ were recorded among 85,458 seniors with RA during 614,915 person-years (6.5 events/1000 person-years). Comparing these HZ cases to 19,995 RA controls, 21.9% of cases versus 10.8% of controls were exposed to prednisone at the time of infection. Multivariate models demonstrated that risk of HZ was higher among current and past use of all DMARD groups. There was a notable increasing trend for higher risk of HZ with increasing steroid doses. Due to low rates of biologic drug exposures in our sample, the estimated effects of these agents were imprecise, but also consistent with a higher risk.

Drug Exposure	Adjusted Odds Ratio [95% Confidence Interval]
Anti-TNF agent [REF = Non-user]	
Current use	1.17 [0.63 2.19]
Past use	1.54 [0.68 3.51]
Anti-IL1 [REF = Non-user]	
Current use	4.02 [0.54 29.63]
Past use	–
Methotrexate [REF = Non-user]	
Current use	**1.44 [1.27 1.62]**
Past use	**1.28 [1.08 1.52]**
Sulfasalazine [REF = Non-user]	
Current use	1.01 [0.77 1.34]
Past use	0.92 [0.66 1.29]
Leflunomide [REF = Non-user]	
Current use	**1.46 [1.03 2.06]**
Past use	1.16 [0.73 1.84]
Hydroxychloroquine [REF = Non-user]	
Current use	**1.89 [1.68 2.13]**
Past use	**1.25 [1.05 1.49]**
Cyclophosphamide [REF = Non-user]	
Current use	**8.35 [1.50 46.58]**
Past use	1.90 [0.57 6.27]
Azathioprine [REF = Non-user]	
Current use	**1.79 [1.18 2.73]**
Past use	1.24 [0.69 2.25]
NSAIDs/COXIBs [REF = Non-user]	
Current use	**1.72 [1.57 1.89]**
Past use	**1.55 [1.42 1.70]**
Other DMARDs [REF = Non-user]	
Current use	**1.73 [1.28 2.33]**
Past use	1.15 [0.83 1.60]
Steroid Use [REF = None]	
Low ≤5 mg prednisone equivalent/day	**1.66 [1.45 1.91]**
Medium 6–9 mg/day	**1.91 [1.46 2.50]**
High 10–19 mg/day	**1.99 [1.67 2.37]**
Very High ≥ 20 mg/day	**3.22 [2.66 3.89]**
Past use	**1.29 [1.17 1.42]**

Conclusions: Our estimates emphasize an association of anti-rheumatic therapies with the occurrence of HZ. Potential limitations of our study include the possibility of incomplete ascertainment of biologic exposures (private insurance is not represented in public payer database; but this is uncommon) and channelling bias (where persons at highest risk for infections may not be prescribed biologics).

Disclosure: J. Widdifield: None; **S. R. Bernatsky:** None; **J. M. Paterson:** None; **N. Gunraj:** None; **J. E. Pope:** None; **J. C. Thorne:** None; **A. A. Cividino:** None; **C. Bombardier:** None.

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The Influence of Systemic Glucocorticoid Therapy upon the Risk of Non-Serious Infection in Patients with Rheumatoid Arthritis. William G. Dixon[3], Abbas Kezouh[2], Sasha R. Bernatsky[1] and Samy Suissa[2]. [1]McGill UHC/RVH, Montreal, QC, Canada, [2]McGill University, [3]The University of Manchester, Manchester, United Kingdom

Background: Glucocorticoid (GC) therapy is a strong risk factor for serious infections in patients with RA. However, the association between GCs and non-serious infections (NSI) is not well studied. Although NSIs are not life-threatening, they are common: respiratory infections alone account for up to 400 general practice consultations annually per 1000 patients. Even a modest increase in relative risk due to GCs may represent a large increase in the attributable risk and a significant health burden.

Methods: Using data from Quebec health administrative databases from 1985–2003, we assembled a cohort of 16,207 patients with RA aged >65. GC and DMARD therapy were identified from drug dispensing records. NSI cases were defined as the first occurrence of either a community physician billing code for infection or community-dispensed anti-infectives. The incidence of NSI was estimated in the whole cohort. The incidence of NSI in GC-exposed and GC-non-exposed person time was calculated in a cohort analysis to enable estimation of the attributable risk. A nested case-control analysis was performed, matching each case to 5 controls. Matching was done on entry date and time in cohort, using risk set sampling. Analysis considered drugs dispensed within 45 days prior to the index date (date of infection for each case-control set), adjusting for age, sex, markers of disease severity, DMARDs and co-morbidity. Oral GC therapy was considered together, then categorised into 5 dose bands. Conditional logistic regression was used to calculate the odds ratio, interpretable as a relative risk.

Results: 13,634 first-episode NSI occurred during 28,695 person years (pyrs), generating an incidence rate of 475 events/ 1000 pyrs. The rate of NSI in GC exposed and unexposed person time was 524 and 388/1000 pyrs, respectively. The attributable risk was therefore 135 events/ 1000 pyrs. In the case-control analysis, GC therapy was associated with an adjusted relative risk (aRR) of 1.20 (95% CI 1.15, 1.25). A positive dose response was seen between risk and GC dose. Methotrexate (MTX) was the most commonly used DMARD, and was associated with a no increased risk of NSI (aRR 1.00 (0.95, 1.04)). Patients currently prescribed sulfasalazine or anti-malarials had a lower rate of infection than patients not prescribed those drugs. Cyclophosphamide was associated with a higher risk of infection (aRR 2.14 (1.51, 3.03)). The results for anti-TNF therapy were inconclusive given the small number of patients exposed to them. All GC risk estimates (including 0–5mg/day) were higher than that seen for MTX.

	Cases n = 13,634	Controls n = 68,170	Adjusted RR* (95% CI)
Oral GC exposure within last 45 days	37.9	32.5	1.20 (1.15, 1.25)
Average daily dose of oral GC therapy			
• <5 mg PEQ	3.2	3.1	1.10 (0.99, 1.22)
• 5–9.9 mg PEQ	17.8	17.1	1.10 (1.04, 1.16)
• 10–14.9 mg PEQ	9.5	7.9	1.25 (1.17, 1.34)
• 15–19.9 mg PEQ	2.7	2.1	1.26 (1.12, 1.42)
• >=20 mg PEQ	4.7	2.3	1.85 (1.68, 2.05)
Any GC: oral or injection	39.2	33.7	1.19 (1.14, 1.24)
Current DMARD use			
• Methotrexate	33.3	33.0	1.00 (0.95, 1.04)
• Sulfasalazine	2.4	3.0	0.79 (0.70, 0.89)
• Leflunomide	0.3	0.3	1.00 (0.71, 1.39)
• CQ/HCQ	29.4	30.7	0.93 (0.89, 0.98)
• Azathioprine	1.9	1.5	1.05 (0.91, 1.22)
• Cyclophosphamide	1.7	0.7	2.14 (1.51, 3.03)
• Gold	7.1	6.5	1.08 (0.99, 1.18)
• Anti-TNF therapy	0.1	0.1	1.48 (0.87, 2.52)
• Others**	1.8	1.7	1.07 (0.92, 1.25)

GC = glucocorticoid, PEQ = prednisolone equivalent, RR = relative risk
*Adjusted for age, sex, markers of disease severity, and co-morbidity
**Includes ciclosporin, mycophenolate mofetil, and D-penicillamine

Conclusion: GC therapy is associated with an increased risk of NSI. The magnitude of the risk increases with dose, and is higher than that seen with MTX (although residual confounding may exist). Whilst the RR is low at 1.20, the absolute risk is high, with one additional infection seen for every 8 patients treated for 1 year.

Disclosure: W. G. Dixon: None; **A. Kezouh:** None; **S. R. Bernatsky:** None; **S. Suissa:** None.

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Three Months of Therapy with DMARDs Is an Inadequate Period of Time To Alter the Treatment in Patients with Early Rheumatoid Arthritis When Treating to a Target of Low Disease State or Remission. Results from Canadian Early ArThritis CoHort (CATCH).

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Objective: The objective of this study was to evaluate the concept of therapy alteration in patients with early rheumatoid arthritis (ERA) not achieving an adequate response by 3 months in a prospective cohort.

The study was designed to assess whether 3 months was an adequate time for decision-making regarding altering therapy in ERA patients who have been on stable DMARDs for 6 months and have not achieved low disease activity state (LDAS) or remission (REM).

Methods: Patients with ERA were studied in the Canadian Early Arthritis Cohort (CATCH), a prospective cohort where data was collected according to a standardized protocol. Patients who were on stable DMARDs therapy (with no dose adjustments after one month of initiating therapy and not receiving oral or parenteral steroids) for 6 months were evaluated. Patients not achieving LDAS or REM by 3 months were examined for the proportion of those achieving LDAS or REM by 6 months. We also evaluated patients achieving LDAS or REM by 6 months who had not achieved these outcomes by 3 months.

Results: 108 patients were evaluated with the baseline mean age of 50 years and disease duration of 6.3 months. Mean patient global assessment of disease activity, pain score and HAQ-DI were 61.2, 65.0 and 1.0 respectively at baseline. At 3 months, 46% and 31% of patients achieved LDAS or REM respectively, while 65% and 52% achieved these states by 6 months. Of 58 patients not in LDAS at 3 months, 26 (45%) achieved LDAS by 6 months. Of 74 patients not in REM by 3 months, 29 (40%) achieved REM by 6 months. Of 56 patients who achieved REM by 6 months, only 27 (48%) achieved it by 3 months.

Although baseline swollen joint count, tender joint count and CRP levels were not significantly different in two groups, patients who achieved LDAS at 6 months had higher pain (71±17 vs 47±32, $p<0.05$) and patients global assessment (77±18 vs 53±32, $p<0.05$) scores at baseline compare to those achieved this state at 3 months. In patients with delayed remission (at 6 months) in addition to the above outcome measures, HAQ-DI (0.6±0.6 vs 1.1±0.6, $p=0.003$) was higher at baseline when compared to patient who achieved remission at 3 months.

Conclusion: While remaining on a stable therapy through 6 months, a substantial proportion of patients who had not achieved an adequate clinical response (LDAS or REM) by 3 months achieved these states by 6 months. Attention should be given to patient reported outcomes when assessing patients with ERA for risk of delayed remission. The data in this real world setting suggest that in a significant number of patients, 3 months was not an adequate period of time to decide on altering therapy based on whether an adequate clinical response had been achieved. Our results support recent guidelines suggesting that a 3 to 6 month time frame is required for optimal treatment decision making when treating to an LDAS or REM target.

Disclosure: P. Akhavan: None; **V. P. Bykerk:** Amgen Inc., 2, Pfizer Inc, 2; **Y. Sun:** None; **J. Hochman:** None; **J. E. Pope:** None; **C. A. Hitchon:** None; **G. Boire:** None; **B. Haraoui:** None; **D. S. Ferland:** None; **J. C. Thorne:** None; **D. A. Weber:** None; **E. C. Keystone:** Amgen Inc., 2, 5, Pfizer Inc, 2, 5; **CATCH Investogators:** Amgen Inc., 2, Pfizer Inc, 2.

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Treating to Target with TNFi in Active Established Rheumatoid Arthritis Results in Longer Drug Survival Than Routine Care with TNFi: Results from the Optimization of Humira RCT.

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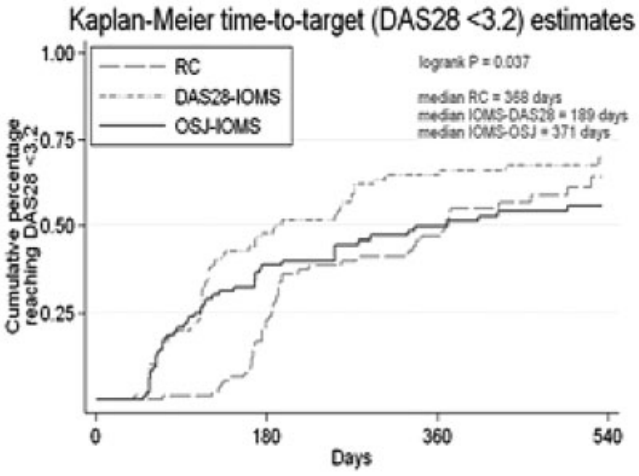
Background: This randomized trial in active RA receiving adalimumab was done to determine if targeted outcomes yielded better results than routine care in established RA and to determine if treating to no swollen joints (0SJC) would be more effective than treating to a DAS<3.2. Drug survival was studied, as the withdrawal rate for TNFi in RA is 20 to 30% annually for the first two years; then decreases thereafter.

Methods: The Optimization of Humira trial was a real-life 18 months RCT in patients with established active RA.; with randomization to: routine care (RC), or treating to clinical target (low DAS28<3.2 or 0/28 SJC). The primary outcome measure was the change in DAS28 at 12 months. Sample size was calculated to show a difference between RC and more intensive (targeted) care, allowing 20% to be previously TNFi experienced.

Results: 309 patients were enrolled. Mean age was 54 years, 80% were female, mean baseline DAS28 was 5.9 and the mean number of previous DMARDs used was 2.7. There were no between groups differences at baseline except for past number of DMARDS used (RC=2.6, DAS=2.9, 0SJC=2.5, $p=0.02$) and 0SJC was younger (51.5). More medication changes for RA (#/100 pt-months) occurred in 0SJC group: 3.3 in RC, 5.1 in DAS and 6.2 in 0SJC, $P<0.035$). 91% of completers were satisfied with treatment at 12 months. Targeted treatment resulted in faster improvement, but RC eventually caught up. At 6 months the change in DAS was −1.9 in RC, =2.4 in DAS and −2.0 in 0 SJC. At 12 months it was −2.4, −2.7 and −2.2 and 18 months: −2.5, −2.7. −2.1. The drop out was 52% in routine care, 27% in the DAS and 22% in the 0 SJC ($p=0.001$). Drop out due to adverse events was 8% in RC, 12% in DAS and 4% in 0SJC ($p=0.018$). The median time to DAS<3.2 was 368 in RC, 189 days in DAS and 371 days in 0SJC. Median time to good/moderate EULAR response was 185 days for RC, 76 days for DAS and 93 days for 0SJC ($p=0.0002$). More in intensive care achieved DAS<2.6 (p=NS). The figure shows time to DAS<3.2. The table demonstrates the markedly different drop outs between routine care and intensive care.



RESULTS		RC	DAS	0 SJC	P-value
# of patients at baseline		109	100	99	
Total # of patients discontinued		57 (52.3)	27 (27)	22 (22.2)	
# of patients discontinued according to visit: n (%)	Visit 2	1 (0.9)	4 (4.0)	0 (0.0)	Overall: *P<0.001* RC vs. DAS: *P<0.001* RC vs. 0 SJC: *P<0.001* DAS vs. 0 SJC: P=0.434
	Visit 4	9 (8.3)	3 (3.0)	2 (2.0)	
	Visit 6	10 (9.2)	11 (11.0)	6 (6.1)	
	Visit 9	7 (6.4)	1 (1.0)	7 (7.1)	
	Visit 12	20 (18.3)	8 (8.0)	7 (7.1)	
	Unknown	10 (9.2)	0 (0.0)	0 (0.0)	
# of patients discontinued according to visit: n (%)	Lost to Follow-up	19 (17.4)	3 (3.0)	5 (5.1)	Overall: *P=0.018* RC vs. DAS: *P=0.014* RC vs. 0 SJC: *P=0.130* DAS vs. 0 SJC: P=0.177
	Withdrawal of Consent	6 (5.5)	5 (5.0)	6 (6.1)	
	Adverse Event	9 (8.3)	12 (12.0)	4 (4.0)	
	Protocol Violation	1 (0.9)	0 (0.0)	2 (2.0)	
	Other	22 (20.2)	7 (7.0)	5 (5.1)	

Conclusions: Treating to target with the same TNFi therapy in established RA may not alter the outcomes vs. routine care for DAS<3.2 by 18 months for those continuing treatment but the drop out rate with treating to a target is very low. A, low disease state occurs earlier in targeted care. The target of 0SJC may be feasible in established RA starting antiTNF treatment but does not look superior to DAS target.

Disclosure: J. E. Pope: Abbott Laboratories, 2; **J. C. Thorne:** Abbott Laboratories, 2; **B. Haraoui:** Abbott Laboratories, 2; **J. Sampalis:** Abbott Laboratories, 2.

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Tumor Necrosis Factor-α Inhibitor Use Does Not Affect Lipid Profiles in Patients with Rheumatoid Arthritis. Stephanie J. Morris[1], Jana L. Antohe[1], Jennifer Sartorius[2], H. Les Kirchner[2], Sorina Dancea[1], Mary Chester Wasko[3] and Androniki Bili[1]. [1]Geisinger Health System, Danville, PA, [2]Geisinger Health System, [3]Univ of Pittsburgh, Pittsburgh, PA

Background: Patients with rheumatoid arthritis (RA) have increased risk of cardiovascular disease (CVD). In some studies of RA patients, tumor necrosis factor-alpha (TNF-α) inhibitors and other biologic agents have been associated with adverse lipid profiles, a risk factor for CVD.This study examined the association of TNF-α inhibitor use with lipid levels in an RA inception cohort in a rural, tertiary health system using Electronic Health Record (EHR).

Methods: Patients diagnosed with RA (ICD-9 code 714.0 at ≥2 office visits with a rheumatologist) from 1/1/2001 – 5/1/2009 were identified through the EHR (n=1539). The RA diagnosis was validated against the American College of Rheumatology criteria by manual review of 100 random charts with 97% concordance. Analysis was restricted to patients with at least one post-RA lipid result (n=706). Outcomes were lipid level results over time by TNF-α inhibitor usage status (infliximab, etanercept, and adalimumab). The lipid panel included low density lipoprotein (LDL), high density lipoprotein (HDL), total cholesterol (TC), and triglycerides. In addition, LDL/HDL and TC/HDL (the atherogenic index) were included as outcomes. Each patient's TNF-α inhibitor use status was evaluated at each lipid measurement date. Body mass index (BMI), erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP) antibodies, diabetes, hypertension, use of glucocorticoids, nonsteroidal anti-inflammatory medications, hydroxychloroquine, methotrexate, and lipid-lowering medications, were controlled for in a random effects, linear regression model. Time is represented as time since RA diagnosis to each lipid result date in years.

Results: 706 incident RA patients with 2851 lipid results were identified and were included in the analysis. The majority of patients were female (69%), and 98% were Caucasian, with median age of 65 years and BMI 29.8 kg/m^2. RF and anti-CCP were positive in 79% and 42% (of the patients who had results recorded in the EHR) respectively. Of the 706 patients, 182 (25.8%) were ever on TNF-α inhibitors. In the regression models, use of TNF-α inhibitors was associated with the following estimated average changes in lipids over time: LDL increase of 0.49 mg/dl (p=0.811), HDL decrease of 0.51 mg/dl (p=0.517), TC increase of 1.64 mg/dl (p=0.505), triglycerides increase of 5.11 mg/dl (p=0.388), LDL/HDL increase 0.063 (p=0.224), and TC/HDL increase of 0.104 (p=0.132).

Conclusions: Use of TNF-α inhibitors in this inception RA cohort was not associated with significant changes in total cholesterol, LDL, HDL, LDL/HDL, or TC/HDL. These results are reassuring, given the widespread use of TNF inhibitors and increased risk of CVD in this patient population.

Disclosure: S. J. Morris: None; **J. L. Antohe:** None; **J. Sartorius:** None; **H. L. Kirchner:** Amgen Inc., 2, Wyeth Pharmaceuticals, 2; **S. Dancea:** None; **M. C. Wasko:** Amgen Inc., 2, Centocor, Inc., 2, 5, UCB, Inc., 5, Wyeth Pharmaceuticals, 2; **A. Bili:** Amgen Inc., 2, Wyeth Pharmaceuticals, 2.

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Urinary Tract Infections in Rheumatoid Arthritis. Colin C. Edgerton[1], Kaleb D. Michaud[3] and Frederick Wolfe[2]. [1]Eisenhower Army Medical Center, Evans, GA, [2]Natilonal Data Bank for Rheumatic Disease, Wichita, KS, [3]Univ of Nebraska Med Ctr, Omaha, NE

Purpose: Recent interest in urinary tract infections in rheumatoid arthritis (RA) has stemmed from the assessment of risk of infection with biologic agents. There have been little data about community acquired urinary tract infections (UTI) until a recent report gave an incidence rate (IR) of ~3% (1). By contrast, an epidemiology study in the general population reported an IR at 10.8% (95% CI 9.4. 12.1) in women (2). We used a large prospective data bank to investigate these differences and to understand risk factor for UTI in RA.

Methods: We used general estimating equations to evaluate the risk of UTI in 17,139 RA patients and 107,546 semiannual observations. Patients self-reported the number of urinary tract infections in the previous 6 months. We evaluated the role of age, sex, antirheumatic drug use, education, BMI, household income, smoking, comorbidity, and the tendency to over-report symptoms. We also calculated the misclassification rate for self-reported events based on 76,493 cases that evaluated for validation.

Results: The estimated IR for UTI, adjusted for 10% overreporting, was 8.9% (8.6, 9.2) overall and 11.4% (11.0, 11.8) in women and 3.3% (2.9, 3.7) in men. Serious events, resulting in hospitalization or requiring intravenous antibiotics was reported in 0.39%. In multivariable analyses, UTI was associated with diabetes, OR 1.2 (95% CI 1.0, 1.3), corticosteroid use OR 1.1 (1.0, 1.2), but not to biologic use, OR 1.0 (0.9, 1.1). Among other factors, UTI was associated with less household income and multiple comorbidities, but not with smoking, BMI, education level or estrogen use. When the study variables were applied to serious infection, the OR increased for prednisone use, 1.9 (1.6, 2.4) and diabetes, 2.0 (1.5, 2.6), but remained non-significant, 0.9 (0.7, 1,1) for biologics. Overall, prednisone was used at 34.9% of observations and biologics at 38.2%.

Conclusions: Based on increased risk associated with prednisone and comorbidity, as well as increased IC compared with the community epidemiology study, we estimate that UTI is slightly increased in RA. These results are 3 times higher than a previous study (1). The Observed rate of serious urinary tract infection was consistent with data from the British Biologics registry (3).

References:

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3. Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006;54(8):2368–76.

Disclosure: C. C. Edgerton: None; **K. D. Michaud:** None; **F. Wolfe:** None.

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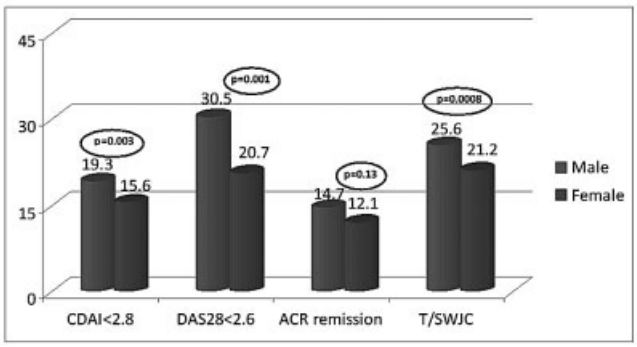
Women with RA Achieve Remission Less Frequently Than Men, Using the CORRONA Database among 6668 Patients. Daniel E. Furst[5], Veena Ranganath[4], Joel M. Kremer[1], James Louie[4], Dinesh Khanna[4], Lawrence Rasouliyan[2] and Jeffrey D. Greenberg[3]. [1]Albany Medical College, [2]ICON, [3]NYU, [4]UCLA, [5]University of California Los Angeles Medical School, Los Angeles, CA

Background: Remission is a commendable and achievable goal for RA patients but it is not clear whether the RA remission rate is different between women and men.

Objectives: To examine the large CORRONA database for differences between remission rates in women and men.

Methods: Logistic regression compared women and men using CDAI<2.8, DAS28<2.6 and ACR remission. Independent variables included: age, gender, disease duration, OA, erosions, RF, Jt tenderness, mHAQ, ethnicity, depression and medications.

Results:



6668 RA pt's were included for CDAI; 1412–1956 for the DAS28 and ACR remission. Women achieved remission less frequently than men. Ethnicity had no effect. Other differences were not clinically significant (eg. W-0.5 more JTC; 0.06 were in HAQ, 2–3 mm worse pain and global VAS). Men had more co-morbidities (eg. diabetes W-6.4%;M-9.0%; MI/CVA-W:33%;M:9.3%)

Conclusion: In the CORRONA database, the remission rate for women was lower than for men.Ethnicity had no effect.

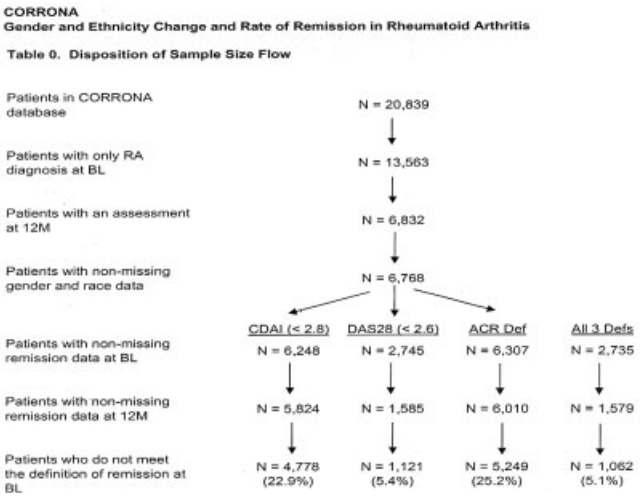


Table 1. Demographic and Clinical Characteristics at Baseline

Characteristic	Male N = 1438	Female N = 4166	p*
Age (years), Mean ± SD	59.6 + 12.2	56.3 + 13.2	<.0001
Disease Duration (years), Mean ± SD	9.1 + 9.3	10.0 + 9.8	0.006
Race, N (%)			0.02
White	1330 (92.5%)	3752 (90.1%)	
Black/African American	67 (4.7%)	245 (5.9%)	
Other	41 (2.9%)	169 (4.1%)	
Marital Status, N (%)			<0.0001
Married	1127 (79.1%)	2687 (64.8%)	
Work Status, N (%)			<.0001
Full time/Part time	735 (52.0%)	1951 (47.4%)	
Not working outside the home	112 (7.9%)	769 (18.7%)	
Student	2 (0.14%)	33 (0.8%)	
Disabled/Retired	565 (40.0%)	1364 (33.1%)	
Presence of Nodules and/or Erosion, N (%)			0.81
Yes	637 (44.3%)	1861 (44.7%)	
Rheumatoid Factor Positivity, N (%)			0.45
Yes	635 (75.9%)	1705 (74.6%)	
ESR, Mean ± SD†	21.4 + 21.5	26.2 + 21.5	<.0001
Tender/Swollen Joint Count, Mean ± SD†	9.8 + 10.0	10.3 + 10.3	0.1
Morning Stiffness in hours, Mean ± SD†	1.2 + 2.5	1.2 + 2.0	0.61
Patient Pain VAS, Mean ± SD†	32.3 + 24.6	34.7 + 25.8	0.003
Patient Global VAS, Mean ± SD†	30.4 + 24.7	32.4 + 25.5	0.01
Physician Global VAS, Mean ± SD†	26.0 + 20.6	27.4 + 20.8	0.03
mHAQ, Mean ± SD	0.32 + 0.42	0.38 + 0.45	<.0001

*P-values derived from Student's t-test and chi-square test for continuous and categorical variables, respectively.
†Component of one of the three primary remission measures.

Table 2. Background Medication and Comorbidities

Characteristic	Male N = 1438	Female N = 4166	p*
Background Prednisone Use, N (%)			0.2
Yes	572 (39.9%)	1576 (38.0%)	
Background TNFi Use, N (%)			<.0001
Yes	462 (32.1%)	1610 (38.7%)	
Background "Strong" DMARD Use, N (%)			0.57
Yes	1018 (70.8%)	2982 (71.6%)	
Background "Weak" DMARD Use, N (%)			0.0005
Yes	162 (11.3%)	624 (15.0%)	
Unusual fatigue in last 8 wks, N (%)†			<.0001
Yes	281 (19.5%)	1232 (29.6%)	
Depression in last 8 wks, N (%)			<.0001
Yes	178 (12.4%)	850 (20.4%)	
MI or Stroke before BL, N (%)			<.0001
Yes	134 (9.3%)	137 (3.3%)	
Diabetes Mellitus before BL, N (%)			0.001
Yes	129 (9.0%)	267 (6.4%)	
Renal Insufficiency before BL, N (%)			0.31
Yes	35 (2.4%)	83 (2.0%)	
Active Liver Disease before BL, N (%)			0.041
Yes	66 (4.6%)	142 (3.4%)	
Joint Surgery in current/previous year**, N (%)			0.96
Yes	62 (4.3%)	181 (4.3%)	
RA Hospitalization before BL***, N (%)			0.3
Yes	72 (5.0%)	181 (4.3%)	

* P-values derived from Student's t-test and chi-square test for continuous and categorical variables, respectively.
** Previously requested joint surgery "in past 6 months". Because of CRF limitations, this is not possible.
If baseline visit occurs July–December we are counting surgeries in the current year. If baseline occurs in the first six months of the year, we are counting joint surgeries in the current OR previous year.
*** Previously requested "in past 6 months". Because of CRF limitations, this is not possible. Any RA Hospitalization before the baseline is counted in the total.

Table 3. Multivariable Logistic Regression of Gender and Race/Ethnicity on Remission (Defined as CDAI <2.8)

Characteristic	OR	Pooled Model (95% CI)	p
Gender			
Female	0.81	(0.68, 0.97)	0.0208
Male		(Ref)	
Race			
Black/African American	1.12	(0.80, 1.57)	0.4998
Other	1.07	(0.72, 1.61)	0.7353
White		(Ref)	
Duration of RA (years)	0.97	(0.96, 0.98)	<.0001
Work Status			
Full time/Part time	1.60	(1.30, 1.98)	<.0001
Not working outside the home	1.22	(0.94, 1.57)	0.1391
Student	0.45	(0.16, 1.27)	0.1316
Disabled/Retired		(Ref)	
Prednisone Use			
Yes	0.68	(0.57, 0.80)	<.0001
No		(Ref)	
TNFi Use	0.80	(0.67, 0.94)	0.0082
Depression	0.64	(0.51, 0.80)	0.0001
RA Hospitalization before BL	0.48	(0.27, 0.83)	0.009
Age (years)	1.00	(1.00, 1.01)	0.2396
RF Positive			
Yes	0.88	(0.69, 1.11)	0.264
No		(Ref)	

Table 4. Multivariable Logistic Regression of Gender and Race/Ethnicity on Remission (Defined as DAS28 <2.6)

Characteristic	OR	Pooled Model (95% CI)	p
Gender			
Female	0.63	(0.45, 0.89)	0.0076
Male		(Ref)	
Race			
Black/African American	0.66	(0.34, 1.27)	0.2089
Other	0.96	(0.48, 1.94)	0.9151
White		(Ref)	
Duration of RA (years)	0.97	(0.95, 0.99)	0.0012
Work Status			
Full time/Part time	1.59	(1.07, 2.35)	0.0205
Not working outside the home	1.07	(0.65, 1.75)	0.7866
Student	0.75	(0.13, 4.34)	0.7443
Disabled/Retired		(Ref)	
Prednisone Use			
Yes	1.03	(0.76, 1.40)	0.8304
No		(Ref)	
TNFi Use	0.63	(0.45, 0.86)	0.0045
Depression	0.52	(0.34, 0.79)	0.0023
RA Hospitalization before BL	0.69	(0.29, 1.63)	0.395
Age (years)	0.98	(0.97, 1.00)	0.0123
RF Positive			
Yes	0.56	(0.35, 0.90)	0.017
No		(Ref)	

Disclosure: D. E. Furst: Abbott Laboratories, 2, 5, 8, 9, Actelion Pharmaceuticals US, 2, 5, 8, 9, Amgen Inc., 2, 5, 9, Bristol-Myers Squibb, 2, 5, 9, Centocor, Inc., 5, 9, Corrona, 3, Genentech and Biogen IDEC Inc, 2, 5, 9, Gilead Sciences, Inc., 2, 5; **V. Ranganath:** None; **J. M. Kremer:** None; **J. Louie:** Abbott Laboratories, 5, Amgen Inc., 5, 8, Genentech and Biogen IDEC Inc, 5, Pfizer Inc, 5, UCB, Inc., 5, Wyeth Pharmaceuticals, 5; **D. Khanna:** Actelion Pharmaceuticals US, 2, 8, Gilead Sciences, Inc., 2, 8, NIAMS-NIH, 2; **L. Rasouliyan:** ICON, 3; **J. D. Greenberg:** Abbott Laboratories, 2, Amgen Inc., 2, Centocor, Inc., 2, Corrona, 1, Pfizer Inc, 8, Wyeth Pharmaceuticals, 8.

ACR Poster Session A
Rheumatoid Arthritis - Human Etiology and Pathogenesis I
Monday, November 8, 2010, 9:00 AM–6:00 PM

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A Novel Splicing Regulatory Mechanism in Generating a Truncated Human Death Receptor 3 (*DR3*) Gene Product That Contributes to the Pathogenesis of Rheumatoid Arthritis. Masaru Mizuhara[2], Akira Hashiramoto[3], Kohsuke Yoshida[1] and Shunichi Shiozawa[4]. [1]Department of Biophysics, Kobe University Graduate School of Health Science, Kobe, Hyogo, Japan, [2]Department of Biophysics, Kobe University Graduate School of Health Science, Kobe, Japan, [3]Department of Biophysics, Kobe University Graduate School of Health Science/Department of Medicine, Kobe University Graduate School of Medicine/The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Hyogo, Japan, [4]Department of Biophysics, Kobe University Graduate School of Health Science/Department of Medicine, Kobe University Graduate School of Medicine/The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan

Purpose: Death Receptor 3 (DR3), a member of tumor necrosis factor receptor superfamily, transmits both apoptosis and NFκB activation signalings. We previously reported a new DR3 haplotype containing 4 single-nucleotide polymorphisms (SNPs) and one 14-nucleotide deletion within exon 5 and intron 5 (GenBank accession Nos. AB051850 to DR3 and AB051851), which resulted in insertion of a portion of intron 5 into the coding sequence to generate a premature stop codon. Based on these mutations, we identified a mutant type of *DR3* gene (*mtDR3*) encoding a truncated *DR3* lacking tramsmembrane domain and death domain as the candidate disease gene for Japanese-Korean patients with rheumatoid arthritis (RA). In this study, we show a specific binding of splicing regulatory proteins on intron 5 in the *mtDR3* gene, which leads to generation of a truncated *DR3* lacking death domain molecule contributing to the pathogenesis of RA.

Methods: The wild type (wt) exon 2, wt intron 5 and mutant intron 5 pre-mRNA were synthesized from *wtDR3* and *mtDR3* genes, respectively, using PCR and DNA transcription and were incubated with nuclear proteins extracted from jurkat cells. The nuclear protein bound to intron 5 pre-mRNA was collected, separated on SDS-Polyacrylamide gels and analysed by silver staining, mass spectrometric and western blotting.

Results: We previously identified that the mutation of *DR3* gene, the polymorphism is: d: g.2590A>T (rs3138155) from the first base of ATG, enhances insertion of a portion of intron 5. As to the cause of exon insertion at intron 5, we have detected 3 nuclear proteins with molecular weight, 100kDa, 70kDa and 60kDa which bound to the mutant type intron 5, but not to wild type intron 5, of DR3 mRNA under silver staining. Mass spectrometric and western blotting identified them as splicing factors, proline- and glutamine-rich (SFPQ), heterogeneous nuclear ribonucleoprotein L (hnRNP L) and non-POU domain-containing octamer-binding protein (NONO), respectively.

Conclusion: As to the cause of exon insertion at intron 5, the truncated *DR3* lacking death domain molecule contributes to the pathogenesis of RA. We have identified 3 splicing regulatory proteins, SFPQ, hnRNP L and NONO, that specifically bound to the intron 5 *mtDR3* to generate a truncated *DR3* gene product.

Disclosure: M. Mizuhara: None; **A. Hashiramoto:** None; **K. Yoshida:** None; **S. Shiozawa:** None.

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BAFF Expression on the Surface of RA Synovial Fibroblasts (RASFib) Facilitates B Cell Responses to IL-15. Yolanda Garcia-Carmona, Marta Benito-Miguel, Alejandro Balsa, Emilio Martin-Mola and Maria Eugenia Miranda-Carus. Hospital La Paz, Madrid, Spain, Hospital La Paz, Madrid, Spain, Hospital La Paz, Madrid

Background: We previously described that IL-15 expressed on RASFib significantly contributes, by a cell-contact dependent mechanism, to the anti-apoptotic action of RASFib on B cells. In addition, whereas exogenous recombinant IL-15 (rhIL-15) has a minimal effect on isolated B cell survival, it significantly potentiates the anti-apoptotic effect of RASFib on B cells. This is attributable to an RASFib-mediated upregulation of the B cell IL-15 receptor.

Objectives: BAFF, a B cell survival factor expressed on RASFib, was tested as a potential candidate involved in upregulating B cell IL-15R.

Methods: Magnetically sorted peripheral blood memory B cells from 20 healthy subjects (CD19+CD20+CD27+, purity >96%) were cultured in the presence or absence of rhIL-15, recombinant human BAFF (rhBAFF), or a combination of both. In addition, B cells were cocultured with RASFib from synovectomy or arthroplasty specimens (n= 10) in the presence or absence of rhIL-15, with or without BAFF neutralizing agents.

Results: Survival of isolated B cells cultured for 6 days in plain medium was below 1% (annexin V-7AAD and JC-1 staining). RhIL-15 had a minimal effect on isolated B cell survival. In contrast, culture of B cells in the presence of rhBAFF resulted in significantly increased survival (22.3+/−3.2% viable cells at 6 days, $p<0.001$) together with upregulation of all three IL-15R chains; in parallel, rhIL-15 potentiated the anti-apoptotic effect of BAFF (32.7+/−4.4% viable cells at 6 days, $p<0.05$).

Flow cytometry of RASFib detached with PBS-EDTA demonstrated surface expression of BAFF together with surface IL-15. In parallel, coculture with RASFib dramatically prolonged B cell survival (55.3+/−8.1% viable cells at 6 days, $p<0.01$) and at the same time upregulated B cell expression of IL-15Ra, b and g chains. RhIL-15 potentiated the anti-apoptotic effect of RASFib (75.1+/−5.2% viable cells, $p<0.05$). In the presence of BAFF neutralizing agents (an anti-BAFF MoAb or a BAFFR-Fc), the effect of RASFib on both B cell survival and B cell expression of IL-15 R was significantly attenuated (28.1+/−4.5 or 27.3 +/−3.8 viable cells, respectively, $p<0.05$). In parallel, rhIL-15 had a lower effect on the survival of B cells cocultured with RASFib in the presence of BAFF neutralizing agents (62.3+/−8.2% viable cells, $p<0.05$ vs conditions without BAFF neutralization). IL-15 blocking agents were not additive with BAFF neutralization in Bcell/RASFib cocultures (28.3+/−4.2% viable cells). In contrast, in the absence of BAFF antagonists, neutralization of IL-15 (with an anti-IL-15 MoAb or an antagonistic IL-15 mutant/Fcg2a fusion protein) was effective at decreasing the antiapoptotic effect of RASFib on B cells (35.5+/−6.2% or 32.8+/−5.7% viable cells, respectively, $p<0.01$). Isotype control MoAbs or Fc fusion proteins used as negative controls had no effect. This indicates that constitutive surface IL-15 expression on RASFib contributes to extending the survival of cocultured B cells when constitutive BAFF activity is spared.

Conclusion: The antiapoptotic effect of RASFib surface IL-15 on cocultured B cells is facilitated by RASFib surface BAFF, through an upregulation of IL-15Ra, b and g chain expression.

Disclosure: Y. Garcia-Carmona: Roche, 2; **M. Benito-Miguel:** Roche, 2; **A. Balsa:** Roche, 2; **E. Martin-Mola:** Roche, 2; **M. E. Miranda-Carus:** Roche, 2.

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Characterization of Fibrinogen-Specific CD4 T Cells Using Peptide-MHC Tetramers. Laura F. Su[1] and Mark M. Davis[2]. [1]Stanford, Mountain View, CA, [2]Stanford

Purpose: Rheumatoid arthritis (RA) is one of the most common debilitating systemic inflammatory conditions. To date, little is known about which autoantigens are involved in RA and how T cells recognizing self-proteins may become pathogenic in disease. Fibrinogen is a common target of autoantibodies in RA patients and a putative T cell autoantigen involved in disease development. The short-term aim of this study is to identify and characterize fibrinogen-specific CD4 T cells in healthy individuals, with the goal of extending the analysis to patients with RA.

Method: Autoantigen-specific T cells were identified directly ex vivo using peptide-MHC tetramers. HLA-DR4 monomers with a tethered thrombin cleavable CLIP peptide were purified from the culture supernatant of a stable HLA-DR4 transfectant cell line by antibody affinity chromatography. The purified monomers were then biotinylated, thrombin cleaved, loaded with peptides, and oligomerized onto a streptavidin backbone labeled with a fluorophore. To identify individuals carrying the HLA-DRB1*0401 (DR4) allele, HLA typing was performed on healthy blood donors and RA patients using sequence-specific primer PCR. Individuals with DR4 allele(s) were selected for T cell repertoire analysis. To identify antigen-specific T cells, blood from DR4 positive individuals were enriched for CD4 cells by rosettasep/ficoll centrifugation. Tetramer staining was performed at room temperature for 1 hour using 10nM of tetramers loaded with peptides from hemagglutinin (HA) and fibrinogen. Memory phenotyping was performed using antibodies against the protein tyrosine phosphatase, CD45RO, and the chemokine receptor, CCR7. Tetramer tagged cells were magnetically enriched and analyzed by flow cytometry.

Results: We are able to identify fibrinogen-specific CD4 T cells in healthy individuals without expansion in culture. The frequency of lymphocytes recognizing fibrinogen is between 0.3 to 22 cells per million CD4 T cells. There does not appear to be significant gender- or age- dependent differences, with similar frequency of fibrinogen-specific lymphocytes seen in male and female, and between young and the older individuals.

Phenotypic characterization of antigen-specific cells using antibodies against CD45RO and CCR7 reveals a memory population that recognizes fibrinogen in most people without an autoimmune disease. The presence of antigen-experienced cells recognizing fibrinogen indicates that the immunological self is not ignorant of these epitopes and suggests that active regulatory mechanisms is involved in preventing inappropriate T cell activation.

Conclusion: Rare antigen-experienced fibrinogen-specific CD4 T cells can be detected in the peripheral blood of healthy individuals. Study is currently ongoing to evaluate the role of regulatory T cells in modulating the activity of fibrinogen-specific T cells and to extend the analysis to patients with RA.

Disclosure: L. F. Su: None; **M. M. Davis:** None.

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Defective ERK Signaling in Hematopoietic Progenitor Cells in Rheumatoid Arthritis. Ines Colmegna[2], Sergei Pryschep[1], Hisashi Oishi[3], Jorg J. Goronzy[3] and Cornelia M. Weyand[3]. [1]Georgia Institute of Technology, [2]McGill University, Montreal, QC, Canada, [3]Stanford University

Background: The main functional property of hematopoietic progenitor cells (CD34+ HPC) is their proliferative response to hematopoietins. HPC from patients with rheumatoid arthritis (RA) are hypo-responsive to growth factor stimulation leading to a decreased cell cycle entry and progression and thus to a restricted expansion capacity. Kinase-based signal transduction pathways are key integration points that link extracellular stimuli to proliferation, differentiation and cell survival. We tested the hypothesis of whether a defect of the extracellular signal-regulated kinase (ERK) pathway underlies the proliferative defect of RA HPC.

Methods: CD34+ cells from patients with rheumatoid factor-positive RA and demographically matched healthy controls were MACS sorted from PBMC. A minimum of 12 RA samples and 12 matched controls were included per experiment. The surface expression of cytokine receptors (IL-3 and IL-6 receptor subunits, c-kit and FLT3) was evaluated by FACS. Baseline and post-cytokine (IL-3, IL-6, FLT3-L and SCF) activation phosphorylation states of ERK 1/2 were determined by flowcytometric single-cell phosphoprotein analysis (Phospho-Flow). Transcripts of ERK target genes (c-Myc and Cyclin D) were quantified by RT-PCR. The co-localization of K-Ras/Raf-B, proximal events in the activation of ERK, was assessed by confocal microscopy in CD34+ cells.

Results: The frequency and density of cytokine receptor expression was similar in RA and controls CD34+ cells. Baseline and post-cytokine activation phosphorylated ERK (pERK) was decreased in RA CD34 compared to demographically matched controls (baseline $p=0.04$, 10' activation $p=0.005$, 15' activation $p=0.006$). Transcripts of ERK modulated genes involved in cell cycle progression (Cyclin D3, and c-Myc) were significantly reduced in RA ($p<0.02$). Confocal microscopy studies demonstrated significantly lower cytokine-induced Ras/Raf colocalization in RA CD34+ cells than in controls. ($p=0.04$) implicating proximal events in the defective ERK activation.

Conclusions: Cytokine evoked signaling responses of the ERK signaling pathway, a key integration network linking extracellular stimuli to proliferation, are defective in RA HPC. Insufficient clustering of K-Ras and Raf-B complexes, decreased phosphorilation of ERK and downregulation of the expression of ERK dependent genes involved in proliferative responses are all consistent with a defect in the ERK pathway.

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Human STEAP4 (Six-Transmembrane Epithelial Antigen of Prostate 4) Regulates Inflammatory Cytokines and the Proliferation of Fibroblast-Like Synoviocyte in Patients with RA. Yoko Tanaka, Isao Matsumoto, Naoto Umeda, Kayo Yamamoto, Yuki Tanaka, Asuka Inoue and Takayuki Sumida. University of Tsukuba

Background: We recently demonstrated that TNFα-induced- adipose related protein (TIARP) plays a crucial role in TNFa-dependent arthritis model such as glucose-6-phosphate isomerase (GPI) -induced arthritis. STEAP4 mRNA and protein expression was reported to be upregulated by TNFα in a dose-dependent manner by using human adipose tissue, however, the function of STEAP4 in other tissue is still unclear. The purpose of this study is to clarify the function of STEAP4 in fibroblast-like synoviocyte (FLS) from RA patients and the relationship between STEAP4 and RA.

Methods: 1) To unravel localization of STEAP4, the expression of EEA1 (known to be a endosome marker) or CD68 in FLS was examined by fluorescence immunohistochemistry (IF). 2) FLS obtained from RA synovium were treated with TNFα (2ng/ml), and the fluctuation of STEAP4 was evaluated by Western blot analysis (WB). 3) FLS obtained from RA was transfected by siRNA specific for STEAP4, and cultured for 24 h. IL-6 mRNA was quantified by real time PCR. 4) GFP-STEAP4 or GFP-empty plasmid DNA were transfected to FLS, then cultured for 24 h with TNFα. Secretion of IL-6, IL-8, MMP3, and GM-CSF was examined by ELISA. 5) Proliferation and apoptosis of GFP-STEAP4 transfectant were investigated by BrdU assay or flow cytometry. 6) The expression of STEAP4 in PBMC was measured before and after therapy with infliximab ($N=40$).

Results: 1) STEAP4 was co-localized with CD68 in the FLS obtained from RA patients. STEAP4, EEA1 and CD68 were clearly co-localized in cytoplasm (endosome and lysosome) of the synovium. 2) In vitro analysis, the expressions of STEAP4 protein in FLS was up regulated by TNFα stimulation confirmed by WB. 3) The expression of IL-6 mRNA was up regulated by STEAP4 siRNA ($p<0.05$). 4) The amount of IL-6, IL-8, GM-CSF secretion were down-regulated by overexpression of STEAP4 ($p<0.05$), although MMP3 were upregulated after TNFα stimulation. 5) Proliferation was decreased and apoptotic cells were increased in GFP-STEAP4 transfectant compared to GFP-empty transfectant. 6) The expression of STEAP4 was decreased after infliximab treatment especially in good responder ($p<0.05$).

Conclusion: STEAP4 expression was observed in rheumatoid synovium, was clearly up regulated by TNFα stimulation, and controlled inflammatory cytokines and proliferation of FLS. In addition, the expression of STEAP4 in PBMC was upregulated by TNF antagonist in RA, suggest that it may play a potential role in the pathogenesis of TNF-α- induced arthritis.

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IL-15 Promotes Osteoclastogenesis Via Phospholipase D Signaling Pathway in Rheumatoid Arthritis. Ji-Min Kim[1], Mi-Kyung Park[2], Mi-La Cho[2], Yong-Geun Jung[1], Su-Jin Moon[1], Seung-Ki Kwok[1], Ji-Hyeon Ju[1], Kyung-Su Park[1], Ho-Youn Kim[1] and Sung-Hwan Park[1]. [1]Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea, Republic of, [2]Rheumatism Research Center, Catholic Research Institute of Medical Science, The Catholic University of Korea, Seoul, Korea, Republic of

Background: Osteoclast plays an important role in the joint destruction in rheumatoid arthritis (RA). Osteoclast formation is enhanced in the presence of receptor activator of nuclear factor κ B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF). Interleukin 15 (IL-15) has also been reported to stimulate the osteoclast differentiation. This study was undertaken to investigate novel signaling molecules essential for the IL-15-mediated osteoclastogenesis.

Methods: Expression of phospholipase D1 (PLD1), RANKL, mitogen-activated protein kinases (MAPKs) and nuclear factor-κB (NF-κB) was determined by immunohistochemistry in the RA synovial tissue. Whether or not IL-15 modulates the expression of various molecules in the RA fibroblast-like synoviocyte (FLS) was examined by quantitative polymerase chain reaction and western blotting. In order to evaluate the effect of IL-15 and phosphatidic acid (PA; active product of PLD metabolism) on the osteoclast formation, peripheral blood monocytes from RA patients were cultured with or without FLS in the presence of M-CSF and RANKL, the traditional osteoclast differentiation condition.

Results: The expression of IL-15, PLD and phosphorylated extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), inhibitor of κB was enhanced in the RA synovial tissue. Expression of RANKL and PLD1 was significantly upregulated by IL-15 in the FLS from RA patients. PA enhanced the RANKL expression, which was inhibited by the blockade of PA production by 1-butanol or PLD1 siRNA. IL-15 and PA also stimulated the osteoclastogenesis through the phosphorylation of NF-κB as well as MAPKs such as ERK and JNK. Regardless of the presence of RA FLS, IL-15-induced osteoclastogenesis in the monocytes cultured with M-CSF and RANKL was suppressed by the blockade of PA production.

Conclusions: PLD1 activation by IL-15 contributed to RANKL-mediated osteoclastogenesis via NF-kB and MAPK signaling pathway in FLS of RA patients. Taken together, our data suggest that PLD1 may be an important mediator of IL-15-induced osteoclastogenesis and can be considered as a new therapeutic target in RA.

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IL-17A and IL-17F Contribute to the Progression of Rheumatoid Arthritis by Inducing a CXCR4-Dependent Invasive Phenotype in Synoviocytes. Arnaud Hot[2], Saloua Zrioual[1], Vanina Lenief[1] and Pierre Miossec[1]. [1]Hospital Edouard Herriot, Lyon, Lyon, France, [2]Immunogenomics and Inflammation Research Unit and Department of Immunology and Rheumatology, Hospital Edouard Herriot, Lyon, France

Objectives: Rheumatoid arthritis (RA) synovium undergoes histological changes characterized by angiogenesis, immune cell infiltration and hyperplasia of synovial lining cells. Among the inflammatory mediators expressed in RA synovium, IL-17 is emerging as a key mediator. The aim of our study was to assess the role IL-17A and IL-17F in synoviocytes migration and invasion.

Methods: IL-17A and IL-17F induced mRNA expression in RA synoviocytes was analyzed using microarrays (Affymetrix, U133 +2) and qRT-PCR. The capacities of IL-17 and IL-17F alone or in combination with TNF-α to induce synoviocyte migration and invasion were tested using Boyden chambers and using transwell matrigel invasion chambers. The specific contribution of CXCR4, the SDF-1 receptor was analyzed using neutralizing antibody. As Hypoxia Induced Factor 1 (HIF1-α) regulates CXCR4 expression, a functional assay (binding DNA assay) was used to evaluate the role of both cytokines in the regulation of HIF1-α expression and activation. To evaluate the role of Hypoxia pathway in RA, 40 RA patients and 20 healthy volunteers (controls) were enrolled for determination of gene expression profiles in whole peripheral blood using U133A Affymetrix microarrays.

Results: IL-17A and IL-17F induced a molecular pattern characterized by inflammation- (LIF, IL-11, IL-23p19, FGF-2) and hypoxia-related genes (SLCA1, CA9, CXCR4). In particular, IL-17A and IL-17F alone or combined with TNF-α induced CXCR4 mRNA in synoviocytes (289 fold for IL17A, 34 fold for IL-17F, 450 fold for the combination of IL-17A with TNF-a). Using immunofluorence microscopy, the expression of CXCR4 at the surface of synoviocyte was confirmed. Moreover, IL-17A and TNF-α induced synoviocyte migration and invasion through a CXCR4-dependent mechanism with a synergistic effect, (6 vs 67 migrated cells/HPF, p≤0,05). The blockade of CXCR4 led to a decrease of synoviocyte migration (- 10 fold, P<0,05). The combination of IL-17A and TNF-α, as the combination of IL-17F and TNF-α in a lesser manner was able to promote the activation of HIF1-α in synoviocytes (2 fold, P=0,0034), and this association was synergic to induce VEGF mRNA expression. To confirm the role of hypoxia pathway in RA, the expression of HIF1-α induced genes was measured in blood of RA patients, and control subjects. Six hypoxia related genes were overexpressed in blood of RA patients as summarized in table 1.

Conclusion: Both IL-17A and IL-17F may contribute to the progression of RA, notably through their effect on synoviocyte aggressiveness. Part of this effect results from a mediated CXCR4/SDF1 pathway and the induction of hypoxia pathway.

Table 1: The observed data from a set of 40 RA patients and 20 controls demonstrated an upregulation of HIF1α-dependent genes.

			median	
gene symbol	Id	RA n = 40	HV (n = 20)	P value
IL6R	1386987_at	411.54	249.5	P<0.0001
TGFB3	209747_at	39.93	34.87	0.0051
TFF3	204623_at	34.67	28.80	0.0001
TF	214064_at	72.40	65.58	0.001
FURIN	201945_at	198.50	145.17	P<0.0001
TERT	207199_at	45.13	36.95	0.0003

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In Rheumatoid Arthritis, Naïve B Cells Prevail in the Peripheral Blood, Whereas Memory B Cells Accumulate in the Joint Compartment, Express ZAP-70 and Characterize the Aggregate Pattern. Alessandro Michelutti[2], Elisa Gremese[2], Barbara Tolusso[2], Francesca Morassi[1], Rosalia Privitera[2], Silvia Canestri[2], Giusy Peluso[2], Silvia L. Bosello[2] and Gianfranco Ferraccioli[2]. [1]Division of Histopathology, Catholic University of Sacred Heart, Rome, Italy, [2]Division of Rheumatology, Catholic University of Sacred Heart, Rome, Italy

Statement of Purpose: To analyse B cell subsets in the peripheral blood of RA, non-RA patients and Healthy Controls (HC) and in the synovial compartment in order to understand whether there is a compartmentalization of some subsets. To examine the phenotypic characteristics of the B cells in the synovial fluid and tissue and their possible relationship with disease activity and with synovial tissue cells and their pattern of distribution.

Materials and Methods: Twelve patients with RA and 15 non-RA arthritides (4 UA, 3 MCA-microcrystal arthritis, 1 SpA, 1 SLE, 4 MOA-monoarthritis, 2 PsA) were examined for B cell subsets in the peripheral blood (PB) and in the synovial fluid (SF) and underwent synovial biopsy. Ten HC matched for sex and age, were enrolled in the study as control group.

Results: The percentage of B cells was similar in RA and in non-RA patients, both in peripheral blood and in the synovial compartment.

Considering the peripheral blood compartment, the percentage of CD19+ B cells (8.0 ± 4.8%), as well as the eBm5 (12.4 ± 5.6%) were lower in RA than in HC (CD19+%: 10.8 ± 3.6%, *p=0.003;* eBm5%: 16.0 ± 7.1%; p=0.06). On the other hand, the percentage of CD19+Zap-70+ B cells were higher in RA than in HC (6.1 ± 5.5%-median 5.0 vs 3.9 ± 3.1%- median 3.1% in HC; *p=0.05*), whereas no differences were seen between RA and non-RA patients (4.1±0.3%, p *=0.22*).

In the SF of RA patients, the percentage of Bm2 +Bm2' were significantly lower than in the PB (3.2 ± 3.2% vs 41.3 ± 20.5% in peripheral blood, *p=0.001*); on the contrary Bm5 were significantly higher in the SF than in the PB (67.9 ± 11.4% vs 21.3 ± 21.1%, *p=0.001*). These data have been confirmed by a significant increase of CD27+ B cells in the SF vs the PB (58.8 ± 18.1% vs 25.1 ± 14.9%, *p=0.001*). More particularly, the percentage of CD27+IgD- was significantly higher in SF (54.7 ± 16.7%) compared to PB (11.1 ± 7.9% in PB, *p=0.001*).

Dividing RA patients with high disease activity (DAS44 > 3.7) from those with a DAS< 3.7, the analysis revealed that Bm1 in the SF were higher in active RA (18.9 ± 8.4% vs 10.7 ± 5.3%, *p=0.04*), whereas eBm5+Bm5 B cells were lower in active RA (75.4 ± 9.4% vs 85.9 ± 6.4%, *p=0.03*). ZAP-70+ B cells correlated with the total number of leukocytes (r=0.32, *p=0.04*), inversely with Bm2+Bm2'%(r=-0.56, *p=0.05*), and with the Bm2+Bm2'/eBm5+Bm5 ratio (r=-0.54, *p=0.05*).

Moreover, the IHC analysis of CD68, CD3, CD20, CD27-CD20, CD38-CD20 and CD138 positive cells in the synovial tissue showed an increased trend in RA vs non-RA synovial tissues (p=ns). ZAP-70+ B cells correlated significantly with CD38+ B cells (r=-0.79, *p=0.04*). Considering the RA synovial biopsies with the aggregate and diffuse patterns, CD27+ B cells characterized the pseudo-follicular/aggregate pattern (128.6 ± 89.3/hpf vs 40.7 ± 31.9/hpf; *p=0.03*).

Conclusions: There is a characteristic accumulation of memory B cells in the joint compartment, with CD27 characterizing the aggregate pattern. In addition, data suggested that these cells are ZAP-70+, which was previously shown to confer to B cells a longer life span. The synovial fluid of patients with active disease contained more "naïve" Bm1 and Bm2-Bm2' cells than patients with less active disease.

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Influence of TNF-α, MMP-3, TIMP-3 and HLA Class II Genes Polymorphisms in the Rheumatoid Arthritis Articular Damage. Renata T. Alarcon[5], Artur R. C. Fernandes[5], Geraldo R. C. Pinheiro[3], Magali J. G. Usnayo[3], Luis C. M. Porto[4], Juliana Cardoso-Oliveira[3], Gustavo M. Fabricio-Silva[3], Ieda M. M. Laurindo[1], Manoel B. Bertolo[2], Mario Yazbek[2], Mariana G. Soares[5], Neusa P. Silva[5], Kaline M. C. Pereira[5] and Luis E. C. Andrade[5]. [1]Universidade de Sao Paulo, Sao Paulo, SP, Brazil, [2]Universidade Estadual de Campinas, Campinas, SP, Brazil, [3]Universidade Estadual do Rio de Janeiro, Rio de Janeiro, RJ, Brazil, [4]Universidade Estadual do Rio de Janeiro, Rio de Janeiro, RF, Brazil, [5]Universidade Federal de Sao Paulo - UNIFESP, Sao Paulo, SP, Brazil

Background: The recent availability of drugs that may alter the course of rheumatoid arthritis (RA) has emphasized the need for predictors of disease outcome in order to assign patients to appropriate treatment. HLA-DRB1 and extra-HLA genes are implicated in the predisposition and progression of RA and polymorphism in some of those may serve as modulators of disease severity. TNF-alpha, matrix metalloproteinase-3 (MMP3) and tissue inhibitor of metalloproteinases-3 (TIMP-3) are integrated in the pathway of joint destruction in RA. Genetic studies of patients with RA can supply data that contribute to define more precisely the groups of patients with good and bad disease progression.

Objective: To evaluate possible associations between cumulative articular damage and polymorphisms in HLA-DRB1, TNF-alpha (-308G/A), MMP3 (-1171 5A/6A) and TIMP3 (-899T/A, -915A/G and -1296T/C) genes in a sample of Brazilian patients with RA.

Methods: We selected 440 RA patients from three university centers in southeast Brazil (São Paulo, Rio de Janeiro, and Campinas). DNA was obtained from peripheral leukocytes. The regions of interest for TNF-alpha, MMP-3 and TIMP-3 were amplified by PCR. Amplicons were digested with appropriate restriction enzymes and the resulting fragments were resolved in agarose gel electrophoresis (RFLP). HLA-DRB1 alleles were determined by PCR using sequence-specific oligonucleotide probes (PCR/SSO) and DRB1*04 alleles by PCR sequence-specific primers (PCR/SSP). Sharp's index was scored in hands and feet X-rays by an experienced blinded radiologist. Derivative Sharp scores were developed according to the mathematical division of hands/feet scores (Sharp-h/f), fingers/wrists scores (Sharp-f/w), and erosion/space narrowing scores (Sharp-e/sn).

Results: There was no ethnic association except for a higher prevalence of MMP3 allele 6A in blacks (83.3%) compared to other races (60%) (p<0.001). There was no association between the studied polymorphisms and total Sharp score. However, patients with predominant feet damage (Sharp-h/f < 1.67) had higher frequency of TIMP3 –1296T (72.6% vs 52.6%, p=0.001) and TIMP3 –915A (71.4% vs 55.5%, p=0.009) alleles as compared with those with predominant hand damage. Predominance of space narrowing (Sharp-e/sn <1.67) was associated with −899 TIMP3 allele A (7.8% vs 0.5%, p=0.007). Sharp-f/w score was not associated with polymorphism in the studied genes. The derived Sharp scores were not associated with HLA-DRB1, weight, height, and BMI.

Conclusions: TIMP-3 polymorphism was significantly associated with the preferential topography of joint destruction and with the predominant type of radiographic changes (erosion versus space narrowing) in rheumatoid arthritis.

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Inhibition of the Recycling of Polyamines Restores DNA Methylation in Rheumatoid Arthritis Synovial Fibroblasts. Emmanuel Karouzakis[1], Christoph Kolling[2], Renate E. Gay[1], Beat A. Michel[1], Steffen Gay[1] and Michel Neidhart[1]. [1]Center of Experimental Rheumatology and Zurich Center of Integrative Human Physiology (ZIHP), University Hospital Zurich, [2]Schulthess Clinic, Zurich

Objective: Global DNA hypomethylation in rheumatoid arthritis synovial fibroblasts (RASF) contributes to their intrinsic activation that leads to cartilage and bone destruction. S-adenosylmethionine (SAM) is the methyl donor during DNA methylation—mediated in somatic cells by DNA methyltransferase 1 (Dnmt1). SAM is also used as substrate in the biosynthesis and recycling of polyamines and metabolized utilizing the key enzymes adenosylmethione decarboxylase (AMD) and spermidine/spermine acetyltransferase (SSAT) resulting in the production of diacetylpolyamines. SSAT recycles spermidine and spermine into putrescine that in turn up-regulate AMD thereby accelerating the consumption of SAM. The aim of this study is to investigate whether the increased recycling of polyamines is associated with the global DNA hypomethylation in RASF.

Methods: RASF (n = 12) and osteoarthritis synovial fibroblasts (OASF, n = 6) were stained for AMD, SSAT, polyamine modulated factor binding protein 1 (PMF-1/PMFBP1), Dnmt1 and analyzed by flow cytometry. 5-methylcytosine (5-MeC) was measured by flow cytometry, diacetylspermine (DASp) in cell culture supernatants and cell extracts was determined by ELISA. S-Adenosylmethionine (SAM) was measured in cell extracts by fluorometry. Small interfering RNAs (siRNA) were used to down-regulating AMD and/or SSAT and diminazene aceturate (DA) was employed to inhibit the activity of SSAT.

Results: The intracellular levels of AMD, SSAT and PMFBP1, as well as the level of DASp in cell culture supernatants, were significantly increased in RASF, compared to OASF (AMD/RASF: 36 ± 5, OASF: 23± 4, p < 0.005; SSAT/RASF: 34 ± 8, OASF: 17 ± 3, p< 0.001; PMFBP1/RASF: 79.0 ± 27.7; OASF: 49.7 ± 7.2 mean fluorescence [mf], p< 0.05). On the other hand, the levels of SAM in cell culture extracts, as well as the amount of Dnmt1 and 5-MeC, were significantly decreased in RASF, compared to OASF (SAM/RASF: 0.95± 0.94, OASF: 3.10±0.25 nM/mg protein, p<0.001; Dnmt1/RASF: 7.2±1.3, OASF: 13.3±1.0 mf, p < 0.001; 5-MeC/RASF: 0.98±0.26, OASF: 2.52±0.37 mf minus background, p<0.001). A significant association was found between the amount of SAM in the cell extracts and the 5-MeC in nuclei (r = 0.69, p<0.005); in addition, parameters of the catabolism and/or recycling of polyamines negatively correlated with SAM, Dnmt1 and 5-MeC (from r = −0.50 to r = −0.83, p < 0.01 to < 0.001). Furthermore, siRNA to SSAT can reduce the expression of AMD (controls: 35.5 ± 10.7, siRNA against SSAT: 27.9 ± 4.8 mf, p= 0.18, n = 4). Similarly, inhibition of SSAT activity by DA significantly reduced the expression of AMD (controls: 33.3 ± 6.6, DA: 19.2 ± 4.8 mf, p<0.05, n = 4). A 2 weeks treatment with DA restored the DNA 5-MeC content of RASF (control: 1.41, DA: 2.75 mf, pool of 4 patients) to levels measured in OASF (2.68 mf, pool of 4 patients).

Conclusion: Intrinsic elevations of PMFBP1 and SSAT enhance the catabolism and recycling of polyamines in RASF. A high consumption of SAM by this pathway is an important factor contributing to the global DNA hypomethylation in these cells. Decreasing SSAT transcription or activity could represent a new therapeutic strategy in RA.

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Interleukin-6 Promotes Pathological Angiogenesis by Modulating Angiopoietin Expression in Rheumatoid Arthritis. Ken Kayakabe[1], Takashi Kuroiwa[2], Noriyuki Sakurai[2], Hidekazu Ikeuchi[2], Akito Maeshima[2], Keiju Hiromura[2] and Yoshihisa Nojima[2]. [1]Department of Medicine and Clinical Science, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan, [2]Department of Medicine and Clinical Science, Gunma University Graduate School of Medicine

Background: Angiogenesis is a part of important factors in the pathogenesis of RA. Pathological angiogenesis is characterized by endothelial proliferation accompanied by increased permeability, in which vascular endothelial growth factor (VEGF) plays a dominant role. Angiopoietin-1 (Ang-1) rather facilitates vessel stabilization by keeping endothelial cell adhesion and has a natural antagonist, Ang-2. Previous studies have shown that interleukin-6 (IL-6) promotes angiogenesis in RA but the precise mechanism is not well determined. In this study we sought to examine whether IL-6 promoted angiogenesis in RA by modulating VEGF/angiopoietin expression.

Methods: Fibroblast-like synovial cells derived from RA patients (FLS) were cultured overnight to confluent. Then, human umbilical vein endothelial cells (EC) were added and co-cultured for 6 days in the presence or absence of recombinant human IL-6 (together with soluble IL-6 receptor), VEGF, or Ang-1. EC were stained with anti-CD31 antibody, and EC proliferation was determined by CD31-positive area analyzed by Image-J (NIH). Cell-cell adhesion of EC was assessed by immunofluorescent staining of CD31. Synovial fluids (SF) were collected from patients with RA (n=25) and osteoarthritis (OA) (n=7), who undertook therapeutic SF aspiration. The levels of VEGF, IL-6, Ang-1, and Ang-2 in culture supernatants or SF were determined by ELISA. Quantitative real-time PCR was performed to examine mRNA expression of Ang-1.

Results: Compared with medium control, IL-6 stimulation at 100 ng/ml in co-culture induced 2.5-fold increase of EC proliferation. VEGF at 10 ng/ml also induced 2.2-fold increase. EC stimulated with IL-6 exhibited irregular shape and decreased cell-cell adhesion, suggesting pathological angiogenesis with increased permeability. In the supernatants of co-culture, IL-6 up-regulated expression of VEGF compared with medium control (81 vs 31 pg/ml) and Ang-2 (5304 vs 1726 pg/ml), while decreased Ang-1 (32 vs 99 pg/ml). Interestingly, adding recombinant Ang-1 in co-culture protected EC from shape change and decrease of cell-cell adhesion induced by IL-6, indicating the critical role of angiopoietins in pathological angiogenesis. In the culture of either FLS or EC alone, we found that cellular source of Ang-1 and VEGF was FLS and that of Ang-2 was EC. In FLS, IL-6 reduced Ang-1 expression compared with medium control, both in protein and mRNA levels, by 75% and 60%, respectively. In ELISA, IL-6 also induced 2.5-fold increase of VEGF expression in FLS and 1.7-fold increase of Ang-2 in EC. In SF, expression of IL-6 (5059 vs 262 pg/ml), VEGF (3137 vs 1715 pg/ml), Ang-1 (104 vs 36 pg/ml) and Ang-2 (9216 vs 1494 pg/ml) were significantly higher in RA than in OA. In RA, IL-6 expression was positively correlated with VEGF (r=0.516, p=0.008), while VEGF negatively with Ang-1 (r=-0.515, p=0.008).

Conclusion: IL-6 not only up-regulates VEGF but also down-regulates Ang-1 signaling. This synergistic effect may play a critical role in the pathological angiogenesis in RA.

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MicroRNA and mRNA Integrated Analysis in Rheumatoid Arthritis Synovial Macrophages. Jong Dae Ji[3], Bit-Na-Ra Lee[5], Tae-Hwan Kim[5], Jae-Bum Jun[5], Dae-Hyun Yoo[5], Kyung-Sun Na[2], Jin-Hyun Woo[4], Sung Jae Choi[4], Young Ho Lee[4], Jeongwon Sohn[1] and Gwan Gyu Song[4]. [1]Department of Biochemistry, College of Medicine, Korea University, Seoul, Korea, [2]Kim's Clinic, Seoul, Korea, [3]Rheumatology, College of Medicine, Korea University, Seoul, Korea, Republic of, [4]Rheumatology, College of Medicine, Korea University, Seoul, Korea, [5]The Hospital for Rheumatic Diseases, Hanyang University, Seoul, Korea

Dysregulated expression of microRNAs (miRNAs) has been shown to be a hallmark of human diseases, and recent studies provide growing evidences that miRNA dysregulation might be play important roles in the pathogenesis of rheumatoid arthritis. Abnormal expression of certain miRNAs was found in peripheral blood mononuclear cells, synovial fibroblasts and synovial tissue from patients with rheumatoid arthritis. To investigate whether abnormal expression of miRNA in rheumatoid arthritis could account for dysregulated expression of certain genes, we compared different expressions of miRNAs and mRNAs in rheumatoid synovial fluid macrophages to normal peripheral blood monocytes, using gene expression oligonucleotide microarray and microRNA microarray.

Comparative analysis of mRNA profiles showed significant different expressions (defined as 2-fold change and $P<0.05$) of 430 genes in RA synovial macrophages, of which 303 (70%) were upregulated and 127 (30%) were downregulated, compared to normal PB monocytes. Among the biological process class, highly represented genes included those involved in cell adhesion, immunity and defense, nucleic acid metabolism and signal transduction. Among molecular function class, highly represented genes included those involved in cell adhesion molecule, defense/immunity protein, receptor, nucleic acid binding and transcription factor. We identified 13 differentially expressed miRNAs in RA synovial macrophages, compared with normal PB monocytes. Out of 13 miRNAs, 9 miRNAs were upregulated and 4 miRNAs were downregulated in RA synovial macrophages. Total 62 genes were predicted as target genes of 13 differentially expressed miRNAs in RA synovial macrophages. Out of these 62 genes, 28 genes were upregulated and 34 genes were downregulated. Among 62 miRNA-targeted dysregulated genes, few genes such as GSTM1, VIPR1, PADI4, CDA, IL21R, CCL5, IL7R, STAT4, HTRA1 and IL18BP have been reported to be associated with rheumatoid arthritis. We validated the differential expression of these genes in RA synovial macrophages using quantitative real time PCR.

In the present study, we observed that several miRNAs are differentially expressed in RA synovial macrophages, and suggest that these dysregulated miRNAs may regulate expressions of several genes associated with the pathogenesis of RA.

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Mitochondrial Mutagenesis in Synovial Tissue Is Associated with *In Vivo* Hypoxia, Inflammation and Oxidative Damage. Monika Biniecka[2], Edward Fox[1], Chin T. Ng[2], Len Harty[2], Ursula Fearon[2], Douglas J. Veale[2] and Jacintha O'Sullivan[2]. [1]Department of Pathology, University of Washington, Seattle, WA, [2]Translation Research Group, Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Co. Dublin, Ireland

Background: Mitochondrial components are highly susceptible to attack by oxygen radicals due to their close proximity to the electron transport chain and the presence of polyunsaturated fatty acid rich membranes. Oxidative damage to mitochondrial DNA (mtDNA) itself can affect genes encoding respiratory chain complexes and transcription, which may lead to further mitochondrial DNA mutations. Moreover, ROS induced oxidative damage could potentially be a major source of mitochondrial genomic instability leading to respiratory chain dysfunction. The aim of this study was to examine the relationship of random mitochondrial DNA point mutations to *in vivo* synovial tissue oxygen level (tpO_2), synovial inflammation and lipid oxidative damage in the inflamed joint of inflammatory arthritis patients.

Method: Oxygen partial pressure in synovial tissue (tpO_2) was measured *in vivo* using a combined oxygen/temperature Licox probe. Synovial membrane biopsies were obtained from the site of the oxygen tension measurement under direct visualization at the time of arthroscopy. The newly validated mitochondrial Random Mutation Capture assay was used to quantitatively evaluate alterations of the mitochondrial genome in synovial tissue biopsies. Expression of inflammatory cell specific markers (CD68 of macrophages and CD3 of T cells) and lipid peroxidation (4-HNE) were quantified by immunohistochemistry.

Results: Twenty subjects were recruited prior to starting therapy with biologic agents (14 patients with RA and 6 patients with PsA). The median synovial tissue pO_2 level was profoundly hypoxic at 25.47mmHg, equivalent to an ambient oxygen tension 3.3%. The mutations detected were mainly transitions i.e. AT>GC and CG>TA, characteristic of mutation following oxidative stress. A statistically significant increase in the frequency of point mutations was detected in synovial biopsies in patients with tpO_2<20mmHg compared to patients with tpO_2>20mmHg ($p<0.05$). Higher *in vivo* tpO_2 was significantly associated with a decrease in the frequency of mtDNA point mutations (p=0.05; r=-0.38). Significantly greater mitochondrial mutation burden correlated with high expression of CD68 (p=0.026; r=0.44) and CD3 (p=0.047; r=0.29) positive cells in the sublining layer of synovial tissue. Higher frequency of random mitochondrial DNA mutations was also significantly associated with higher synovial 4-HNE cytoplasmic expression in lining and sublining layers of the synovium (p=0.04; r=0.46 and p=0.03; r=0.44 respectively).

Conclusion: Higher frequency of random mitochondrial mutations was significantly associated with reduced *in vivo* oxygen level, with higher microscopic inflammation and oxidative stress. This data implicates that alterations in the mitochondrial genome may be a consequence of severe hypoxic levels in the inflamed joint.

Disclosure: M. Biniecka: None; **E. Fox:** None; **C. T. Ng:** None; **L. Harty:** None; **U. Fearon:** None; **D. J. Veale:** Abbott Immunology Pharmaceuticals, 2, 5, 8, Centocor, Inc., 5, 8, GlaxoSmithKline, 2, 5, 8, Mundipharma, 2, 8, Opsona, 2, 8, Pfizer Inc, 5, 8, Schering-Plough, 5, 8, Wyeth Pharmaceuticals, 2, 5, 8; **J. O'Sullivan:** None.

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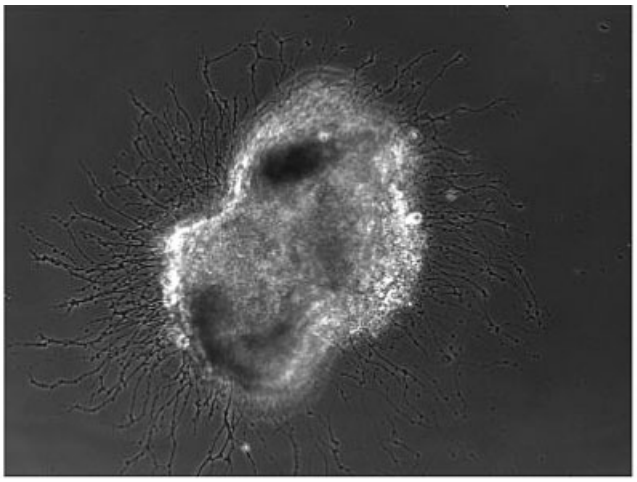
Nerve Fiber Repulsion by Semaphorins—More Redundancy Than Expected in the Rheumatoid Arthritis Joint. Susanne Klatt, Alexander Fassold and Rainer H. Straub. University Hospital Regensburg, Regensburg, Germany, University Hospital Regensburg, Regensburg, Germany

Background: The loss of sympathetic nerve fibers (SNF) is a general principle in inflammatory diseases. Since sympathetic neurotransmitters exert antiinflammatory effects at increased concentrations, their loss in inflamed tissue is reasonable to overcome infection and ensure proper wound healing. However, this mechanism is unfavorable in chronic autoimmune diseases like rheumatoid arthritis (RA). It is generally accepted that semaphorins are the major factors which are involved in guidance and repulsion of nerve fibers, respectively. Additional factors that might influence sympathetic nerve fiber repulsion need to be investigated. Recent findings indicate increased concentrations of norepinephrine, dopamine and 17beta-estradiol in synovial tissue of patients suffering from RA. The aim of this project was to test the effects of these substances on growth and repulsion of sympathetic nerve fibers in vitro.

Methods: In order to study the effect of different factors on nerve fiber repulsion a neurite outgrowth assay was established. In this assay the behavior of nerve fibers from sympathetic trunk ganglia of postnatal mice could be investigated using time-lapse microscopy.



Results: Both investigated semaphorins 3F and 3C induced a repulsion of SNF. Semaphorin 3F repelled 80 % to 100 % of sympathetic nerve fibers, whereas Semaphorin 3C only repelled 30 %. Interestingly, TNF repelled nerve fibers with variable effects (from 10% to 100%) although the variability is unexplained. High concentrations of dopamine and norepinephrine (10^{-6}M) induced significant, but slight nerve fiber repulsion up to 20 % in comparison to controls. Stimulation with low concentrations of 17beta-estradiol (10^{-10}M) led to repulsion of sympathetic nerve fibers. Lower concentrations of norepinephrine (10^{-8}M) seemed to favour nerve fiber outgrowth.

Conclusions: The outgrowth assay enabled us to study the influence of pathogenetically relevant factors which may be involved in nerve fiber growth and repulsion. We assume that not only specific axon guidance molecules like semaphorins, but rather the interplay of other factors, which are elevated in inflamed tissue predominantly influence nerve fiber growth and repulsion during the course of rheumatoid arthritis.

Disclosure: S. Klatt: None; **A. Fassold:** None; **R. H. Straub:** None.

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Phosphoinositide 3-Kinase Delta (PI3Kδ) Regulation and Function in RA. Beatrix Bartok[2], David Boyle[2], Christian Rommel[1] and Gary S. Firestein[3]. [1]Intellikine, [2]UCSD, San Diego, [3]UCSD

Purpose: Phosphoinositide-3 kinases (PI3K) are emerging as drug targets to treat inflammation and autoimmune diseases. Expression of PI3Kγ and PI3Kδ isoforms is relatively selective for leukocytes and regulate innate and adaptive immune responses. They belong to Class I PI3Ks which also include PI3Kα and β isoforms. Unlike PI3Kγ and PI3Kδ, the a and b isoforms are ubiquitously expressed which limits their targeting potential for rheumatic disease. Analysis of genetically modified mice that lack PI3Kγ or δ activity revealed complementary but nonredundant functions in leukocytes. Recently, PI3Kδ expression was observed in cultured fibroblast-like synoviocytes (FLS). The goal of our study was to assess the potential role of PI3Kδ and its downstream target Akt in synovial inflammation.

Methods: Immunohistochemistry (IHC) was used to analyze PI3Kδ expression in RA FLS and synovial tissue. Quantitative real-time PCR (qPCR) was used to determine PI3Kδ mRNA levels and protein expression was quantified with Western blot analysis. PI3K mediated activation of Akt and GSKb was detected using Western blot analysis using phospho-specific antibodies. A selective PI3Ka, PI3Kb and panPI3K inhibitors were used in FLS cultures. An MTT assay was used to quantify cell survival in response to H_2O_2.

Results: PI3Kδ was detected in RA synovial tissue by IHC, with the greatest intensity in the intimal lining layer, which contains FLS. Modest sublining staining was also observed in scattered mononuclear cells. PI3Kδ expression was confirmed in cultured FLS in chamber slides by IHC and by Western blot analysis of FLS extracts (n=4). PI3Kδ mRNA level was 2.5-fold greater in RA compared with OA synovium (n=6 each, $p < 0.05$). PI3K pathway activation in cultured FLS was analyzed by evaluating Akt and GSKb phosphorylation. Only low levels of P-Akt and P-GSKβ were detected in response to IL-1, TNF, LPS or TGFβ. However, a rapid and sustained 140-fold increase in Akt phosphorylation and 3-fold increase in GSKβ phosphorylation was induced by PDGF. To determine relative contribution of PI3Kδ to Akt and GSKβ activation, FLS were pre-incubated with PI3Ka, b, δ or pan PI3K inhibitors. Based on the inhibition of P-Akt, PI3Kδ contributed 55±5% and PI3Kα was responsible 40±5% of Akt phosphorylation. PI3Kδ inhibition had no effect on P-GSKβ levels. We also assessed the effect of PI3Kd inhibition on FLS proliferation and cell death in vitro compared to PI3Kα and pan PI3K inhibition. PDGF stimulation decreased FLS cell death by 50% in response to H_2O_2 and was completely reversed by PI3Kδ inhibition.

Conclusions: PI3Kδ is expressed in the rheumatoid synovial intimal lining. It also plays a novel role in FLS survival, which could contribute to synovial lining hyperplasia. PI3Kδ inhibitors in RA could provide anti-inflammatory effects in RA due to suppression of leukocyte function as well as novel disease modifying effects by decreasing FLS survival.

Disclosure: B. Bartok: None; **D. Boyle:** None; **C. Rommel:** Intellikine, 3; **G. S. Firestein:** Intellikine, 2.

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Platelet Microparticle Proteome: Insight into Role of Microparticles under Different Stimulatory Conditions. Roopa Shree Subbaiah[5], K. C. Sekhar Rao[1], Peter Nigrovic[2], David Lee[4], Masaru Miyagi[1], Eric Boilard[3] and Reuben Gobezie[6]. [1]Case Center for Proteomics and Bioinformatics, School of Medicine, Case Western Reserve University, Cleveland, OH, [2]Center for Adults with Pediatric Rheumatic Illness (CAPRI), Pediatric and Adult Rheumatology, Children's Hospital Boston, Brigham and Women's Hospital, Boston, MA, [3]Department of Rheumatology and Immunology, CHUL, QC, Canada, [4]Division of Rheumatology, Immunology and Allergy, Brigham & Women's Hospital, Boston, MA, [5]The Department of Orthopaedic Surgery, Case Western Reserve University, School of Medicine, University Hospitals of Cleveland, Cleveland, OH, [6]The Department of Orthopaedic Surgery, Case Western Reserve University, School of Medicine, University Hospitals of Cleveland, Cleveland, OH

Background/Purpose: Platelets are well known for their role in thrombosis, but they contribute also to other physiologic and pathologic functions including inflammation. Our recent work demonstrated that platelets can contribute to joint inflammation through the release of small membrane vesicles called microparticles, which are frequently the most abundant cellular element in inflammatory synovial fluid. Generated upon contact with extracellular matrix via the platelet collagen/laminin receptor glycoprotein VI (GPVI), platelet microparticles (pMP) promote inflammation via interleukin 1 and potentially other mechanisms. Since GPVI is not the only stimulus that can induce pMP production, we employed a quantitative proteomic approach to determine whether pMPs remain identical across multiple pathways of platelet activation, or whether diverse activating stimuli engender production of microparticles that are biologically distinct.

Methods: Platelets from a healthy donor were stimulated by three different agonists, collagen-related peptide (CRP, a synthetic GPVI agonist), thrombin and adenosine diphosphate (ADP). Formed pMP were purified and analyzed using high throughput mass spectrometric analysis through a quantitative proteomic approach. Unstimulated platelets were used as control. The Mascot search engine was used for protein identification. Data analysis was done using Genego software.

Results: Mass spectrometry data analysis of the three different proteome sets indicated important differential effect of major agonists in the generation of pRPs. Microparticles generated via GPVI ligation were rich in molecules pertaining to

lipid mediators, strongly suggesting an inflammatory function, while MPs from thrombin possessed multiple procoagulant molecules. In addition, MPs from CRP stimulation contained additional molecules that further activate the immune system as compared to thrombin stimulated MPs. ADP stimulated pathway was observed in all three datasets. Ongoing studies are being carried out to confirm and extend these results.

Conclusions: Our results provide evidence for the differential functions of microparticles released by platelets under various stimulation conditions. In particular, a proteomic approach substantiates the proinflammatory nature of pMPs produced upon contact with collagen, while other pathways may elicit pMP with prothrombotic or other functions. These findings represent a novel observation in fundamental platelet biology and support the possibility that blockade of GPVI may represent a promising therapy for inflammatory arthritis while leaving intact the important hemostatic activity of platelets.

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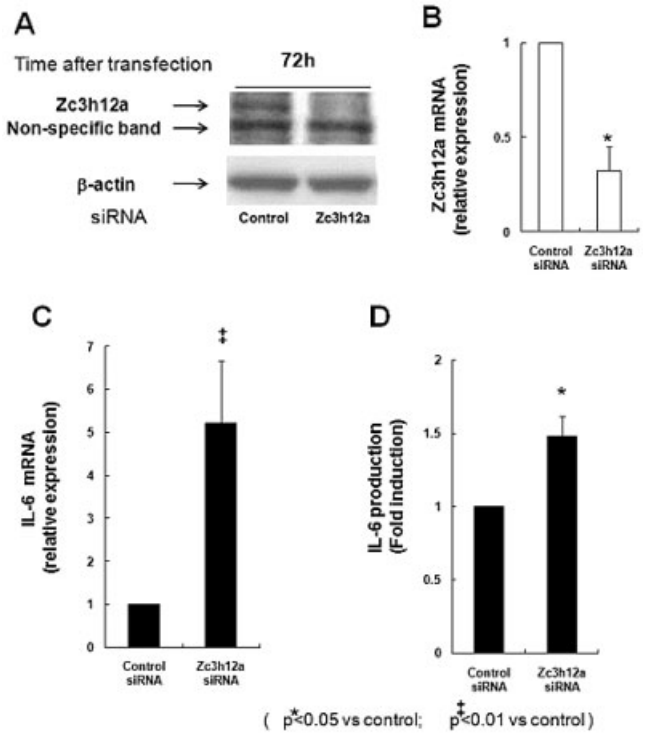
Post-Transcriptional Regulation of IL-6 Production by Zc3h12a in Fibroblast-Like Synovial Cells. Tomohiro Koga, Satoshi Yamasaki, Akitomo Okada, Shin-ya Kawashiri, Hideki Nakamura, Atsushi Kawakami and Katsumi Eguchi. Nagasaki University, Nagasaki, Japan, Nagasaki University, Nagasaki, Japan

Objective: Zc3h12a is a RNA binding protein with a CCCH-type finger motif, known to regulate mRNA metabolism. Previous reports suggest that Zc3h12a acts as a negative regulator of inflammatory processes because it is engaged in the degradation of IL-6 We investigate the effect of Zc3h12a on IL-6 production in fibroblast-like synovial cells (FLS) from rheumatoid arthritis (RA) patients.

Methods: The expression of Zc3h12a in FLS was determined by western blot and polymerase chain reaction. To knock down the expression of Zc3h12a in FLS, siRNA for Zc3h12a was transfected by lipofection method. The supernatants were collected after the siRNA transfection for the quantification of IL-6 production. Cell proliferation was analyzed by the Cell Counting Kit-8 assay after Zc3h12a knock down.

Results: Protein and mRNA for Zc3h12a were demonstrated in all the FLS from RA patients. Zc3h12a transcripts were induced by LPS and IL-1β in FLS. The production of IL-6 as well as its transcripts expression was significantly increased by knocking down of Zc3h12a. Proliferation of Zc3h12a knocked down FLS was significantly promoted in the presence of recombinant soluble IL-6 receptor (sIL-6R). Knocking down of Zc3h12a also induced the activation of signal tranducer and activator of transcription 3 (STAT3).



Conclusion: Our data suggests that Zc3h12a is a novel IL-6 regulator in FLS, which may be involved in the progression of RA.

Disclosure: T. Koga: None; **S. Yamasaki:** None; **A. Okada:** None; **S.-y. Kawashiri:** None; **H. Nakamura:** None; **A. Kawakami:** None; **K. Eguchi:** None.

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Role of IL-17 in Pannus Formation and Osteoclastogenesis in Rheumatoid Arthritis. Hiroshi Ito[2], Hidehiro Yamada[3], Toshiko Nozaki Shibata[2], Hirofumi Mitomi[2], Kiyomi Matsuo[2], So Nomoto[1] and Shoichi Ozaki[4]. [1]Department of Orthopaedic Surgery and Rheumatology, Saiseikai Yokohama Tobu Hospital, [2]Division of Rheumatology, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan, [3]Division of Rheumatology, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan, [4]Division of Rheumatology, St. Marianna University School of Medicine, Kawasaki, Japan

Objectives: IL-17 plays a critical role in the pathogenesis of murine model of arthritis. There are, however, controversies whether IL-17 plays as a pro-inflammatory mediator in rheumatoid arthritis (RA). We studied an exact role of IL-17 in RA using a human cellular model of pannus.

Methods: Inflammatory cells that infiltrated synovial tissue (ST) from patients with RA were collected without enzyme digestion, and designated as ST-derived inflammatory cells as previously reported in Arthritis Rheum 2007;56:2875-85. ST-derived inflammatory cells were cultured in the presence or absence of IL-17 and/or indomethacin, and the morphologic change was observed for 4 weeks. Cytokines produced in the culture supernatants were measured by ELISA kits. Osteoclastic activity was assessed by the development of resorption pits in calcium phosphate-coated slides.

Results: Primary culture of the ST-derived inflammatory cells resulted in a 3-dimensional macroscopic tissue growth, during which TNF-alpha, M-CSF and MMP-9, but not IL-17, were produced in the supernatant. Culture of ST-derived inflammatory cells on calcium phosphate-coated slides resulted in the development of a numerous number of resorption pits. ST-derived inflammatory cells produced IL-17 when stimulated with exogenous Toll-like receptor (TLR) ligands. Exogenous addition of IL-17 dramatically enhanced production of IL-6 and PGE2 from ST-derived inflammatory cells in a dose dependent manner. When endogenous PGE2 production was blocked by indometacin, IL-17 enhanced pannus-like tissue growth, the production of TNF-alpha and M-CSF, and the development of resorption pits, while exogenous addition of PGE1 suppressed their activities.

Discussion: The present study suggests that IL-17 induces negative feedback regulation through the induction of PGE2, while it stimulates pro-inflammatory pathways such as inflammatory cytokine production, pannus formation and osteoclastogenesis in RA. The study also suggests that stimulations of innate immunity via TLR induces and/or exacerbates rheumatoid synovitis mainly through induction of IL-6.

Disclosure: H. Ito: None; **H. Yamada:** None; **T. N. Shibata:** None; **H. Mitomi:** None; **K. Matsuo:** None; **S. Nomoto:** None; **S. Ozaki:** None.

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Role of Raf Kinase Inhibitor Protein in Cytokines, Matrix Metalloproteinases Regulation and Invasiveness of Rheumatoid Fibroblast-Like Synobiocytes. Joong Kyong Ahn[1], You Sun Lee[2], Eun-Jung Park[3], Ji-Won Hwang[3], Ji-Min Oh[3], Jaejoon Lee[3], Chan-Hong Jeon[4], Eun-Mi Koh[3] and Hoon-Suk Cha[3]. [1]Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, [2]Masan Samsung Hospital, Sungkyunkwan University School of Medicine, [3]Samsung Medical Center, Sungkyunkwan University School of Medicine, [4]Soonchunhyang University College of Medicine

Objective: Raf kinase inhibitor protein (RKIP) is a protein that directly interacts with the kinase domain of Raf-1, and has been shown to modulate many processes, including Alzheimer's disease, diabetes and cancer. RKIP negatively regulates the Raf/MEK/ERK pathway by interfering with the activity of Raf-1. Also, RKIP-1 interferes with the activity of the IKK complex and prevents the movement of NF-κB to the nucleus. The role of RKIP in rheumatoid fibroblast-like synoviocytes (FLS) is not known. The present study was performed to investigate the expression and function of RKIP in rheumatoid arthritis (RA) FLS.

Methods: RKIP expression was measured in synovial tissue (ST) and FLS by Western blot analysis. Plasmid containing RKIP or control vector, RKIP small interfering RNA (siRNA), or control siRNA were transfected into FLS using the Amaxa system. Expression of cytokines and matrix metallo-

proteinases (MMPs) mRNA were examined by quantitative real-time PCR. Phosphorylated MAP kinases were measured in RA FLS by Western blot analysis. NF-κB EMSA was performed after TNFa stimulation in RKIP-overexpressed FLS. In vitro cell invasion assay was performed to measure the invasiveness of RA FLS according to RKIP silencing.

Results: RKIP protein was detected in RA ST and FLS, which was similar to osteoarthritis ST and FLS (n=4 each). RKIP overexpression decreased IL-6, IL-8, MMP-1, and MMP-3 mRNA expression (40.76±24.38%, 32.16±18.93%, 31.25±25.09%, and 30.39±14.16% inhibition, respectively) in TNF-α-stimulated RA FLS (n=4), but these results did not reach statistical significance except the result of IL-6 mRNA (p=0.001). RKIP silencing by siRNA resulted in significantly increased MMP-1 and MMP-3 mRNA expression (1.8±0.4 and 2.3±0.8 fold increase, respectively) in TNF-α-stimulated RA FLS (n=3, p=0.01 for each). RKIP silencing also increased IL-6 and IL-8 mRNA expression (1.4±0.3 and 2.1±0.8 fold increased, respectively) in TNF-α-stimulated RA FLS (n=3), but it's not statistical significant. RKIP overexpression suppressed TNF-α-induced ERK phosphorylation. However, p38 and JNK phosphorylation by TNF-α were not affected by RKIP overexpression. RKIP overexpression also suppressed TNF-α-induced NF-κB activation measured by EMSA. RKIP silencing resulted in significantly higher invasion index in TNF-α-stimulated RA FLS compared to controls (10.33±1.45 vs. 4.00±0.58, n=3, p=0.02).

Conclusion: RKIP plays an important role in inflammatory cytokine and MMP production by regulating ERK and NF-κB activation in RA FLS. These results suggest that RKIP might be a potential therapeutic target for RA.

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Sublining CD79a+ B Cell Correlates with Joint Destruction in Rheumatoid Arthritis. Ying-qian Mo[2], Lie Dai[1], Dong-hui Zheng[3], Lang-jing Zhu[2], Xiu-ning Wei[4] and Bai-yu Zhang[2]. [1]Department of Rheumatology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, [2]Department of Rheumatology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, [3]Department of Rheumatology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, [4]Department of Rheumatology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China., China

Objectives: The potent efficacy of B cell-depletion therapy (rituximab) in the treatment of patients with RA has revitalized interest in the pathogenic role of B cells. Recent data indicated the importance of understanding which B cell was critical to RA pathogenesis in designing therapeutic strategies to target B cells. Thus, we aimed to evaluate the distribution and densities of synovial B lineage cells in a large and well-documented cohort of Chinese RA patients, and to determine which type of these B cells correlate with disease activity and joint destruction in RA.

Methods: Synovium was obtained from 69 patients with active RA (defined as $DAS_{28} \geq 3.2$) by needle biopsy and controlled with 14 patients with osteoarthritis (OA) and 15 with orthopedic arthropathies (Orth.A). Serial sections from paraffin blocks were stained for CD68 (macrophage), CD3 (T cell), CD20 (B cell), CD38 (plasmocyte), CD79a (B lineage cell from pre-B cell to plasmocyte stage), CD21 (follicular dentritic cell) and CD34 (endothelial cell) by immunohistochemistry. Quantitative analysis was performed to evaluate cell densities. Radiographic joint destruction of both hands was evaluated by standard Sharp score.

Results: (1) Sublining CD79a+ cell density in RA group (1381.8±1328.2/mm^2) was significantly higher than those in OA group (335.9±727.3/mm^2, $p<0.001$) or Orth.A group (417.9±548.3 /mm^2, $p=0.003$). Receiver operating characteristic curve (ROC) analysis showed high synovial expression of CD79a differentiated RA well from OA ($p=0.001$) or Orth.A ($p=0.003$); (2) Spearman's rank order correlation test showed significant correlation of sublining CD79a+ cell density in RA synovium with synovitis score ($r=0.714$, $p<0.001$) or CD3+ T cell density ($r=0.714$, $p<0.001$); (3) Sublining CD79a+ cell density was significantly higher in long-standing RA patients (disease duration>2 years, n=45, 1633.5±1443.9/mm^2) than those in early RA patients (disease duration≤2 years, n=24, 891.1±912.2/mm^2, $p=0.045$); and correlated significantly with CRP ($r=0.281$, $p=0.033$); (4) Sublining CD79a+ B cell density in RA group correlated significantly with total joint space narrowing score ($r=0.444$, $p=0.002$), erosion score ($r=0.485$, $p=0.001$) and Sharp score ($r=0.458$, $p=0.001$) and Erosive RA showed higher sublining CD79a+ cells density (n=42, 1527.6±1374.9/mm^2) compared with non-erosive RA (n=27, 771.3±919.3/mm^2, $p=0.028$).

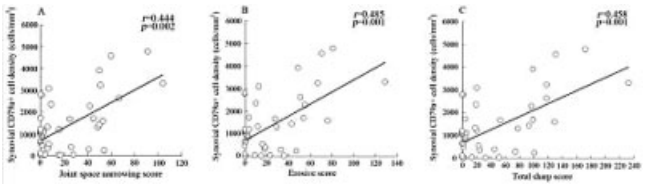

Fig. 1. Spearman's rank correlation analysis for sublining CD79a+ B cell density and radiological Sharp score in RA. A, Correlation between sublining CD79a+ B cell density and joint space narrowing score; B, Correlation between sublining CD79a+ B cell density and erosion score; C, Correlation between sublining CD79a+ B cell density and total Sharp score. (RA: rheumatoid arthritis)

Conclusions: Our results indicate that synovial B lineage cells play a vital role in the maintenance of immune response in rheumatoid synovitis via interaction with T cells and sublining CD79a+ B cell may be involved in the pathogenic process of joint destruction in RA.

Disclosure: Y.-q. Mo: None; **L. Dai:** None; **D.-h. Zheng:** None; **L.-j. Zhu:** None; **X.-n. Wei:** None; **B.-y. Zhang:** None.

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SUMO-2/3 Regulates Apoptosis and MMP Expression in RA Fibroblast-Like Synoviocytes. Svetlana Frank[3], Simon Strietholt[3], Christine Seyfert[2], Thomas Pauly[1], George Kollias[4], Thomas Pap[5] and Marvin A. Peters[3]. [1]Department of Nephrology and Rheumatology, Heinrich-Heine University, [2]Department of Orthopaedic Surgery, Zeisigwaldkliniken, Chemnitz, Germany, [3]Institute of Experimental Musculoskeletal Medicine, University of Muenster, Muenster, Germany, [4]Institute of Immunology, Biomedical Sciences Research Center, Vari, Greece, [5]University Hospital Münster, Münster, Germany

Background: Posttranslational modification through SUMOylation has emerged as an important way by which proteins can be modified to change their intracellular localization, stability and gene expression. Previous data have shown that the overexpression of SUMO-1 contributes to the activation of RA fibroblasts like synoviocytes (RA-FLS) through a SUMO-1/SENP1 dependent mechanism. Based on these data, we investigated the expression of SUMO-2/3 in human RA and in hTNFtg mice and studied its role in regulating both apoptosis and the expression of disease specific MMPs

Methods: Synovial tissue samples were obtained from RA and osteoarthritis (OA) patients at joint replacement surgery and used for histological analysis as well as for the isolation of fibroblast like synoviocytes. Using specific antibodies in immunohistochemical and Western blot analyses, we studied the expression of SUMO-2/3 in fibroblasts from the human samples as well as from hTNF-tg and wt mice. Knockdown of SUMO-2/3 was performed using specific siRNA against both SUMO-2 and -3. The apoptotic response of the fibroblasts was measured using a Caspase-3/7 assay after induction of cell death with 100ng/ml Fas ligand over 13h. MMP-1 and MMP-3 production in FLS from RA and OA patients was measured by ELISAs.

Results: Immunohistochemistry and Western blot analyses revealed a clear upregulation of SUMO-2/3 expression in all RA synovial tissue samples and in RA-FLS compared to OA control samples. These data were confirmed in tissue sections of hTNFtg mice, as well as in FLS from these mice. Knockdown of SUMO-2/3 by siRNA sensitized RASF to Fas-mediated apoptosis. Furthermore, TNF-alpha and IL-1β induced upregulation of MMP-3 was significantly stronger after knockdown of SUMO-2/3 in RA- and OA-FLS. Interestingly, the expression of MMP-1 was not affected.

Conclusions: Our results demonstrate that the posttranslational modification of target proteins by SUMO-2/3 and specifically increased levels of SUMO-2/3 in RA-FLS contribute to the resistance of these cells against Fas-mediated apoptosis. Moreover, our data indicate that SUMO-2/3 is involved in the regulation and TNF-alpha stimulated production of MMP-3. Therefore, we hypothesize that SUMO-2/3 are novel players contributing to the specific activation of RASF and, thus, to the disease process of RA.

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The 6-O Extracellular Endosulfatases as Novel Regulators of Synovitis. Yoon Hoon Hong[1], Shuhei Otsuki[1], Shugeru Miyaki[1], Beatriz Caramez[2], Noboru Taniguchi[1] and Martin Lotz[1]. [1]The Scripps Research Institute, La Jolla, CA, [2]The Scripps Research Institute, La Jolla, CA

Purpose: As receptors or co-receptors, the heparan sulfate proteoglycans (HSPG) modulate the binding and signaling of various ligands to their specific receptors. The sulfation pattern of HSPG is critical in determining binding or release of ligands. The recently identified extracellular sulfatases (Sulf-1, -2) exert novel signaling mechanisms by regulating the binding of ligands to the 6-O sulfate on HSPG and thereby can modulate several signaling pathways that are involved in inflammation. The aim of this study was to analyze expression patterns of Sulf-1 and Sulf-2 and their role in experimental arthritis.

Method: Sulf expression in normal and arthritic human and murine knee joints and in cultured human fibroblast-like synoviocytes (FLS) were analyzed by real-time PCR, immunohistochemistry and western blotting. The role of Sulf in arthritis pathogenesis was analyzed by using the antigen-induced arthritis (AIA) model in wild-type, Sulf1−/− and Sulf2−/− mice. IL-6, an important mediator in arthritis, was measured by ELISA in FLS subjected to Sulf silencing or over-expressing with siRNA or cDNA transfection.

Results: Synovial tissues from humans with rheumatoid arthritis (RA) and mice with AIA showed increased expression of Sulf-1 and Sulf-2 than tissues from human osteoarthritis (OA) or surgically-induced OA in mice or normal knee. Cultured FLS from RA patients showed higher Sulf-1 and Sulf-2 expression as compared to FLS from OA patients. Treatment of FLS with IL-1β or TNFα increased Sulf-1 expression was more prominently than Sulf-2. The severity of AIA was significantly reduced in Sulf1−/− but not in Sulf2−/− mice and this was associated with reduced synovial leukocyte infiltration and pro-inflammatory cytokine expression such as IL-1β and IL-6. Sulf-1 over-expression in FLS enhanced and Sulf-1 silencing reduced IL-6 expression but did not alter the basal or IL-1β induced expression of Cox-2, MMP-3 or MMP-13.

Conclusion: Increased Sulf expression is observed in arthritic synovium and in IL-1β or TNFα activated FLS. Sulf-1 plays an important role in arthritis pathogenesis and this is at least in part mediated by the controlling IL-6 production. Thus, Sulf-1 represents a novel therapeutic target for inflammatory arthropathies.

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The Critical Role of STAT3 in the Th17 Differentiation of RA Synovial T Cells. Ji Hyeon Ju, Mi-La Cho, Ji Min Kim, Yong-Geun Jeong, Seung-Ki Kwok, Kyung Su Park, Sung-Hwan Park and Ho-Youn Kim College of Medicine, The Catholic University of Korea

Objective: STAT3, a signal transduction molecule of inflammatory cytokines such as IL-6, IL-21 and IL-23, plays an important role during the differentiation of CD4+ T cell into Th17 cells (Th17). Since Th17 is the pathogenic cell in autoimmune arthritis, STAT3 has also been suspected to be closely involved in the pathophysiology. This study aims to investigate the mechanism of rheumatoid arthritis (RA) related to the differentiation of Th17 and to identify the role of STAT3.

Method: Cytokine levels in the peripheral blood and synovial fluid of RA patients were measured with ELISA. Immunohistochemical staining of RA synovium was performed to investigate the relationship between synovitis and the expression of STAT3. CD4+ T cells, isolated from peripheral blood and synovial fluid of normal individuals and RA patients, were respectively stimulated with factors leading to Th17 differentiation (anti-CD3 1 μg/ml, anti-CD28 1 μg/ml, IL-23 5 ng/ml, TGF-β 2 ng/ml, IL-6 10 ng/ml, anti-IFN-γ 10 μg/ml, anti-IL-4 μg/ml) or regulatory T cells (Treg) differentiation (anti-CD3 1 μg/ml, anti-CD28 1 μg/ml, TGF-β 20 ng/ml, IL-2 5 ng/ml), as known. STAT3 siRNA was transfected to CD4+ T cells during the differentiation of Th17 cells, which was followed by FACS, RT-PCR and ELISA analyses in order to investigate the impact of STAT3 in Th17 and Treg differentiation.

Result: IL-6, a Th17 related cytokine, was significantly increased in RA synovium ($P<0.01$). The number of Th17 cells in the synovial tissue was significantly higher in RA patients than in normal population. STAT3 and p727S-STAT3 expressions were significantly increased in RA synovium, and their expressions were positively related to the severity of synovitis such as infiltration of inflammatory cells and synovial proliferation ($r=0.68$, $P<0.05$). When STAT3 siRNA was transfected to the CD4+ T cell differentiation in normal individuals, IL-17 and IL-22 expressions and Th17 population decreased, whereas TGF-β expressions and Treg population increased ($P<0.05$). In contrast to the STAT3 inhibition, when STAT5, the transcription factor for Treg, was inhibited, the number of Th17 was increased and that of Treg was decreased ($P<0.05$). Similar findings were observed in the CD4+ T cells isolated from peripheral blood of RA patients. Notably, T cells from RA synovial fluid were significantly decreased in differentiating into Th17 (RASF 0.2% < RAPB 0.5% < HCPB 0.7%, $P<0.05$) while increasing the proportion of Treg (RASF 20% > RAPB 10%, HCPB 11%, $P<0.05$).

Conclusion: The downstream signaling of STAT3 plays a critical role in CD4+ T cell differentiating into Th17 as well as Treg. Inhibition of STAT3 in CD4+ T cells of RA synovium effectively attenuated the differentiation of Th17. By simultaneously achieving Th17 inhibition and Treg stimulation, the regulation of STAT3 promises a novel strategy for RA treatment.

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TNFα-Driven IL-32 Expression in Rheumatoid Arthritis Synovial Tissue Amplifies an Inflammatory Cascade. Bas Heinhuis[4], Marije I. Koenders[4], Piet L. van Riel[2], Charles A. Dinarello[3], Mihai G. Netea[1], Wim B. van den Berg[4] and Leo A. B. Joosten[1]. [1]Department of Medicine, Radboud University Nijmegen Medical Centre, Nijmegen the Netherlands, [2]Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, [3]Division of Infectious Diseases, University of Colorado Denver, Aurora, CO, [4]Rheumatology Research & Advanced Therapeutics, Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen the Netherlands

Statement of Purpose: To investigate the interplay between IL-32 and TNFα in chronic inflamed synovial tissue and to assess whether anti-TNFα treatment of RA patients modulates synovial IL-32 expression.

Methods: To study the interplay between IL-32 and TNFα, we first investigated the induction of IL-32γ by TNFα stimulation in human synovial fibroblasts donated by arthritis patients and compared it with other stimuli such as TLR ligands or IL-1β. Second, we investigated the production of TNFα through intracellular overexpression of IL-32γ followed by LPS stimulation in human THP1 cells. Additionally, we determined the induction of IL-1β, IL-6, and CXCL8. Third, the role of endogenous IL-32 was studied by silencing IL-32γ in human synovial fibroblasts and subsequently IL-6 and CXCL8 levels were determined. Fourth, overexpression of intracellular IL-32γ using an adenovirus expressing human IL-32γ followed by TNFα stimulation was done in synovial fibroblasts to investigate induction of proinflammatory cytokines. Fifth, modulation of TNFα mRNA stability was investigated in human THP1 cells transduced with an adenoviral vector expressing human IL-32γ. IL-1β, IL-6, and CXCL8 mRNA stability was determined. Finally, immunohistochemistry was applied to study IL-32 expression in synovial biopsies from RA patients.

Summary of the Results: Synovial fibroblasts stimulated with TNFα showed potent induction of IL-32γ expression when compared to IL-1β, TLR ligands or medium. Moreover, TNFα induced IL-32γ expression is specific since IL-1β stimulation induced primarily IL-6 and CXCL8. Of high interest, overexpression of intracellular IL-32γ in human THP1 cells followed by LPS exposure resulted in significant production of TNFα, IL-1β, IL-6, and CXCL8. Furthermore, silencing of endogenous IL-32γ showed potent down-regulation of IL-6 and CXCL8 whereas overexpression of IL-32γ resulted in enhanced production of IL-6 and CXCL8 in human synovial fibroblasts. To investigate the mechanism how IL-32γ is capable of amplifying the inflammatory cascade resulting in a self perpetuating loop between IL-32γ and TNFα, we studied mRNA stability. Enhanced expression of intracellular IL-32γ resulted in delayed TNFα, IL-1β, and CXCL8 mRNA decay. In contrast, IL-6 mRNA stability was not regulated by IL-32γ. Of high interest, treatment of RA patients with anti-TNFα resulted in significant reduction of IL-32 protein expression in synovial tissue.

Conclusions: TNFα is a potent specific inducer of endogenous IL-32 expression and IL-32 itself contributes to a prolonged TNFα production. This results in a self perpetuating loop between IL-32γ and TNFα resulting in potent induction of several proinflammatory cytokines and chemokines. This auto-inflammatory loop can potentially be intervened by silencing IL-32 or anti-TNFα treatment. Targeting IL-32 might be a novel therapy to counteract the auto-inflammatory cascade of TNFα-IL-32-TNFα present in chronic inflamed synovial tissue of RA patients.

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Underexpression of TIM-3 and Blunted Galectin-9-Induced Apoptosis of CD4+ T Cells in Rheumatoid Arthritis. Jaejoon Lee[4], Ji-Min Oh[6], Ji Won Hwang[6], Eun-Jung Park[6], Eun-Kyung Bae[3], Joong Kyong Ahn[1], Yoo Sun Lee[2], Eun-Mi Koh[5] and Hoon-Suk Cha[4]. [1]Kangbook Samsung Hospital, Sungkyunkwan University School of Medicine, [2]Masan Samsung Hospital, Sungkyunkwan University School of Medicine, [3]Samsung Biomedical Research Institute, [4]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of, [5]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of, [6]Samsung Medical Center, Sungkyunkwan University School of Medicine

Purpose: T cell immunoglobulin- and mucin-domain-containing molecule-3 (TIM-3) is a novel transmembrane protein involved in the negative regulation of Th1 cell-mediated immunity by interacting with its ligand galectin-9. Galectin-9 has been shown to induce apoptosis of TIM-3 expressing Th1 cells in vitro and in vivo. We have previously demonstrated that, in rheumatoid arthritis (RA) patients, TIM-3 is expressed in the synovial tissues and that TIM-3 mRNA expression in the peripheral mononuclear cells is inversely correlated with disease activity as measured by DAS28. We hypothesize that galectin-9 induced apoptosis of Th1 cells in RA is impaired because of aberrantly low TIM-3 expression which may lead to augmented Th1 response. This study was therefore undertaken to investigate the expression of TIM-3 from CD4+ T cells and galectin-9-mediated apoptosis of CD4+T cells from RA patients and healthy controls.

Methods: CD4+T cells from RA patients and healthy controls were isolated from peripheral blood mononuclear cells and then were activated. The expression of TIM-3 mRNA in CD4+T cells was measured using real-time PCR. After CD4+T cells were activated in the presence of graded doses of galectin-9 or control, galectin-9 induced cytotoxicity and apoptotic activity of CD4+ T cells were analyzed using MTT assays and annexin V staining, respectively.

Results: TIM-3 mRNA expression was significantly lower in CD4+T cells from RA patients compared to those in healthy controls ($p=0.028$). CD4+T cell survival as measured by MTT assay when incubated with galectin-9 (15nM) was significantly higher in RA patients than in healthy controls ($p=0.002$). The increased survival trend of CD4+ T cells from RA patients was maintained at higher dose of galectin-9 (50nM), but did not reach statistical significance ($p=0.078$). Apoptotic activity of CD4+ cells from healthy controls as measured by annexin V staining increased with graded doses of galectin-9 (0nM vs. 30nM, 0nM vs. 90nM, $p=0.016$ each). However, apoptotic activity of CD4+T cells from RA patients did not change despite the stimulation with galectin-9.

Conclusion: Galectin-9-mediated apoptosis of CD4+ T cells is dysfunctional in RA patients. Blunted galectin-9-mediated apoptosis may be exerted through underexpression of TIM-3 that negatively regulates Th1 response. Our data suggest that TIM-3 and its interaction with galectin-9 may play an important role in the pathogenesis of RA and may represent a potential therapeutic target.

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ACR Poster Session A
Rheumatoid Arthritis Treatment - Small Molecules, Biologics and Gene Therapy: Safety, Non-Biologic DMARDs, Switching Biologics I
Monday, November 8, 2010, 9:00 AM–6:00 PM

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Appearance of Non-Rheumatoid Arthralgia after Tocilizumab Treatment in RA Patients with High Disease Activity. Osamu Saiki[2] and Hiroshi Uda[1]. [1]Sakai Onshinkai Hospital, Sakai, Japan, [2]Shiraishi Hospital, Imabari, Japan

Purpose: Tocilizumab, IL-6 receptor antagonist, is one of essential biologics to treat RA patients and several side reactions have been reported, but appearance of non-rheumatoid arthralgia after tocilizumab injection has not been discussed. We experienced several RA patients who developed additional non-rheumatoid somatic arthralgia after tocilizumab treatment. We conducted this study to examine which patients develop non-rheumatoid arthralgia and to clarify how the pain is appeared and how we should take care of these patients.

Patients and Method: We treated RA patients with tocilizumab who had not responded to MTX and/or TNF inhibitors. When we treated RA patients with tocilizumab, we examined CRP and other blood tests in addition to clinical symptoms. Serum levels of IL-6 and TNF-α were also examined before and after tocilizumab treatment.

Results: Sixty-eight RA patients were treated with 8mg/kg tocilizumab every 4 week. Among 68 RA patients, 25 patients developed non-rheumatoid arthralgia. They suffered from severe pains of large joints such as shoulder pain and lumbago, and the quality and the site of pain was quite different from those of RA. The pain started one day after receiving tocilizumab injection and lasted for one week or longer. The magnitude of pain reduced time by time. When the non-rheumatoid arthralgia was appeared, the levels of CRP had fallen down from high levels (more than 50 mg/L) to low levels (under 5mg/L). In the patients experienced non-rheumatoid arthralgia, the serum CRP levels before tocilizumab therapy were significantly higher (113 ± 57 mg/L) than those in patients without non-rheumatoid arthralgia (31 ± 18 mg/L) and the serum levels of IL-6 were very high at 28 days after first tocilizumab treatment and they were significantly higher than in those without non-rheumatoid arthralgia. But the serum levels of high sensitive TNF-α were less than 2.8 pg/mL in both patients.

Conclusion: In tocilizumab treatment, RA patients with high disease activity develop non-rheumatoid arthralgia more frequently than those with low disease activity. In the patients who developed non-rheumatoid arthralgia, the levels of IL-6 but not CRP or TNF-α were selectively high suggesting that the pain would preferentially relate to IL-6 rather than CRP or TNF-α. The elevation of IL-6 levels is due to blocking of IL-6 receptor by tocilizumab treatment. However, the relationships between appearance of non-rheumatoid arthralgia and the high levels of IL-6 were remained to uncertain.

Disclosure: O. Saiki: None; **H. Uda:** None.

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Are Venous Thrombotic Events (VTE) Increased in Patients with Rheumatoid Arthritis (RA) Treated with Anti-TNF Therapy? Results from the British Society for Rheumatology Biologics Register (BSRBR). Rebecca Davies, James Galloway, Kath D. Watson, Mark Lunt, BSRBR Control Centre Consortium, Deborah P. M. Symmons, Kimme L. Hyrich and on Behalf of the British Society for Rheumatology Biologics Register. University of Manchester

Background: Case reports have shown that TNF decreases platelet activation and inhibits thrombus formation, and so blocking TNF may contribute to thrombus formation. Research looking at the role of such therapies on venous thrombotic events (VTE) in RA patients has produced conflicting results with more recent studies documenting an increased risk, particularly in post-orthopaedic surgery patients. The aims of this analysis were (1) to compare rates of VTE in RA patients treated with anti-TNF vs. non-biologic disease modifying anti-rheumatic drugs (nbDMARDs) alone and (2) to compare the rates between each individual anti-TNF and nbDMARDs.

Methods: To 31/10/2009, 11,881 anti-TNF and 3,673 biologic-naive nbDMARD control patients had been recruited to the BSRBR, a UK national register of active RA patients on biologic therapy. All patients were followed by regular hospital and patient questionnaires. This on-drug analysis, limited to first biologic only, followed all patients until first VTE (defined as deep venous thrombosis or pulmonary embolism), death, treatment discontinuation or last follow-up date, whichever came first. Cox proportional hazards models were used to compare rates of VTE between cohorts. Inverse probability of treatment weighting (IPTW) was used to adjust for the confounding effect of baseline differences between groups, including age, gender, diabetes, steroid use, smoking, BMI, hypertension, disease duration, severity and year of entry into the study. Surgery was entered into the model as a time-varying covariate, with patients viewed as being at increased risk for 90 days post-procedure. Missing baseline data were accounted for using multiple imputation.

Results: The anti-TNF cohort was younger (mean 56 v 60 years), had a higher proportion of females (76 v 72%) and more severe disease (mean DAS28/HAQ: anti-TNF 6.6/2.0, nbDMARD 5.1/1.5). The median duration of follow up was 4.3 years (IQR 2.9, 5.4) in the anti-TNF cohort, and 3.0 years (IQR 1.7, 4.2) in the nbDMARD cohort.

A total of 204 first VTE's were reported (160 anti-TNF, 44 nbDMARD). 13% of anti-TNF and 7% of nbDMARD VTE events were reported within 90 days of hip or knee replacement. Overall there was no difference in the rate

of VTE between anti-TNF and nbDMARD treated patients (adjusted HR 0.9 (95% CI 0.5, 1.6). The risk was similar across all anti-TNF agents.

Conclusion: Anti-TNF therapy is not associated with an increased risk of VTE in RA patients. There is also no difference in VTE risk between the anti-TNF drugs.

Table: Patient characteristics and incidence of VTEs.

	nbDMARD	All anti-TNF	ETN**	INF**	ADA**
Subjects (n)	3673	11881	4139	3475	4267
Exposure (pyrs)	11418	32811	13648	9549	9614
Surgeries, n	1210	4370	1922	1243	1205
Hip/knee replacement, n	545	2564	1129	750	685
All VTE events: n	44	160	55	67	38
VTE within 90 days of surgery, n (%)	5 (12)	34 (21)	10 (19)	17 (24)	7 (18)
VTE within 90 days hip/knee replacement, n (%)	3 (7)	20 (13)	6 (11)	9 (13)	5 (13)
VTE incident rate/1000 pyrs	3.9 [2.8, 5.2]	4.9 [4.2, 5.7]	4.0 [3.0, 5.2]	7.0 [5.4, 8.9]	4.0 [2.8, 5.4]
VTE adjusted HR*	Ref	0.9 [0.5, 1.6]	0.6 [0.3, 1.2]	1.1 [0.6, 2.1]	0.9 [0.4, 1.8]

*Adjusting for potential confounders was performed using an inverse probability of treatment weighted propensity model.
Including age, gender, diabetes, baseline steroid exposure, smoking, BMI, hypertension, surgery, disease duration, disease severity and year of entry into study.
**ETN = Etanercept, INF = Infliximab, ADA = Adalimumab

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Assessment of Cardiovascular Markers after 24 Weeks of Abatacept or Rituximab Therapy in Patients with Rheumatoid Arthritis. Sylvain Mathieu[3], Gauthier Szymanski[1], Jean-Jacques Dubost[2], Natacha Mrozek[4], Geoffroy Marceau[1], Jean-Michel Ristori[4] and Martin Soubrier[4]. [1]Biochimie, CHU Gabriel Montpied, Clermont-Ferrand, France, [2]Humatologie, CHU Gabriel Montpied, Clermont-Ferrand, France, [3]Rhumatologie, CHU Gabriel Montpied, Clermont-Ferrand, France, [4]Rhumatologie, CHU Gabriel Montpied, Clermont-Ferrand, France

Background: Increased incidence of cardiovascular disease has been observed in rheumatoid arthritis (RA). Several studies have attributed this excess cardiac risk to biological inflammation. Effective control of inflammation may be of benefit in reducing cardiovascular risk in RA patients.

Objectives: To investigate the effects of abatacept and rituximab treatment in active RA on markers of atherosclerosis: arterial stiffness measured by augmentation index (AIx) and pulse wave velocity (PWV), lipoproteins, pro-brain natriuretic peptide (pro-BNP) and soluble levels of Receptor for Advanced Glycation Endproducts (sRAGE).

Methods: PWV, AIx, clinical status, lipoproteins, systemic inflammation, pro-BNP and s-RAGE were assessed at baseline and after 24 weeks of abatacept and rituximab therapy.

Results: Thirty RA patients, including 27 women, with a mean age of 58.0 ± 11.6 years and a longstanding disease of about 11 years received rituximab therapy. Of these 30 patients, 90% had rheumatoid factor, 80% anti-CCP antibody and 93.3% were erosive. Nineteen patients had failed to respond to TNF alpha inhibitor treatments.

Seventeen RA patients (14 female), with a mean age of 60.6 ± 14.1 years were treated by abatacept. Of these 17 patients, 47.1% had positive rheumatoid factors, 76.5% had positive anti-CCP antibody, and all were erosive. Twelve patients were non-responders to TNF alpha inhibitor treatments and 7 (41.1%) to rituximab treatment.

1) Arterial stiffness. After abatacept treatment, no change was observed in PWV (8.6 ± 4.2 vs. 9.4 ± 3.1 m/s; p=0.09) and AIx (29.9 ± 10.6 vs. 30.1 ± 9.3%; p=0.98). With rituximab, an improvement in AIx was obtained (AIx: 29.1 ± 8.0% vs. 31.7 ± 10.5%; p=0.024) but not to a level of significance for PWV (7.9 ± 2.7 vs. 8.1 ± 3.4 m/s; p=0.620).

2) Lipoproteins and other cardiovascular risk markers. After both treatments, a significant increase in the level of apolipoprotein A1 (apoA1) and a tendency to a decrease in the apolipoprotein B/apoA1 ratio were obtained. No change was found in levels of pro-BNP, sRAGE or apoB.

3) Disease activity. DAS28 ESR and DAS28 CRP were significantly improved after both rituximab and abatacept. We found a decrease in parameters of biological inflammation, significant after rituximab and not significant after abatacept.

Conclusion: This study shows that arterial stiffness, occurring in RA, was not improved after 6 months of abatacept or rituximab therapy, nor pro-BNP and s-RAGE. However, the treatment did have a beneficial effect on lipid profile and so it would be interesting to have an assessment over a longer period, especially since abatacept and rituximab are not anticytokine therapies.

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Before Beginning Anti-TNF, a Better Targeted Screening and a Twice Decrease Frequency of Latent Tuberculosis (TB) with IFN gamma Release Assays (IGRA) Compared with Tuberculin Skin Test. Results in 396 Patients from the ETAT Study. Xavier Mariette[3], Gabriel Baron[3], Frédéric Lioté[3], Philippe Goupille[4], René-Marc Flipo[1], Bernard Combe[2], Florence Tubach[3], Dominique Emilie[3], Dominique Salmon[3], Marc Leman[3], Guislaine Carcelain[3] and Philippe Ravaud[3]. [1]Lille University, [2]Montpellier University, [3]Paris University, [4]Tours University

Background: In spite of screening for latent tuberculosis (TB) with tuberculin skin test (TST), reactivation of TB remains a non rare severe complication in patients treated with TNF blockers, mainly with monoclonal antibodies. Great hope came from a more efficient screening of latent TB with specific IFN gamma release assays (IGRA).

Objective: To compare TST and 2 IGRA in a large cohort of patients with different immune mediated inflammatory diseases (IMID) before introduction of anti-TNF.

Methods: 396 patients with IMID were screened for latent TB with TST and with 2 IGRA, Quantiferon Gold and T-Spot TB, before beginning anti-TNF. 126 patients (32%) had rheumatoid arthritis, 178 (45%) had spondyloarthritis and 92 (23%) had Crohn's disease. 238 patients (60%) received an immunosuppressive treatment and 144 (36%) received steroids.

Results: 138 patients (35%) had positive skin test (> 5mm) and 66 (17%) had positive IGRA (either Quantiferon Gold or T-Spot TB), p< 0.0001. Interestingly, 122 patients (31%) had discordant results between TST and IGRA, 97 (25%) with positive TST and negative IGRA and 25 (6%) with negative TST but positive IGRA. The discordant results in the different diseases are indicated in the table.

		IGRA + in all patients (n = 396)			IGRA + in RA patients (n = 126)			IGRA + in SpA patients (n = 178)			IGRA + in CD patients (n = 92)		
		No	Yes	Tot	No	Yes	Tot	No	Yes	Tot	No	Yes	Tot
TST + (> 5 mm)	No	233	25	258	79	13	92	85	7	92	69	5	74
	Yes	97	41	**138 (34.9%)**	24	10	**34 (27.0%)**	58	28	**86 (48.3%)**	15	3	**18 (19.6%)**
	Tot	330	**66 (16.7%)**	396	103	**23 (18.3%)**	126	143	**35 (19.7%)**	178	84	**8 (8.7%)**	92
P (IGRA + vs TST+			<0.0001			0.07			<0.0001			0.03	

Proportion of positive results was higher with T-Spot TB than with Quantiferon Gold: 59/396 (15%) versus 39/396 (10%), p= 0.0006.Concordance between the 2 IGRA tests was good: 91% [88–94], kappa= 0.61 [0.49–0.73].

In multivariate analysis, the factors influencing positivity of IGRA (one or the other) were to be born in a TB endemic area (OR=2.9 [1.5–5.7]) and not to be vaccinated with BCG (OR=3.7 [1.3–10.8]).

The number of indeterminate results was greater with T-Spot TB than with Quantiferon Gold TB: 29/396 (7.3%) versus 11/396 (2.8%), p=0.002. Among the 29 indeterminate tests with TsSpot TB, 25 were negative with Quantiferon Gold, 3 were positive and 1 was indeterminate. Among the 11 indeterminate tests with Quantiferon Gold, 8 were negative with TsSpot TB, 0 were positive and 3 were indeterminate. No factor influences an indeterminate result of IGRA, and in particular neither steroid use nor immunosuppressant use.

All the patients were treated with antibiotics depending of the IGRA tests (1 or the other). No patient developed TB with 1 year of follow-up.

Conclusion: In this large series of almost 400 patients assessed for latent TB before anti-TNF, IGRA are positive in twice less cases than TST and 31% of the patients had discordant results between TST and IGRA, ¾ with positive TST and negative IGRA and ¼ with negative TST and positive IGRA. Using IGRA for screening of latent TB seems more effective than TST for better targeting the population at risk of TB with anti-TNF treatment but

the sensitivity and the specificity of each of the tests will have to be assessed in the sub-group of patients with certain latent TB on clinico-radiological arguments independently of the results of the tests.

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Better Results Are Achieved with Switching Directly to Biologics Than Switching Via DMARD Combinations in RA Patients Who Have Failed Methotrexate as Their Initial DMARD: Real Life Data from NOR-DMARD. Elisabeth Lie[2], Till Uhlig[2], Knut Mikkelsen[3], Synøve Kalstad[5], Erik Rødevand[4], Cecilie Kaufmann[1] and Tore K. Kvien[2]. [1]Buskerud Central Hospital, Norway, [2]Diakonhjemmet Hospital, Norway, [3]Lillehammer Hospital for Rheumatic Diseases, Lillehammer, Norway, [4]St. Olavs Hospital, Norway, [5]University Hospital of Northern Norway, Norway

Background: Combination of methotrexate (MTX) with an anti-TNF agent is generally considered more effective than combinations with synthetic DMARDs in RA pts who have failed MTX. Many countries require use of at least two DMARDs before start of a biologic agent and the relative benefit of these different strategies in real life is not clarified. The objective of this study was to examine the value of switching via MTX+DMARD combinations vs switching directly to MTX+aTNF after failing MTX mono.

Methods: The NOR-DMARD registry includes pts >18 yrs of age with inflammatory arthropathies starting treatment with DMARDs or biologicals in 5 centres. Pts are consecutively included and followed longitudinally. For the current analyses we included RA pts with <5 yrs disease duration who had failed on MTX (but no other DMARDs), and who were started on MTX+aTNF (group I) or MTX+DMARDs (group IIa). From group IIa we identified a subgroup of pts who received MTX+anti-TNF after failure of the MTX+DMARD combination (i.e. failed ≥2 DMARDs) (group IIb). We compared effectiveness and disease states between group I and group IIa and between group I and group IIb. Survival analyses (Kaplan-Meier) were based on 1- and 2-yr data.

Results: Group I included 85 pts (37 etan(ercept), 25 infl(iximab), 23 ada(limumab)) and group IIa 125 pts (56 MTX+sulfasalazine, 43 triple, 24 MTX+antimalarials, 2 MTX+leflunomide). In groups I/IIa 73%/70% were RF pos (p=0.60), 61%/69% were female (p=0.25), mean age was 50/53 yrs (p=0.15), median(IQR) disease duration was 1.2(0.6–2.3)/1.1(0.5–1.8) yrs (p=0.24). Baseline disease activity was similar (mean DAS28 4.94/4.97, MHAQ 0.79/0.70, SF6D 0.57/0.58, all differences N.S). 6-month disease activity states and responses were superior for group I vs group IIa (table). 1- and 2-yr drug survival were superior for group I vs group IIa (p<0.001/ p=0.001). 31 of the 125 pts who received MTX+DMARDs were later started on secondary MTX+aTNF (group IIb; 11 etan, 12 infl, 8 ada). These pts (68% female, 81% RF pos) were at baseline not significantly different from the remaining pts in group IIa. At start of MTX+aTNF mean DAS28/MHAQ/SF6D were 5.46/0.74/0.59. On average group IIb pts reached a less favourable disease activity state than group I (table). Mean 6-month change in SF6D was 0.13 for group I vs 0.02 for group IIb (p<0.001). Drug survival was superior for group I vs group IIb at 1 yr (p=0.09) and 2 yrs (p=0.02).

Disease states, remission and response rates at 6 months

	Group I MTX + aTNF	Group IIa MTX + DMARDs	Group IIb MTX + aTNF	*P**	*P***
DAS28	3.20 (1.42)	4.13 (1.38)	3.95 (1.49)	0.001	0.06
CDAI	11.3 (9.7)	18.3 (13.1)	16.2 (10.2)	0.001	0.06
MHAQ score (0–3)	0.34 (0.36)	0.46 (0.43)	0.52 (0.37)	0.09	0.06
SF6D	0.68 (0.12)	0.66 (0.13)	0.64 (0.10)	0.23	0.16
DAS28 <2.6	30.4%	12.9%	10.5%	0.02	0.12
CDAI <2.8	15.8%	8.0%	5.0%	0.16	0.44
EULAR good resp.	37.8%	20.9%	29.4%	0.05	0.54

*group I vs. group IIa; **group I vs. group IIb

Conclusion: In these pts who were MTX failures, MTX+anti-TNF was superior to MTX+DMARDs in terms of disease states reached, response and remission rates, and retention to therapy. Furthermore, the subgroup of pts receiving MTX+aTNF after failing the MTX+DMARD combination reached less favourable disease activity states and a lower remission rate than pts receiving MTX+aTNF after having failed MTX only. These data may suggest that delayed initiation of TNF inhibitor can reduce the achieved clinical benefit.

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Characterization of Laboratory Parameters in Long-Term Extension Studies of Tocilizumab in Rheumatoid Arthritis. William Rigby[3], Daniel E. Furst[8], Warren Rizzo[1], Alexandra Balbir-Gurman[5], Moshe Zilberstein[6], Emma Vernon[7], Joel M. Kremer[2], Andrea Rubbert-Roth[9] and Ronald F. van Vollenhoven[4]. [1]Advanced Arthritis Care, Scottsdale, AZ, [2]Albany Medical College, Albany, NY, [3]Dartmouth Medical School, Lebanon, NH, [4]Karolinska University Hospital, Stockholm, Sweden, [5]Rambam Health Care Campus, Haifa, Israel, [6]Roche, Nutley, NJ, [7]Roche, Welwyn, UK, [8]UCLA Medical Center, Los Angeles, CA, [9]University of Cologne, Cologne, Germany

Purpose: Tocilizumab (TCZ) is a fully humanized monoclonal antibody that targets interleukin-6-receptor signal transduction. Efficacy and safety of TCZ in patients with RA have been demonstrated in 7 phase 3 studies. The objective of this analysis was to assess the effects of TCZ on laboratory parameters in patients with RA using pooled data from clinical trials (OPTION, TOWARD, RADIATE, AMBITION, and LITHE) and ongoing long-term extension studies.

Methods: This was a pooled analysis of patients who received ≥1 TCZ dose (in OPTION, TOWARD, RADIATE, AMBITION, LITHE, GROWTH95, and GROWTH96) from initial exposure through August 28, 2009. Data were examined using descriptive statistics.

Results: A total of 4009 patients received TCZ with a median (mean) treatment duration of 3.1 (2.7) years and a total observation time of 10,994 patient-years (PY). Mean CRP levels decreased from 2.43 mg/dL at baseline to 0.17 mg/dL at first assessment (week 2) and have remained at or near normal levels (0.13 mg/dL at week 192). Mean ESR decreased from 46 mm/h at baseline to 17 mm/h at week 2 and to 8 mm/h at week 192. Mean hemoglobin/albumin levels increased from 134.0/38.1 g/L at baseline to 143.0/41.6 g/L at week 6 and to 149.0/42.1 g/L at week 192. Clinically significant decreases in neutrophil counts occurred in 4.5% (grade 3: ANC = 0.5-<1.0 × 10^9/L) and 0.7% (grade 4: ANC = <0.5 × 10^9/L) of patients, and there was no apparent correlation between decreased neutrophil counts and serious infections. Continued exposure to TCZ was not associated with increased incidences of CTC grade 3/4 decreases in neutrophil counts. A decrease in platelet counts to ≥25 to <50 × 10^9/L occurred in 0.4% of patients and to <25 × 10^9/L in 0.5% of patients. There was no apparent correlation between decreased platelet count and serious bleeding event. Increased ALT/AST levels from normal at baseline to >3 to 5× ULN and >3× ULN occurred in 7.9%/2.7% and 10.3%/3.3% of patients. Most transaminase elevations >3× ULN were single, transient occurrences. An increase in LDL from <130 mg/dL at baseline to ≥130 mg/dL at last observation was reported in 22.6% (63/279) of patients who were receiving lipid-lowering medication and in 37.4% (761/2033) of patients who were not receiving lipid-lowering medication. Lipid profile changes were not associated with increased cardiovascular events over a median duration of 3.1 (range, 0–4.6) years.

Conclusions: Treatment with TCZ led to marked improvements in CRP levels and ESR as early as week 2. Among patients with increases in lipid levels, hepatic transaminases, neutrophil counts, or platelet counts, no clear increase in associated clinical events was noted; this could have been a result of monitoring and treatment adjustments that occurred in this longitudinal study. Regular monitoring of these parameters should be employed during routine use of TCZ in patients with RA.

Disclosure: W. Rigby: Genentech, a member of the Roche Group, 5, 8, Roche, 2; **D. E. Furst:** Abbott Laboratories, 2, 5, 8, 9, Actelion Pharmaceuticals US, 2, 5, 8, 9, Amgen Inc., 2, 5, 9, Biogen Idec, 5, 9, Bristol-Myers Squibb, 2, 5, 9, Centocor, Inc., 5, 9, Corrona, 3, Genentech and Biogen IDEC Inc, 2, 5, 9, Gilead Sci; **W. Rizzo:** None; **A. Balbir-Gurman:** Abbott Laboratories, 9, Roche, 9, Schering-Plough, 9; **M. Zilberstein:** Roche, 3; **E. Vernon:** Roche, 3; **J. M. Kremer:** Abbott Laboratories, 2, 5, Amgen Inc., 2, 5, Bristol-Myers Squibb, 2, 5, Centocor, Inc., 2, 5, Genentech and Biogen IDEC Inc, 2, 5, Pfizer Inc, 2, 5, Roche, 2, 5, UCB, Inc., 5; **A. Rubbert-Roth:** Abbott Laboratories, 5, Chugai, 5, Essex, 5, Roche, 2, 5, 8, UCB, Inc., 5, Wyeth Pharmaceuticals, 2, 5; **R. F. van Vollenhoven:** Roche, 2, 5.

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Disease Activity, Calendar Year, and Physician Preference Are Associated with Switching of Biologic Agents for Reasons of Inadequate Efficacy. Jeffrey R. Curtis[3], Ying Shan[4], Joel M. Kremer[2], Jeffrey D. Greenberg[1] and George Reed[4]. [1]Millburn, NJ, [2]The Center for Rheumatology, Albany, NY, [3]University of Alabama - Brimingham, Birmingham, AL, [4]University of Massachusetts

Background: As new biologic agents have become available, the impact of having additional options on the decision to switch is unclear. We evaluated factors associated with switching biologic medication regimen in a large U.S. registry of rheumatoid arthritis (RA) patients.

Methods: Using CORRONA data through 12/31/2009, eligible patients had RA newly treated with an anti-TNF agent with ≥ 6 months of follow-up. The outcome was discontinuing or switching to a different biologic within one year due to inadequate efficacy. Individuals switching for other reasons were excluded.

Factors associated with switching for lack of efficacy were evaluated using logistic regression, with a focus on CDAI and calendar year. Clustering at the physician level was estimated using random effects. We tested the hypotheses that switching would be more likely as new biologics were available over time after controlling for disease activity, and that physician preference for switching would be significant even after adjustment.

Results: Among 3,351 patients initiating an anti-TNF medication, 1,328 were eligible for analysis. Baseline characteristics were mean±SD 46.2 years, 80% women, 90% RF+, mean RA duration 9.5±9.2 years, mean CDAI 21.9±14.5, mean MD global 34±22, mean DAS28 4.5±1.5, 37% steroids, 62% 1st biologic, 30% 2nd biologic, 8% 3rd biologic.

Among these, 125 switched their biologic regimen for lack of efficacy; 44 (35%) switched within 6 months. Numerous factors were different among patients who switched versus those persistent: CDAI (22.4 vs. 12.5, $p < 0.001$), change in CDAI (−2.7 vs. −9.7, $p = 0.002$), MD global (−7.6 vs. −14.4, $p = 0.04$), change in swollen joints (−0.1 vs. −3.3, $p = 0.001$), change in patient global (0.1 vs. −11.8, $p = 0.008$).

As shown (Table), calendar year was associated with switching even after controlling for disease activity. Patients with moderate disease activity (CDAI 10–21) were even more likely than low or high disease activity to be switched over time (p value for interaction between moderate disease activity × calendar year = 0.03). There was a small but significant effect of clustering by physician in the decision to switch for lack of efficacy (OR=1.2, 95%CI 1.1–66.5).

Factors Associated with RA Patients Switching Their Biologic Medication Regimen for Lack of Efficacy

	Odds Ratio (95% CI)
Clinical Disease Activity Index (CDAI)	
<10 (referent)	1.0
10–21	4.0 (2.3–6.9)
> = 22	7.7 (4.6–14.7)
Change in CDAI	
>=10 unit improvement (referent)	1.0
Improvement between 1 and 10 units	1.3 (0.8–2.2)
No improvement, or worsening	1.6 (0.9–2.6)
Calendar Year	
2002–2005 (referent)	1.0
2006–2007	2.0 (1.1–3.7)
2008–2009	3.4 (1.9–6.0)
Number of prior biologics used	
1 (referent)	1.0
2	1.7 (1.1–2.6)
3	1.4 (0.7–2.7)

Conclusion: The availability of new biologic agents in recent years has increased the likelihood of switching for reasons of lack of efficacy, especially for patients with moderate disease activity, and after controlling for clinical response. Physician preference also was significantly associated with the decision to switch. The future availability of new agents will likely further motivate medication switching.

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Early Clinical Response to Treatment Predicts Long-Term Outcome in RA Patients: 5 Year Follow-Up Results of a MTX-Based Tight Control Strategy (CAMERA). M. F. Bakker[1], J. W. G. Jacobs[1], P. M. J. Welsing[1], S. A. Vreugdenhil[4], C. van Booma-Frankfort[2], S. P. Linn-Rasker[3], E. Ton[1], F. P. J. G. Lafeber[1] and J. W. J. Bijlsma[1]. [1]Rheumatology & Clinical Immunology, University Medical Center Utrecht, The Netherlands, [2]Rheumatology, Diakonessenhuis Utrecht, the Netherlands, [3]Rheumatology, Meander Medical Center Amersfoort, the Netherlands, [4]Rheumatology, St. Antonius Hospital Nieuwegein, the Netherlands

Background: The CAMERA trial showed that an intensive, tightly controlled MTX-based strategy after 2 years of treatment is more effective in early RA when compared to a conventional MTX-based strategy. The aim of this investigation was to compare the long-term effects of the intensive strategy in CAMERA with those of the conventional strategy in early RA and to investigate the predictive value of an early response for long-term outcome.

Methods: The clinical (DAS28) and radiographic (mean yearly radiographic progression rate) outcome at 5 years was compared between strategies and tested with independent t-tests. Patients of the CAMERA trial were classified as early good-, moderate- or non-responders after 6 months of treatment according to the EULAR criteria. Whether early response to treatment had additional predictive value to that of established baseline predictors (rheumatoid factor, joint damage and disease activity) was investigated by multivariate linear regression analysis, taking into account the 2 treatment strategies.

Results: Of the 299 patients, 5 years data were present of 205 (102 intensively, 103 conventionally treated) patients. Analysis showed no indication for missing data due to selective drop-out. The mean (SD) DAS28 at 5 years of treatment was 2.68 (1.0) and 2.75 (1.3) for intensively and conventionally treated patients respectively. The median (IQR) radiographic progression rates at 5 years were 1.4 (0.1–3.6) and 0.8 (0.0–3.2), respectively. There was no significant difference for clinical and radiological outcomes between the initial treatment strategies. According to the EULAR criteria, 68, 84, and 45 patients had an early good-, moderate-, and non-response, respectively. Patients with an early good-, moderate- or non-response respectively had a mean DAS28 at 5 years of 2.39 (1.2), 2.69 (1.1), and 3.11 (1.2) and a median radiographic progression rate of respectively 0.6 (0.0–2.2), 1.5 (0.2–3.6), and 2.5 (0.5–6.2). Early good-responders showed significantly better results for clinical (p=.09 and p=.001) and radiological (p=.013 and p=.001) outcomes at 5 years when compared to those with early moderate- and non-response, respectively. About 2/3 of the early good-responders and 1/4 of the early non-responders had been allocated to the intensive treatment strategy. The multivariate regression analysis with inclusion of known predictors showed that early response to treatment is an independent predictor of long-term outcome, both within the tight control and conventional strategy.

Conclusions: The difference in effect between treatment strategies diminished over the years. An early good-response to treatment independently predicts significantly better long-term outcomes irrespective of the treatment strategy. Effects of continuation of tight control in those patients who still have active disease needs further study.

References:

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Disclosure: M. F. Bakker: None; **J. W. G. Jacobs:** None; **P. M. J. Welsing:** None; **S. A. Vreugdenhil:** None; **C. van Booma-Frankfort:** None; **S. P. Linn-Rasker:** None; **E. Ton:** None; **F. P. J. G. Lafeber:** None; **J. W. J. Bijlsma:** None.

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Early Development of Antibodies Against Infliximab Predicts Withdrawal Due to Adverse Drug Reactions in Patients with Rheumatoid Arthritis. Sophine B. Krintel[2], Veit Peter Grunert[4], Merete L. Hetland[1], Julia S. Johansen[3], Matthias Rothfuss[4] and Ursula Klause[4]. [1]DANBIO Registry and Department of Rheumatology at Copenhagen University Hospital, Hvidovre and Glostrup, Hvidovre, Denmark, [2]DANBIO Registry and Department of Rheumatology at Copenhagen University Hospital, Hvidovre and Glostrup and Department of Medicine at Copenhagen University Hospital, Herlev, Valby, Denmark, [3]Medicine and Oncology at Copenhagen University Hospital, Herlev, Denmark, [4]Roche Diagnostics GmbH, Penzberg, Penzberg, Germany

Background: Some patients with rheumatoid arthritis (RA) treated with TNFalpha inhibitors develop adverse drug reactions (ADR) or secondary treatment failure. The objectives were to investigate the frequency of

antibodies against infliximab in patients with RA during treatment with infliximab, and to determine if development of such antibodies was associated with withdrawal due to early ADR and/or treatment failure.

Methods: Between October 1999 and August 2008 serum samples were collected from 218 Danish patients with RA (80% females, median age = 56 years, disease duration = 10.1 years, 65% RF positive, median DAS28(CRP) = 5.0 (IQR =4.2–5.9)) who initiated treatment with infliximab according to national guidelines. The levels of anti-infliximab antibodies (AB) were determined pre-infusion at baseline (week 0), weeks 6 and 14 (or at withdrawal) by the IMPACT Indirect Assay (Roche Diagnostics). Based on 100 blood donors and all 218 baseline samples, a preliminary cutoff for the assay was defined. A sample was considered positive (AB+) if the signal was at least two fold above the highest signal seen in any blood donor or baseline sample, otherwise as negative (AB-).

Clinical assessments were performed at weeks 0, 2, 6, and then every 8th week until termination of treatment. Clinical evaluation (including tender and swollen joint counts (28 joints), CRP, DAS28(CRP) score, and reason for withdrawal) was obtained from the DANBIO Registry. ADR was defined as any adverse event leading to withdrawal of infliximab treatment. Lack of efficacy (LOE) was defined as withdrawal due to high disease activity despite adequate treatment.

Results: In total 28 (13%) patients withdrew due to ADR before week 50 and 46 (21%) due to LOE (median DAS28 4.9 (IQR= 4.35 – 5.65)). Among patients withdrawn due to ADR, 18 withdrew due to infusion reactions. At week 6, 31 patients were AB+, and 15 (48%) of those withdrew due to ADR before week 50. Only 12 (13%) of the 94 AB- patients at week 6 withdrew due to ADR before week 50. Compared to AB- patients, the AB+ patients had a HR of ADR of 5.06 at week 6 ($p<0.0001$), see Table. Patients who withdrew due to infusion reaction were primarily AB+ at week 6 (n=15; 83%). After 14 weeks of treatment, 43 patients were AB+ and 16 (37%) of those withdrew due to ADR before week 50. Compared to AB- patients, the AB+ patients had a HR of ADR of 3.30 at week 14 ($p=0.0009$), see Table. There was no association between development of AB at week 6 and 14 and withdrawal due to LOE, see Table.

	Reason for withdrawal	
	ADR	LOE
Week 6	31/15 vs. 94/12*	27/11 vs. 112/31*
	5.06 (2.36–10.84), p < 0.0001#	1.70 (0.85–3.38), p = 0.13#
Week 14	43/16 vs. 88/12*	40/13 vs. 109/33*
	3.30 (1.56–6.99), p = 0.0009#	1.17 (0.62–2.29), p = 0.63#

*: Number of AB+/withdrawals vs. AB−/withdrawals
#: Hazard Ratio (95% CI), p-value

Conclusions: Early development of antibodies against infliximab predicted withdrawal due to adverse drug reactions in patients with RA within the first year of infliximab treatment. The findings suggest that anti-infliximab antibody measurement 6 weeks after start of treatment represents a promising approach to identify which RA patients that are at increased risk of developing adverse drug reactions.

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Effect of Switching Anti–Tumor Necrosis Factor Agents on Clinical Outcomes for Patients with Rheumatoid Arthritis. Amir Goran[2], Sanjoy Roy[1], Marco DiBonaventura[2], Jochen Ertl[2] and Mary Cifaldi[1]. [1]Abbott Laboratories, Abbott Park, IL, [2]Kantar Health, New York, NY

Background and Purpose: Tumor necrosis factor antagonists (anti-TNFs) have led to better management of rheumatoid arthritis (RA), and their efficacy is well-established for patients who have failed disease-modifying antirheumatic drugs (DMARDs). The utility of switching to a second anti-TNF agent, after the first fails, is therefore a topic of immense clinical interest. We assessed outcomes of switching from 1 anti-TNF agent to another on a range of clinical measures.

Methods: Data were extracted from medical charts of patients with RA who were treated with an anti-TNF agent and then switched to a second biologic DMARD by rheumatologists in the United States. Outcomes frequently used in clinical practice were assessed: swollen and tender joint counts (SJC and TJC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and physician-reported severity. Mixed models assessed improvements over time, from initiation to discontinuation of the first and then the second anti-TNF agent, controlling for age, sex, time on and between treatments, years since diagnosis, concomitant use of methotrexate, psychiatric comorbidity, and Charlson Comorbidity Index. Subgroups were also analyzed by reason for switching in the following order: lack of/inadequate response to the first agent, side effects/tolerability issues, or other reasons (eg, compliance or cost).

Results: Data were analyzed for 399 patients with RA who switched to a second biologic agent after a mean (SD) of 1.6 (1.7) years on the first therapy. Of 215 who switched to a second anti-TNF agent, 148 switched for lack of/inadequate response, 31 for intolerability, and 36 for other reasons. Mean age was 51.3 years, mean RA duration was 6.5 years, 71.2% were women, and 80.9% were white. After failure on the first anti-TNF agent, patients treated with a second anti-TNF agent for a mean (SD) of 1.3 (1.6) years achieved overall improvements of 65.6%, 69.5%, and 25.5% for TJC, SJC, and severity, respectively (all $p<0.001$); improvements were significantly greater with the second anti-TNF agent compared with the first. CRP (54.2%) and ESR (46.5%) showed similar overall improvements (both $p<0.001$), but there was no difference before and after switching to the second anti-TNF agent. Continued improvement after switching anti-TNF therapies was observed for all patients, except for those who switched due to other reasons. For patients who switched due to inadequate response, significantly greater improvement on all measures was observed during therapy with the second anti-TNF agent compared with the first, whereas the intolerability group experienced steady and significant improvements on both the first and second anti-TNF agent.

Conclusions: For patients with RA who failed a first anti-TNF agent, including those who failed because of lack of response or tolerability issues, significant improvements on SJC, TJC, ESR, CRP, and disease severity were observed after switching to a second anti-TNF agent. Overall improvements were similar or better than those observed in most randomized, controlled trials of an anti-TNF agent as the first biologic therapy, thus demonstrating the value of switching to a second anti-TNF when the first fails.

Disclosure: A. Goran: Kantar Health (contractor for Abbott), 3; **S. Roy:** Abbott Laboratories, 1, 3; **M. DiBonaventura:** Kantar Health (contractor for Abbott), 3; **J. Ertl:** Kantar Health (contractor for Abbott), 3; **M. Cifaldi:** Abbott Laboratories, 1, 3.

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Efficacy and Safety of Ocrelizumab in Patients with Active Rheumatoid Arthritis Who Had an Inadequate Response to Methotrexate: Results from the Phase III STAGE Trial. William F. C. Rigby[2], Hans Peter T. Tony[7], Kurt R. Oelke[5], Bernard G. Combe[8], Andrew J. Laster[1], Helen Travers[6], Carlos A. Von Muhlen[4], Elena Fisheleva[6], Carmen Martin[6] and Wolfgang Dummer[3]. [1]Arthritis & Osteoporosis Consultants of the Carolinas, Charlotte, NC, [2]Dartmouth Medical School, Lebanon, NH, [3]Genentech Inc, San Francisco, CA, [4]Pontifical Catholic University of Rio Grande do Sul, Porto Alegre, Brazil, [5]Rheumatic Disease Center, Glendale, WI, [6]Roche, Welwyn Garden City, UK, [7]Universitätsklinikum Würzburg, Wuerzburg, Germany, [8]Université Montpellier, Montpellier, France

Purpose: B-cell targeted therapy using anti-CD20 antibodies has demonstrated clinical benefit in patients (pts) with rheumatoid arthritis (RA). This phase III study investigated the efficacy and safety of ocrelizumab (OCR), a humanized anti-CD20 antibody, + methotrexate (MTX) vs MTX alone in pts with active RA who have had an inadequate response to MTX.

Methods: STAGE was a phase III, international, randomized, placebo (PBO)-controlled, parallel-group study, consisting of a 48-wk double-blind PBO-controlled period and open-label extension. A total of 1015 pts with active RA (revised 1987 ACR criteria) with SJC ≥4, TJC ≥4, CRP ≥0.6 mg/dL, RF+ and/or anti-CCP+, and on stable MTX (7.5–25 mg/wk) were randomized (1:1:1) to PBO (n=324), OCR 200 mg × 2 (n=344), or OCR 500 mg × 2 (n=347). Pt baseline characteristics were generally well balanced between treatment groups (means: age 51 yr; SJC 17; TJC 27; CRP 2.4 mg/dL; DAS28 6.4; RA duration 7.4 yr). Two OCR/PBO courses (each consisting of 2 infusions given 14 days apart) were given at days 1/15 and wks 24/26, with methylprednisolone 100 mg iv as premedication. Co-primary endpoints were ACR20 response at wk 24 and at wk 48. Secondary endpoints included change in van der Heijde-modified total Sharp score (mTSS) and ACR50/70 responses at 24 and 48 wks. Pts were allowed to continue the same corticosteroid dose from baseline.

Results: Key efficacy and safety data are shown in Table 1.

	PBO (n=319)	OCR 200 mg x 2 (n=343)	OCR 500 mg x 2 (n=343)
Efficacy[a], %			
Wk 24			
ACR20	35.7	56.9 (p<0.0001)	54.5 (p<0.0001)
ACR50	16.3	31.8 (p<0.0001)	31.2 (p<0.0001)
ACR70	5.6	14.3 (p=0.0002)	12.2 (p=0.0023)
Wk 48			
ACR20	27.6	58.3 (p<0.0001)	62.1 (p<0.0001)
ACR50	12.9	39.9 (p<0.0001)	36.7 (p<0.0001)
ACR70	6.6	20.7 (p=0.0001)	22.4 (p=0.0001)
Radiographic[b]			
Mean change in mTSS, 48 wks	1.74	0.26 (p<0.0001)	-0.03 (p<0.0001)
Safety 48 wks, pts with at least one event (%)			
	[n=320]	[n=343]	[n=343]
AEs	79.4	82.2	83.7
SAEs	11.6	7.6	11.1
Infections	54.1	54.8	56.6
SIEs	3.1	3.2	6.1
IRRs	9.7	20.1	23.3
Serious IRRs	0	0.3	0.6
Deaths, n	1	0	3
Serious infection rates			
Total pt-years	287.08	310.59	311.88
Serious infections[c]	10	11	27
Serious infections/100 pt-yrs (95% CI)	3.48 (1.67, 6.41)	3.54 (1.77, 6.34)	8.66 (5.71, 12.60)

All comparisons (OCR vs PBO) using Cochran-Mantel-Haenszel test, stratified for rheumatoid factor (RF) status and region (US/RoW).
[a]Missing data set to non responder.
[b]Van Elteren test: mITT (pts with 1 BL and at least 1 post-BL X-ray): n=305 for PBO, n=322 for OCR 200 mg x 2, and n=329 for OCR 500 mg x 2. Missing data were extrapolated/interpolated.
[c]Multiple occurrences of the same event in one individual counted multiple times.

Both OCR doses showed statistically significant improvements (vs PBO) in ACR20/50/70 at wks 24 and 48. At wk 48, both OCR doses showed statistically significant ($p<0.0001$) inhibition of progression of joint damage (PJD; change from baseline in mTSS) relative to PBO (85% and 100% inhibition for 200 mg and 500 mg, respectively). Frequency of AEs, serious AEs, and overall infections were comparable. Serious infectious events (SIEs) were reported with similar frequency with OCR 200 mg and PBO (pts with at least 1 SIE: 3.2% and 3.1%, respectively), but were more frequent with OCR 500 mg (6.1%). Two opportunistic infections were reported (1 *Mycobacterium kansasii* infection with OCR 200 mg; 1 fungal esophagitis infection with OCR 500 mg). Four deaths were reported (1 rheumatoid vasculitis with PBO; 3 [1 respiratory failure, 1 sepsis, 1 myocardial infarction] with OCR 500 mg).

Conclusions: Both OCR doses met the primary efficacy endpoints and significantly improved the signs and symptoms of RA at wks 24 and 48. The efficacy of both doses of OCR was generally comparable. Both OCR doses showed inhibition of PJD. More SIEs were reported with OCR 500 mg compared with OCR 200 mg and PBO.

Disclosure: W. F. C. Rigby: Genentech and Biogen IDEC Inc, 5, 8, Roche, 2, 5, 8; **H. P. T. Tony:** Abbott Laboratories, 8, Chugai, 8, ESSEX, 8, Roche, 2, 8, Wyeth Pharmaceuticals, 8; **K. R. Oelke:** None; **B. G. Combe:** Roche, 5, 8; **A. J. Laster:** Abbott Laboratories, 5, Amgen Inc., 5, Eli Lilly and Company, 5, Genentech and Biogen IDEC Inc, 5, GlaxoSmith-Kline, 5, Roche, 5; **H. Travers:** Roche, 1, 3; **C. A. Von Muhlen:** Roche, 2; **E. Fisheleva:** Roche, 3; **C. Martin:** Roche, 1, 3; **W. Dummer:** Roche, 1, 3.

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First Experiences with Pregnancies in RA Patients (pts) Receiving Tocilizumab (TCZ) Therapy. Andrea Rubbert-Roth[4], Philippe M. Goupille[1], Shahrzad Moosavi[3] and Antony Hou[2]. [1]Hopital Trousseau, Tours, France, [2]Inland Rheumatology Clinical Trials, Upland, CA, [3]Roche, Nutley, NJ, [4]University of Cologne, Cologne, Germany

Purpose: TCZ, an IL-6 receptor inhibitor, reduces signs and symptoms of RA and inhibits joint damage progression in RA pts. Women of childbearing potential were required to use a reliable contraception method in TCZ clinical trials. However, pregnancies did occur during TCZ use in clinical studies. TCZ has an FDA label of pregnancy category C (no adequate and well-controlled studies in humans; should be used in pregnant women only if potential benefit justifies potential risk to fetus). The purpose of this analysis was to describe pregnancies and their outcomes in RA pts receiving TCZ in clinical studies.

Methods: The analysis included all pregnancies reported in RA pts who received TCZ in one phase 1 study, five phase 3 trials (OPTION, TOWARD, RADIATE, AMBITION, LITHE), and 2 ongoing open-label extension studies (GROWTH95/96). Pts received 1 dose of TCZ 10 mg/kg in the phase 1 study, TCZ 4 or 8 mg/kg Q4W in phase 3 trials, and TCZ 8 mg/kg Q4W in extensions. Cutoff date was August 28, 2009.

Results: A total of 4009 pts (10,994 pt-years) were included. Thirty-three pregnancies were reported in 32 pts, despite a requirement for contraceptive use. All pts had received TCZ 8 mg/kg, except 1 pt who received TCZ 4 mg/kg. Of 32 pts, 26 received TCZ + MTX and 6 received TCZ monotherapy or a concomitant DMARD other than MTX. Most of the 32 pts conceived while using a condom as a primary or secondary contraception method followed by hormonal contraceptive. Some pts used more than one method. Two patients did not use any contraceptive method. Pt age at conception was 19 to 42 y; 10 were ≥35 y. In pts who continued their pregnancies, TCZ and MTX were stopped when the pregnancy was known. Thirteen of 33 pregnancies were therapeutically aborted, 7 (3 pts were ≥35 y) spontaneously aborted, and 11 resulted in term delivery. Outcome was unknown for 2 pregnancies (1 lost to follow-up; 1 outcome not confirmed). Of 7 spontaneous abortions, all occurred within ~2 months of conception; all pts received TCZ 8 mg/kg, and 5 received concomitant MTX at conception. Of 11 term deliveries, 10 were of healthy newborns (1 infant died of ARDS 3 days after emergency cesarean section for intrapartum fetomaternal hemorrhage due to placenta previa). All mothers who delivered to term had received TCZ 8 mg/kg; 9 had received concomitant MTX, and 2 had received TCZ monotherapy.

Conclusions: The amount of clinical trial data about pregnancy outcomes in women exposed to TCZ during pregnancy is limited. The low number of cases and the high rate of therapeutic abortions, as well as concomitant medication use, limit the conclusions that can be drawn regarding the safety of TCZ during pregnancy. Physicians should be aware of the pregnancy information in local prescribing information and advise women of childbearing potential to use reliable methods of contraception before initiating treatment with TCZ. Hormonal contraceptives are substrates of CYP450, and the effect of TCZ on the reliability of hormonal contraceptives is being assessed in a separate clinical trial. A pregnancy registry is being established to assess pregnancy outcomes in women exposed to TCZ during pregnancy.

Disclosure: A. Rubbert-Roth: Abbott Immunology Pharmaceuticals, 5, Chugai, 5, Essex, 5, Roche, 2, 5, 8, UCB, Inc., 5, Wyeth Pharmaceuticals, 2, 5; **P. M. Goupille:** None; **S. Moosavi:** Roche, 3; **A. Hou:** Abbott Laboratories, 8, Coviden, 8, Pfizer Inc, 8, Pricara, 8.

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Golimumab and Cardiovascular Disease Markers in Inflammatory Arthritides. Bruce Kirkham[3], Mary C. Wasko[8], Joan M. Bathon[4], Elizabeth C. Hsia[2], Roy M. Fleischmann[6], Mark C. Genovese[7], Eric L. Matteson[5], Hongjuan Liu[1] and Mahboob U. Rahman[2]. [1]Centocor Research and Development, Inc., [2]Centocor Research and Development, Inc./Univ. of Pennsylvania School of Medicine, Malvern, PA, [3]Guy's and St. Thomas' Hospital, London, United Kingdom, [4]Johns Hopkins Univ., School of Medicine, Baltimore, MD, [5]Mayo Clinic, Rochester, MN, [6]Rheumatology Associates, Dallas, TX, [7]Stanford University, Sunnyvale, CA, [8]Univ. of Pittsburgh

Purpose: To assess the effect of golimumab (GLM), a human anti-tumor necrosis factor (TNF) agent, +/− methotrexate (MTX), on serum lipid profiles and inflammatory markers associated with cardiovascular disease (CVD).

Methods: Serum lipids, including LDL subfractions and inflammatory CV markers (e.g., high sensitivity [hs]CRP, VEGF, ICAM-1, SAA, fibrinogen, IL-6) and markers of insulin sensitivity (fasting glucose, fasting insulin, HbA1c, HOMA-IR, QUICKI) were assessed in 2 phase 3 GLM trials in RA pts (MTX-naïve in GO-BEFORE and MTX inadequate responders [IR] in GO-FORWARD). Changes from baseline to wk14 or 24 were compared between the PBO+MTX (n=293) and combined GLM (50&100 mg)+MTX (n=496) groups (grps).

Results: In GO-FORWARD, total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels increased in the GLM+MTX compared with PBO+MTX grp, whereas atherogenic ratios (TC/HDL, LDL/HDL, Apo B1/A1) were not substantially changed. Favorable changes in LDL subfractions (increase in large, decrease in small LDL, increase in mean LDL particle size) were seen in GLM grps. In GO-BEFORE, increases in TC and LDL and favorable changes in LDL subfractions were seen in both the MTX and GLM

grps; in contrast, HDL increase and Apo B/A1 decrease were observed in GLM but not MTX grp. Most inflammatory CV markers improved significantly with GLM+MTX vs PBO+MTX in both studies (hsCRP and ICAM-1 shown in table as representative data). Markers of insulin sensitivity remained unchanged at wks14/24 in patients treated with GLM.

Conclusion: This is the first demonstration of favorable changes in LDL subfractions with anti-TNF therapy. Despite increases in TC and LDL, atherogenic indices remained stable and CV-related inflammatory markers improved with GLM treatment. These findings are consistent with published epidemiologic data suggesting, a beneficial effect of anti-TNF agents on CV events. No significant changes in insulin sensitivity parameters were observed.

Table. Median or median % changes

	Pbo + MTX		GLM 50 + 100 mg Combined + MTX		Median % change from baseline	
	BL	Wk 14/24	BL	Wk 14/24	Pbo + MTX	GLM (50 + 100) + MTX
GO-FORWARD (MTX-IR)						
LIPID MARKERS (mg/dL)						
Triglycerides	103.5	108.0	108.0	113.0	1.9	3.7
Total cholesterol	194.0	199.0	198.5	213.0###	1.0	8.4***
HDL	61.0	59.0	60.5	62.0###	0.0	5.4**
T chol/HDL	3.17	3.26	3.35	3.37#	1.90	2.78
LDL	107.5	111.0	112.0	121.0###	3.3	11.6**
LDL subfractions						
Mean LDL size (nM)	21.3	21.2	21.2	21.6###	0.0	1.0***
Large LDLs (mmol/L)	465.5	465.0	457.0	537.0###	3.4	21.5***
Small LDLs (mmol/L)	543.0	641.0	648.0	484.0##	4.3	−10.5***
ApoB/A1	0.52	0.54	0.57	0.54	−1.08	−3.78
INFLAMM. MARKERS						
hsCRP (mg/dL)	7.0	6.0	9.7	2.1###	−10.4	−70.7***
ICAM-1 (ng/mL)	340.0	320.0	340.0	296.0###	0.0	−12.2***
MARKERS OF INSULIN SENSITIVITY						
Fasting glucose (mg/dL)	85.0	85.0	83.0	86.0	2.44	1.26
Fasting insulin (uIU/mL)	8.0	9.0	10.0	10.0	2.33	−2.68
HbA1c (%)	5.6	5.6	5.7	5.5	0.0	−1.75
HOMA-IR	1.6	1.87	2.08	2.22	10.71	−2.26
QUICKI	0.15	0.15	0.15	0.15	−1.72	0.36
GO-BEFORE (MTX-naïve)						
LIPID MARKERS (mg/dL)						
Triglycerides	114.0	113.5	107.0	114.0	−2.0	4.1
Total cholesterol	193.0	199.0##	191.0	202.0###	4.0	4.1
HDL	58.0	56.0	57.0	59.0##	0.6	2.5
T chol/HDL	3.28	3.56#	3.37	3.34	4.8	0.79
LDL	109.0	116.0###	108.0	115.5##	6.3	2.7
LDL subfractions						
Mean LDL size (nM)	21.2	21.4##	21.2	21.5###	0.5	0.9
Large LDLs (mmol/L)	406.0	479.0##	464.5	544.0###	11.8	8.0
Small LDLs (mmol/L)	679.0	538.0	644.5	516.0###	−10.4	−16.9
ApoB/A1	0.56	0.59	0.58	0.53##	−2.0	−3.84
INFLAMM. MARKERS						
hsCRP (mg/dL)	13.4	4.5###	12.4	2.1###	−49.6	−71.7*
ICAM-1 (ng/mL)	338.0	330.0	345.0	300.0###	−0.7	−12.5***
MARKERS OF INSULIN SENSITIVITY						
Fasting glucose (mg/dL)	88.0	89.0	88.0	91.0	2.43	3.23
Fasting insulin (uIU/mL)	10.0	10.0	10.0	10.0	0.0	0.0
HbA1c (%)	5.7	5.7	5.7	5.6	−1.54	−2.90
HOMA-IR	2.3	2.07	2.2	2.04	7.50	−0.82
QUICKI	0.15	0.15	0.15	0.15	−1.20	0.13

#, ##, ###p ≤ 0.05, 0.01, 0.001, resp., for within-group change from baseline.
*, **, ***p ≤ 0.05, 0.01, 0.001, resp., GLM + MTX vs Pbo + MTX

Disclosure: B. Kirkham: Centocor Research and Development, Inc., 2, 9; **M. C. Wasko:** Centocor Research and Development, Inc., 2, 9; **J. M. Bathon:** Centocor Research and Development, Inc., 2, 9; **E. C. Hsia:** Centocor Research and Development, Inc., 3; **R. M. Fleischmann:** Centocor Research and Development, Inc., 2, 9; **M. C. Genovese:** Centocor Research and Development, Inc., 2, 9; **E. L. Matteson:** Centocor Research and Development, Inc., 2, 9; **H. Liu:** Centocor Research and Development, Inc., 3; **M. U. Rahman:** Centocor Research and Development, Inc., 3.

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Golimumab and Cardiovascular Disease: Carotid Artery Ultrasound Evaluation and Cardiovascular Adverse Events. Joan M. Bathon[5], Mary Chester Wasko[7], Bruce Kirkham[4], Pierre-Jean Touboul[6], Elizabeth C. Hsia[3], Weichun Xu[2], Jiandong Lu[1] and Mahboob U. Rahman[3]. [1]Centocor Research and Development, Inc., Malvern, PA, [2]Centocor Research and Development, Inc., [3]Centocor Research and Development, Inc./Univ. of Pennsylvania School of Medicine, Malvern, PA, [4]Guy's & St. Thomas' Hospital, London, United Kingdom, [5]Johns Hopkins University, Baltimore, MD, [6]Paris-Diderot University, London, United Kingdom, [7]University of Pittsburgh, Pittsburgh, PA

Objective: To evaluate the effect of golimumab on changes in ultrasound measurements of carotid arteries in an exploratory study of patients with rheumatoid arthritis (RA), and to evaluate cardiovascular (CV) adverse events (AEs) in 5 large randomized, controlled studies of golimumab in patients with RA, ankylosing spondylitis (AS), or psoriatic arthritis (PsA).

Methods: Carotid ultrasound measures were performed at baseline and weeks 24 and 52 in a subset of the GO-BEFORE study, in which patients with RA & naïve to methotrexate (MTX) were randomized to subcutaneous injections every 4 weeks of placebo (PBO) + MTX, golimumab 100 mg + PBO, golimumab 50 mg + MTX, or golimumab 100 mg + MTX. Common carotid artery (CCA) intima-media thickness (IMT), distensibility coefficient (DC), interadventitial (IA) diameter, and plaque counts were determined. CCA-IMT measurements were done by automated edge detection using M'ATH software. Carotid ultrasound analyses included only those subjects (n = 392) with a non-missing measurement at baseline and a follow-up time point. CV events reported as serious AEs by investigators (not adjudicated) from the GO-BEFORE, GO-FORWARD (RA), GO-AFTER (RA), GO-REVEAL (PsA), and GO-RAISE (AS) randomized, controlled studies, in which golimumab (50 mg and 100 mg) with or without MTX was compared with PBO with or without MTX, were compiled through week 100 or 104.

Results: In the ultrasound analyses (n = 77 to 96 per group), mean (±standard error) changes in CCA-IMT for the golimumab groups were not statistically significantly different from PBO + MTX except for the 100 mg + MTX group at week 24 and the 50 mg + MTX group at week 52, suggesting a trend of increase in CCA-IMT with golimumab treatment, albeit variable over time (Figure). There was a trend of improvement in DC in GLM + MTX groups; however, changes in DCs and IA diameters for the golimumab groups were not statistically significantly different from PBO + MTX. No changes were observed in the number of plaques detected. In the 5 golimumab studies, 639 patients received PBO (for 339 patient years [py]), 1245 patients received 50 mg (for 1626 py), and 1377 patients received 100 mg (for 2069 py). Sudden death, myocardial infarction, or stroke occurred in 2 patients on PBO (0.59 events per 100 patient-years [95% confidence interval: 0.07, 2.13]), 4 patients on 50 mg (0.25 [0.07, 0.63]), and 10 patients on 100 mg (0.48 [0.23, 0.89]). Ischemic CV events occurred in 4 patients on PBO (1.18 [0.32, 3.02]), 7 patients on 50 mg (0.43 [0.17, 0.89]), and 11 patients on 100 mg (0.53 [0.27, 0.95]).

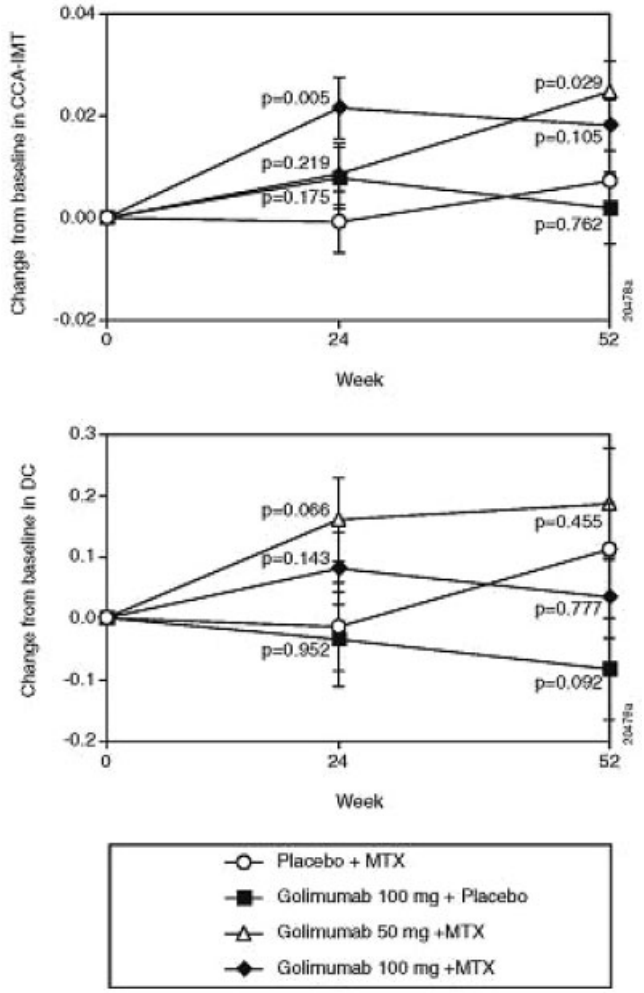

Figure. Changes (mean ± standard deviation) from baseline to weeks 24 and 52 in CCA-IMT and DC.

Conclusion: Changes in subclinical measures of CV disease in response to GLM +/− MTX over 52 weeks were variable, in that trends towards worsening

of CCA-IMT, but improvement in DC, were observed. Because patients receiving GLM did not appear to have an increased incidence of CV events through two years, the clinical relevance of the carotid ultrasound results are unclear.

Disclosure: J. M. Bathon: Centocor Research and Development, Inc., 2, 9; **M. C. Wasko:** Centocor Research and Development, Inc., 2, 9; **B. Kirkham:** Centocor Research and Development, Inc., 2, 9; **P.-J. Touboul:** Centocor Research and Development, Inc., 2, 9; **E. C. Hsia:** Centocor Research and Development, Inc., 3; **W. Xu:** Centocor Research and Development, Inc., 3; **J. Lu:** Centocor Research and Development, Inc., 3; **M. U. Rahman:** Centocor Research and Development, Inc., 3.

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Hepatitis B Virus Reactivation in Rheumatoid Arthritis and Ankylosing Spondylitis Patients Using Anti-TNFα Agents: A Retrospective Analysis of 52 Cases with or without Anti-Viral Prophylaxis. Han Hee Ryu[5], Eun Young Lee[5], Kichul Shin[4], In Ah Choi[5], Chul Kim[5], Yoon Jong Lee[5], Bin Yoo[7], Min-Chan Park[6], Yong-Beom Park[6], Sang-Cheol Bae[1], Wan Hee Yoo[3], Sung Il Kim[2], Jun Wan Kim[5], Eun Bong Lee[5] and Yeong Wook Song[5]. [1]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Korea, [2]Division of Rheumatology, Department of Internal Medicine Pusan National University Hospital Institutes, Busan, Korea, [3]Division of Rheumatology, Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine, Jeonju, Korea, [4]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea, Republic of, [5]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea, [6]Divsion of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea, [7]Divsion or Rheumatology, Department of Internal Medicine, University of Ulsan, Asan Medical Center, Seoul, Korea

Background: Anti-TNFα agents are widely used in the treatment of inflammatory arthritis such as rheumatoid arthritis (RA) and ankylosing spondylitis (AS). However, TNFα is also an important mediator contributing to the normal host immune response against infectious agents, in particular intracellular microorganisms. It is noteworthy that there are a number of case reports describing hepatitis B virus (HBV) reactivation in otherwise asymptomatic carriers under anti-TNFα treatment. Nevertheless, there is no established consensus describing whether this subset of patients would benefit from HBV anti-viral prophylaxis.

Objectives: To investigate the incidence and characteristics of HBV reactivation in HBsAg carriers with RA and AS after initiating anti-TNFα agents.

Methods: We retrospectively collected clinical data from 52 cases of HBsAg carriers with RA or AS who initiated anti-TNFα treatment at 7 centers nationwide. Periodic data of liver function tests and HBV DNA titers were utilized to assess HBV reactivation by 1) elevated HBV DNA level by ≥1 log10 compared with baseline, and 2) increase of AST or ALT above 2 times of the upper normal limit at the same period. YMDD mutation was checked in lamivudine-treated patients who developed HBV reactivation.

Results: Four patients were excluded from the analysis (three with high baseline transaminase, one died due to hepatocellular carcinoma). Among the 48 patients, 19 patients began anti-viral prophylaxis (14 lamivudine, 5 entecavir) with or shortly after starting anti-TNFα treatment. The remainder 29 patients without prophylaxis were treated with anti-viral agents if needed at the discretion of the clinician. The median duration of anti-TNFα treatment was 72 weeks in both groups. Of the 29 patients who did not receive primary prophylaxis, 2 patients (6.9 %) developed viral reactivation within a year of anti-TNFα treatment. In the prophylaxis group, 1 patient developed viral reactivation (5.2 %) at week 64 of anti-TNFα therapy. This single case of viral reactivation among the prophylaxis group was owing to YMDD mutation under lamivudine. There was not one case of reactivation in 5 patients who received entecavir as primary prophylaxis during the study period.

Conclusions: The rate of HBV reactivation in patients under anti-TNFα therapy without anti-viral prophylaxis was 6.9 % among the study population. Anti-viral prophylaxis did help preventing HBV reactivation, except for 1 case of YMDD mutation after using lamivudine. A larger prospective study is warranted to elucidate whether long-term anti-viral prophylaxis would be crucial in HBsAg carriers starting anti-TNFα treatment.

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Individual Dose Response Relation for MTX: Prediction of the Optimally Effective Dose in Patients with Early Rheumatoid Arthritis. Paco M. J. Welsing[1], Marije F. Bakker[2] and Johannes W. G. Jacobs[2]. [1]Rheumatology & Clinical Immunology and Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands, [2]Rheumatology & Clinical Immunology, University Medical Center Utrecht, The Netherlands

Background: In early RA, disease activity should be controlled as soon as possible. MTX is the DMARD of first choice and the dose is usually stepwise increased from a low (insufficient) dose until optimal disease control. Clinical intuition is that the optimally effective dose is different for each individual patient. The aim of this investigation was to determine the MTX dose needed for optimal response in individual patients and to explore whether this 'lowest optimally effective MTX dose (LOED)' and the level of disease activity reached can be predicted, to aid optimal MTX-based treatment.

Methods: Within the CAMERA trial the efficacy of a tight control and conventional MTX-based strategy in early RA were compared. Oral MTX was up-titrated from 7.5mg/wk until 30mg/wk (or maximal tolerable dose), if necessary. Per patient a power curve was fitted through the DAS28 measurements over time to control for natural variation in disease activity. Using the individual curves the highest MTX-dose which still resulted in a clinically relevant improvement in disease activity, defined as a decrease >0.15 DAS28 units per month, was determined.

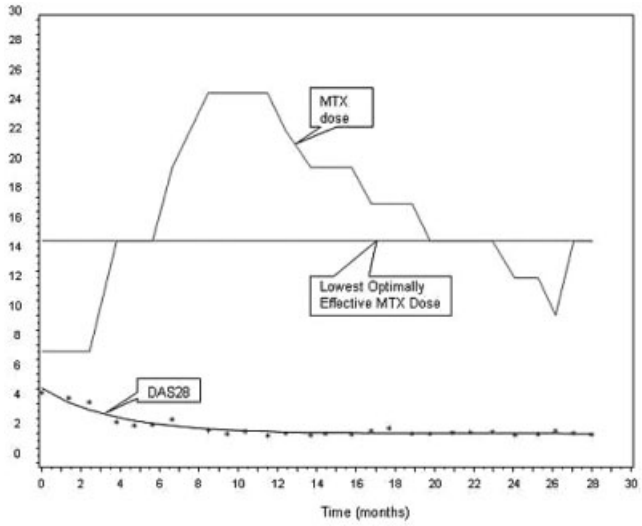

Figure 1. Shows an example of one patient's dose response curve and the LOED.

Using multinomial logistic regression the association of demographic and clinical characteristics at baseline with LOED was studied. Further, using linear regression, the association of demographic and clinical characteristics, including LOED, with the level of disease activity reached was investigated. All models were corrected for treatment strategy. A sensitivity analysis varying the definition of clinically relevant improvement was performed.

Results: For 290 of 299 patients a dose response curve could be estimated; the fit of the curves was found to be adequate. In 208 patients a LOED could be determined. The most common LOEDs were 7.5mg, 15mg, 20mg, and 25mg; higher LOEDs were found more frequent in the tight control strategy arm of the trial. Patients with a LOED of 7.5mg usually only showed an initial improvement in DAS28, probably due to 'regression to the mean'. The highest MTX dose reached was higher than the average LOED. Higher baseline disease activity and higher body height were predictive of higher LOEDs. A lower DAS28 reached was related to a higher LOED next to male gender and a lower DAS28 at baseline. Sensitivity analyses did not change these results.

Conclusion: Different 'optimally effective MTX doses' (after which no further clinically relevant improvement occurs) can be determined for different RA patients and might be predicted by

baseline patient and disease characteristics. The level of disease activity reached is related to this optimally effective MTX dose next to baseline characteristics. Usual dosing strategies with MTX monotherapy might result in over- and undertreatment. Based on these results, a starting dose of at least 15 mg/wk MTX might be a good choice.

Disclosure: P. M. J. Welsing: None; **M. F. Bakker:** None; **J. W. G. Jacobs:** None.

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Long-Term Effect of Anti TNF-Alpha Therapies on Insulin Resistance, Body Composition and Adipokines in Rheumatoid Arthritis Patients. Esmeralda Delgado-Frias[3], Vanesa Hernández-Hernández[2], Iván Ferraz-Amaro[1], Juan Carlos Quevedo[1], Jose R. Muñiz, Maria T. Arce-Franco, Judith Lopez-Fernandez, Andres Franco-Maside and Federico Diaz-Gonzalez. [1]La Laguna, S/C Tenerife, Spain, [2]La Laguna, S/C Tenerfe, Spain, [3]Hospital Universitario de Canarias, Tenerife, La Laguna, S/C Tenerife, Spain

Introduction: It has been suggested that tumor necrosis factor alpha (TNFalpha), a cytokine that plays a key role in rheumatoid arthritis (RA) pathogenesis, may act as a link between inflammation and cardiovascular disease apparently through several effects including the induction of insulin resistance (IR). The purpose of this study was to clarify if long-term modulation of inflammatory activity by TNFalpha inhibitors has some influence on insulin sensitivity, and if this effect is related to changes in body fat distribution, body composition, physical activity or levels of adipokines (cytokines secreted by adipocytes) in active RA patients.

Methods: Sixteen patients with RA (mean age 50.8±14.6 years, mean duration of disease 6.3±2.7 years) who were receiving anti-TNFalpha agents in addition to methotrexate because of active disease were followed up during one year. Disease activity was assessed by DAS28 (Disease Activity Score), IR was determined by using Homeostatic Model Assessment-2, body composition was evaluated by multifrequency bioelectric impedance analysis, physical activity by accelerometry, abdominal fat distribution by magnetic resonance imaging, and serum level of several key adipokines were quantified by ELISA. All examination and assessments were done at baseline (prior to TNF-alpha treatment) and after 3 and 12 months of treatment.

Results: Body mass indices had increased significantly after one year (25.7±3.2 vs 28.06±4.5 kg/m2, p=0.02) of treatment with anti-TNFalpha. Body composition in terms of fat and fat-free mass had not changed between visits except for a significant elevation of body cell mass (25.5±4.6 vs 26.6±3.1 kg, p=0.02). Values of visceral intraabdominal and subcutaneous abdominal adipose tissue were not modified due to treatment. In spite of a significant improvement in DAS28, patients' physical activity remained stable during the follow up. Basal levels of insulin resistance, beta cell function production or insulin sensitivity did not change along the study. Only insulin sensitivity exhibited a significant increase after 3 months (110[94–138] vs 118[107–156] %, p=0.045) but no longer by the end of the study. Basal levels of adiponectin, visfatin, leptin, ghrelin, resistin, and apelin did not change in response to anti-TNFalpha treatment; only retinol binding protein 4 showed a significant change (51.7±32.7 vs 64.9±28.4 μg/mL, p=0.03) at the end of the study.

Conclusions: Insulin resistance, adiposity, body composition, and adipokine serum levels are not significantly affected by long-term inhibition of TNFalpha in RA patients. Our findings question the suggested beneficial role of anti-TNFalpha treatments in insulin resistance.

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Long-Term Safety of Abatacept: Integrated Analysis of Clinical Program Data of up to 7 Years of Treatment. Marc C. Hochberg[7], Rene Westhovens[4], Richard Aranda[2], Sheila M. Kelly[2], Nadar Khan[2], Keqin Qi[2], Ramesh Pappu[2], Ingrid Delaet[2], Allison Luo[2], Anne Torbeyns[3], Larry W. Moreland[6], Roger B. Cohen[5], Sheila Gujrathi[2] and Michael E. Weinblatt[1]. [1]Brigham & Womens Hospital, Boston, MA, [2]Bristol-Myers Squibb, Princeton, NJ, [3]Bristol-Myers Squibb, Braine-l'Alleud, Belgium, [4]Catholic University of Leuven, Leuven, Belgium, [5]Fox Chase Cancer Center, Philadelphia, PA, [6]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [7]University of Maryland, Baltimore, MD

Background: Integrated analyses of clinical trial data are important to assess long-term (LT) safety and detect rare events. Here the authors present an integrated analysis of safety data from the abatacept RA clinical trial program up to December 2009, including 12,132 patient–years (p–y) of exposure.

Methods: Data from eight abatacept RA clinical trials were classified into short-term (ST) and LT periods and analyzed. ST data included six double-blind (6- or 12-month), placebo-controlled periods, one non-randomized Phase II study and one non-randomized Phase III study. The LT data included the open-label (OL) periods of these eight studies. Safety assessments, presented for all patients receiving ≥1 dose of abatacept, included adverse events (AEs), serious AEs (SAEs), mortality and events of clinical interest. Incidence rates (IRs) per 100 p–y with 95% CIs were calculated for the ST, LT and cumulative (ST+LT) periods.

Results: The cumulative period included 4149 patients with 12,132 p–y of exposure; 1165 had ≥5 years' exposure. Mean (range) exposure was 35.6 (1.9–104.2) months. The ST period included 3173 patients (2331 p–y) and the LT period included 3256 patients (9752 p–y). IRs for the ST, LT and cumulative periods are presented (Table). Annual IRs (95% CIs) per 100 p–y for SAEs did not increase with increasing abatacept exposure: Year 1, 19.13 (17.67–20.67); Year 2, 14.39 (12.80–16.11); Year 3, 12.82 (11.09–14.74); Year 4, 10.53 (8.76–12.57); Year 5, 10.18 (8.11–12.62); Year 6, 7.09 (4.54–10.55); Year 7, 8.90 (4.74–15.22). During the cumulative period, the IR (95% CI) of hospitalized infection was 2.64 per 100 p–y (2.35–2.95). The IRs (95% CIs) for the most common serious infections were; pneumonia: 0.46 (0.34–0.59); urinary tract infection: 0.20 (0.13–0.30); cellulitis: 0.18 (0.11–0.28). There were few opportunistic infections (0.36 [0.27–0.49]), with only eight cases of tuberculosis (0.07 [0.03–0.13]) observed overall. The IRs (95% CIs) for non-melanoma skin cancer and solid tumors in the cumulative period were 0.73 (0.58–0.90) and 0.59 (0.46–0.75) per 100 p–y, respectively.

Table. Safety events during the short-term, long-term and cumulative periods

		ST (n = 3173)	LT (n = 3256)	Cumulative (n = 4149)
P-y exposure		2331	9752	12,132
Deaths	Patients with event, n	12	60	73
	Incidence rate*	0.51 (0.27–0.90)	0.62 (0.47–0.79)	0.60 (0.47–0.76)
Overall SAEs	Patients with event, n	400	1086	1373
	Incidence rate*	18.15 (16.41–20.02)	14.31 (13.47–15.18)	14.61 (13.85–15.41)
Serious infections†	Patients with event, n	85	260	332
	Incidence rate*	3.68 (2.94–4.55)	2.79 (2.46–3.15)	2.87 (2.57–3.19)
Malignancies (excluding NMSC)	Patients with event, n	16	72	88
	Incidence rate*	0.69 (0.39–1.11)	0.74 (0.58–0.93)	0.73 (0.58–0.89)
Lung cancer	Patients with event, n	5	13	18
	Incidence rate*	0.21 (0.07–0.50)	0.13 (0.07–0.23)	0.15 (0.09–0.23)
Lymphoma	Patients with event, n	1	8	9
	Incidence rate*	0.04 (0.00–0.24)	0.08 (0.04–0.16)	0.07 (0.03–0.14)
Autoimmune events	Patients with event, n	48	NP	232
	Incidence rate*	2.07 (1.53–2.75)	NP	1.99 (1.74–2.26)
Acute infusional events‡	Patients with event, n	225	NP	377
	Incidence rate*	11.61 (10.14–13.22)	NP	3.90 (3.52–4.32)

*Data show incidence rates per 100 p-y (95% confidence interval); in only six studies ST period, n = 2368, period, n = 3755: ST = short term; LT = long term; SAE = serious adverse event; NMSC = skin cancer; NP = analyses not performed

Conclusions: The integrated safety data from 4149 patients with 12,132 p–y of exposure up to 7 years demonstrate that abatacept is generally well tolerated. No new safety events were identified over time, and the types and IRs of safety events (including events of clinical interest) in the LT and cumulative periods were generally consistent with those in the ST period, indicating that the abatacept safety profile remains stable with increasing duration of exposure.

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[2]Genovese MC, et al. *Ann Rheum Dis* 2008;**67:**547–54
[3]Westhovens R, et al. *Ann Rheum Dis* 2009;**68:**1870–7

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Long-Term Safety of Rituximab: Follow-Up of the Rheumatoid Arthritis Clinical Trials and Retreatment Population. Ronald van Vollenhoven[5], Paul Emery[2], Clifton O. Bingham[4], Edward C. Keystone[9], Roy M. Fleischmann[8], Daniel E. Furst[7], Katherine Macey[6], Marianne Sweetser[1], Patricia Lehane[6], Pam Farmer[3] and Simon G. Long[6]. [1]Biogen Idec Inc, [2]Chapel Allerton Hospital, Leeds, United Kingdom, [3]Genentech Inc, [4]Johns Hopkins University, Baltimore, MD, [5]Karolinska Institute, Stockholm, Sweden, [6]Roche Products Ltd, [7]University of California Los Angeles Medical School, Los Angeles, CA, [8]University of Texas Southwestern Medical Center, Dallas, TX, [9]University of Toronto, Toronto, ON, Canada

Objective: To evaluate the long-term safety of rituximab (RTX) in rheumatoid arthritis (RA) patients (pts) in clinical trials.

Methods: Pooled observed case analysis of safety data from pts treated with RTX plus methotrexate (MTX) in a global clinical trial program. Pts were offered RTX retreatment based on physician decision of clinical need and the criteria for retreatment included assessment of active disease (defined as either SJC and TJC ≥8 or DAS28 ≥2.6). Pts who received placebo during placebo-controlled study periods were pooled to provide a placebo population.

Results: As of September 2009, 3189 pts had been treated with RTX providing 9342 pt-yrs exposure. The analysis includes >9 yrs of follow-up with up to 15 courses of RTX. More than 1500 pts were followed for >3 yrs and 587 pts for >5 yrs with 1724, 1392, 1036 and 656 pts receiving ≥3, ≥4, ≥5 and ≥6 courses, respectively. Other than infusion-related reactions (IRR), the safety profile of RTX was similar to the placebo population or general RA populations. In the RTX group, the most frequent adverse event (AE) was IRR; most were CTC grade 1 or 2 and occurred after the first infusion of the first course (23.0%), with 0.5% considered serious (over all courses). Rates of serious AEs (SAEs) and infections generally remained stable over time and over multiple RTX courses, and in patients in long-term follow-up (>5 yrs).

	All exposure (n = 3188) 9342 pt-yrs	Long term (>5 yrs) (n = 587) 3386 pt-yrs	Pooled placebo (n = 818) 575 pt-yrs
AE rate/100 pt-yrs (95% CI)	309.4 (305.9–313.0)	285.1 (279.5–290.9)	353.1 (341.5–365.0)
SAE rate/100 pt-yrs (95% CI)	16.2 (15.4–17.0)	15.5 (14.2–16.9)	15.5 (13.2–18.2)
Infection rate/100 pt-yrs (95% CI)	94.3 (92.3–96.3)	83.2 (80.2–86.3)	100.8 (94.7–107.3)
Serious infection rate/100 pt-yrs (95% CI)	4.35 (3.94–4.79)	3.19 (2.64–3.85)	4.29 (3.17–5.80)

The overall serious infection rate was 4.35 events/100 pt-yrs (3.19 events/100 pt-yrs in pts treated for >5 yrs) and was comparable to that observed in the placebo population (4.29 events/100 pt-yrs). The most frequent serious infections were of the lower respiratory tract, predominantly pneumonia (2%). Serious opportunistic infections were rare with the rate comparable to the placebo population (0.04/100 pt-yrs in RTX all exposure compared to 0.1/100 pt-yrs in pooled placebo). Rates of myocardial infarction (0.49 events/100 pt-yrs) and stroke (0.25 events/100 pt-yrs) were consistent with rates in the general RA population (0.34–0.59 events/100 pt-yrs and 0.112–0.76 events/100 pt-yrs, respectively).[1–4]

Conclusions: In long-term follow-up of RA pts treated with RTX in clinical trials, no new safety signals were observed in all exposed pts, or in pts with >5 yrs exposure. RTX has remained generally well tolerated over time and over multiple courses, with a safety profile similar to that of the pooled placebo population and consistent with published data on pts with moderate to severe RA.

1. Pharmetrics Claims Database, 2006.
2. British Society for Rheumatology Biologics Register, 2007.
3. Nurses' Health Study, 2003.
4. General Practice Research Database, 2003.

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Low-Dose Glucocorticoid Chronotherapy of Rheumatoid Arthritis: 12 Week Efficacy and Safety of Modified-Release (MR) Prednisone. Frank Buttgereit[2], Daksha P. Mehta[3], John R. Kirwan[1], Jacek Szechinski[7], Maarten Boers[12], Rieke Alten[10], Jerzy Supronik[8], István Szombati[9], Ulrike Römer[4], Stephan Witte[5], Amy Grahn[6] and Kenneth G. Saag[11]. [1]Bristol Royal Infirmary, Bristol, United Kingdom, [2]Charite University Med-Berlin, Berlin, Germany, [3]Ctr Arthritis & Osteoporosis, Elizabethtown, KY, [4]Horizon Pharma GmbH, Mannheim, Germany, [5]Horizon Pharma GmbH, Mannheim, Germany, [6]Horizon Pharma, Inc., Northbrook, IL, [7]Med. University Dept. of Rheumatology, Wroclaw, Poland, [8]NZOZ Centrum Medyczne, Bialystok, Poland, [9]OEC, Budapest, Hungary, [10]Schlosspark-Klinik, UnivMed, Berlin, Germany, [11]University of Alabama-Birmingham, Birmingham, AL, [12]VU University Medical Center, Amsterdam, The Netherlands

Background: In patients with rheumatoid arthritis (RA), nocturnal increases in proinflammatory cytokines are implicated in the typical early morning symptoms, joint stiffness and pain. Glucocorticoid (GC) chronotherapy with a novel modified-release (MR) prednisone tablet enables delivery of prednisone during the night to specifically target the nocturnal rises in inflammatory mediators and symptoms. This novel approach has shown clinically relevant reduction of morning stiffness (MS) compared to conventional, immediate-release (IR) prednisone, thereby improving the benefit-risk ratio of GC therapy. Here we present efficacy and safety data of low-dose prednisone chronotherapy in patients with RA, not adequately controlled by disease-modifying antirheumatic drug (DMARD) therapy.

Methods: In this 12-week, double-blind, placebo (PBO)-controlled study, patients (n=350) were randomized 2:1 to receive MR prednisone 5 mg or PBO once daily in the evening in addition to their standard RA therapy. The primary endpoint was the percentage of patients achieving a 20% improvement in RA signs and symptoms according to American College of Rheumatology criteria (ACR20) at week 12. A key secondary objective was the relative reduction of MS at week 12. Secondary efficacy endpoints included ACR50 and ACR70 responses, and other measures of clinical efficacy, inflammatory markers, adverse events (AEs) and other safety parameters.

Results: Compared to PBO + DMARD, MR prednisone + DMARD treatment produced a higher ACR20 response (48.5% vs 28.6%, P<0.001), a higher ACR50 response (22.7% vs 9.2%, P<0.003) and ACR 70 response (7.0% vs 2.5%, P<0.1) at week 12. Greater improvements were also seen in morning symptoms and in individual RA core set measures in the MR prednisone group vs. PBO group at week 12. The incidence of adverse events (AEs) on MR prednisone was similar to PBO (43% vs 49%), with more AEs related to RA signs and symptoms (arthralgia and RA flare) in the PBO arm than in the MR prednisone arm (29.4 % vs 16.9 %). There were no clinically relevant differences between treatment groups in vital signs, hematology, biochemistry values or in markers for bone turnover, osteocalcin and urine CTX I.

Conclusion: Even at 5 mg per day, low-dose prednisone chronotherapy is effective in the treatment of signs and symptoms of RA with a short-term safety profile similar to placebo.

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Metanalysis on the Effect of TNF-Inhibitors on Lipid Profile. Claire Immediato Daien[1], Yohan Duny[3], Thomas Barnetche[2] and Jacques Morel[1]. [1]Département de Rhumatologie, Hôpital Lapeyronie, Montpellier, France, [2]Département de Rhumatologie, Hôpital Pellegrin, Bordeaux, France, [3]Institut Universitaire de Recherche Clinique, Service de Biostatistiques, Epidémiologie et Santé Publique, Montpellier, France

Background: Patients with Rheumatoid arthritis (RA) have an increased risk for cardiovascular diseases. Lipidic changes related to inflammation have been described in RA. TNF inhibitor (TNFi) therapy is an effective treatment that controls inflammation.

Objective: To assess modification of lipid levels after initiation of TNFi in RA patients.

Methods: The search strategy used Medline database until March 2010 and abstracts of 2009 EULAR/ACR congress. The Mesh terms used were: ("Lipids"[Mesh] OR "Dyslipidemia"[Mesh]) AND "Arthritis, Rheumatoid-"[Majr:NoExp] AND ("TNFR-Fc fusion protein"[Substance Name] OR "infliximab"[Substance Name] OR "adalimumab"[Substance Name] OR "anti-TNF"). Values of total cholesterol (TC), LDL, HDL, triglycerides (TG), atherogen index (AI), and apoB/A were collected before and after TNFi initiation. Three time-points were defined as following: short term from 2 weeks to 2 months, mid-term at 3 months and long term from 6 to 12 months. Paired-data statistic analysis was performed with the logiciel Comprehensive Metanalysis®. Standardized mean differences were obtained using fixed or random effects model (Peto and Dersimonian & Laird method respectively). Random effects model was used when there was evidence of heterogeneity. The percentage of variability beyond chance was estimated using the I^2 statistic. Publication biais was assessed using the Egger's test. The Trim and Fill Analysis for publication biais was performed using Duval and Tweedie's method.

Results: The search led to 31 articles and 1 ACR abstract. Sixteen articles were excluded as they were out of topic or reviews/comments. Three other articles were also excluded because of missing p-values and/or confidence intervalls. Thus, 13 studies were included for the different meta-analyses. Ten of them included patients only treated with monoclonal antibodies, 1 with etanercept and two with respectively 47 and 21% of soluble receptors. The follow-up varied from 2 weeks to 2 years. TNFi were found to increase HDL levels at short term (+0.4 mmol/L; CI95% 0.3–0.5; p<0.0001; I2 4.4%), mid-term (+0.4 mmol/L, CI95% 0.2–0.6; p<0.0001; I2 0%) and long term (+0.3 mmol/L; CI95% 0.1–0.4; p<0.0001; I2 36%) as well as TC (short term: +0.4mmol/L; CI95% 0.3–0.5; p<0.0001, I2 0%; mid-term: +0.2 mmol/L; CI95% 0.1–0.3; p=0.002; I2 34%; long term: +0.2; CI95% 0.0–0.3; p=0.02; I2 25%). At short term, LDL levels were also increased (+0.4mmol/L; CI95% 0.3–0.6; p<0.0001; I2 0%) but not at mid-term (p=0.88; I2 55%) or long term (p=0.83; I2 72%). AI did not variate at short (p=0.3; I2 38%) and long term (p=0.3; 47%). TG levels increased at short term (+0.2; CI95% 0.0–0.3; p=0.009, I2 0%) and long term (+0.2; CI95% 0.1–0.3; p=0.03; I2 55%). ApoB/A tended to decrease at mid-term (−0.1; CI95% −0.3–0.0; p=0.08; I2 50%) and decreased at long term (-0.3 mmol/L; CI95% −0.5 –0.1; p<0.0001; I2 0%). No publication biais were found except for 4 analyses. These analyses remained significant after performing Duval and Tweedie method.

Conclusion: Initiation of TNFi led to a persistant increase of TC and HDL. LDL and AI remained unchanged at long term. TG were increased and apoB/A decreased at long term after initiation of TNFi.

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Methothrexate Directly Inhibits RANKL Expression and Osteoclasts Formation in Very Early Arthritis. Shankar Revu, Petra Neregård, Erik Afklint and Anca Irinel Catrina Department of Medicine, Rheumatology Unit, Karolinska University Hopsital and Karolinska Institute, Stockholm, Sweden

Objective: Methotrexate (MTX) is one of the most widely used therapies in rheumatoid arthritis (RA). However, in the long term, patients treated with methotrexate may experience joint deterioration and subclinical inflammation even after clinical remission. Bone biology is governed by the RANKL/RANK/OPG system that determines the balance between bone formation by osteoblasts and bone resorbtion by osteoclasts. Herein we investigated MTX effects on the RANKL/RANK/OPG system in vivo and in vitro.

Methods: 16 patients with newly diagnosed RA (mean disease duration 1 week) were started on MTX 10 mg once a week and increased with 10 mg each week until a stable dose of 20 mg once a week was reached. Patients were naïve for other disease modifying anti rheumatic drugs. Synovial biopsies were obtained by needle arthroscopy at baseline and 8 weeks after initiation of therapy. X-ray of hands and feet were obtained at baseline and 1 year after diagnosis. Immunohistochemical analysis was performed to detect RANKL, RANK and OPG in the synovial biopsies. We further investigated the in vitro effect of MTX on synovial fluid derived mononuclear cells, SFMC (by immunohistochemistry), osteoblasts (by rtPCR and Western blot) and osteoclasts formation (tartrate-resistant acid phosphatase staining and dentine pit formation assay). Statistical analysis was performed using the Wilcoxon and Mann Whitney test when appropriate.

Results: 9 patients (56%) were responders to therapy according to EULAR criteria. 2 patients were having erosions at inclusion and 5 more developed erosions at 1 year follow-up in both the responder and non responder group. MTX treatment decreased synovial inflammation with a significant reduction of synovial cellularity. In parallel MTX decreased synovial RANK expression and the RANKL/OPG ratio, mainly in the subgroup of RA patients with no radiological progression at 1 year follow up. We confirmed the effect on RANK expression in SFMC cultured in vitro with MTX. A decrease of the RANKL/OPG ratio was also observed in cultured osteoblasts as demonstrated both at the mRNA and protein levels. MTX blocks osteoclastogenesis from PBMC despite presence of M-CSF and RANKL indicating that MTX directly inhibits osteoclastogenesis.

Conclusions: MTX directly affects the RANKL/RANK/OPG system and inhibits osteoclasts formation providing an explanation for the bone-sparing effect of MTX observed in a subgroup of RA patients.

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Non-Infectious Pulmonary Complications of Biologic Agents for Rheumatic Diseases—A Systematic Literature Review. Andreas Hadjinicolaou[2], Shweta Bhagat[1] and Andrew Ostor[1]. [1]Rheumatology Research Unit, Addenbrooke's Hospital, Cambridge, Cambridge, United Kingdom, [2]University of Cambridge, United Kingdom

Background: Systemic inflammatory diseases, such as rheumatoid arthritis (RA) as well as their treatment with disease modifying anti-rheumatic drugs (DMARDS) and anti-TNFα agents may be complicated by a variety of pulmonary disorders. Due to the influx of new biologic agents, we undertook this systematic literature review (SLR) to identify if any of these were associated with non-infectious lung disease.

Methods: A SLR was conducted in PubMed, the Cochrane Library and EMBASE for reviews, meta-analyses, randomized controlled trials(RCT), clinical trials, case series and reports published up to and including May 2010 using the terms "rituximab" "anakinra" "certolizumab" "golimumab" "tocilizumab" "abatacept" and "efalizumab" in the advanced search option. Search results were assessed by two independent reviewers. Meeting abstracts from the European League Against Rheumatism and the British Society of Rheumatology annual meetings were included. We manually reviewed references of all the selected publications to complement our search with published data not identified in the initial search or with unpublished data from the Food and Drug Administration (FDA), the European Agency for the Evaluation of Medicinal Products (EMEA) and manufacturers. Identified articles were included if they reported a possible relationship of biologic agents with lung toxicity, excluded other potential causes or failed to exclude drug-induced causality. A total of 9 RCTs, 15 clinical studies, 10 case series, 35 case reports were identified.

Results: This SLR revealed possible relationships between some biologic agents and interstitial lung disease (ILD) and other drug-related pulmonary toxicities. No cases of pulmonary toxicity were found with golimumab, certolizumab and efalizumab.

Rituximab(RTX) appeared to have a higher reported rate of ILD as we identified 65 papers reporting at least one case of pulmonary toxicity (148 cases in total). However, RTX was given for a rheumatic disease only in 7 of these studies. In 3 studies in RA and lupus, out of a total of 403 patients involved, there were 3 cases of lung toxicity (1 of ILD and 2 of interstitial

pneumonitis, 1 of which was fatal). 4 case reports of RTX (3 given for RA and 1 for lupus) reported 2 cases of Bronchiolitis Obliterans Organising Pneumonia and 2 of ILD with1 death.

3 RCTs of Tocilizumab enrolling a total of 589 patients reported 6 pulmonary adverse events (2 - ILD, 1 - allergic pneumonitis, 3 - interstitial pneumonia). There was 1 case report of fatal exacerbation of RA induced ILD with tocilizumab.

2 RCTs with a total of 1596 patients on Anakinra for RA refractory to DMARDS reported 3 cases of ILD with 2 fatalities.

In all the non-fatal cases, lung pathology was reversible with drug discontinuation and administration of high dose steroid treatment.

Conclusion: Although the number of reports of pulmonary complications with the newer biologic agents is small, the associated morbidity and mortality is substantial. Drug discontinuation is essential and treatment should be instituted expediously in order to optimise outcomes. Clinicians should remain vigilant for non-infectious pulmonary disease in any patient treated with biologic agents.

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Parenteral MTX as an Initial Treatment Strategy for Early Rheumatoid Arthritis: Results from a Nationwide Cohort. Vivian P. Bykerk[2], David S. Rowe[3], Janet E. Pope[5], CATCH Scientific Advisory Committee[1], Ashley Bonner[1] and J. Carter Thorne[4]. [1]Canada, [2]Mt Sinai Hospital, Toronto, ON, Canada, [3]Saba University School of Medicine, Stouffville, ON, Canada, [4]Southlake Regional Health Care, Newmarket, ON, Canada, [5]St Joseph Health Care London, London, ON, Canada

Background: Previous studies have established the value of prompt diagnosis and intervention in patients with Early Rheumatoid Arthritis (ERA). While there is a growing body of literature on parenteral administration of methotrexate (pMTX) at optimal doses (≥ 20 mg weekly) there is still no clear recommendation for a standard route and dosage. The Canadian early Arthritis Cohort (CATCH) is a multi-centre observational prospective "real world" cohort for patients with early inflammatory arthritis. With CATCH, there is an opportunity to evaluate the relative effectiveness of different therapeutic strategies in ERA.

Objectives: 1. Compare effectiveness of early optimal doses of pMTX (≥ 20 mg weekly within 100 days of baseline) with other treatment strategies

2. Assess achievement of clinical outcomes: a) DAS28-defined remission (DAS28<2.6) during 12 months; b) LDAS (DAS28<3.2) during 12 months; and "sustained remission" (CATCH target outcome of 2 consecutive visits with DAS28<2.6) at 6 and 12 months.

Methods: CATCH is a study of usual care in over 20 sites across Canada. Patients were selected from the available cohort (n = 898). Only those with baseline DAS28 scores ≥ 2.6 and available data at 6 and/or 12 months were chosen for analysis. At time of abstract submission, 593 patients were eligible. Patients receiving early optimal pMTX (n=126) and those receiving all other treatment regimens (n=467) were compared for achievement of clinical outcomes within the first year as above. Baseline clinical and demographic characteristics were evaluated and compared. Nonparametric analysis and binary logistic regression models were used to assess outcomes between groups.

Results: Patients receiving early optimal pMTX were more likely to achieve LDAS (67% vs. 52%) and DAS28 <2.6 (53% vs. 40%) within the first year ($p<0.05$). Patients in the early optimal pMTX group were also more likely to be on Combination DMARDs during this time ($p<0.01$). Parenteral MTX was found to be a significant predictor of good clinical outcomes in a binary logistic regression model. Baseline differences between groups were assessed - overall, patients on early optimal pMTX were more likely to have baseline predictors of poor clinical outcomes, though were less often seropositive at baseline (50% vs. 65%).

Conclusions: The data are compelling that pMTX ≥ 20 mg should be considered as 1st line therapy in ERA. Results will be reported with updated data at time of conference.

Disclosure: V. P. Bykerk: Amgen Inc., 2, Pfizer Inc, 2; **D. S. Rowe:** Roche, 9; **J. E. Pope:** None; **CATCH Scientific Advisory Committee:** None; **A. Bonner:** None; **J. C. Thorne:** None.

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Polymorphisms in the Folate Metabolism Gene MTHFR (C677T and A1298C) Are Not Associated with Methotrexate Adherence: Findings from the Veteran's Affairs Rheumatoid Arthritis (VARA) Registry. Lisa A. Davis[2], Grant W. Cannon[5], Roger Wolff[6], Leah Haverhals[3], Ted R. Mikuls[7], Andreas M. Reimold[1], Gail S. Kerr[8], John S. Richards[8], Dannette S. Johnson[4] and Liron Caplan[2]. [1]Dallas VAMC, Dallas, TX, [2]Denver VAMC, Aurora, CO, [3]Denver VAMC, [4]Jackson VAMC, Jackson, MS, [5]Salt Lake City VAMC, Salt Lake City, UT, [6]Salt Lake City VAMC, [7]Univ of Nebraska Med Ctr, Omaha, NE, [8]Washington, D.C. VAMC, Washington, DC

Background: Methylenetetrahydrofolate reductase (MTHFR) polymorphisms have been associated with specific toxicities of methotrexate (MTX) in rheumatoid arthritis patients. The most commonly studied polymorphisms MTHFR A1298C and C677T (CC and TT homozygotes respectively) have been associated with the occurrence of liver function abnormalities, alopecia, and headache, though other studies are equivocal. These polymorphisms are more common in Caucasians than in other ethnic groups. To examine whether these polymorphisms influence treatment, we studied the relationship of MTHFR A1298C and C677T genotypes with the MTX medication possession ratio (MPR), a measure of medication adherence.

Methods: Quantitative Real-Time PCR was used to genotype 1,054 randomly selected VARA registry participants for MTHFR A1298C and C677T polymorphisms. Patients' medication histories were abstracted from the VA Pharmacy Benefits Management (PBM) database to determine patients' MPR for MTX. Of the 1,054 subjects, MTX MPR data was available on 826. The average weighted MPR (awMPR, outcome variable) was calculated as the proportion of treatment time that the patient had drug available, weighted by course duration. Significant time gaps were defined as greater than 90 days. Linear regression was used to examine the associations of the MTHFR polymorphisms with MTX awMPR. Covariates included in the initial model were patient baseline demographics (age, race, education, co-pay requirements) and markers of RA activity and severity (mean DAS28, mean MDHAQ, aCCP status, nodules [ever], erosions [ever]). Model selection was based on a variation of the backward stepwise procedure that examined groups of conceptually-related variables simultaneously, with a p-value < 0.05 required for inclusion into the final model. The MTHFR A1298C and C677T homozygous genotypes were forced into the final model. A similar linear regression was performed restricted to Caucasian subjects.

Results: MTHFR A1298 and C677T homozygotes were 11.5% and 9.81% of the population, respectively. These MTHFR polymorphisms were not associated with MTX awMPR. In the linear regression model of all patients, older age was associated with an increase in awMPR (see table). In the model limited to Caucasians, no significant predictor of awMPR was found.

Conclusions: Although MTHFR polymorphisms may play a role in specific toxicities related to MTX, we found no evidence that MTHFR status influences patients' medication adherence.

Table. All participants

variable	univariate analysis				multivariate analysis			
	coef	p-value	95% CI		coef	p-value	95% CI	
Age, years	0.002	0.058	0.000	0.004	0.003	0.031	0.000	0.005
Education, years	0.008	0.133	−0.002	0.019	0.009	0.080	−0.001	0.020
Sex (male)	0.037	0.394	−0.047	0.120				
Caucasian	0.015	0.618	−0.043	0.072				
African-American	0.007	0.833	−0.059	0.073				
Hispanic	−0.044	0.453	−0.160	0.072				
Current tobacco	−0.013	0.647	−0.066	0.041				
Former tobacco	0.025	0.294	−0.022	0.073				
Never tobacco	−0.023	0.433	−0.081	0.035				
Average DAS	0.001	0.943	−0.019	0.021				
Average MDHAQ	0.001	0.943	−0.019	0.021				
Average pain score	−0.004	0.360	−0.012	0.004				
RF positive (ever)	0.007	0.846	−0.067	0.082				
anti-CCP positive (ever)	0.031	0.384	−0.039	0.100				
Rheumatoid nodules (ever)	0.009	0.737	−0.043	0.061				
Radiological changes (ever)	−0.006	0.831	−0.059	0.048				
Erosions (ever)	0.001	0.968	−0.053	0.055				
Disease duration, years	0.001	0.465	−0.001	0.003				
Medication copay required	−0.028	0.507	−0.112	0.056				
MTHFR 1298 CC	−0.036	0.347	−0.110	0.039	−0.060	0.191	−0.149	0.030
MTHFR677 TT	−0.006	0.890	−0.085	0.074	−0.025	0.607	−0.118	0.069

Disclosure: L. A. Davis: None; **G. W. Cannon:** None; **R. Wolff:** None; **L. Haverhals:** None; **T. R. Mikuls:** None; **A. M. Reimold:** None; **G. S. Kerr:** None; **J. S. Richards:** None; **D. S. Johnson:** None; **L. Caplan:** None.

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Pooled Analysis of Observational Studies on Lymphoma Incidence among Rheumatoid Arthritis (RA) Patients Initiating Etanercept Therapy. Peter McCroskery[2], Virgil C. Dias[2], Scott Stryker[3], Bojena Bitman[3], Sean Z. Zhao[2] and Debra J. Zack[1]. [1]Amgen Inc, Thousand Oaks, CA, [2]Amgen Inc., Thousand Oaks, CA, [3]Amgen Inc.

Background: There have been several studies suggesting an association between tumor necrosis factor (TNF) inhibitors, including etanercept, and the development of lymphoma in RA patients. Other studies have noted a 2- to 4-fold increase in reported lymphomas in biologic-naïve RA patients compared with the general population (Askling et al, Ann Rheum Dis 2009,68: 648–653), and suggested the increased risk may be attributable to the underlying disease, particularly in patients with chronic active disease. We now present a surveillance analysis of the incidence of lymphoma in patients conducted as a post-marketing commitment to the US Food and Drug Administration.

Methods: The data used in this analysis were from 2 Amgen-sponsored long-term extension studies in patients with late/early and early RA, 2 US registries (RADIUS 1/2) and 3 EU registries (BSRBR and RABBIT, which enrolled patients receiving any biologic drugs and conventional disease modifying antirheumatic drugs, and ARTIS, which enrolled patients receiving any biologic drug). Crude incidence rates and age- and sex-adjusted standardized incidence ratios (SIRs) of lymphoma were estimated based on total patient-years (pt-yrs) of follow-up (since first etanercept exposure) and total pt-yrs of etanercept exposure (through 30 days after last etanercept exposure) using country-specific lymphoma rates.

Results: This study collected data from 24,266 RA patients who accumulated a total 93,260 pt-yrs of observation since the first date of etanercept exposure. The mean exposure to etanercept was 2.7 years. Sixty-two lymphomas were reported, compared with the expected number of 27.3 from country-specific rates, yielding an overall SIR of 2.3 (95% confidence interval [CI]: 1.7 to 2.9), in the total follow-up period. The data from the etanercept exposure period yielded an SIR of 3.0 (CI: 2.3 to 3.9). Variability in the SIRs for lymphoma in the US studies and the EU registries was noted.

Studies	Total Pt-Yrs	Observed Count/ Expected Count	SIR (95% CI)
Lymphoma Incidence in Total Follow-up Period			
US Studies	28818	27/10.5	2.6 (1.7 to 3.9)
RADIUS I and II	21443	13/7.7	1.7 (0.9 to 2.9)
016.0018	4440	7/1.7	4.2 (1.7 to 8.6)
016.0023	2935	7/1.1	6.3 (2.5 to 13.0)
EU Registries	64442	35/16.8	2.1 (1.5 to 2.9)
BSRBR Registry	32427	26/9.1	2.9 (1.9 to 4.2)
RABBIT Registry	4177	1/0.9	1.1 (0.0 to 5.9)
ARTIS Registry	27838	8/6.8	1.2 (0.5 to 2.3)
Total	93260	62/27.3	2.3 (1.7 to 2.9)
Lymphoma Incidence in Etanercept Exposure Period			
US Studies	21218	21/7.6	2.8 (1.7 to 4.2)
RADIUS I and II	13869	10/4.8	2.1 (1.0 to 3.8)
016.0018	4427	6/1.7	3.6 (1.3 to 7.8)
016.0023	2921	5/1.1	4.5 (1.5 to 10.6)
EU Registries	43720	35/11.1	3.2 (2.2 to 4.4)
BSRBR Registry	19286	26/5.2	5.0 (3.2 to 7.3)
RABBIT Registry	4054	1/0.9	1.1 (0.0 to 6.3)
ARTIS Registry	20380	8/5.0	1.6 (0.7 to 3.2)
Total	64938	56/18.7	3.0 (2.3 to 3.9)

CI, Confidence interval; Pt-Yrs, Patient-Years

Conclusions: Overall, the data from the long-term Amgen extension studies and both US and EU registries appear to show a 2- to 4-fold increased risk of lymphoma in RA patients receiving etanercept, though there was variability in SIRs from different sources. This analysis, combined with the observation that the risk of lymphoma in biologic-naïve and biologic-exposed RA patients is similar, supports the interpretation that there is no additional risk for lymphoma in patients receiving etanercept above the already increased risk of lymphoma in RA patients.

Disclosure: P. McCroskery: Amgen Inc., 1, 3; **V. C. Dias:** Amgen Inc., 1, 3; **S. Stryker:** Amgen Inc., 1, 3; **B. Bitman:** Amgen Inc., 1, 3; **S. Z. Zhao:** Amgen Inc., 3; **D. J. Zack:** Amgen Inc., 1, 3.

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Post-Marketing Surveillance Program of Tocilizumab for RA in Japan – Interim Analyses of 3,881 Patients. Takao Koike[2], Masayoshi Harigai[8], Shigeko Inokuma[3], Naoki Ishiguro[6], Junnosuke Ryu[7], Tsutomu Takeuchi[5], Syuji Takei[4], Yoshiya Tanaka[10], Hisashi Yamanaka[9] and Kyoko Ito[1]. [1]Chugai Pharmaceutical Co.Ltd, [2]Hokkaido University, Japan, [3]Japanese Red Cross Medical Center, [4]Kagoshima University, Kagoshima City, Japan, [5]Keio University, Toyko, Japan, [6]Nagoya University, [7]Nihon University, [8]Tokyo Medical and Dental University, Tokyo, Japan, [9]Tokyo Womens Med Univ, Shinjuku-ku, Tokyo, Japan, [10]U Occupa & Environ Hlth, Kitakyushu, Japan

Purpose: An all-cases post-marketing surveillance (PMS) program has been implemented to investigate the safety and efficacy of tocilizumab (TCZ) in Japanese patients with rheumatoid arthritis (RA).

Methods: The PMS study has enrolled all patients with RA who were treated with TCZ in Japan after its launch in April 2008 with a tracking period of 28 weeks for each patient. All adverse events (AEs) and adverse drug reactions (ADRs) during the tracking period and disease activity score 28 (DAS28) at week 0 and week 24 were collected. AEs and ADRs were classified using MedDRA, ver11.1. The present analysis included 3,881 patients whose case report forms were completed by 15th July 2009.

Results: Baseline data of the patients were as follows: mean age, 58.5 y/o (range 16.0–87.0, 36.2% of them were ≥65 y/o); mean disease duration of RA, 10.7 yrs. (38.3% of them were ≥10 yrs); respiratory, cardiac, or hepatic comorbidities, 13.5%, 4.7%, or 4.5%, respectively; previous TNF inhibitors, 62.0%; concomitant methotrexate and glucocorticoid, 50.0% and 75.1%, respectively. Incidences of total and serious ADRs were 35.5% and 7.2%, respectively. The most frequent ADR and serious ADR were infection and infestation with an incidence of 9.6% and 3.4%, respectively. Among serious infections, bacterial pneumonia was the most frequently reported (1.4%). Regarding opportunistic infections, 4 cases of tuberculosis (3 pulmonary and 1 peritoneal tuberculosis) and 6 cases of *Pneumocystis jirovecii* pneumonia were reported. Logistic regression analysis identified risk factors for the development of serious infection (odds ratio, 95% confidence interval): presence of respiratory comorbidities (2.970, 1.959–4.502), higher prednisolone dose at the baseline (>5 mg/day) (2.297, 1.299–4.061), older age (≥65 y/o) (1.762, 1.170–2.651) and longer disease duration (>10 yrs.) (1.561, 1.032–2.361). The malignancies as AE were reported in 17 patients (0.4%) without any specific patterns. Gastrointestinal disorders were reported in 3.0% of cases with 5 cases (0.1%) of gastrointestinal tract perforations. All these patients recovered. Anaphylactic shock/reactions were reported in 8 patients (0.2%). Although dyslipidemia and elevated liver function tests were reported in 5.9% and 6.6% of the patients, respectively, these laboratory test abnormalities accompanied neither serious cardiovascular diseases nor serious hepatic disorders. Twenty-eight out of 3,881 patients died with causes of death in the following order of occurrence (expressed as a percentage): infection, 32%; respiratory disease, 20%; cardiovascular disease, 24%; cerebrovascular disease, 12%. The standardized mortality rate (SMR), with Japanese general population in 2008 as a control, was 1.66, which was similar to those reported in the Japanese cohort study [1].

Conclusions: The results from the interim analysis of the PMS study revealed that TCZ was well tolerated in the real world for Japanese patients with RA.

Reference

1. Nakajima A, et al. Mortality and cause of death in Japanese patients with rheumatoid arthritis based on a large observational cohort, IORRA. Scand J Rheumatol 2010;First article:1–8.

Disclosure: T. Koike: Abbott Immunology Pharmaceuticals, 5, 8, Bristol-Myers Squibb, 5, Chugai, 8, Eisai, 8, Mitsubishi-Tanabe, 8, Takeda Pharmaceuticals, 8, Wyeth Pharmaceuticals, 8; **M. Harigai:** Abbott Immunology Pharmaceuticals, 5, Bristol-Myers Squibb, 2, 5, Chugai, 2, 5, Eisai, 2, 5, Janssen Pharmaceutica Product, L.P., 5, Mitsubishi-Tanabe, 2, 5, Takeda Pharmaceuticals, 2, 5, Wyeth Pharmaceuticals, 2, 5; **S. Inokuma:** None; **N. Ishiguro:** Astellas, 8, Chugai, 8, Eisai, 8, Mitsubishi-Tanabe, 8, Takeda Pharmaceuticals, 8; **J. Ryu:** None; **T. Takeuchi:** Abbott Immunology Pharmaceuticals, 5, Astellas, 5, AstraZeneca, 5, Bristol-Myers Squibb, 5, Chugai, 5, Mitsubishi-Tanabe, 5, Pfizer Inc, 5, Wyeth Pharmaceuticals, 5; **S. Takei:** None; **Y. Tanaka:** Abbott Immunology Pharmaceuticals, 5, Astellas, 5, Chugai, 5, Eisai, 5, Mitsubishi-Tanabe, 5, Takeda Pharmaceuticals, 5; **H. Yamanaka:** Abbott Immunology Pharmaceuticals, 2, 5, Bristol-Myers Squibb, 2, 5, Chugai, 2, 5, Eisai, 2, 5, Hoffmann-La Roche, Inc., 5, Janssen Pharmaceutica Product, L.P., 2, 5, Mitsubishi-Tanabe, 2, 5, Otsuka Pharmaceutical, 2, 5, Takeda P; **K. Ito:** Chugai, 3.

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Predictive Risk Factors of Severe Infections in RA Patients Treated with Abatacept in Real Life: Results from the Orencia and Rheumatoid Arthritis (ORA) Registry. Jacques-Eric Gottenberg[11], Philippe Ravaud[5], Thomas Bardin[7], Patrice Cacoub[6], Aain Cantagrel[12], Bernard Combe[9], Maxime Dougados[3], René-Marc Flipo[8], Bertrand Godeau[4], Loic Guillevin[3], Eric Hachulla[8], Xavier Le Loët[10], Thierry Schaeverbeke[2], Jean Sibilia[11], Gabriel Baron[5] and Xavier Mariette[1]. [1]Bicetre Hospital, [2]Bordeaux Hospital, [3]Cochin Hospital, [4]Henri Mondor Hospital, [5]Hotel Dieu Hospital, [6]La Pitié Hospital, [7]Lariboisière Hospital, [8]LIlle Hospital, [9]Montpellier Hospital, [10]Rouen Hospital, [11]Strasbourg Hospital, [12]Toulouse Hospital

Objective: Little data is available regarding the rate and predicting factors of severe infections in patients with rheumatoid arthritis treated with abatacept (ABA) in daily practice. We therefore addressed this issue using real-life data from the "Orencia and Rheumatoid Arthritis" (ORA) registry.

Methods: ORA is an independent registry promoted by the French Society of Rheumatology dedicated to RA patients with abatacept. At baseline, 3, 6 months and every 6 months or at disease relapse, during 5 years, standardized information are prospectively collected by trained clinical nurses in each center. Central reviewing of charts of patients with SAEs is performed by the two coordinators of the study.

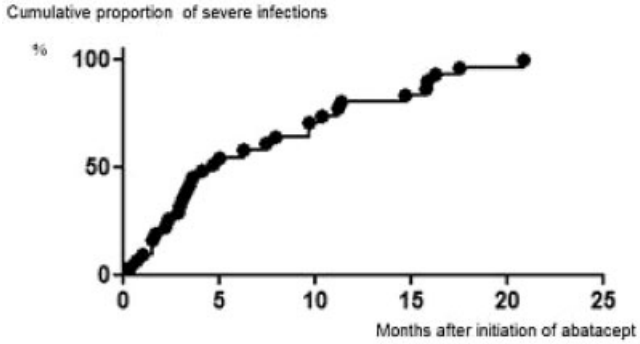
Results:

- Baseline characteristics and comorbidities

1036 patients (78.9% of women) were included. Median age of patients was 58 years and median disease duration was 12 years. 5.8% of patients had a history of cancer, 33.6% a record of severe infection, and 11.4% had diabetes. Follow-up was 557 patient/years on April 30th, 2010.

-Rate of severe infections

35 severe infections occurred, including 31 severe infections during treatment with ABA and/or within the 6 months following ABA discontinuation. Thus, 5.6 severe infections/100 patient-years were observed. No opportunistic infection was observed. Severe infections occurred after a median duration of 4.6 months (range: 2.4–11.2 months) after abatacept initiation.



- Predicting factors of severe infections

The analysis was carried out on the 709 patients who already had at least 1 follow-up visit (at least 3 months of follow-up). On univariate analysis, age, history of cancer, record of previous severe infections, diabetes, a higher number of previous synthetic DMARDs and a lower number of previous anti-TNF were associated with a higher risk of severe infection. Previous treatment with rituximab, disease activity or low IgG levels at initiation of abatacept were not significantly associated with an increased risk of severe infection. On multivariate analysis, history of cancer (OR 3.7 CI95% [1.0–13.9], P=0.05), record of severe infections (2.7 [1.1–6.7], P= 0.03) and diabetes (3.5 [1.3–9.7], P= 0.01) were significantly associated with a higher risk of severe infection.

Conclusion: In ORA registry, severe infections in patients treated with abatacept were slightly more frequent than in clinical trials. This might be related to the fact that a high proportion of patients with comorbidities, who would have been excluded from controlled trials, are treated with ABA in real life. The greatest risk of severe infections occurs within the first 6 months after ABA, as it was also reported with anti-TNF or rituximab. In patients treated with abatacept, predicting factors of severe infections include history of cancer, record of severe infections and diabetes.

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Pregnancy Outcomes in Patients with Autoimmune Diseases Treated with Rituximab. Eliza F. Chakravarty[1], Elaine Murray[2], Ariella Kelman[2] and Pamela Farmer[3]. [1]Mountain View, CA, [2]Genentech, South San Francisco, CA, [3]Genentech

Background: Rituximab is a monoclonal antibody to CD20 causing CD20+B-cell depletion. It is approved for treatment of adults with moderately-to severely-active rheumatoid arthritis (RA) with inadequate response to TNF antagonists, and has been studied in other autoimmune diseases. Despite counseling to avoid pregnancy, some women may become pregnant after rituximab treatment. Almost half of all U.S. pregnancies are unplanned, including those in women with underlying medical conditions. Data on pregnancy outcome following rituximab treatment is important when counseling women who inadvertently become pregnant, or are pregnant and need to assess therapeutic options for severe disease.

Methods: Utilizing the rituximab global drug safety database, we reviewed all reports of pregnancy following rituximab use (spontaneous reporting or during clinical trials) among women treated for autoimmune conditions (RA, systemic lupus erythematosus (SLE), idiopathic thrombocytopenia purpura (ITP), and multiple sclerosis). Patients may have received concomitant treatment with known teratogens and abortifacients such as methotrexate.

Results: Of 172 pregnancy reports identified through February 2010, 16 were ongoing, 11 reported paternal exposure, and 40 did not report pregnancy outcomes. Eight patients received rituximab during an established pregnancy for the treatment of profound autoimmune hematologic disease. Of the 105 reports with known outcomes, 56 (53%) resulted in live births, 27 (26%) in spontaneous abortion, and 20 (19%) pregnancies were terminated. One maternal death occurred from an intracerebral hemorrhage in a woman treated for ITP; and one pregnancy ended in fetal demise at 20 weeks from an umbilical knot. There was one neonate death at six weeks of life of an infant delivered to a rituximab treated woman with SLE, who also received mycophenolate mofetil and warfarin while pregnant. Mean gestational age at delivery was 37.3± 2.5 weeks. 73% of live births were full term, and 27% were prior to 37 weeks gestational age. One congenital malformation was reported: clubfoot in one of a set of twins. Six infants had hematological abnormalities at birth: 3 with transient leucopenia, and 3 with thrombocytopenia. Most were mild and transient, although one infant, born to a mother treated with rituximab during the third trimester for profound ITP, had a cerebral hemorrhage of unreported severity. Three neonatal infections were reported: febrile illness at 3 weeks of age, chorioamnionitis, and vertical transmission of CMV; none occurred in infants with cytopenias.

Conclusions: Women should continue to be counseled to avoid pregnancy after rituximab exposure; however, inadvertent pregnancy can occur. Few congenital malformations or infections were seen among exposed neonates, and it is difficult to determine if rituximab, concomitant medications, underlying diseases, or other factors contributed. This data provides information that can be used to counsel women in making decisions during pregnancy.

Disclosure: E. F. Chakravarty: None; **E. Murray:** Genentech and Biogen IDEC Inc, 3; **A. Kelman:** Genentech and Biogen IDEC Inc, 3; **P. Farmer:** Genentech and Biogen IDEC Inc, 3.

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Pulmonary Function in Patients with Rheumatoid Arthritis Treated with Anti-TNF Biologic Agents. Andrew J. Odden[1], Ann J. Impens[2], Elena Schiopu[2], Kevin Flaherty[1] and Kristine Phillips[2]. [1]University of Michigan, [2]University of Michigan, Ann Arbor, MI

Background: Initiation of anti-tumor necrosis factor (TNF) therapy has been associated with a range of pulmonary pathology in patients with rheumatoid arthritis (RA), including usual interstitial pneumonitis and granulomatous lung disease. It has been suggested that preexisting interstitial lung disease may predispose patients with rheumatoid arthritis treated with anti-TNF agents to the development of worsening pulmonary disease. There have been no known quantitative studies of lung function in patients with RA-associated interstitial lung disease treated with anti-TNF biologics.

Method: This retrospective cohort study identified patients at a single large referral center who were diagnosed with rheumatoid arthritis, had

coexisting interstitial lung disease, and were treated with anti-TNF therapy. Data recorded included demographics, comorbidities, mortality, chest CT, lung biopsy results, and pulmonary function tests including spirometry and DLCO. Patients were included who had spirometry measurements within one year prior to and within six months after initiating anti-TNF therapy. The baseline FEV1 and FVC were compared with FEV1 and FVC six months after therapy using the paired samples test.

Results: Seventy-four patients were identified with rheumatoid arthritis and interstitial lung disease and had been treated with anti-TNF biologic therapy. Demographic, treatment, and PFT data were gathered for this cohort. Of these, 23 had spirometry measured at least one year prior to starting anti-TNF therapy and again within six months after initiation of therapy. There was no statistically significant difference in FEV1 (2.067 liters vs. 2.097 liters, paired difference 0.030 liters, 95% CI −0.104 to 0.164) or FVC (2.664 liters vs. 2.668 liters, paired difference 0.004 liters, 95% CI −0.141 to 0.150) from baseline to six months after starting anti-TNF therapy.

Conclusion: In this retrospective cohort study, there was no statistically significant change in either FEV1 or FVC from baseline to six months after initiation of anti-TNF biologic therapy. Our study suggests that the use of anti-TNF therapy, an important component of the management of patients with rheumatoid arthritis, does not worsen pulmonary function with short term treatment (six months) in patients with pre-existing lung disease. This study is limited by its small sample size and the short interval between baseline and follow-up spirometry, both of which may have limited our ability to detect a clinically significant difference in lung function. Larger prospective studies are needed to determine the safety of using anti-TNF agents in patients with rheumatoid arthritis and interstitial lung disease.

Disclosure: A. J. Odden: None; **A. J. Impens:** None; **E. Schiopu:** None; **K. Flaherty:** None; **K. Phillips:** None.

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Rate of Serious Infections in RA Patients Who Subsequently Receive Other Biologic Therapies after Discontinuing Rituximab Treatment. Mark C. Genovese[8], Ferdinand Breedveld[4], Paul Emery[2], Stanley B. Cohen[6], Ed C. Keystone[9], Eric L. Matteson[5], Laura Burke[7], Akiko Chai[3], William Reiss[3], Marianne Sweetser[1] and Tim Shaw[7]. [1]Biogen Idec, [2]Chapel Allerton Hospital, Leeds, United Kingdom, [3]Genentech, [4]Leiden Univ, [5]Mayo Clinic, Rochester, MN, [6]Rheumatology Associates, Dallas, TX, [7]Roche, [8]Stanford Univ, Sunnyvale, CA, [9]University of Toronto, Toronto, ON, Canada

Purpose: Rituximab (RTX) selectively targets CD20+ B-cells and is approved for treatment of RA patients (pts) who had an inadequate response to ≥1 TNF-inhibitor(s) (TNFi). The pharmacodynamic effect of RTX may be long lasting. The safety of treatment with other biologic disease-modifying antirheumatic drugs (BDMARDs) during this period of peripheral B-cell depletion in pts who have discontinued RTX is an important clinical question. The purpose of this analysis is to describe the rate of serious infection events (SIEs) in pts treated with RTX, who subsequently received a BDMARD.

Methods: Pts with moderately-to-severely active RA who received RTX + methotrexate within an international clinical trial program were included. Following completion or withdrawal from their studies, pts entered safety follow-up (SFU) and peripheral B-cell counts were monitored for ≥48 wks. During SFU, pts were permitted to receive BDMARDs. All SIEs, defined as serious adverse events or infections that required IV antibiotics, were collected.

Results: As of Sept 2009, 3189 RA pts had received ≥1 course of RTX providing 9365 pt-yrs of follow-up (SIE rate / 100 pt-yrs: 4.34 [95% CI: 3.93, 4.78]). Of pts who entered SFU, 283 pts were subsequently treated with BDMARD (median time 8.5 mo [range: 0.1–52] after last RTX infusion). 87 (30.7%) pts received their BDMARD < 6 mo of their last RTX infusion. 230 of the 283 pts received TNFi after RTX. Median follow-up time after receipt of the subsequent BDMARD was 11 mo (7—17). At the time of receiving further BDMARD treatment, 83% had peripheral B-cell counts below lower limit of normal (LLN) (<80 cells/μL). During treatment with RTX and prior to receipt of the BDMARD, the 283 pts had 6.01 SIEs / 100 pt-yrs (Table). Following initiation of BDMARD, the SIE rate was 4.97 / 100 pt-yrs. Median time to SIE after initiating BDMARD was 11 mo (range: 2—21). In 43 pts who received abatacept (ABA) as their 1st subsequent BDMARD post RTX, there was 1 SIE before and 1 after receiving ABA (97.7 total pt-yrs). Overall, the infections were variable and typical for RA pts, with no opportunistic or fatal infections. In subgroup analysis of 174 patients with CD19+ counts <20 cells/ μL at the time of receipt of their next BDMARD, SIE rate / 100 pt-yrs was 6.28 (3.79, 10.42). In pts who received BDMARD <6 mo (n= 87) or ≥6 mo (n= 196) post RTX, SIE rates were 5.04 (2.26, 11.22) and 4.94 (2.66, 9.18), respectively.

Table. Rate of SIEs in Pts Receiving Biologic DMARDs following RTX

	All Pts Receiving Any Biologic after RTX (n = 283)		Pts Receiving a TNFi after RTX (n = 230)	
	Before Biologic	After Biologic	Before TNFi	After TNFi
Total exposure, pt-yrs	365.83	321.84	282.16	265.89
# SIEs	22	16	17	12
SIE per 100 pt-yrs (95% CI)	6.01 (3.96, 9.13)	4.97 (3.05, 8.12)	6.03 (3.75, 9.69)	4.51 (2.66, 7.95)

CI – confidence interval

Conclusion: In this updated analysis, the use of other BDMARDS in RA pts previously treated with RTX was not associated with an increase in the rate of serious infections. The rate of serious infections is consistent with rates seen in long-term safety analyses.

Disclosure: M. C. Genovese: Genentech and Biogen IDEC Inc, 2, 5; **F. Breedveld:** None; **P. Emery:** Roche, 2; **S. B. Cohen:** Genentech and Biogen IDEC Inc, 5; **E. C. Keystone:** Genentech and Biogen IDEC Inc, 5, 8, Roche, 2, 5, 8; **E. L. Matteson:** Genentech and Biogen IDEC Inc, 2; **L. Burke:** Roche, 3; **A. Chai:** Genentech and Biogen IDEC Inc, 3; **W. Reiss:** Genentech and Biogen IDEC Inc, 3; **M. Sweetser:** Biogen Idec, 3; **T. Shaw:** Roche, 3.

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Rates of Tuberculosis and Nontuberculous Mycobacterial Disease among Rheumatoid Arthritis Patients Who Use Anti-Tumor Necrosis Factor alpha Therapy; from the SAfety of Biologic ThERapy (SABER) Study. K. L. Winthrop[2], John Baddley[4], Lang Chen[4], Liyan Liu[1], Carlos G. Grijalva[8], Nivedita M. Patkar[3], Fenlong Xie[4], Elizabeth Delzell[4], Timothy Beukelman[6], Lisa J. Herrinton[1], Kenneth G. Saag[7] and Jeffrey R. Curtis[5]. [1]Kaiser-Permanente, [2]OSHU, [3]Univ of AL at Birmingham, Birmingham, AL, [4]Univ of AL at Birmingham, [5]University of Alabama-Birmingham, Birmingham, AL, [6]University of Alabama-Birmingham, Birmingham, AL, [7]University of Alabama-Birmingham, Birmingham, AL, [8]Vanderbilt

Background: Rheumatoid arthritis (RA) patients who use anti-tumor necrosis factor alpha therapies (anti-TNF) are at increased risk for tuberculosis. Serious infections due to environmental nontuberculous mycobacteria (NTM) have also been reported in such patients. In the United States, there is no population-based data for patients with rheumatic diseases estimating the risk of TB and NTM.

Methods: We identified new users of anti-TNF therapy among a cohort of rheumatoid arthritis (RA) patients during the years 2000–2007 from three data sources: Kaiser-Permanente Northern California, MAX + 'dual eligible' (MAX + Medicare) data from the national Centers of Medicare and Medicaid Services (years 2000–2005), and Tennessee Medicaid. We used validated electronic medical record (Kaiser) and administrative claims data (CMS and Tenncare) algorithms to identify and describe cases of TB and NTM within this cohort. We calculated incidence rates using total anti-TNF exposure time (current use required) for each patient during the study time-period. We compared TB incidence rates with the rate of TB reported by the US Centers for Disease Control in the United States general population during this same time-period.

Results: Among 29500 new users of anti-TNF therapy for RA, we identified 24 NTM and < 11 TB cases and calculated incidence rates of 66.7 (40–93) and 45.9 (14–78) per 100,000 patient-years respectively. The rate of TB in the US general population was 5.1/100,000 during the same study time-period. 80 (%) and 93 (%) of NTM and TB patients were female respectively, with median age in 5 year increment (range) of 50 (25–75 and 55 (25–80+). NTM patients were more likely to be white (50%) than TB patients (40%). Pre-existing chronic obstructive pulmonary disease or bronchiectasis was more frequent among NTM patients (35%) than among TB patients (33%).

Conclusion: In the United States, a region of low TB prevalence, the rate of TB among RA patients who start anti-TNF therapy is 9 fold higher than the general US population. However, NTM disease was more common than tuberculosis among these RA patients. Rheumatologists should continue to screen for latent TB infection prior to prescribing anti-TNF therapy and remain vigilant for NTM disease, particularly in those with a history of underlying lung disease.

Disclosure: K. L. Winthrop: Amgen Inc., 5, Genentech and Biogen IDEC Inc, 5, Oxford Immunotech, 2, Wyeth Pharmaceuticals, 5; **J. Baddley:** None; **L. Chen:** None; **L. Liu:** None; **C. G. Grijalva:** None; **N. M. Patkar:** None; **F. Xie:** None; **E. Delzell:** Amgen Inc., 2; **T. Beukelman:** None; **L. J. Herrinton:** None; **K. G. Saag:** Amgen Inc., 2, 5, 8, AstraZeneca, 5, Aventis Pharmaceuticals, 5, Eli Lilly and Company, 2, 5, Genentech and Biogen IDEC Inc, 5, GlaxoSmithKline, 2, 5, Merck Pharmaceuticals, 2, 5, NicOx, 5, Nitec, 5, Novartis Pharmaceuticals Corp; **J. R. Curtis:** Amgen Inc., 2, Centocor, Inc., 2, 5, Corrona, 2, 5, Roche, 5, 8, UCB, Inc., 2, 5, 8.

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Real Life Analysis of the Romanian Experience in Switching from Anti-TNF Based Therapy to Rituximab. Ioan Ancuta[1], Catalin Codreanu[2], Ruxandra Maria Ionescu[4], Horatiu Bolosiu[5], Magda Parvu[3] and Lia Georgescu[6]. [1]"Dr. I. Cantacuzino" Hospital, Bucharest, Romania, [2]"Dr. I. Stoia" Center for Rheumatic Diseases, Bucharest, Romania, [3]"N. Gh. Lupu" Clinical Hospital, Bucharest, Romania, [4]"Sfanta Maria" Clinical Hospital, Bucharest, Romania, [5]Rheumatology Clinic, Cluj - Napoca, Romania, [6]Rheumatology Clinic, Tirgu-Mures, Targu - Mures, Romania

Background: The rheumatoid arthritis is a chronic disorder affecting physical function and patient's quality of life, and its treatment carries therefore important costs for the National Health Insurance House (NHIH). In case of an inadequate response with the first anti-TNF medication, a largely used option is currently to continue the treatment with drugs from the same class, either by modifying dosage/frequency of the initial ones, or by prescribing different anti-TNF. Using the available data from NHIH, we researched if continuing with a second anti-TNF brings both the expected benefits for the patients and is reasonably cost effective for NHIH, versus switching to rituximab (RTX) after the initial medication, instead of using again anti-TNF drugs.

Methods, Materials and Analytical Procedures Used: The analysis was performed for 200 patients (78% women with an average age of 55 and 22% men, average age 54) who were all prescribed in the first stage anti-TNF alpha medication. In the second stage, 102 patients were treated with RTX for 3 courses (after one anti-TNF-IR), while 98 of them received a 2nd anti-TNF medication and after an inadequate response to that were treated with 3 courses of RTX. The median time for follow-up was 1.5 years for each arm. We evaluated the effectiveness of the 2 treatment approaches by calculating the Δ between DAS28 measured after and before each stage of the therapy. The financial efficiency was computed as ratio of average cost per DAS28 point for each strategy.

Summary of the Results: Patients had a good response to the first anti-TNF alpha medication, the medium duration of the treatment being 2.43 years. Average DAS28 before treatment was found 6.43, and 3.88 after (medium ΔDAS28 = −2.55). For the 98 patients having a second anti-TNF alpha therapy we noticed an increase of DAS28, the medium ΔDAS28 reaching 0.96, evidencing development of resistance to the anti-TNF medication. For the 102 patients that switched to RTX in the second treatment stage, DAS28 decreased, reaching ΔDAS28 = −2.39. Over the 3 RTX cycles, DAS28 decreased consistently for all patients but reached its lowest value for the patients having RTX after the first anti-TNF, (ΔDAS28 = −3.9).

Conclusions: Repeating anti-TNF alpha medication after an initial a-TNF inadequate response did not bring benefits to the patients, as DAS28 increased during the second stage of the treatment. The incomplete immunosuppression caused by the first anti-TNF medication could lead to development of resistance to treatment which becomes significant during the next stage. Introducing RTX right after the first anti-TNF inadequate response proved to be the most effective option, leading to cumulating of clinical benefits and to consolidation of lower DAS28 response with each following RTX cure. This strategy is also more efficient, as the cost per DAS28 point decreased compared with introducing RTX only after the second anti-TNF. Therefore the balance cost-benefits is clearly in favor of initiating a RTX medication immediately after the first anti-TNF therapy and this shall be our recommendation for NHIH.

Disclosure: I. Ancuta: Abbott Immunology Pharmaceuticals, 8, Merck Pharmaceuticals, 8, Roche, 8; **C. Codreanu:** None; **R. M. Ionescu:** None; **H. Bolosiu:** None; **M. Parvu:** None; **L. Georgescu:** None.

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Real Life Treatment with Rituximab in TNF Blocker Non-Responders Is Superior to Treatment with a Second TNF Blocker. Joern Kekow[4], Ulf Müller-Ladner[2], Hendrik Schulze-Koops[1], Ralf Link[3], Steffen Breuer[3] and Monika Kobialko[3]. [1]Division of Rheumatology, University of Munich, Germany, [2]Justus-Liebig University Giessen, Kerckhoff Clinic, Bad Nauheim, Germany, [3]Roche Pharma AG, Grenzach-Wyhlen, Germany, [4]Specialized Hospital for Rheumatology & Orthopaedics, Vogelsang-Gommern, Vogelsang-Gommern, Germany

Background: Treatment with biologics has led to a fundamental change in the therapy of rheumatoid arthritis (RA). However, 30% of patients treated with TNF blockers still do not sufficiently respond to therapy. Switching to a 2nd TNF blocker vs. second generation biologic such as rituximab is still a matter of debate, especially which option might be superior in that situation. The objective of this trial was to assess the efficacy of one course with 2 × 1g rituximab compared to an alternative TNF blocker in RA patients with one previous TNF blocker failure in a real life setting.

Methods: This was a non-interventional, retrospective cohort study with a mean observation period of 6.6 months (median 6.32, range 1.64–20.76). Of 196 patients (77% females; rituximab n=90) with active RA (DAS28 ≥ 3.2), 43.9% had previously received adalimumab and etanercept each, and 12.2% infliximab.

Results: Both cohorts were comparable regarding age (rituximab 56.6±11.1; TNF blocker 57.4±13.1 years), duration of disease (10.0±7.8 vs. 9.7±7.6 years), DAS28 (5.6±1.0 vs. 5.4±1.0) and concomitant DMARD therapy (77.8% vs. 77.4%) at initiation of 2nd treatment (baseline). The mean DAS28 reduction was significantly greater after 6.6 months treatment in the rituximab group as compared to the patients treated with a 2nd TNF blocker (-1.64 [95%-CI: −1.92; −1.36] vs. −1.19 [95%-CI: −1.42; −0.96], p=0.0133), see Figure 1 (left). This cohort difference was similar in the 156 patients seropositive for RF (−1.66 [95%-CI: −1.98; −1.34] vs. −1.17 [95%-CI: −1.43; −0.91], p=0.0176) and more pronounced in the 132 patients seropositive for CCP: a significant difference (p=0.0295) could already be observed after 12 weeks with further improvement until month 6.6 (−1.75 [95%-CI: −2.07; −1.43] vs. −1.06 [95%-CI: −1.34; −0.78], p=0.0016), see Figure 1 (right). The results from the 23 seronegative patients also favored rituximab but this difference was not significant. More rituximab than TNF blocker patients reached moderate/good EULAR response: 82.2% vs. 71.7%; with a significant difference in the CCP subgroup: 85.3% vs. 67.2% (p=0.0128).

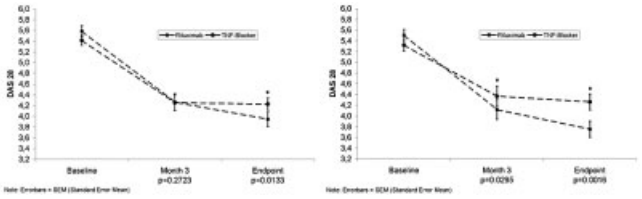

Figure 1. Course of the mean DAS28 (±SEM) in all patients (left) and CCP positive patients (right)

Conclusion: The results from this non-interventional, retrospective cohort study indicate that treatment with rituximab is superior to a 2nd TNF blocker therapy in RA patients after failure of the first TNF inhibitor in terms of clinically significant improvement as measured by the DAS28 score. An even stronger difference in clinical response was found in the patients seropositive for CCP. This observational data of a real life setting confirm the data of rituximab in TNF blocker non-responders as shown in the REFLEX study. In addition to previous publications we could show that CCP may be a useful predictive biomarker for response to rituximab in patients with TNF blocker treatment failure.

Disclosure: J. Kekow: None; **U. Müller-Ladner:** Roche, 5, 8; **H. Schulze-Koops:** Roche, 2, 5; **R. Link:** Roche, 3; **S. Breuer:** Roche, 3; **M. Kobialko:** Roche, 3.

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Risk of Malignancies in Patients with Rheumatoid Arthritis Treated with Biologic Therapy: Meta-Analysis of Controlled Trials. Maria A. Lopez-Olivo[4], Juan A. Martinez-Lopez[2], Jean H. Tayar[7], Jose Polo Cueto[5], Eduardo N. Pollono[3], M. Rosa Gonzales-Crespo[1], Stephanie Fulton[6] and Maria E. Suarez-Almazor[7]. [1]Hospital 12 de Octubre, [2]Spanish Society of Rheumatology, Spain, [3]Texas Tech University Health Science Center - Paul Foster School of Medicine, [4]The University of Texas M.D. Anderson Cancer Center, Houston, TX, [5]The University of Texas MD Anderson Cancer Center, [6]University of Texas, MD Anderson Cancer Center, Houston, TX, [7]UT M D Anderson Cancer Ctr, Houston, TX

Background: Biologic response modifiers (BRM) provide an important therapeutic alternative in patients with rheumatoid arthritis. Because these biologic agents interfere with the immune system, there are concerns regarding their safety and an increased risk of malignancies. The objective of this study was to assess the risk of malignancies in patients with rheumatoid arthritis enrolled in clinical trials of BRMs, in order to update the information reported in previous reviews of RCTs and determine if the newly approved BRMs have an increased risk for malignancies.

Methods: We searched for clinical trials on the use of abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab,

rituximab, and/or tocilizumab for the treatment of rheumatoid arthritis, published through April 29, 2009. Sources included electronic databases (MEDLINE, EMBASE, and Web of Science). Review of 12,480 citations revealed 55 controlled trials. Two independent reviewers evaluated risk of bias in the methods of selected studies using the risk of bias instrument (Cochrane Collaboration) and extracted data. Information on reported number of malignancies, type and time of occurrence when available was collected.

Results: Fifty-three trials with 23,696 patients were included. Compared with placebo, patients in the TNF antagonists group were 1.38 times more likely to develop malignancy at one year, but this was not statistically significant (95% CI, 0.76, 2.48) with a 0.33% (95% CI: −0.16%, 0.82%) absolute risk difference between groups. The number needed to harm was 305 (95% CI: 122, ∞) for one additional malignancy within a treatment period of 12 mo. No statistically significant risk of developing a specific type of malignancy was found in the TNF antagonist-treated patients compared to placebo. Total number of solid malignancies (breast, lung, colon, prostate) were greater for patients treated in tocilizumab group compared to placebo (RR: 6.47, 95% CI: 0.34, 124.16) and skin cell carcinoma was increased when certolizumab was given in combination with methotrexate against placebo plus methotrexate (RR 3.56, 95% CI 0.18, 68.63), but these results were not statistically significant.

Conclusions: On the basis of the studies reviewed here, there is no evidence that BRMs for the treatment of the RA confide a greater risk for malignancies, but further long-term studies and continuing post-marketing surveillance are required.

Disclosure: M. A. Lopez-Olivo: None; **J. A. Martinez-Lopez:** None; **J. H. Tayar:** None; **J. Polo Cueto:** None; **E. N. Pollono:** None; **M. R. Gonzales-Crespo:** None; **S. Fulton:** None; **M. E. Suarez-Almazor:** AHRQ, 2, Amgen Inc., 8, Bristol-Myers Squibb, 8, NIH, 2, Roche, 8.

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Risk of Malignancy during Anti-TNF alfa Therapy in Patients with Rheumatoid Arthritis: Systematic Review and Meta-Analysis of Registries, Long-Term Extension Studies and Randomized Controlled Trials.

Pierre Le Blay[3], Gael Mouterde[4], Thomas Barnetche[1] and Bernard G. Combe[2]. [1]Bordeaux University Hospital, [2]Hopital Lapeyronie, Montpellier, France, [3]Hopital Lapeyronie, France, [4]Hopital Lapeyronie

Background: TNF antagonists have shown their efficacy in rheumatoid arthritis (RA) and are now widely used. Some data derived from randomized control trials (RCTs) suggest that anti-TNF might be associated with an increased risk of malignancy [1], but results from long term safety follow up and registries are controversial.

Objective: To assess the risk of malignancy in TNF antagonists treated-RA patients, by performing a systematic review and meta-analysis based on data from registries, long term extension studies, and RCTs of 2 newly licensed anti-TNF.

Method: A systematic review of literature was performed until January 2010. Bibliographic references were selected from Embase and Medline databases, and abstracts from both the EULAR and the ACR annual meetings.The Mantel-Haenszel method was used to provide a common odds-ratio (OR) estimate and 95% confidence interval (CI) in anti-TNF– versus disease modifying antirheumatic drug (DMARDs) treated patients for registries and for certolizumab and golimumab RCTs. Statistical heterogeneity was assessed on the basis of the Q test (χ^2), using a significance level of 0.05. OR and 95% CI were shown on forest plots. Standardized Incidence Ratio (SIR), versus the general population, were extracted for long term extension studies and registries.

Results: The literature search identified 641 articles and 110 abstracts of which respectively 25 and 2 were selected for analysis. Retrieved data allowed meta-analysis on 4 registries and 5 RCTs. Based on registries (40128 Patient-years (PY) in anti-TNF treatment group and 59862 PY under DMARD treatment in control group), the pooled OR for malignancy was 0.81 (95% CI 0.71–0.94), without significant heterogeneity.

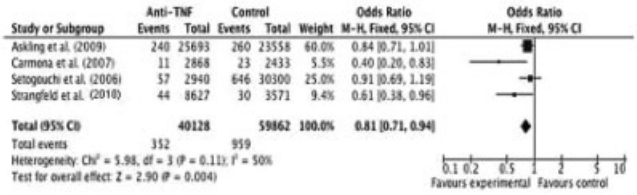

Figure 1. Meta-analysis of registries for risk of total malignancy.

In golimumab and certolizumab RCTs, the pooled OR for total malignancy and for non melanoma skin cancers were respectively 1.07 (95% CI 0.35–3.25) and 0.83 (95% CI 0.24–2.87), without heterogeneity.

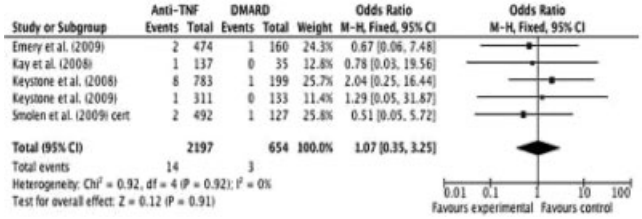

Figure 2. Meta-analysis for risk of total malignancy with certolizumab and golimumab.

Among 3 long term extension studies, no increase in the incidence of total malignancy was noted (SIRs ranging from 0.84 to 1.07). A similar observation was made in 4 registries (21225 PY), (SIRs ranging from 0.74 to 1.36, none being statistically significantly higher than 1).

Conclusion: This meta-analysis of registries did not find an increased risk of malignancy in anti TNF treated-RA patients. Data from long term extension studies and RCTs with new TNF antagonists confirmed these results.

[1]Bongartz and al., JAMA 2006

Disclosure: P. Le Blay: None; **G. Mouterde:** None; **T. Barnetche:** None; **B. G. Combe:** None.

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Rituximab vs TNF-Inhibitor Cycling in Patients Who Previously Failed to TNF-Inhibitors: The MIRAR Study.

Juan-Jesús Gómez-Reino[1], Raimon Sanmartí[2], Ana-Belen Romero[3] and Laura Monclus[3]. [1]Hospital Clínico Universitario / Xeral de Galicia, Santiago de Compostela, [2]Hospital Clinic, Barcelona, [3]Roche

Purpose: Rituximab (RTX) is used to deplete B cells, and control disease activity in, mainly, anti-TNF failing RA patients. Another option is to switch to another anti-TNF, and it is not yet clear which of these two options is the more successful strategy. The objective of this study is to compare in a clinical setting the effectiveness of RTX treatment vs. an alternative anti-TNF in RA patients failing to an anti-TNF.

Methods: Multicentre, prospective, 3-year observational study of a cohort of patients with RA who received either RTX or an alternative anti-TNF, having previously inadequate response to at least 1 anti-TNF. Assessments included DAS28, EULAR response and HAQ at 9–12 months. At the time of this analysis, more evaluable patients were included since last published results[1]. All analysis were done with SAS 9.1.3. Appropriate tests were used for comparisons.

Results:

Table 1. Baseline patient characteristics

	Rituximab	TNF-inhibitor	P-value
Female	346 (81.41%)	958 (79.77%)	0.4646
Age (mean SD)	55.73 (12.47)	54.55 (13.46)	0.2583
>4 years since diagnosis of RA	292 (86.65%)	787 (78.23%)	0.0008
Extra-articular manifestations of RA	137 (44.05%)	255 (26.18%)	<0.0001
Prior number of TNF inhibitors failure			<0.0001
1	210 (60.69%)	762 (79.89%)	
≥2	136 (39.31%)	229 (20.11%)	
Previous use of ≥2 DMARDs	193 (94.15%)	860 (87.31%)	0.0053
Previous toxicity with DMARDs	78 (38.61%)	291 (29.82%)	0.0141

Significantly more patients in RTX had > 4 years since diagnosis, extra-articular manifestations, ≥ 2 DMARDs and ≥ 2 previous number of anti-TNF, toxicity with DMARDS (Table 1) and higher DAS28. At 9–12 months, change in DAS28 is significantly larger in RTX (-1.84) than alternative anti-TNF (-1.34) (P=0.0156; difference: 0.4999, 95% CI: 0.0954, 0.9043) (Figure 1). EULAR good-mod. response rate is better in RTX

(82.56%) than alternative anti-TNF (70.83%) (P= 0.04); Probability of good-moderate response is affected by baseline DASS28 (OR= 2.532, 95% CI: 1.837, 3.489). There were no differences in change of HAQ (P= 0.3141) nor in proportion of patients with HAQ > 0.22 (P= 0.1754).

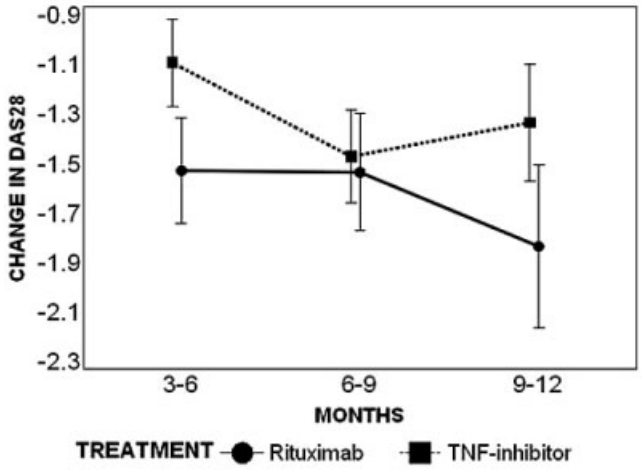

Figure 1. mean (95% confidence intervals) changes in DAS28

Conclusion: Data from the MIRAR Study confirms that switching to RTX provides an alternative therapeutic option to TNF cycling in patients with RA who have previously failed TNF inhibitor therapy. DAS28 reduction was significantly higher in the RTX group.

Disclosure: J.-J. Gómez-Reino: Roche, 2; **R. Sanmartí:** Roche, 2; **A.-B. Romero:** Roche, 3; **L. Monclus:** Roche, 3.

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Rituximab vs. Anti-TNF after Failure of Anti-TNF: An Observational Study. Katerina Chatzidionysiou[2] and Ronald Van Vollenhoven[1]. [1]Karolinska University Hospital, Stockholm, Sweden, [2]Karolinska University Hospital, Stockholm

Background: The purpose of this study was to determine whether patients who had failed one or more anti-TNFs achieve better results when switching to another anti-TNF or when switching to rituximab.

Methods: The Stockholm registry ''STURE'' was used. Treatment results at 3 and 6 months were analysed by 1) biologic used; 2) whether as second, third or fourth biologic; 3) type of TNF switch; and 4) reason for discontinuation (lack of efficacy or intolerance).

Results: A total of 850 patients switched to an alternative biologic, 679 to a TNF antagonist and 171 to rituximab. There was a significant improvement in the DAS28 scores for both RTX and anti-TNF groups from baseline to 6 months. The mean (S.D.) reduction of DAS28 was 1.79 (1.35) for the RTX group and 1.37 (1.44) for the anti-TNF group (p=0.03). Specifically, mean ΔDAS28 was 1.15 (1.4) for infliximab and adalimumab taken together and 1.58 (1.46) for etanercept. A significant difference was observed between rituximab and anti-TNF monoclonal antibodies (p=0.002, 95% CI = 0.24; 1.06) but not between rituximab and etanercept (p=0.32, 95% CI = −0.21; 0.6).

In figure 1 the mean improvements in DAS28 can be seen according to the type of TNF switch. Having failed a TNF soluble receptor, RTX was significantly better than an anti-TNF monoclonal antibody (p=0.03). For patients who had failed a TNF monoclonal antibody RTX leads to numerically but not significantly greater reductions in DAS28 than an alternative anti-TNF antibody or etanercept.

When the reason for discontinuation of previous treatment was intolerance, rituximab achieved significantly greater reduction in DAS28 compared to anti-TNF, 2.05 (1.17) versus 1.52 (1.26) (p=0.04).

Conclusion: In this observational cohort, patients who had failed anti-TNF had slightly better overall results when treated with rituximab than with another anti-TNF, but both options provided clinical benefits. The superiority of rituximab was observed when compared to anti-TNF monoclonal antibodies but not to etanercept. Unexpectedly, the advantage of RTX was most clearly seen in patients who had failed anti-TNF due to intolerance.

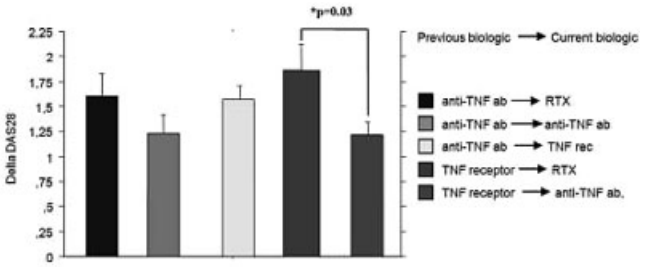

Figure 1. Change in DAS28 at 6 months for patients who switched from an anti-TNF monoclonal antibody (aTNFab) or a TNF soluble receptor-construct to rituximab or an alternative anti-TNF.

Disclosure: K. Chatzidionysiou: None; **R. Van Vollenhoven:** Roche, 2, 5.

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Safety and Tolerability of Tocilizumab in Long-Term Extension Studies of Rheumatoid Arthritis. Mark C. Genovese[5], Anthony Sebba[7], Andrea Rubbert-Roth[6], Juan J. Scali[1], Moshe Zilberstein[3], Emma Vernon[4] and Ronald F. van Vollenhoven[2]. [1]Durand University Hospital, Buenos Aires, Argentina, [2]Karolinska University Hospital, Stockholm, Sweden, [3]Roche, Nutley, NJ, [4]Roche, Welwyn, UK, [5]Stanford University Medical Center, Palo Alto, Palo Alto, CA, [6]University of Cologne, Cologne, Germany, [7]University of South Florida, Palm Harbor, FL

Background: Tocilizumab (TCZ) is an effective RA therapy that targets interleukin-6-receptor (IL-6R) signal transduction. The objective of this analysis was to assess the longer-term safety of TCZ in RA patients using pooled data from clinical trials (OPTION, TOWARD, RADIATE, AMBITION, and LITHE) and ongoing long-term extension studies.

Methods: Pooled analysis of patients who received ≥1 TCZ dose in the core or extension studies (GROWTH95 and GROWTH96) from initial exposure through August 28, 2009.

Results: A total of 4009 patients received TCZ with a median (mean) treatment duration of 3.1 (2.7) years and a total observation time of 10,994 patient-years (PY). The AE rate was 321.1/100 PY (95% CI: 317.8, 324.5); infections were the most frequent AE (70.7/100 PY). The SAE rate was 14.6/100 PY (95% CI: 13.9, 15.4); infections were the most frequent SAE (4.5/100 PY; 95% CI: 4.1, 4.9). Rates of SAEs and serious infections were stable over time (Table). The rate of deaths was 0.4/100 PY (95% CI: 0.3, 0.6). The rate of malignancies was 0.8/100 PY, excluding nonmelanoma skin cancer (NMSC); the rate of NMSC was 0.3/100 PY. The overall rate of malignancies did not exceed reported background rates (SEER database), and overall rates, including NMSC, have remained stable with continued TCZ therapy (Table). GI perforations, including potential occurrence of sequelae from GI perforations (eg, abscess, strictures), occurred at a rate of 2.6/1000 PY (95% CI: 1.8, 3.8); 59% (17/29) of these patients had colonic diverticular perforations. Preliminary epidemiologic data revealed that although the GI perforation rate was higher than in the general population, it was similar to rates in the RA population. Rates/100 PY of myocardial infarction and stroke were 0.3 (95% CI: 0.2, 0.4) and 0.2 (95% CI: 0.1, 0.3), respectively, were stable over time (Table), and did not exceed expected rates in the RA population (myocardial infarction, 0.3–0.8/100 PY; stroke, 0.5–0.7/100 PY). Eight patients experienced anaphylactic reactions and withdrew from the study. The rate of AEs leading to withdrawal was 5.4/100 PY; the most common AEs leading to withdrawal were laboratory abnormalities (1.2/100PY, primarily transaminase elevations), infections/infestations (1.0/100PY), and neoplasms (benign, malignant, or unspecified, 0.7/100PY).

Table. Event Rate Per 100 PY (95% CI) Over 12-Month Periods

	0–12	13–24	25–36	37–48
AEs	416.6 (409.8, 423.4)	296.5 (290.4, 302.7)	271.7 (265.4, 278.0)	250.7 (243.0, 258.5)
SAEs	15.7 (14.4, 17.1)	13.7 (12.4, 15.1)	15.1 (13.6, 16.6)	13.6 (11.8, 15.5)
Serious infections	4.6 (3.9, 5.4)	3.9 (3.2, 4.6)	5.1 (4.3, 6.1)	4.6 (3.6, 5.8)
Malignancies[a]	0.9 (0.6, 1.3)	1.1 (0.8, 1.5)	1.3 (0.9, 1.8)	1.4 (0.9, 2.1)
MI	0.3 (0.1, 0.5)	0.2 (0.1, 0.4)	0.3 (0.1, 0.5)	0.5 (0.2, 1.0)
Stroke	0.3 (0.1, 0.5)	0.1 (0.0, 0.3)	0.2 (0.1, 0.4)	0

[a]Including NMSC.

Conclusions: Rates of SAEs, serious infections, malignancies, and CV events have remained stable with continued exposure to TCZ. These results suggest that the longer-term safety profile of TCZ is not different from that established in the phase 3 studies.

Disclosure: M. C. Genovese: Roche, 2, 5; **A. Sebba:** Abbott Laboratories, 8, Amgen Inc., 2, 5, Bristol-Myers Squibb, 2, Genentech and Biogen IDEC Inc, 2, Novartis Pharmaceuticals Corporation, 2, 5, Roche, 2, 5, 8; **A. Rubbert-Roth:** Abbott Laboratories, 5, Chugai, 5, Essex, 5, Roche, 2, 5, 8, UCB, Inc., 5, Wyeth Pharmaceuticals, 2, 5; **J. J. Scali:** None; **M. Zilberstein:** Roche, 3; **E. Vernon:** Roche, 3; **R. F. van Vollenhoven:** Roche, 2, 5.

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Safety of Combination Therapies in Early RA: A Systematic Comparison between Combination DMARDs and TNF Inihibitors with Methotrexate. Margaret H. Y. Ma[2], Andrew P. Cope[1] and David L. Scott[2]. [1]Surrey, United Kingdom, [2]Academic Department of Rheumatology, King's College London

Background: The use of combination regimes plays a central role in the contemporary treatment of early Rheumatoid Arthritis. As these therapies become increasingly intensive and aggressive, drug toxicity is now a crucial issue. The aim of this study was to systematically evaluate the frequency and type of adverse effects associated with combination disease-modifying anti-rheumatic drugs (DMARDs) and tumour necrosis factor inhibitors (TNFi) combined with methotrexate (MTX) when compared with MTX monotherapy.

Methods: A systematic literature search of Cochrane Library, EMBASE, Pubmed and Ovid Medline identified 15 relevant RCTs from 1960 to March 2010. The following outcome measures were assessed: patient withdrawal due to toxicity, total adverse events, serious adverse events (total and by individual systems), nausea, malignancy and deaths. Review Manager 5 was used for meta-analysis.

Results: The preliminary search identified 459 citations. Out of these, seven RCTs compared combination DMARD therapies with MTX monotherapy, seven RCTs compared TNFi/MTX with MTX monotherapy and one RCT included both treatment arms. Table 1 shows the baseline characteristics of the trials.

Table 1. Trial Characteristics.

Study	Year	Disease duration (mths)	Follow-up (mths)	Jadad Score (1-5)	No. Pts	Combination arm therapies	MTX Monotherapy Arm: Mean Age (yrs)	Female (%)	RF+ve (%)	ESR	DAS	Combination Arm: Mean Age (yrs)	Female (%)	RF+ve (%)	ESR	DAS
Combination DMARDs																
CARDERA [14]	2008	<24	24	5	467	MTX[a]/CsA/Pred	54	67	66	-	5.8[a]	55	67	72	-	5.6[a]
Dougados et al [15]	1999	<12	12	4	209	MTX/SSZ	50	74	62	46	4.1	52	77	71	38	4.2
BeST (step down) [13]	2005	<12	12	3	508	Step down[c]	54	68	67	-	4.5[d]	55	65	65	-	4.5[d]
Haagsma et al [16]	1999	<12	12	4	103	MTX/SSZ	55	66	94	20	4.3	57	66	94	21	5.0
CIMESTRA [17]	2006	<6	12	5	163	MTX/CsA/IA steroids	51	78	59	27	5.5[e]	53	64	70	28	5.3[e]
Ichikawa et al [18]	2005	<24	24	4	71	MTX/Bucillamine	53	70	85	77	-	49	71	96	68	-
Marchesoni et al [19]	2003	<24	12	2	61	MTX/CsA	49	90	74	65	5.1[e]	47	93	63	44	5.2[e]
O'Dell [20]	2006	<12	24	4	66	MTX/Doxycycline	56	79	100	-	-	50	67	100	-	-
TNF inhibitor/Etoricoxcate																
Bejarano et al [21]	2008	<24	12	5	148	MTX/Adalimumab	47	53	95	-	6.0[e]	47	58	86	-	5.9[e]
PREMIER [22]	2006	<35	24	4	799	MTX/Adalimumab	52	74	-	-	6.3[e]	52	72	-	-	6.3[e]
COMET [23]	2008	<24	12	5	274	MTX/Etanercept	52	73	-	49	-	51	74	-	48	-
Quinn [24]	2005	<12	12	5	20	MTX/Infliximab	53	-	60	-	-	51	-	70	-	-
BeST (TNF/MTX) [13]	2005	<12	12	3	508	MTX/Infliximab	54	68	67	-	4.5[d]	54	66	64	-	4.5[d]
Dorey et al [25]	2005	<12	12	2	44	MTX/Infliximab	54	73	64	-	5.2[e]	50	60	67	-	5.5[e]
ASPIRE [26]	2004	<36	12	4	1049	MTX/Infliximab	50	75	71	43	6.7[e]	50	68	73	44	6.7[e]
Taylor et al [27]	2004	<36	12	4	24	MTX/Infliximab	51	-	-	36	5.1[e]	55	-	-	28	5.4[e]

No pts = number of patients randomised, mths = months, yrs = years, RF = rheumatoid factor, MTX (oral) = Methotrexate, CsA = Ciclosporin A, Pred = prednisolone, IA= intra-articular, SSZ = sulfasalazine, [a]DAS28, [b]DAS44, [c]DAS28CRP, [d]7.5-15mg, [e]7.5-15mg, [f]7.5-20mg, [g]7.5-25mg, [h]7.5-30mg, [i]10-20mg, [j] 4-8mg

There were more patient withdrawals using combination DMARDs therapy (OR 2.33, 95% CI 1.43, 3.77) and TNFi/MTX when (OR 1.44 95% CI 1.05, 1.98) compared to MTX monotherapy (Table 2). More patients reported nausea when using combination DMARDs therapy (OR 2.06 95% CI 1.30, 3.27) and there were more serious adverse events using TNFi/MTX (OR 1.66 95% CI 1.26, 2.20, Table 2).

Table 2: Meta-analysis of toxicity outcomes TNFi/MTX = Tumour necrosis factor inhibitors with methotrexate, MTX = methotrexate, Combo DMARDs = combination DMARDs therapy

Outcome	Treatment	No. Studies	MTX monotherapy: Cases	Total	%	Range	Combination Therapies: Cases	Total	%	Range	Fixed effects Pete OR (95% CI)	Heterogeneity	p value
Toxicity Withdrawals	TNFi/MTX	8 [14-20]	67	1058	6.3	0-34	102	1160	8.8	0-35	1.44 (1.05, 1.98)	10.77	ns
	Combo DMARDs	8 [13, 21-27]	28	505	5.5	0-8	58	511	11.4	0-23	2.33 (1.43, 3.77)	3.53	ns
Nausea	TNFi/MTX	2 [21, 23]	69	349	19.8	16-33	74	341	21.7	24-50	0.89 (0.61, 1.28)	2.13	ns
	Combo DMARDs	3 [14-16]	46	221	18.1	35-117	66	229	30.0	10-33	2.06 (1.30, 3.27)	11.62	0.003
Serious Adverse events	TNFi/MTX	4 [13, 21, 23, 26]	85	758	11.2	0-34	147	854	17.2	13-51	1.66 (1.26, 2.20)	24.74	<0.001
	Combo DMARDs	3 [13, 14, 16]	29	278	10.4	0-23	40	285	14.0	0-23	1.43 (0.86, 2.38)	1.34	ns
Serious Infections	TNFi/MTX	5 [13, 21-23, 25, 26]	23	1029	2.4	0-8	38	1137	3.3	0-19	1.35 (0.82, 2.24)	3.81	ns
	Combo DMARDs	4 [13, 14, 16, 17]	11	358	3.1	0-7	5	365	1.4	0-2	0.46 (0.17, 1.24)	0.99	ns
Malignancy	TNFi/MTX	5 [13, 21-23, 26]	8	1015	0.8	0-4	10	1122	0.9	0-4	1.15 (0.46, 2.93)	2.53	ns
	Combo DMARDs	5 [13, 14, 16, 17, 19]	7	388	1.8	0-5	4	393	1.0	0-2	0.58 (0.18, 1.89)	1.08	ns

However, the remaining outcomes (total numbers of adverse events, the number of serious infections, malignancies and deaths) did not differ significantly between the combination treatment arms and MTX monotherapy arms. Events in individual systems were rare and did not show major differences between groups.

Conclusion: Our systematic review showed that combination therapies using synthetic or biological agents increased patient withdrawals due to toxicity when compared to monotherapy. There were more serious adverse events using biologics with methotrexate whereas nausea was an issue for combination synthetic DMARDs. However, there were no significant differences in total numbers of adverse events, serious infections, malignancies and deaths. Events reported in individual system were too rare to draw definitive conclusions. Based on the available evidence, intensive therapies in early rheumatoid arthritis appear to be justified.

Disclosure: M. H. Y. Ma: None; **A. P. Cope:** None; **D. L. Scott:** None.

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Scleritis: A New Paradoxical Effect of Etanercept? A Series of 3 Cases and a Systematic Literature Review of Etanercept-Associated Inflammatory Eye Disease. Cécile Gaujoux-Viala[1], Cecilia Giampietro[2], Thomas Gaujoux[3], Hang-Korng Ea[4], Philippe Orcel[4] and Frédéric Lioté[4]. [1]Paris 6 – Pierre et Marie Curie University; Rheumatology, Pitié-Salpêtrière Hospital, Paris, France, [2]Paris 6 – Pierre et Marie Curie University; Rheumatology, Pitié-Salpêtrière Hospital, Paris, France 2University of L'Aquila, L'Aquila, Italy, [3]Paris 7 University, Medicine Faculty; AP-HP, Lariboisière Hospital, Ophtalmology Department, Paris, France, [4]Paris Diderot University, School of Medicine; Lariboisière Hospital, AP-HP, Rheumatology Department, Paris, France

Background: The widespread use of TNFα antagonists has led to the recognition of paradoxical adverse effects, defined as the onset or exacerbation of disorders that are usually improved by TNFα antagonists. Cutaneous psoriasis, Crohn disease and uveitis exacerbations have been extended reported. Scleritis, a serious and sight threatening ocular inflammatory disease, has recently been described like another possible paradoxical event of anti-TNF-α and particulary of etanercept.

Objectives: 1) to report 3 cases of severe bilateral scleritis caused by administration of etanercept for rheumatoid arthritis, and 2) to review the literature related to inflammatory eye diseases associated with the use of etanercept.

Methods: 1) Three cases of severe bilateral scleritis during etanercept therapy were analyzed. 2) A systematic review of the literature in PUBMED, EMBASE, Cochrane library and hand search was performed until May 2010 using terms as etanercept, Enbrel, scleritis, uveitis, orbital myositis and inflammatory eye disease.

Results: 1) Three patients with seropositive rheumatoid arthritis developped for the first time during their long-lasting disease (disease duration: 9, 20 and 21 years), scleritis or sclero-uveitis 7–28 months after the initiation of etanercept. In all patients the underlying disease had well responded to anti-TNF alpha therapy. Ocular inflammation underwent remission after discontinuation of etanercept and no other relapses were observed. Interestingly, 1 patient experienced a worsening of symptoms after rechallenge of treatment and drug discontinuation led to rapid resolution.

2) 34 cases of inflammatory eye diseases believed to be associated with the use of etanercept have been reported in the literature: 26 uveitis, 7 scleritis, 1 orbital myositis, concerning 14 RA, 8 juvenile idiopathic arthritis, 10 ankylosing spondylitis and 2 psoriatic spondylarthropathy. Mean age of patients was 44.1 $\pm$ 13.7 years and 84.6% were women. The mean rheumatic disease duration was 11.8 $\pm$ 9.6 years. Regarding the time-to-onset, the average time between the beginning of etanercept therapy and the onset of symptoms was 12.3 $\pm$ 9.1 months, with exposure times ranging between 1 and 36 months. Dechallenge was performed in 19 patients, leading to resolution of symptoms. Rechallenge was done in 6 cases.

Conclusion: Ocular inflammation is paradoxically a potential adverse event of etanercept even in previously uninvolved eyes. Patients being treated with TNFα soluble receptors should be closely monitored for the development of ocular signs and symptoms in order to detect flares secondary to etanercept therapy and necessitating discontinuation.

Disclosure: C. Gaujoux-Viala: None; **C. Giampietro:** None; **T. Gaujoux:** None; **H.-K. Ea:** None; **P. Orcel:** None; **F. Lioté:** None.

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Serious Infections with Ocrelizumab in Rheumatoid Arthritis: Pooled Results from Double-Blind periods of the Ocrelizumab phase III RA program. P Emery[1], W Rigby[2], PP Tak[3], T Dörner[4], MC Genovese[6], G Ferracioli[7], E Martin-Mola[8], M Dougados[9], H Travers[10], E Fisheleva,[10] W Dummer[11]. [1]Univ of Leeds, Leeds, United Kingdom; [2]Dartmouth, Lebanon, NH; [3]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands; [4]Charité Univ Hospital, Berlin, Germany; [5]Oklahoma Univ Health Sci Ctr, Oklahoma City, OK; [6]Standford Univ, Palo Alto, CA; [7]Catholic Univ, Rome, Italy; [8]La Paz Univ Hospital, Madrid, Spain; [9]Hopital Cochin, Paris, France; [10]Roche, Welwyn Garden City, United Kingdom; [11]Genentech, South San Francisco, CA

Purpose: Ocrelizumab (OCR), a novel humanized monoclonal antibody that selectively targets CD20+ B cells, has been studied in 4 phase III randomized clinical trials in different patient (pt) populations with active rheumatoid arthritis (RA). Here, we report safety data from the double-blind, placebo (PBO)-controlled (DBPC) periods in phase III studies.

Methods: The OCR RA program includes 4 randomized, DBPC globally conducted trials assessing the safety and efficacy of OCR given as 2 infusions of 200 mg or 500 mg (400 mg × 1 in FEATURE) every 6 months in combination with methotrexate (MTX) or leflunomide (LEF). STAGE studied OCR in combination with MTX vs MTX alone in pts with an inadequate response (IR) to MTX. SCRIPT included pts with an IR to at least one TNF inhibitor and was conducted in combination with either MTX or LEF. FEATURE investigated a single infusion regimen (400 mg) in pts who failed MTX and/or biologic DMARDs. FILM included pts who were MTX-naïve. Pooled safety data was analyzed for the DBPC periods of the RA phase III trials (48 wks in STAGE and SCRIPT, 52 wks in FILM, and 24 wks in FEATURE). Frequencies and rates (events per 100 pt-yrs) of serious infection events (SIEs) were assessed by dose and region. Pts who received either 200 mg × 2 or 400 mg × 1 were grouped together in pooled analyses.

Results: SIE rates in each treatment group of each study are shown in **Table**. Increased SIE rates were predominantly seen with OCR 500 mg × 2. Following pooling of the 4 studies by treatment group, the weighted difference from PBO in the number of pts with at least one SIE was calculated to be 0.6 (95% CI: −1.3 to 2.4) for OCR 200 mg × 2 and 2.4 (95% CI: 0.3 to 4.5) for OCR 500 mg × 2. Thus, statistically significant increases in the number of pts experiencing an SIE were only seen in the 500 mg group. In a sub-analysis of SIE rates in one year trials, pooled by dose and region (Asia vs Other), OCR pts in Asia had relatively higher rates compared to rates seen in pts from non-Asian (Other) regions (**Table**), although the imbalance was also seen in non-Asian regions vs PBO. There were 9 opportunistic infections in 9 pts in OCR-treated pts comprised of 2 de novo pulmonary tuberculosis, 1 Pneumocystis jiroveci suspected, 1 hepatitis B, 1 Mycobacterium kansasii infection, 1 esophageal candidiasis, 1 Varicella pneumonia, 1 histoplasmosis, 1 fungal pneumonia and there was one 1 Mycobacterium abscessus reported on PBO. None of these events resulted in death. No cases of PML were observed. 2 fatal infections (both pneumonias) occurred in the OCR 500-mg group in STAGE.

Conclusions: The pooled SIE rates were increased for OCR 500, but not OCR 200 compared to the PBO group in the DBPC periods with the imbalance primarily driven by rates in Asia. A detailed evaluation of risk factors for SIEs is underway. The same infection-related safety signal seen in the OCR high-dose has not been observed with rituximab.

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Table 1. Summary of serious infection event rates

No. pts with SIE/No. pts in treatment group (%)	Placebo	OCR 200 mg × 2 or OCR 400 mg × 1	OCR 500 mg × 2
STAGE	10/320 (3.1%)	11/343 (3.2%)	21/343 (6.1%)
SIE rate/100 pt-yrs 95% CI	**3.5** (1.7–6.4)	**3.5** (1.8–6.3)	**8.7** (5.7–12.6)
SCRIPT	7/277 (2.5%)	14/277 (5.1%)	12/282 (4.3%)
SIE rate/100 pt-yrs 95% CI	**3.7** (1.7–6.9)	**6.9** (4.0–11.0)	**6.3** (3.6–10.2)
FEATURE	2/64 (3.1%)	5/248 (2.0%)	NA
SIE rate/100 pt-yrs 95% CI	**7.0** (0.8–25.2)	**4.4** (1.4–10.3)	NA
FILM	6/207 (2.9%)	5/196 (2.6%)	10/202 (5.0%)
SIE rate/100 pt-yrs 95% CI	**3.0** (1.1–6.5)	**2.6** (0.9–6.1)	**7.1** (3.9–11.9)
***Pooled weighted Difference OCR minus PBO (95% CI)**		**0.6** (−1.3–2.4)	**2.4** (0.3–4.5)

Region†	Placebo Asia	Placebo Other	OCR 200 mg × 2 Asia	OCR 200 mg × 2 Other	OCR 500 mg × 2 Asia	OCR 500 mg × 2 Other
STAGE (No. pts in subgroup)	N=24	N=296	N=35	N=308	N=37	N=306
SIE rate/100 pt-yrs 95% CI	**4.5** 0.1–25.2	**3.4** 1.6–6.5	**0** 0–11.4	**4.0** 2.0–7.1	**15.0** 4.9–35.0	**7.9** 5.0–12.0
SCRIPT (No. pts in subgroup)	N=37	N=240	N=36	N=241	N=38	N=244
SIE rate/100 pt-yrs 95% CI	**0** 0–11.0	**4.2** 1.9–8.1	**15.1** 4.9–35.2	**5.6** 2.9–9.8	**14.3** 4.6–33.3	**5.0** 2.5–9.0
FILM (No. pts in subgroup)	n=21	N=186	N=17	N=179	N=20	N=182
SIE rate/100 pt-yrs 95% CI	**4.8** 0.1–26.6	**2.8** 0.9–6.5	**0** 0–22.0	**2.9** 0.9–6.7	**30.1** 11.0–65.5	**4.5** 2.0–8.9
****Pooled**	N=82	N=722	N=88	N-728	N=95	N=732
No. SIEs	2	23	5	28	16	41
Total pt-yrs exposure	76.77	657.53	82.24	666.68	88.47	675.13
SIE rate/100 pt-yrs 95% CI	**2.6** 0.3–9.4	**3.5** 2.2–5.3	**6.1** 2.0–14.2	**4.2** 2.8–6.1	**18.1** 10.3–29.4	**6.1** 4.4–8.2

*Patients with at least one serious infection adverse event
**Includes STAGE, SCRIPT and FILM only. Naive pooling, not weighted by study size.
†Asia includes China, Hong Kong, Indonesia, Malaysia, Philippines, Republic of Korea, Singapore, Taiwan, Thailand, and Japan; Other includes North and South America, Europe, and South Africa. CI=confidence interval; NA=not applicable

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Subsequent Therapy of Patients with Biologic Response Modifiers after a Diagnosis of Coccidiomycosis Infection. Sara Taroumian[3], Jeffrey R. Lisse[5], Eric P. Gall[5], Rafael G. Grau[5], Neil M. Ampel[2], Susan E. Hoover[4], James Yanes[4] and Berchman Vaz[1]. [1]Tucson, AZ, [2]Southern Arizona VA Health Care System, Tucson, AZ, [3]The University of Arizona Department of Internal Medicine, Tucson, AZ, [4]The University of Arizona Section of Infectious Diseases, Tucson, AZ, [5]The University of Arizona Section of Rheumatology, Arizona Arthritis Center, Tucson, AZ

Background: Coccidioides (cocci) are dimorphic fungi endemic to California, Arizona, New Mexico, Texas, Mexico, and Central and South America (1). Annually, approximately 100,000 people in the endemic areas of the United States are diagnosed (dx) with primary cocci (2). Chronic and disseminated disease may occur in up to 5% of patients (3); immunocompromised patients are very high risk.

Methods: A chart review of all patients seen at least once in a university-based outpatient rheumatology clinic in Tucson, AZ between 2007–2009 identified 298 patients who received biologic response modifiers (BRM), including anti-TNF drugs (TNF). Twenty four patients developed cocci during treatment with BRM. The review emphasized the mode of dx, clinical manifestations, antifungal treatments, the duration of treatment, and the course of action taken after the dx was made.

Results: Twenty four patients developed cocci during treatment. Prior to cocci dx, 3/24 patients were taking only cytotoxic agents and 2/24 were on unclear immunosuppressive agents. The following table summarizes the medications at the time of dx in the remaining patients.

Medications at the Time of Cocci Diagnosis:

Biologic Response Modifier (BRM)	BRM alone	Cytotoxic agent (one or two in combo with BRM) (Methotrexate, Leflunomide, Azathioprine)
Infliximab (Inf)	9/24	3/24
Etanercept (Etr)	1/24	3/24
Adalimumab (Ada)	0/24	3/24

Mode of Cocci Diagnosis	Pos serologies only (EIA)	Pos serol plus CXR/CT chest findings w/o pulm symptoms	Dissemination to skin, joint or lungs with pulm symptoms
Number of Patients	4/24	13/24	6/24

After the dx was made, all TNFs and DMARDs were held in 13/24 patients. 5/24 continued TNFs and/or DMARDs w/o any change in their regimen and 4/24 continued/started DMARDs but anti-TNFs were held. Two remaining patients had an unclear course of treatment after their cocci dx. Of the 13 patients in whom all TNFs and DMARDs were held, 11/13 were

restarted on either a DMARD alone or in combination with a TNF; 2 were not restarted. 17/24 patients had non-disseminated cocci. 4/17 were treated with Fluconazole (Fluc) until their cocci serol turned negative. 2/17 were lost to follow up. These patients continued to receive anti-TNFs w/o any cocci reactivation. 6/24 patients had severe cocci with dissemination to skin or joints. 5/6 patients will continue Fluc as long as they need to be treated w/ an immunosuppressive agent. Of all the patients reviewed in this study, 4/24 were found to have some evidence of cocci reactivation.

Conclusions: Despite clinicians' hesitation in treating a patient with BRM after dx of cocci, restarting BRM appears to be safe in some patients with non-disseminated disease. Patients with severe or disseminated disease who need to be treated with BRM most likely need to also continue treatment with an antifungal agent.

Disclosure: S. Taroumian: None; **J. R. Lisse:** Centocor, Inc., 2, Genentech and Biogen IDEC Inc, 2, UCB, Inc., 2; **E. P. Gall:** None; **R. G. Grau:** None; **N. M. Ampel:** None; **S. E. Hoover:** None; **J. Yanes:** None; **B. Vaz:** None.

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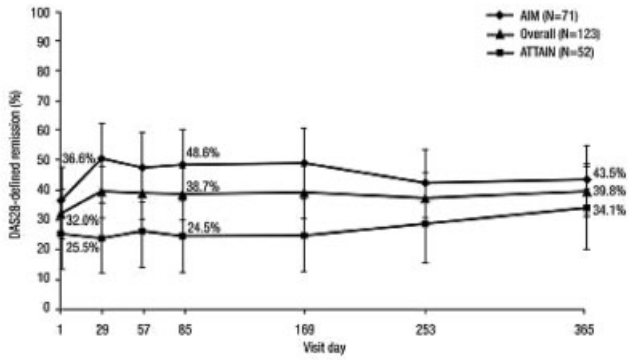
Switching Patients (pts) with Rheumatoid Arthritis (RA) from Intravenous (IV) to Subcutaneous (SC) Abatacept Is Well Tolerated and Sustains Previously Established Efficacy. Edward C. Keystone[9], Joel M. Kremer[6], Anthony S. Russell[7], Jane H. Box[1], Carlos Abud-Mendoza[5], Mario Alberto Garza Elizondo[4], Allison Luo[2], Richard Aranda[2], Ingrid Delaet[2], Rene Swanink[3], Sheila Gujrathi[2] and Michael E. Luggen[8]. [1]Box Arthritis and Rheumatology of the Carolinas, Charlotte, NC, [2]Bristol-Myers Squibb, Princeton, NJ, [3]Bristol-Myers Squibb, Braine-l'Alleud, Belgium, [4]Faculty of Medicine, Universidad Autónoma de Nuevo León, Monterrey, NL, Mexico, [5]Regional Unit of Rheumatology, Faculty of Medicine and Central Hospital, University of San Luis Potosí, San Luis Potosi, Mexico, [6]The Center for Rheumatology, Albany, NY, [7]University of Alberta, Edmonton, AB, Canada, [8]University of Cincinnati College of Medicine, Cincinnati, OH, [9]University of Toronto and Mount Sinai Hospital, Toronto, ON, Canada

Background: IV abatacept is effective and well tolerated in pts with RA[1,2]. For some pts, the flexibility and convenience of self-administered treatment is desirable. Here, we evaluate the safety, immunogenicity and maintenance of efficacy in pts who switched from long-term IV abatacept to SC abatacept formulation.

Methods: This was an open-label, single-arm trial. Consenting and eligible pts completing ~5 years of the AIM (Abatacept in Inadequate Responders to Methotrexate)[1] or ATTAIN (Abatacept Trial in Treatment of Anti-TNF INadequate Responders)[2] IV abatacept trials were enrolled and self-administered SC abatacept 125 mg/week via ready-to-use, prefilled syringes (no IV loading months, clinically indicated adjustments were allowed. Safety for the first 3 months administered). Initially, pts were maintained on the same stable doses of corticosteroids, DMARDs and analgesics received during the IV trials; after 3 after switching from IV abatacept was the primary endpoint, reported in all pts who received ≥1 dose of SC abatacept. Immunogenicity, reported up to Month 3, was assessed by ELISA and electrochemiluminesence (ECL). Proportions of pts achieving Low Disease Activity State (LDAS; DAS28 [CRP] ≤3.2) and DAS28-defined remission (DAS28 [CRP] <2.6) are reported over 1 year. Data are as-observed for patients with available data at the visit of interest.

Results: In total, 123 pts entered the study (AIM, n=71; ATTAIN, n=52); mean age was 54.3 years, mean DAS28 was 3.4 and mean tender and swollen joint counts were 8.9 and 4.8, respectively. At Month 3, 120 (97.6%) pts were ongoing; no pts discontinued due to lack of efficacy. By Month 3, adverse events (AEs) were reported in 49 (39.8%) pts overall. One pt (0.8%) discontinued due to an AE (musculoskeletal pain, unlikely related to treatment) and one pt (0.8%) experienced a serious AE (worsening RA, unrelated to treatment). Two (1.6%) pts had local injection site reactions (erythema, pain); both were mild in intensity. Overall, 8/122 (6.6%) pts had a positive abatacept-induced antibody response by ELISA; six of those eight had a positive response before enrollment. No pt had a positive response based on ECL. The proportions of pts (95% CI) achieving LDAS and remission was sustained after switching from IV to SC abatacept (N=123); LDAS: Day 1, 43.4% (34.6–52.2); Month 3, 54.6% (45.7–63.6); Year 1, 51.3% (42.1–60.5). Remission is shown in Figure 1.



Visit day	1	29	57	85	169	253	365
AIM, n	71	69	69	70	71	71	69
ATTAIN, n	51	50	49	49	48	45	44
Overall, n	122	119	118	119	119	116	113

Error bars represent 95% confidence intervals

Conclusions: These data demonstrate that switching pts from IV to SC abatacept is well tolerated, with few and mild local injection site reactions, and is associated with low immunogenicity. Furthermore, efficacy was sustained and not compromised following the switch.

References:
[1]Kremer JM, et al. *Ann Intern Med* 2006;**144:**865–76
[2]Genovese MC, et al. *N Engl J Med* 2005;**353:**1114–23

Disclosure: E. C. Keystone: Abbott Laboratories, 2, 5, 8, Amgen Inc., 2, 5, 8, AstraZeneca, 2, Bristol-Myers Squibb, 2, 5, 8, Centocor, Inc., 2, 5, Genentech and Biogen IDEC Inc, 5, Hoffmann-La Roche, Inc., 2, 5, 8, Novartis Pharmaceuticals Corporation; **J. M. Kremer:** Abbott Laboratories, 2, 5, Amgen Inc., 2, 5, Bristol-Myers Squibb, 2, 5, Centocor, Inc., 2, 5, Genentech and Biogen IDEC Inc, 2, 5, Merck Pharmaceuticals, 2, 5, Pfizer Inc, 2, 5, Roche, 2, 5; **A. S. Russell:** Bristol-Myers Squibb, 5, 8, 9, GlaxoSmithKline, 5, 8, 9, Pfizer Inc, 5, 8, 9; **J. H. Box:** Box Arthritis and Rheumatology of the Carolinas PLLC, 4, Bristol-Myers Squibb, 5, 8; **C. Abud-Mendoza:** None; **M. A. Garza Elizondo:** None; **A. Luo:** Bristol-Myers Squibb, 1, 3; **R. Aranda:** Bristol-Myers Squibb, 1, 3; **I. Delaet:** Bristol-Myers Squibb, 1, 3; **R. Swanink:** Bristol-Myers Squibb, 3; **S. Gujrathi:** Bristol-Myers Squibb, 3; **M. E. Luggen:** Bristol-Myers Squibb, 2.

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The Effect on MTX Polyglutamate Concentration Profile after Changing from Oral to Subcutaneous Methotrexate in Rheumatoid Arthritis. Lisa K. Stamp[4], John L. O'Donnell[1], Peter Chapman[3], Mei Zhang[2], Jill James[3], Christopher Frampton[5] and Murray Barclay[5]. [1]Canterbury Health Laboratories, Christchurch, New Zealand, [2]Canterbury Health Laboratories, [3]Christchurch Hospital, [4]University of Otago, Christchurch, New Zealand, [5]University of Otago

Background: The pharmacokinetics of oral methotrexate (MTX) in RA have been described previously (1). Some patients may change from the oral to subcutaneous (SC) route of administration to try to reduce adverse effects or improve disease control. The aim of this study was to determine the effect of changing from oral to SC administration of MTX on the concentrations of red blood cell MTX polyglutamates (RBC $MTXGlu_n$).

Methods: Twenty-two patients on stable dose weekly oral MTX were changed to SC weekly MTX at the same dose. Trough RBC $MTXGlu_n$ concentrations were measured by HPLC in samples taken weekly until week 8, then fortnightly until week 16 and then 4-weekly until week 24. Median concentrations were fitted to a standard first-order exponential model with Graph Pad Prism 5.0.

Results: Of the 22 patients, 72.7% were female and mean age was 53.4 years (32–70). The mean duration of RA was 7.3 years (0.75 – 21). All patients were receiving 20mg MTX weekly followed by folic acid 5mg/week four days later. There were no dose changes during the study period.

RBC $MTXGlu_3$, $MTXGlu_4$, and $MTXGlu_5$ concentrations increased significantly from week 0 to week 24, by factors of 1.3, 1.9 and 2.6-fold respectively. However, there was no significant change in RBC $MTXGlu_1$ or $MTXGlu_2$ concentrations. There was a significant reduction in the proportion of RBC $MTXGlu_1$ and $MTXGlu_2$ and increase in the proportions of RBC $MTXGlu_3$, $MTXGlu_4$, $MTXGlu_5$ and $MTXGlu_{3-5}$ contributing to the total RBC MTXGlu from week 0 to week 24.

$MTXGlu_3$, $MTXGlu_4$, $MTXGlu_5$ and $MTXGlu_{3-5}$ concentrations fitted

the first-order exponential model well whilst $MTXGlu_1$ and $MTXGlu_2$ fitted poorly (Figure). The half-life of accumulation was 8.9 weeks for $MTXGlu_3$, 12.2 weeks for $MTXGlu_4$ and 9.9 weeks for $MTXGlu_5$ and 10.4 weeks for $MTXGlu_{3-5}$. The time to achieve 90% of steady state was 29.8 weeks for $MTXGlu_3$, 40.4 weeks for $MTXGlu_4$ and 33.2 weeks for $MTXGlu_5$ and 34.5 weeks for $MTXGlu_{3-5}$.

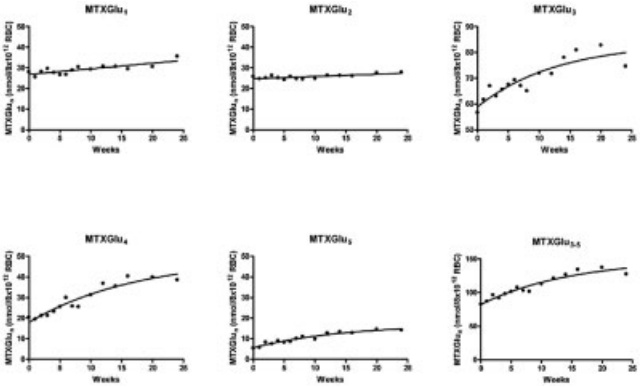

Figure 1. Median $MTXGlu_n$ concentrations and fitted curves over 24 weeks.

Conclusions: Changing from oral to SC MTX resulted in an alteration in the ratio of short and long chain MTX polyglutamates. It took at least 6 months for long chain MTX polyglutamates to reach 90% of steady state after changing to SC administration. However, the time to reach steady state was shorter than that observed in patients commencing oral MTX. Adequate time must be allowed to determine clinical response to a change in route of administration of MTX.

Reference:

1. Dalrymple JM, Stamp LK, O'Donnell JL, Chapman PT, Zhang M, Barclay ML. Pharmacokinetics of Oral Methotrexate in Patients with Rheumatoid Arthritis. Arthritis Rheum 2008;58:3299–308.

Disclosure: L. K. Stamp: None; **J. L. O'Donnell:** None; **P. Chapman:** None; **M. Zhang:** None; **J. James:** None; **C. Frampton:** None; **M. Barclay:** None.

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TNF Switch after Failure of One or More TNF Inhibitors—Results of an Observational Study. Katerina Chatzidionysiou[2] and Ronald Van Vollenhoven[1]. [1]Karolinska University Hospital, Stockholm, Sweden, [2]Karolinska University Hospital, Stockholm

Background: The optimal alternative treatment for those patients who fail an anti-TNF is not clearly described. The purpose of this study was to determine whether patients who had failed one or more anti-TNFs benefit from switching to another anti-TNF and whether the type of switch is significant.

Methods: The Stockholm registry ''STURE'' was used and treatment results at 3 and 6 months were analysed according to DAS28 reductions and EULAR responses by type of TNF switch, number of switches and reason for discontinuation (lack of efficacy or intolerance).

Results: 850 patients who had previously failed a TNF inhibitor switched to another biologic: 679 switched to an alternative TNF antagonist, 308 to etanercept, 294 to adalimumab and 77 to infliximab. By the end of 6 months statistically significant improvements in DAS28 were observed ($p<0.0001$ for etanercept and adalimumab and $p=0.006$ for infliximab). At 3 and 6 months significantly greater reductions in DAS28 were observed for etanercept compared to the anti-TNF monoclonal antibodies taken together (1.56 ± 1.34 vs. 1.14 ± 1.26, $p=0.005$ and 1.58 ± 1.46 vs. 1.15 ± 1.4, $p=0.01$, respectively). At 6 months the percentage of EULAR good/moderate/no responders was 16.6/38.7/44.7 for the anti-TNF monoclonal antibodies and 29.4/35.3/35.3 for etanercept ($p=0.009$). Table 1 summarizes the response to therapy according to the type of switch. The difference between etanercept and monoclonal antibodies was observed both for the second and the third switch. At 6 months the subgroup of patients who discontinued previous anti-TNF monoclonal antibody for reason of loss of efficacy achieved significantly better results when switched to etanercept than when switched to an alternative antibody (ΔDAS28 2.11 ± 1.5 vs. 1.09 ± 1.43, $p=0.008$).

Table 1. Response to therapy with an alternative TNF inhibitor (monoclonal antibody or soluble TNF receptor) according to DAS28 reductions and EULAR response during the first 6 months.

	TNF monoclonal ab ↓ TNF monoclonal ab	TNF monoclonal ab ↓ Etanercept	Etanercept ↓ TNF monoclonal ab
ΔDAS28 at 3 months	1.15 ± 1.51	1.56 ± 1.33	1.15 ± 1.12
ΔDAS28 at 6 months	1.24 ± 1.5	1.57 ± 1.45	1.22 ± 1.25
EULAR Good response	20.9%	29.4%	15.4%
EULAR Moderate response	29.8%	35.3%	41.9%
EULAR No response	49.3%	35.3%	42.7%

Conclusion: In this observational cohort patients having failed anti-TNF therapy do benefit from switching to other TNF inhibitors. Better results were observed when switching from a TNF monoclonal antibody to etanercept rather than to an alternative antibody, especially when the reason for failure of the first was loss of efficacy.

Disclosure: K. Chatzidionysiou: None; **R. Van Vollenhoven:** Roche, 2, 5.

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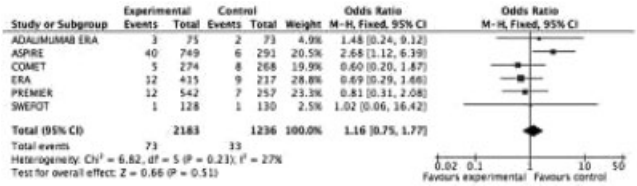
TNF Therapy and the Risk of Serious Infection and Malignancy in Patients with Early Rheumatoid Arthritis: A Meta-Analysis of Randomized Controlled Trials. Andrew E. Thompson[2], Janet E. Pope[1] and Scott W. Rieder[3]. [1]St Joseph Health Care London, London, ON, Canada, [2]University of Western Ontario, London, ON, Canada, [3]University of Western Ontario

Background: The efficacy of TNF-inhibition has been shown in numerous trials including patients with both early and established rheumatoid arthritis (RA). As a result, TNF-inhibition has significantly improved the signs and symptoms, function, radiographic progression and quality of life for patients with RA. The most important side effects of TNF-inhibition are the risks of serious infection and the potential for malignancy. Although product monographs include warnings & precautions about these side effects they do not provide an estimate of risk. Meta-analysis of published clinical trial data and registry data are common methodologies used to estimate this risk. However, the challenge with current meta-analytic data and on-going registry data is the inclusion of heterogeneous populations with varying degrees of co-morbidity. This heterogeneity makes it very difficult to understand and communicate risk for individual patients. It is important to know if early RA has the same risk of serious infection or malignancy compared with older patients with long-standing RA and multiple co-morbidities.

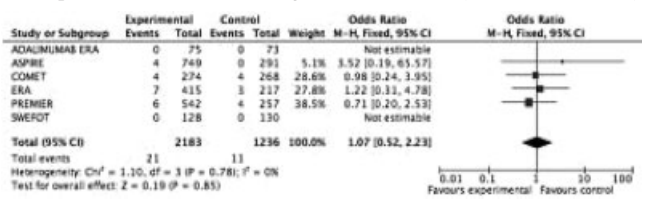
Objective: To conduct a meta-analysis of the rates of serious infection and malignancy in patients with early rheumatoid arthritis who have were started on anti-TNF therapy and were naïve to DMARD/Methotrexate therapy.

Methods: A systematic literature search was conducted through the summer of 2009. All studies included were randomized, double-blind, placebo-controlled of patients with early rheumatoid arthritis who were started on anti-TNF therapy without prior DMARD/Methotrexate use. Six trials met our inclusion criteria that included 2183 patients receiving biologic therapy and 1236 patients receiving control therapy. All data extracted was from published trials.

Results: A pooled odds ratio (Mantel-Haenszel methods with a continuity correction designed for sparse data) was calculated for serious infections (requiring hospitalization) and malignancies. The pooled odds ratio for serious infections was 1.16 (95% CI, 0.75–1.77).



The pooled odds ratio for malignancies was 1.07 (95% CI, 0.52–2.23).



There was no significant difference between the anti-TNF therapy and the control therapy in both serious infection rates and malignancy rates.

Conclusions: While other meta-analyses have shown an increased risk of serious infection and malignancy in patients taking anti-TNF therapy, our results show that there is not an increased risk when the patients have early disease and haven't previously failed DMARD/Methotrexate therapy.

Disclosure: A. E. Thompson: Abbott Laboratories, 5, Amgen Inc., 5, Bristol-Myers Squibb, 5, Roche, 5, Takeda Pharmaceuticals North America, 5, UCB, Inc., 5; **J. E. Pope:** Abbott Laboratories, 5, Actelion Pharmaceuticals US, 5, Amgen Inc., 5, Bristol-Myers Squibb, 5, Roche, 5, UCB, Inc., 5, Wyeth Pharmaceuticals, 5; **S. W. Rieder:** None.

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Treatment with Infliximab Improves Clinical Response and Physical Function in Patients with Moderate or Severe Rheumatoid Arthritis Actively Switch from Etanercept or Adalimumab Therapy. Roy M. Fleischmann[8], John A. Goldman[2], Marjatta Leirisalo-Repo[4], Ellen I. Zanetakis[7], Hisham S. El-Kadi[1], Herbert L. Kellner[6], Rebecca Bolce[3], Jim Wang[5], Raphael Dehoratius[3] and Dennis Decktor[3]. [1]Arthritis and Osteoporosis Association, Freehold, NJ, [2]Atlanta Center for Clinical Research, [3]Centocor Ortho Biotech Services, LLC, [4]Helsinki University Central Hospital, Helsinki, Finland, [5]Johnson and Johnson Pharmaceutical Research and Development, LLC, [6]Medizinische Poliklinik/Munich University Hospital, Munchen, Germany, [7]Oklahoma Center for Arthritis Therapy, Tulsa, OK, [8]University of Texas SW Medical Center, Dallas, TX

Background: Anecdotal evidence suggests that RA pts with active disease, despite tx with SC TNFα inhibitors, respond to infliximab (IFX). The dosing flexibility described in the IFX prescribing information allows for the tx of continued active disease by adjusting dose for achievement of specific targeted clinical outcomes.

Purpose: To evaluate the safety & efficacy of IFX in RA pts with moderate or severe RA despite tx with etanercept (ETN) or adalimumab (ADA).

Methods: This is a Phase 4, multicenter, open-label, assessor-blinded, active switch study of IFX in pts with active RA who received MTX and had inadequate response (DAS28 score $\geq$ 3.6 and $\geq$ 6 swollen and $\geq$ 6 tender joints) to ETN or ADA. Pts were on stable dose of $\geq$ 7.5 mg/wk of MTX for $\geq$4 wks prior to screening. Pts receiving ETN were switched no less than 1 wk and no more than 2 wks after the last dose; pts receiving ADA were switched no less than 2 wks and no more than 4wks after the last dose. Pts received open-label 3 mg/kg IFX infusions at wks 0, 2, and 6. Pts who either achieved/maintained EULAR response at wks 14 or 22 remained on current IFX dose. IFX dose was increased by 2 mg/kg for pts who did not achieve/lost response. EULAR response was evaluated at wk 10 post induction (primary endpoint) and following incremental increases in IFX dose in pts not adequately responding to the initial IFX doses. Physical function was assessed using HAQ.

Results: Of the 203 pts enrolled, data for 197 were evaluable. 60.9% and 39.1% of pts were previously treated with ETN or ADA, respectively. Baseline demographics were reported previously.[1] EULAR response was achieved by 49.7% of pts at wk 10 (55.6%, per protocol analysis) and 51.8% at wk 26 (61%, per protocol analysis) with/without dose adjustment. Among pts responsive to 3mg/kg induction dose, 45% maintained response through wk 26. ACR 20, 50, and 70 responses were achieved in 28.4%, 12.2 %, and 1.5% of pts at wk 10, respectively. These responses improved to 35.5% (ACR20), 18.3% (ACR50), and 7.1% (ACR70) at wk 26. Mean CDAI and SDAI were 40.1 and 41.2, respectively, at baseline and significantly improved to 21.45 ($p< 0.001$) and 22.28 ($p<0.001$), respectively, at wk 26. 48.3% of pts previously treated with ETN and 57.1% of pts previously treated with ADA achieved a EULAR response at wk 26. Changes from baseline at wk 10 and 26 in DAS 28, HAQ, SJC, and TJC are described (Table). At least 1 AE and serious AE were reported in 70.4% and 4.9% of pts, respectively; 6.9% of pts experienced at least 1 infusion reaction (1.6% of infusions were associated with an infusion reaction).

Conclusion: RA pts actively switched from tx with ETN or ADA to IFX, without a washout period, demonstrated a statistically significant and clinically important improvement in EULAR response and physical function. IFX was generally well-tolerated with no new safety signals observed.

Table. Summary of mean (SD) change from baseline at wks 10 and 26

	Baseline	Change from baseline to wk 10	Change from baseline to wk 26
DAS28 (ESR)	6.193 (0.981)	−1.076 (1.146)*	−1.468 (1.437)*
DAS28 (CRP)	5.701 (0.896)	−1.088 (1.090)*	−1.436 (1.312)*
HAQ improvement	1.334 (0.577)	−0.173 (0.455)*	−0.223 (0.497)*
SJC	17.335 (10.537)	−6.960 (10.686)*	−8.283 (11.380)*
TJC	30.188 (16.893)	−10.460 (14.067)*	−13.197 (14.304)*

*$p < 0.001$

1. R. Fleischmann, J. Goldman, M. Leirisalo-Repo et al. *Ann Rheum Dis* 2010; 69(Suppl3):531.

Disclosure: R. M. Fleischmann: Centocor Ortho Biotech Services, LLC, 2, 9; **J. A. Goldman:** Centocor Ortho Biotech Services, LLC, 2, 9; **M. Leirisalo-Repo:** Centocor Ortho Biotech Services, LLC, 2, 9; **E. I. Zanetakis:** Centocor Ortho Biotech Services, LLC, 2, 9; **H. S. El-Kadi:** Centocor Ortho Biotech Services, LLC, 2, 9; **H. L. Kellner:** Centocor Ortho Biotech Services, LLC, 2, 9; **R. Bolce:** Centocor Ortho Biotech Services, LLC, 3; **J. Wang:** Johnson and Johnson Pharmaceutical Research and Development, LLC, 3; **R. Dehoratius:** Centocor Ortho Biotech Services, LLC, 3; **D. Decktor:** Centocor Ortho Biotech Services, LLC, 3.

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Varicella Zoster Virus (VZV) Infections Are Increased in Patients with Rheumatoid Arthritis (RA) Treated with Anti-TNF Therapy; Results from the British Society for Rheumatology Biologics Register (BSRBR). James Galloway[1], Alison Moseley[2], Lousie Mercer[2], Will Dixon[2], Bo Fu[2], Andrew Ustianowski[2], Kath Watson[2], Mark Lunt[2], BSRBR Control Centre Consortium[2], Kimme Hyrich[2], Deborah Symmons[2] and on Behalf of the British Society for Rheumatology Biologics Register[2]. [1]University of Manchester, Manchester, United Kingdom, [2]University of Manchester

Introduction: VZV infection is highly prevalent with 95% of adults showing seropositivity. The initial infection typically occurs in childhood causing chicken pox. Reactivation later in life results in herpes zoster (shingles). The immune defence against both chicken pox and herpes zoster is T-cell mediated. Anti-TNF therapy interacts with this pathway and hence theoretically predisposes to VZV associated disease. The aim of this study was to compare rates of herpes zoster in rheumatoid arthritis (RA) patients treated with anti-TNF agents or non-biologic disease modifying anti-rheumatic drugs (DMARDs); and to compare the rates for the individual anti-TNF agents.

Methods: The BSRBR was established in 2001 to evaluate the safety of anti-TNF therapies etanercept (ETN), infliximab (INF) and adalimumab (ADA) in patients with RA. The anti-TNF treated cohort was recruited alongside a comparator group with active disease (DAS28 >4.2) treated with DMARDs. Patients were recruited between 01/10/2001 and 30/06/2008 and followed up by consultant and patient questionnaires. For this analysis patients were followed until the first episode of herpes zoster infection, death or 31/12/2009, whichever came first. An infection was attributed to anti-TNF if diagnosed while the patient was actively receiving the drug (up to the date of the first missed dose). A Cox proportional hazards model was used to compare rates between cohorts and adjustment was made for differences in baseline characteristics including age, gender, disease severity, disease duration, baseline steroid exposure and co-morbidity using an inverse probability of treatment weighting propensity model.

Results: (see table)

Three hundred and twenty two herpes zoster infections occurred in the anti-TNF cohort: IR 7.8/1000 (pyrs) (95% CI 7.0, 8.7) and 46 in the DMARD cohort (IR 4.0/1000 pyrs (95% CI 3.0, 5.4) (Table). The adjusted hazard ratio for herpes zoster was 2.2 (95% CI 1.4, 3.6). A greater proportion of the cases in the anti-TNF cohort were severe (defined as herpes zoster being a primary reason for hospitalisation, requiring intravenous antivirals or being multidermatomal) 6% vs 0.02%. A similar pattern of risk was seen for each anti-TNF therapy with no statistical difference between etanercept and the monoclonal antibodies. In total, 12 cases of chicken pox infection were reported in the anti-TNF cohort and none in the DMARD cohort.

Conclusion: Anti-TNF therapy is associated with a significantly increased risk of VZV associated disease. This information would support the evaluation of VZV vaccination in an RA population.

Table. Baseline characteristics and incidence of VZV infections

	DMARD	All anti-TNF	ETN	INF	ADA
Subjects, n	3,666	11,864	4,136	3,472	4,256
Mean age, years (SD)	60 (12)	56 (12)	56 (12)	56 (12)	57 (12)
Female gender, (%)	2648 (72)	9038 (76)	3190 (77)	2624 (76)	3224 (76)
Disease Duration: years, median (IQR)	6 (1–15)	11 (6–19)	12 (6–19)	12 (6–19)	10 (5–18)
Baseline steroid use: n (%)	834 (23)	5243 (44)	1977 (48)	1609 (46)	1657 (39)
DAS28, mean (SD)	5.1 (1.3)	6.6 (1.0)	6.6 (1.0)	6.6 (1.0)	6.5 (1.0)
Exposure (pyrs)	11,417	41,235	17,977	10,484	12,773
Shingles events (n)	46	322	121	103	98
Shingles incident rate/1000 pyrs	4.0 [3.0, 5.4]	7.8 [7.0, 8.7]	6.7 [5.6, 8.0]	9.8 [8.0, 11.9]	7.7 [6.2, 9.3]
Shingles adjusted HR*	Ref	2.2 [1.4, 3.6]	2.2 [1.3, 3.6]	2.5 [1.5, 4.0]	2.1 [1.2, 3.7]
Chicken pox (n)	0	12	6	3	3

*Adjusting for potential confounders was performed using an inverse probability of treatment weighted propensity model including age, gender, co-morbidity, smoking, baseline steroid exposure, disease duration, disease severity and year of entry into study. Missing baseline data were replaced using multiple imputation.

Disclosure: J. Galloway: None; **A. Moseley:** None; **L. Mercer:** None; **W. Dixon:** None; **B. Fu:** None; **A. Ustianowski:** None; **K. Watson:** None; **M. Lunt:** None; **BSRBR Control Centre Consortium:** None; **K. Hyrich:** None; **D. Symmons:** None; **on Behalf of the British Society for Rheumatology Biologics Register:** None.

ACR Poster Session A
Systemic Lupus Enrythematosus - Animal Models
Monday, November 8, 2010, 9:00 AM–6:00 PM

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Altered microRNA Expression in the Murine Tri-Congenic B6.Sle123 Model. Barry Garchow[1], Yiu Tak Leung[3], Roberto Caricchio[2] and Marianthi Kiriakidou[1]. [1]Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, [2]Temple Univ Med Office Bldg, Philadelphia, PA, [3]Thomas Jefferson University Hospital, Philadelphia, PA

Statement of Purpose: microRNAs (miRNAs) have emerged over the last decade as a conserved class of non-coding RNAs that regulate gene expression. Current evidence supports a key role for miRNAs in the development and function of the immune system and emerging evidence underscores the importance of this pathway in autoimmunity. However, the expression and function of miRNAs in SLE and the signaling pathways regulated by miRNAs in lupus remain largely unknown.

Research in our laboratory focuses on the function of miRNAs in the tri-congenic mouse model B6.Sle123. Autoimmune disease in B6.Sle123 is characterized by autoantibodies, lymphosplenomegaly and glomerulonephritis, strongly resembling human lupus. We studied miRNA expression in mouse lupus B and T cells over the course of twelve months; before manifestation of renal disease and as it progresses from mild proteinuria to fatal nephrotic syndrome.

Methods: Mice (B6.Sle123 and C57BL6/J) were sacrificed at 2, 6 and 12 months of age and their spleens harvested. Splenocytes from individual mice were FACS purified into CD19+, CD3+CD44lowCD62Lhigh and CD3+CD44lowCD62Lhigh cell populations. For quantitative real-time PCR, total RNA from purified cells was reverse-transcribed using microRNA specific stem-loop primers. RT products were amplified by real-time PCR. Fold expression differences were calculated using the ΔΔCt method. For Northern blotting, total RNA from purified cells was separated on 15% urea-polyacrylamide gels, blotted and UV crosslinked. microRNAs were visualized by autoradiography and quantitated using the GelQuant software. For Western blotting, total protein from purified cells were separated by PAGE and blotted on nitrocellulose membranes. Bands were visualized by chemiluminescence and quantitated with ImageJ software.

Data Summary: We asked if altered microRNA expression in B6.Sle123 B and T lymphocytes correlates severity of renal disease. Here we report that several microRNAs are differentially expressed in B and T lymphocytes from lupus mice and their expression correlates with the severity of lupus nephritis. All eight miRNAs that we showed as upregulated in B cells from mice with severe SLE nephritis (miR-21, 34a, 221, 222, 223, 155 and 142-5p) and have been also recently reported as upregulated in human lupus nephritis.

Conclusions: Our findings show that several microRNAs with known key roles in the development and function of lymphocytes are differentially expressed in B6.Sle123 derived B and T cells and their expression correlates with the severity of renal disease. Correlation of our results with recently published data of miRNA expression in PBMCs from patients with lupus nephritis indicates that B6.Sle123 is a suitable model to study the miRNA function in lupus. We are now focusing on identifying miRNA-dependent signaling pathways that are uniquely affected in this model, in which disease manifestations and disordered mechanisms overlap with those in human SLE. In our studies we employ novel in vivo experimental methods to knock down endogenous miRNAs in B and T cells in order to dissect these pathways.

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Amelioration of Lupus Nephritis by a Macromolecular Prodrug of Dexamethasone in NZB/W F1 Mice. Fang Yuan[2], Richard K. Nelson[2], Xin-ming Liu[2], Karen A. Gould[2] and Dong Wang[1]. [1]Univ Nebraska Med Ctr, Omaha, NE, [2]University of Nebraska Medical Center

Purpose: Though developed with specific molecular targets, most lupus nephritis drugs do not have tissue specificity to renal inflammation sites, leading to limited efficacy and potentially severe systemic side effects. To address this problem, we propose to develop P-Dex, a macromolecular prodrug of dexamethasone (Dex) using N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer, which would specifically target the kidneys of lupus nephritis subjects to improve efficacy and reduce systemic toxcities associated with Dex phosphate treatment.

Methods: Female NZB/W F1 lupus-prone mice (16-wk-old) were treated with Dex phosphate (1.32 mg/kg, daily i.p. injections for 8 wks) and P-Dex (250 mg/kg, monthly i.v. injections for 8 wks) with HPMA homopolymer (PHPMA) and saline as controls. The overall doses of P-Dex and Dex phosphate are equivalent in terms of Dex content. Albuminuria was measured weekly using Ablustix. Mean arterial pressure (MAP) was measured by the tail cuff method every 4 wks. Serum was isolated from blood collected from the saphenous vein every 4 wks. Mice were sacrificed 1 wk after cessation of treatment (wk 9). Kidneys were harvested for histological assessment of nephritis. Femurs were harvested for bone mineral density (BMD) analysis.

Results: P-Dex treatment of NZB/W F1 mice resulted in an attenuated onset of nephritis (as measured by durable albuminuria $\geq$ 2 or 100 mg/dL). At wk 9, the incidence of albuminuria was 0% in the P-Dex group, whereas the incidence of albuminuria was 100% in saline treated group, 70 % in PHPMA group and 46.7% in Dex phosphate group ($p<0.001$). A significant improvement of hypertension (MAP was reduced from 134 ± 16 mmHg to 110 ± 11 mmHg, $p < 0.01$) was only found in P-Dex treated group. Furthermore, the P-Dex treated group had a significantly higher femur BMD value than the Dex phosphate group ($p < 0.001$). No significant difference in BMD value was found among the P-Dex, saline and PHPMA groups.

Conclusion: P-Dex displayed highly efficient attenuation of lupus nephritis and improved renal function, compared to the treatment with equivalent dose Dex phosphate. It also significantly reduced the bone loss caused by long-term Dex phosphate treatment. Collectively, these data suggest that the macromolecular prodrug of dexamethasone could provide more effective amelioration of lupus nephritis with reduced systemic toxicity.

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An Intrinsic B Cell Defect That Affects Toll-Like Receptor Signaling Supports Autoimmunity in New Zealand Black Chromosome 13 Congenic Mice. Christina Loh[2], Evelyn Pau[3], Nan-Hua Chang[1] and Joan E. Wither[2]. [1]University Health Network, [2]University of Toronto, Toronto, ON, Canada, [3]University of Toronto

Purpose: Introgression of a New Zealand Black (NZB) chromosome 13 interval onto the B6 background (denoted, c13) is sufficient to produce many of the hallmarks of lupus, including, high titre anti-chromatin antibody (Ab) production, abnormal B and T cell activation, and renal disease. In this study we sought to characterize the immune defects leading to these pathogenic abnormalities.

Methods: Bone marrow (BM) chimeras were generated by reconstituting lethally irradiated B6, B6.Thy1aIgHa, or B6.CD45.1 mice with B6, B6.Thy1aIgHa, B6.CD45.1, c13, c13.Ig, or various mixtures of BM cells.

Anti-hen egg lysozyme (HEL) immunoglobulin (Ig) and/or soluble HEL transgenes (Tg) were crossed onto the c13 mouse strain (denoted, c13.Ig and c13.Ig.sHEL) to assess B cell tolerance. Antibody production was measured by ELISA and splenic cellular profiles were examined by flow cytometry. For Toll-like receptor (TLR) stimulation, splenocytes from 10–14 week old B6, c13, B6.Ig, or c13.Ig mice were cultured in the presence of poly(I:C) (TLR3), imiquimod (TLR7), or ODN1826 (TLR9) and/or HEL for 72 hrs. Proliferation was measured by CFSE dilution.

Results: Serologic and cellular characterization of hematopoietic radiation chimeras and anti-HEL Ig transgenic mice revealed that the autoimmune phenotype in c13 mice could be transferred by BM cells. Assessment of mixed hematopoietic chimeric and c13.Ig mice indicated that autoreactive congenic B cells were required for disease initiation. Examination of c13.Ig.sHEL mice, a classic model of B cell anergy, revealed that B cell anergy was intact in congenic mice. However, there was enhanced selection and/or survival of endogenous B cells resulting in high titer anti-chromatin and -Sm/RNP antibody production in these mice. Given the preferential generation of anti-nuclear over anti-HEL antibodies, we examined whether nucleic-acid sensing TLR signaling was altered in these mice. Congenic B cells were hyper-responsive to the TLR3 ligand, polyinosine-polycytidylic acid (poly(I:C)), a double stranded RNA analogue, demonstrating enhanced proliferation, survival, and induction of intracellular TLR3 expression as compared to control B cells. Using mixed cell cultures, this response was found to be intrinsic to congenic B cells.

Conclusions: An intrinsic defect affecting self-reactive B cell selection and/or function that is associated with TLR3-hyper-responsiveness is required for initiation of autoimmunity in NZB chromosome 13 congenic mice.

Disclosure: C. Loh: None; **E. Pau:** None; **N.-H. Chang:** None; **J. E. Wither:** None.

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Breach of B Cell Tolerance in New Zealand Black Chromosome 1 Congenic Mice. Nan-Hua Chang[1], Evelyn Pau[3], Christina Loh[3] and Joan E. Wither[2]. [1]Toronto Western Research Institute, Toronto, ON, Canada, [2]University Health Network, Toronto, ON, Canada, [3]University of Toronto

Purpose: The production of anti-nuclear antibodies in lupus indicates a breach of B cell tolerance, however the precise defects that lead to this breach are unknown. Our laboratory has produced C57BL/6 (B6) congenic mice with homozygous NZB chromosome 1 intervals and localized the genetic locus leading to autoantibody production in these mice to a 96–100 cM interval, which contains *Nba2*. In this study we have backcrossed anti-hen egg white lysozyme (HEL) Ig and soluble HEL transgenes (double Tg, dTg) onto the B6.NZBc1(96–100 cM) background to assess B cell anergy.

Methods: Serum IgM and IgG anti-HEL antibody production was measured by ELISA. Splenic B cell populations were characterized by flow cytometry. Upregulation of CD86 and B cell apoptosis was determined by flow cytometry following stimulation of splenocytes with anti-IgM $F(ab)'_2$ Ab or HEL for 18 hrs. To quantify phosphatidylinositol 3,4,5,-triphosphate production ($PI(3,4,5)P_3$), splenocytes were stimulated with anti-IgM $F(ab)'_2$ Ab for 5 min, fixed with 1% paraformaldehyde, stained intracellularly with an anti-$PI(3,4,5)P_3$ Ab. Calcium flux was measured by stimulating Indo-1-labeled immature anti-HEL Ig Tg B cells (generated by culturing bone marrow in IL-7 for 5 days) with anti-IgM $F(ab)'_2$ Ab.

Results: B6.NZBc1(96–100 cM) dTg B cells produced increased levels of IgM and IgG anti-HEL Abs indicating a breach of B cell anergy in these mice. IgM^a down-regulation and the proportion of T1, T2, follicular and marginal zone B cells were similar in B6 and B6.NZBc1(96–100 cM) dTg mice, however B6.NZBc1(96–100 cM) dTg mice had an increased proportion of IgM^a B cells expressing edited Ig-lambda light chains. Following stimulation with anti-IgM Ab or sHEL, B cells from B6.NZBc1(96–100cM) dTg mice demonstrated enhanced up-regulation of CD86 and decreased apoptosis, suggesting defective anergy induction. To gain further insight into the mechanism leading to this defect, upregulation of $PI(3,4,5)P_3$ was contrasted in B6 and B6.NZBc1(96–100 cM) dTg B cells following Ig receptor cross-linking. B6.NZBc1(96–100 cM) dTg B cells demonstrated enhanced generation of $PI(3,4,5)P_3$, indicating that altered B cell signaling leads to the B cell anergy defect. Consistent with this possibility, calcium mobilization was impaired in naïve immature anti-HEL Ig Tg B cells from B6.NZBc1(96–100cM) mice following Ig receptor cross-linking

Conclusion: Our findings demonstrate that genetic loci within the NZB chromosome 1 (96–100 cM) interval lead a breach of B cell anergy.

Disclosure: N.-H. Chang: None; **E. Pau:** None; **C. Loh:** None; **J. E. Wither:** None.

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Dysfunction of Hematopoietic Stem Cells in Lupus Mice. Haitao Niu[2], Luokun Xie[3], Laurence Marguerite Morel[4], Betty Diamond[1] and Yong-rui Zou[3]. [1]Feinstein Institute for Medical Research, Manhasset, NY, [2]The Feinstein Institute for Medical Research, Manhasset, NY, [3]The Feinstein Institute for Medical Research, [4]University of Florida

Background: Systemic lupus erythematosus (SLE) is a multi-organ autoimmune disorder. Among the various clinical manifestations of SLE, leukopenia and lymphopenia represent the most prevalent initial abnormality, and are associated with higher disease activity. The specific cause of leukopenia and lymphopenia in SLE is unknown. Conceivably, the chronic inflammatory milieu may impair the maturation and survival of hematopoietic cells. Alternatively, hematopoietic stem cells (HSCs) of SLE patients may be functionally defective, thereby resulting in poor hematopoietic regeneration. We investigated whether HSC function is impaired in a mouse model of SLE, and whether the change in HSC function is a cell-intrinsic event or affected by the microenvironment of SLE.

Materials and Methods: We determined whether HSCs undergo functional changes in B6.Sle1.2.3 triple congenic (TC) mice. TC mice are C57/BL6 mice that carry three NZM2410-derived major lupus susceptibility loci and develop severe systemic autoimmunity and fatal nephritis. 7-month-old TC female mice with high levels of autoantibodies and proteinuria were selected for the studies. B6 female mice were used as controls. *First, we examined whether the pool size of HSCs was changed in TC mice.* We determined the HCS cellularity in the bone marrow (BM) by flow cytometry. Primitive hematopoietic cells were detected with antibodies for lineage negative (Lin^-: B220, CD3, CD4, CD8, CD11b, Gr1, TER119) and $c\text{-}Kit^+$ and $Sca\text{-}1^+$ (referred to as LSK cells). Long-term reconstituting HSCs (LT-HSCs) were further identified as $CD48^-$ $CD34^-CD150^+$ LSK cells. *Second, we examined whether the pathological microenvironment of lupus mice alters HSC quiescence* by measuring the cell-cycle status of HSCs based on their content of pyronin stained RNA and Hoechst stained DNA. *Third, we examined whether HSC localization was altered in lupus mice* by determining the HSC frequency in the periphery. *Lastly, we analyzed HSC function by transplantation assays.* To do so, 2×10^6 BM cells from TC or control C57/BL6 mice ($CD45.2^+$) were transferred into irradiated B6.SJL mice ($CD45.1^+$). Four months later, hematopoietic reconstitution was determined by the frequencies of donor derived ($CD45.2^+$) HSCs, lymphocytes and myeloid lineage cells.

Results: We found that LT-HSCs were 4-fold more abundant in the BM of TC mice than that in control mice. This expansion of the HSC compartment was accompanied by an increase in the number of cycling HSCs in the BM and mobilization of HSCs in the periphery in TC mice. More importantly, HSCs from TC mice transplanted into healthy recipients displayed altered HSC function, indicating a cell-intrinsic defect. Finally, we found that HSCs from TC mice showed a bias towards differentiation into the myeloid versus the lymphoid lineage.

Conclusion: Our data demonstrate that HSC function is altered in lupus mice through a cell-autonomous process. The dysfunction of HSCs in lupus mice may contribute to lymphopenia observed in SLE patients. These results highlight the importance of restoring HSC function for lupus therapy.

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Engraftment of PBMC from SLEand ACL Donors into BALB-Rag2−/− IL2Rgc-KO Mice: A Promising Model for Studying SLE. Danieli Andrade[1], Milena Vukelic[2], Patricia B. Redecha[1], Xiaoping Qing[1], Giorgio Perino[3], Jane E. Salmon[2] and Gloria C. Koo[4]. [1]Hospital for Special Surgery, NY, NY, [2]Hospital for Special Surgery, New York, NY, [3]Hospital for Special Surgry, NY, NY, [4]Hospital for Speicail Surgery, New York, NY

Purpose: Our goal was to construct a SLE mouse model that resembles the human disease and has human cells which may be studied to define pathophysiology and targeted for treatments.

Methods: We infused peripheral blood mononuclear cells (PBMC) from SLE patients into the severe combined immuno-deficient mouse, BALB-Rag2 −/− IL2Rgc −/− mice (DKO), which lack T, B and NK cells. PBMC from 5 SLE patients (5 anti-dsDNA positive and 2 of these were ACL positive) and 4 normal donors (ND) at 3–5 ×106/mouse were infused IV and IP to non- irradiated 4–5 weeks old DKO mice, 2–5 DKO mice/donor. We evaluated the engraftment of human CD45+ cells and lymphocyte subsets.

We monitored the plasma human IgG concentration, anti-dsDNA antibody, anti-cardiolipin (CL) antibody, proteinuria, and performed histologic examination of the liver and kidney.

Results: We found 100% engraftment of human PBMC in 38 DKO mice studied. In both SLE-DKO and ND-DKO mice, we found 5–10% human CD45+ cells in the PBMC fraction 2 weeks post engraftment, and these cells expanded to 50–80% at 4–6 weeks. PBMC from both SLE-DKO and ND-DKO mice contained 70–90% human CD3+ cells. In SLE-DKO mice, as reported in SLE patients, there were fewer CD3+4+cells (5.1±1.9 %) and more CD3+8+ cells (81.6± 3.9 %), significantly different from that in ND-DKO mice, which had normal distribution of CD3+CD4+ (66.2 ±2.5 %) and CD3+8+ (16.5 ± 2.1%) cells in the PBMC (SLE-DKO vs. ND-DKO: P<1.3E-08 for CD4+, P< 2.1E-07 for CD8+ populations). CD19+ B cells were present mainly in the peritoneum and bone marrow, and CD11c cells were found in the spleen. Human CD45+ cells, assessed by FACS analyses, were also present in the lung, liver, and kidney. There was no significant difference in plasma human IgG levels between SLE-DKO and ND-DKO mice (32.3 ±13 and 26.4 ±7 ug/ml, respectively). Anti-dsDNA antibodies were found in SLE-DKO mice (3.97 ± 1.6 IU/ml) and lower in ND-DKO mice (2.2 ± 0.7 IU/ml, DKO=1 ± 0.02), but not significantly different between the 2 groups (P<0.25). Strikingly, levels of ACL antibody were higher in all SLE-DKO mice infused with cells from an ACL positive patient (SLE-DKO, 8.5 ±1.4 vs ND-DKO, 3.6 ± 0.2 GCL-U; P<0.019, un-engrafted DKO, 3.6 ± 0.8 GCL-U). SLE-DKO mice had evidence of nephritis. After 4–6 weeks of engraftment, they had proteinuria, (SLE-DKO: 93.5 ± 25 ug/mg; ND-DKO: 22 ± 3.3 ug/mg albumin/creatinine; P<0.01; un-engrafted DKO:17.8 ug/mg). Kidney sections showed human IgG deposits. In SLE- DKO mice engrafted with PBMC from an ACL-positive patient, we found micro-thrombi in the glomeruli of the kidney, and the liver showed fibrosis and necrosis. By 4–5 weeks after engraftment, 50% of the SLE-DKO mice died, whereas ND-DKO lived >7 weeks (SLE-DKO vs ND-DKO, P<0.04).

Conclusion: We have created a novel humanized SLE-DKO mouse that exhibits many characteristics of immunologic and clinical features of SLE. Importantly, we recapitulated clinical manifestations of APS in mice infused with PBMC from an ACL-positive patient. The SLE - DKO mouse promises to be an excellent model to study the pathophysiology of SLE and test human-specific therapies. Supported in part by NIH fund, R01 AR03889 and CNPQ 200591/2008-8.

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Enhancement of IL-17 and Interferon-gamma Inflammatory Pathways in IRF9$^{-/-}$ MRL/*lpr* Mice with Disrupted Type I Interferon Signaling. Alvina D. Chu[2], Nicole H. Kattah[3], Michael T. Wong[3], Catherine Tadina[3] and Paul J. Utz[1]. [1]Stanford Univ Schl of Med, Stanford, CA, [2]Stanford University School of Medicine, Palo Alto, CA, [3]Stanford University School of Medicine

Purpose: Multiple inflammatory pathways have been implicated in the pathogenesis of systemic lupus erythematosus (SLE) including those involving type I interferons (IFNs), IFN-gamma, and IL-17. The development of an IFN gene signature, isotype-switched autoantibodies, and kidney disease in the pristane-induced BALB/c model of SLE has been correlated with the predominance of type I IFNs in diseased mice. The role of type I IFNs in the development of disease is less clear in the MRL/*lpr* mouse model of SLE, in which IFN-gamma has been demonstrated to play an important role. Using a newly-generated MRL/*lpr* strain lacking IRF9, a protein crucial for the transcription of type I IFN-regulated genes, we aimed to determine how disruption of type I IFN signaling alters the autoantibody profiles and inflammatory features of disease, including IFN-gamma and IL-17 production by lymphocyte subsets.

Methods: IRF9$^{-/-}$ BALB/c mice were backcrossed to the MRL/*lpr* background for 8 generations. Serum and urinary protein measurements were collected monthly from age-matched female IRF9$^{-/-}$ and IRF9$^{+/+}$ MRL/*lpr* littermates. At 18 weeks of age, sera were analyzed for isotype-specific autoantibodies directed against lupus autoantigens by ELISA. Cells isolated from the spleen and lymph nodes were analyzed for cytokine production including IL-17A and IFN-gamma by ELISPOT, intracellular cytokine staining by flow cytometry, and quantitative RT-PCR analysis.

Results: Despite a defect in type I IFN signaling, IgG autoantibodies targeted against Sm/RNP, RiboP, and whole histones were detected in IRF9$^{-/-}$ MRL/*lpr* mice, including those of the IgG2a subtype. An analysis of cytokine pathways revealed increased IL-17A and IFN-gamma production by splenocytes in the IRF9$^{-/-}$ samples compared to IRF9$^{+/+}$ samples by ELISPOT and quantitative RT-PCR. IRF9$^{-/-}$ samples demonstrated greater IFN-gamma production by flow cytometry, particularly in the CD4^{+} T-cell compartment.

Conclusions: Taken together, these results demonstrate that disruption of the type I IFN signaling pathway at IRF9 in MRL/*lpr* mice does not significantly alter IgG autoantibody profiles or class switching to the IgG2a subtype. Autoantibody production correlated with an enhancement of IL-17 and IFN-gamma, supporting a role for Th17 and Th1 interactions with autoreactive B cells in this model. These results are strikingly different from those of pristane-induced IRF9$^{-/-}$ BALB/c mice, highlighting the heterogeneity of genetic backgrounds and disease mechanisms in lupus-like disease. On a broader scale, these results hold implications for the development of new treatment strategies for human SLE, where modulation of type I IFNs in some patients may potentially result in the enhancement of other inflammatory pathways influencing disease.

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Epistatic Interactions between Lupus Susceptibility Loci on New Zealand Black Chromosomes 1 and 13 Lead to Marked Expansion of Dendritic Cell Populations but Have Little Effect on Autoimmunity. Yui Ho Cheung[2], Evelyn Pau[2] and Joan E. Wither[1]. [1]University Health Network, Toronto, ON, Canada, [2]University of Toronto, Toronto, ON, Canada

Purpose: In previous work we have shown that mice with introgressed homozygous NZB chromosome 1 (63.1 to 192.1 Mb; B6.NZBc1) or 13 intervals (48 to 113 Mb; B6.NZBc13) have high titer IgG anti-nuclear antibodies and develop glomerulonephritis. In this study we have produced bicongenic mice with both NZB intervals, to determine whether interactions between the two loci lead to exacerbation of the autoimmune phenotype.

Methods: Splenic cellular populations were examined by flow cytometry. Serum levels of autoantibodies were measured by ELISA and the presence of glomerulonephritis (GN) determined by light microscopy. Cytokine mRNA levels in freshly isolated splenocytes were examined using real time PCR. Splenic TLR responses were assessed by measurement of cytokine production following stimulation.

Results: B6.NZBc1c13 mice demonstrated marked expansion of the CD11c+ dendritic cell (DC) compartment (5 fold as compared to B6 mice and 2–3 fold as compared to single congenic mouse strains). Increases in both the plasmacytoid DC population (B220+CD11c+NK1.1-) and myeloid DC population (CD11b+CD11c+) contributed to this expansion. Despite these cellular changes, the levels of IgM and IgG autoantibodies, and severity of GN in bicongenic mice were similar to single congenic mice. However, bicongenic mice had significantly elevated levels of total IgA and IgA anti-chromatin, -ssDNA and -dsDNA antibodies when compared with single congenic mouse strains. Consistent with the increased IgA production, bicongenic mice had markedly increased levels of baff mRNA and the number of BAFF-producing myeloid DC in their spleens. mRNA levels of tnf were also increased in bicongenic mice. In contrast, the levels of Type I IFN and IFN-inducible genes were reduced in the spleens of 8 mo old bicongenic mice. To gain further insight into the immune mechanism leading to reduced production of Type I IFN in these mice, freshly isolated splenocytes from young and old mice were stimulated with various TLR ligands. At 8 wks of age, TLR-induced IFNα and TNFα secretion was similar in bicongenic and B6 mice. Despite the ~5 fold expansion of pDC in 8-mo-old mice, levels of IFN-α secretion were reduced in bicongenic mice, indicating a marked reduction in secretion of IFNα on a per cell basis, whereas TNFα production was relatively preserved. To further examine the regulation of cytokine production in bicongenic mice, DC were expanded by culturing bone marrow cells isolated from 8 wk old mice with FLT3L for 7 days and stimulated with various TLR ligands. DC from bicongenic mice demonstrated increased TNFα but not IFNα production following stimulation with TLR7 ligands.

Conclusions: Epistatic interactions between lupus susceptibility loci on NZB chromosomes 1 and 13 lead to marked expansion of DC populations with little impact on the autoimmune phenotype. DC from bicongenic mice appear to be shifted towards TNFα production which may lead to the impaired production of IFNα and reduced disease severity in older mice.

Disclosure: Y. H. Cheung: None; **E. Pau:** None; **J. E. Wither:** None.

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Hypercholesterolaemia and Autoimmunity Interact in a Mouse Model of Systemic Lupus Erythematosus To Enhance Both Atherosclerosis and Renal Inflammation, but by Distinct Mechanisms. Myles J. Lewis[2], Talat H. Malik[2], Liliane M. Fossati-Jimack[2], Daniele Carassiti[2], Terence H. Cook[2], Dorian O. Haskard[1] and Marina Botto[1]. [1]Imperial College, London, United Kingdom, [2]Imperial College

Background: Although SLE is known to accelerate atherosclerosis, the underlying mechanisms are not known. We explored the hypothesis that hypercholesterolaemia and autoimmunity interact in driving both arterial wall and renal pathology through immune-complex deposition.

Methods: Atherosclerosis prone low density-lipoprotein receptor deficient mice ($Ldlr^{-/-}$) were crossed with B6.129-*Sle16* congenic autoimmune mice, which develop high titres of lupus autoantibodies, and studied on low fat (LF) and high fat (HF) diets at 22 weeks of age.

Results: The *Sle16* locus significantly increased atherosclerosis in $Ldlr^{-/-}$ mice, as measured by *en face* aortic lesion area (LF $p<0.0001$; HF $p<0.002$) and by aortic root lesion analysis (LF $p<0.05$; HF $p<0.0001$). Unexpectedly, aortic root lesions in *Sle16*.$Ldlr^{-/-}$ mice had significantly less complement C3 than those in $Ldlr^{-/-}$ mice, but similar IgG deposition. The *Sle16* locus caused a reduction in serum C3, associated with renal immune-complex deposition. *Sle16*.$Ldlr^{-/-}$ mice showed augmented renal inflammation, with enhanced glomerular C3 deposition compared to B6.129-*Sle16* mice, but again no difference in glomerular IgG deposits.

Conclusions: The data suggest that hypercholesterolaemia enhances immune complex-mediated renal damage by amplifying complement activation, but do not support a role for arterial wall immune complex deposition and complement activation in accelerated atherosclerosis. On the contrary, systemic complement depletion by immune-complexes may contribute to atherogenesis by reducing the protective role of complement in disposal of apoptotic debris. The results predict that aggressive treatment of hyperlipidaemia in SLE may reduce lupus nephritis, as well as reduce accelerated atherosclerosis.

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IL-17 Promotes Autoimmunity in Pristane-Induced Lupus. Elaine V. Lourenco, Chunlin Cai, Bevra H. Hahn and Antonio La Cava. UCLA

IL-17 promotes inflammatory responses in several autoimmune conditions. Although it has been shown that IL-17 can be found elevated in systemic lupus erythematosus (SLE) patients and in lupus mice, it has not yet been directly proven that this association underlies a promoting role of this cytokine in the development and/or progression of the disease. To test whether IL-17 can facilitate the development of SLE, we treated IL-17-deficient or wild-type mice with pristane, a hydrocarbon oil that induces a lupus-like disease characterized by the development of lupus-associated autoantibodies and glomerulonephritis. Wild type and IL-17-deficient mice were treated with pristane or saline, and serological and pathological evaluations were done at serial times points post treatment. It was found that pristane promoted hypergammaglobulinemia that was more prominent in wild type than in IL-17-deficient mice, and the difference became statistically significant by three months post-treatment ($p<0.04$) and was maintained thereafter ($p<0.001$). IL-17-deficient mice treated with pristane also developed lower serum levels of anti-single-stranded DNA and anti-chromatin antibodies in comparison with wild type mice treated with pristane, and the onset of glomerulonephritis of the kidney was as well delayed in the IL-17-deficient mice. These results suggest that the presence of IL-17 facilitates the development of murine lupus-like disease induced by pristane. The formal demonstration that IL-17 has a promoting role in the accelerated development of serological and pathologic manifestations of SLE may have implications in the targeting of this pro-inflammatory cytokine for therapeutic purposes in the disease.

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IL-21 Promotes Autoimmune Features in Chronic Graft Versus Host Disease by Enhancing T Follicular Helper Development and B Cell Response. Vinh Nguyen[3], Irina G. Luzina[1], Qing Chen[1], Horea Rus[1] and Violeta Rus[2]. [1]Baltimore, MD, [2]Univ of Maryland Schl of Med, Baltimore, MD, [3]University of Maryland School of Medicine, Baltimore, MD

Studies in murine models of lupus have indicated increased production of IL-21 and attenuation of autoimmune features following IL-21 blockade. IL-21 exerts an autocrine effect on T follicular B helper cells (TFH) cells and also stimulates B cell proliferation, plasma cell (PC) differentiation and germinal center (GC) expansion. To determine whether IL-21 promotes systemic lupus through effects on TFH cells or B cells, we assessed the effect of IL-21/IL-21R signaling on B cells independent from the effect on CD4 T helper cells using IL-21R−/− or IL-21R+/+ mice as donor or hosts in the P-into-F1 and Bm12-into-B6 models of chronic Graft Versus Host Disease (cGVHD). cGVHD induced by injection of IL-21R−/− CD4 cells from B6 mice into B6D2F1 hosts was characterized by a decrease in the expansion of donor CD4, TFH and GC cells and decrease in levels of anti-ssDNA antibody (Ab). When cGVHD was induced by injecting Bm12 spleen cells into IL-21R−/− B6 mice, parameters of cGVHD including B cell activation assessed by MHC class II upregulation, GC B cell and PB/PC differentiation, IgG anti-dsDNA Ab production were significantly decreased compared to IL-21+/+ hosts. The decreased B cell activation and autoantibody titers in the IL-21R−/− hosts were unlikely to be the result of defective priming of donor T cells or activation of host dendritic cells as CD4+ T cells exhibited similar expression of CD44 and CD69 and proliferated more efficiently in IL-21R−/− hosts than in IL-21R+/+ hosts. Similarly, DC displayed similar expression of CD80, CD86. Consistent with the decrease in GC B cells, splenic GCs in IL-21R−/− hosts detected by immunohistochemistry staining on day 7, 14 and 28, were smaller, ill-formed and disrupted compared to those in IL-21R+/+ hosts. Long-term studies showed decreased severity of lupus-like renal disease in the IL-21R−/− hosts. These results suggest that IL-21 promotes autoimmune features in lupus by enhancing both the expansion of TFH cells and the differentiation of autoreactive B cells into autoAb producing cells.

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Interferon Regulatory Factor-5 (IRF-5) Is Critical for the Development of Lupus in MRL/lpr Mice. Yoshifumi Tada[3], Seiji Kondo[4], Shigehisa Aoki[2], Syuichi Koarada[3], Hisako Inoue[3], Rie Suematsu[3], Akihide Ohta[1] and Kohei Nagasawa[3]. [1]Department of Clinical Nursing, Saga University, Saga, Japan, [2]Department of Pathology, Saga University, Saga, Japan, [3]Department of Rheumatology, Saga University, Saga, Japan, [4]National Hospital Organization Kyushu Medical Center, Fukuoka, Japan

Objective: Interferon Regulatory Factor-5 (IRF-5) is a transcription factor that mediates intracellular signals activated by engagement of the Toll-like receptors (TLRs). IRF-5 polymorphisms are associated with increased or decreased risk of systemic lupus erythematosus (SLE) in various human populations but the precise role of IRF-5 in SLE development is not understood. We examined the role of IRF-5 in the development of murine lupus.

Methods: We crossed gene-targeted IRF-5-deficient (IRF-5−/−) mice to MRL/Mpj-lpr/lpr (MRL/lpr) mice and examined the progeny for survival, glomerulonephritis, autoantibody (autoAb) levels, immune system cell populations, and dendritic cell (DC) functions.

Results: We show that IRF-5−/−MRL/lpr mice survive longer than control IRF-5+/+MRL/lpr mice and display only very mild glomerulonephritis. The glomerular deposition of IgG and C3, and the infiltration of CD4+T cells and macrophages into glomeruli was significantly decreased in IRF-5−/−MRL/lpr mice. Anti-nuclear antibodies, anti-dsDNA antibodies, anti-Sm antibodies, and anti-RNP antibodies were decreased in mouse serum, and numbers of activated CD4+ T cells were reduced in the spleen. Splenic DCs from IRF-5−/−MRL/lpr mice produced lower levels of inflammatory cytokines when treated in vitro with TLR7 or TLR9 ligands or immune complexes. Interferon-α production in response to CpG was also decreased.

Conclusion: Our results show that IRF-5 is a crucial driver of lupus development in mice, and indicate that IRF-5 may be an attractive new target for therapeutic intervention to control disease in SLE patients.

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Interferonα Causes SLE by Expanding CD3$^+$ CD4$^-$ CD8$^-$ Double Negative T Cell (DN T Cell). Chieri Akiyama[1], Eriko Honda[1], Akira Hashiramoto[2], Dean W. Felsher[3] and Shunichi Shiozawa[2]. [1]Department of Biophysics, Graduate School of Health Science, Kobe University, Kobe, Hyogo, Japan, [2]Department of Biophysics, Graduate School of Health Science, Kobe University/Department of Medicine, Graduate School of Medicine, Kobe University/The Center for Rheumatic Disease, Kobe University Hospital, Kobe, Japan, [3]Stanford University, School of Medicine, Division of Oncology, Department of Medicine and Pathology, Stanford, CA

Objective: Interferon alpha (IFNα) has been suggested to cause systemic lupus erythematosus (SLE), however, the direct proof for this is lacking. We showed by solely increasing IFNα in doxycycline-inducible transgenic mice (IFNα Tg mice) that IFNα induces autoantibodies including serum anti-dsDNA antibody, serum immune complex (IC) and lupus-like tissue injuries (Uchimura C *et al*. Arthritis Rheum 56 (suppl.9):S200).

We now show that IFNα causes SLE by expanding CD3$^+$ CD4$^-$ CD8$^-$ double negative T cell (DN T cell) to induce lupus glomerulonephritis.

Methods: Mouse IFNα (mIFNα) cDNA, amplified by RT-PCR, was subcloned into pTet Splice vector under the control of TetOp promoter to generate TetOp-mIFNα. This was microinjected into fertilized eggs of C57BL/6 to generate TetOp-mIFNα Tg mice. The EμSR-tTA Tg mice of FVB/N background was mated with TetOp-mIFNα Tg mice to obtain double Tg mice (IFNα Tg mice). Serum IFNα was measured using Mu-IFN-α ELISA kit. Serum autoantibodies and IC were measured with ELISA, referring to pooled sera of MRL/*lpr* female adult mice (arbitrary units).Proteinuria were measured semiquantitatively using urine dipsticks. Frozen kidney sections were stained for C3 and IgG using immunofluorescent antibodies. To detect intracellular IFNα, splenocytes (1×10^6/ml) were stimulated with ionomycin and phorbol 12-myristate 13-acetate for 4 h in the presence of blefeldin A. Cells were then stained with anti-CD4 and anti-CD8 antibodies, followed by fixation, permeabilization with saponin and treatment with anti-IFNα antibody. The CD3$^+$ (5×10^6), CD4$^+$(5×10^6), CD8$^+$ (5×10^6), and DN(3×10^5) subsets derived from the IFNα Tg mice of 30 weeks after cessation of Dox were transferred twice into naïve recipients, and renal histopathology was studied 21 days after transfer.

Results: In IFNα Tg mice, pathological lesion consisted of IC-deposited glomerulonephritis, interstitial lung disease, liquefaction and positive lupus band test in the skin epidermis, onion skin lesion in the spleen and inflammatory infiltrates to salivary gland and bile duct. Activated effector CD4$^+$ and CD8$^+$ T cells producing IFNα were increased, in which IFNα^+CD8$^+$ T cell with effector phenotype, i.e., full-matured CTL, and in particular, activated CD3$^+$CD4$^-$CD8$^-$ double negative T cell (DN T cell) was increased. The DN T cells not only infiltrated to the glomerular lesions of IFNα Tg mice but also induced *de novo* glomerulonephritis when transferred into naïve recipients. Thus, IFNα is responsible for the core manifestation of SLE except for anti-Sm autoantibody.

Conclusion: IFNα causes SLE by expanding CD3$^+$ CD4$^-$ CD8$^-$ double negative T cell (DN T cell) to induce lupus glomerulonephritis.

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IRF4-Deficient Lupus-Prone MRL/*lpr* Mice Lack Serum Ig/Auto-Abs and Th17 Cells but Develop Non-Immune Complex-Mediated Diffuse Proliferative Glomerulonephritis and Dermatitis/Ear Necrosis. Hideharu Sekine[4], Takeshi Machida[1], Eiji Suzuki[3], Efrain Martinez Avila[3], Phil Ruiz[5], Christopher M. Reilly[6] and Gary S. Gilkeson[2]. [1]Fukushima Medical University, Fukushima, Japan, [2]Med Univ of South Carolina, Charleston, SC, [3]Medical University of South Carolina, Charleston, SC, [4]Medical University of South Carolina/Fukushima Medical University, Charleston, SC, [5]University of Miami, Miami, FL, [6]Virginia Tech, VA

The transcription factor interferon regulatory factor 4 (IRF4) is a member of the IRF family of transcription regulators and required for Ig-production/maturation of B cells and development of Th17 cells. We found that the Irf4 gene is over-expressed in CD4$^+$ T cells in lupus-prone MRL/*lpr* mice compared to non-lupus mice. To investigate the role of IRF4 in the development of lupus, we analyzed disease expression in *Irf4*$^{-/-}$ MRL/*lpr* mice until time of sacrifice.

Sera and urine were collected biweekly from groups of *Irf4*$^{-/-}$ and wild-type MRL/*lpr* mice starting at 12 weeks. Serum Ig/anti-dsDNA Ab levels and urinary albumin excretion levels were measured by ELISA. Mice were sacrificed at 24 weeks of age and ear, back skin and kidneys were removed for pathological analysis. Splenic immune cell populations were analyzed by flow. To determine Th1/Th2/Th17 cell numbers, splenic CD4$^+$ T cells from 12 weeks old MRL/*lpr* mice were purified by magnetic selection, cultured with PMA/ionomycin, and IFN-γ, IL-4 or IL-17 production was detected by flow and ELISPOT assay.

Unlike wild-type MRL/*lpr* mice, all *Irf4*$^{-/-}$ MRL/*lpr* mice had undetectable levels of serum Ig and anti-dsDNA Abs and no albuminuria. *Irf4*$^{-/-}$ MRL/*lpr* mice had no glomerular immune complex (IC)/C3 deposits, epithelial cell reaction, crescent formation or renal vasculitis, however, they had significant dermatitis/ear necrosis and pathologic observable nephritis characterized by diffuse glomerular hypercellularity and mesangial matrix expansion consistent with diffuse proliferative glomerulonephritis. *Irf4*$^{-/-}$ MRL/*lpr* mice showed significantly increased numbers of splenic CD4$^+$ T cells ($66.7\pm6.6\times10^6$ vs $41.4\pm5.8\times10^6$; $p = 0.016$) while all other splenic immune cells were significantly decreased compared to wild-type controls. Notably, splenic CD19$^+$/IgM$^+$ B cells and CD8$^+$ T cells were significantly decreased/absent in *Irf4*$^{-/-}$ MRL/*lpr* mice compared to wild-type MRL/*lpr* mice. Bone marrow analysis revealed B cell development arrest before the stage of CD19$^+$/B220^{high}/CD43^{low} immature B cells in *Irf4*$^{-/-}$ MRL/*lpr* mice. Flow/ELISOPT assay showed absence of IL-17 producing cells in *Irf4*$^{-/-}$ MRL/*lpr* mice, however, they had significantly increased numbers of IFN-γ producing cells ($59.2\pm20.2\times10^6$ vs $6.6\pm1.5\times10^6$; $p = 0.027$) and IL-4 producing cells ($4.30\pm0.27\times10^6$ vs $0.39\pm0.08\times10^6$; $p < 0.0001$) compared to control MRL/*lpr* mice.

Our results indicate that IRF4 is required for the full expression of lupus like renal disease in MRL/*lpr* mice, most likely by maintenance/modulation of autoreactive B cells and specific T cell subsets. Importantly, development of proliferative glomerulonephritis and skin disease were still present in *Irf4*$^{-/-}$ MRL/*lpr* mice indicating that their pathogenesis, in these mice, is independent of autoAb/IC-mediated mechanisms or Th17 cells, and is most likely induced by Th1 and/or Th2 cells. Absence of IL-17 producing CD4$^+$ T cells and significantly increased numbers of IFN-γ or IL-4 producing CD4$^+$ T cells in the spleens of *Irf4*$^{-/-}$ MRL/*lpr* mice suggested a dual role of IRF4 for development of Th17 cells and inhibition of Th1 and Th2 cell development in MRL/*lpr* mice.

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Long-Term Anti-CD20 Treatment Reduces Antibody-Secreting Ells in NZB/W Lupus Mouse. Wensheng Wang[2], Terasa Owen[2], Travis Ichikawa[2] and Jennifer H. Anolik[1]. [1]University of Rochester, Rochester, NY, [2]University of Rochester Medical Center, Rochester, NY

Objective: Although anti-CD20 antibody efficiently depletes most B cells, B-cell depletion (BCD) has shown variable efficacy in clinical trials as a therapy for systemic lupus erythematosus (SLE). To better understand the mechanisms of action of anti-CD20 and the effect on SLE, a lupus-prone mouse model was used to study the alteration in antibody-secreting cells after B cell depletion.

Methods: For short-term treatment, NZB/NZWF1 female mice (24–30 wks old) with durable proteinuria $>$ 2+ (100 mg/dl) were dosed weekly $\times$ 4 with anti-mCD20 antibody (IgG2a, a gift from Biogen Idec)(n=6) or control antibody IgG2a and sacrificed 1 wk after the last treatment. To study longer-term effects of BCD, 27 wk old NZB/NZWF1 female mice with high titer anti-dsDNA antibodies were dosed weekly with anti-mCD20 antibody or control IgG via retro-orbital injection. One group was treated weekly $\times$ 4 (n= 6) and sacrificed 8 wks later. Another was treated weekly $\times$ 12 (n= 6) and sacrificed 1 wk after the last treatment. Cells from spleen, bone marrow (BM) and kidney were collected and total IgG and dsDNA antibody secreting cells (ASC) were determined by ELIspot.

Results: Nephritis improved after anti-mCD20 treatment (neither 4 wks nor 12 wks treated mice were found to develop nephritis [3+ proteinuria]) compared to control (5/6 mice developed nephritis 4+). Although BCD was efficient (>90% B220+ cell depletion), there was no difference in the numbers of anti-dsDNA-secreting cells and total IgG-secreting cells in either spleen, BM or kidney after 4 treatments of anti-mCD20, over the short-term (evaluation 1 wk after the last treatment- see Table) or long-term (evaluation 8 wks after the last treatment, data not shown). Interestingly, in untreated mice the ratio of anti-dsDNA/total IgG-secreting cells in the kidney was significantly higher than in spleen and BM (p<10-4) suggesting that the kidney is a reservoir of either production or maintenance of autoreactive ASCs. In

striking contrast, long-term treatment with anti-mCD20 resulted in significant decreases in total IgG and anti-dsDNA-secreting cells in spleen. In addition, the average size of total IgG-secreting cell spots from kidney decreased significantly, suggesting a shift in the antibody producing capacity after anti-mCD20.

Short-term Treatment

	IgG			dsDNA		
	Ctrl	a-CD20	*t-test*	Ctrl	a-CD20	*t-test*
Spleen	115.6 ± 35.6	61.9 ± 17.5	0.12	3.4 ± 1.0	2.6 ± 0.58	0.3
BM	15.9 ± 4.2	21.2 ± 3.2	0.26	0.66 ± 0.17	0.46 ± 0.11	0.28
Kidney	68.3 ± 4.1	81.5 ± 21.0	0.11	30.3 ± 8.8	37.3 ± 8.3	0.18

Long-term Treatment

	IgG			dsDNA		
	Ctrl	a-CD20	*t-test*	Ctrl	a-CD20	*t-test*
Spleen	132.2 ± 23.0	4.21 ± 3.66	0.0011	2.03 ± 0.30	0.21 ± 0.15	0.00091
BM	33.27 ± 7.02	12.9 ± 4.54	0.032	0.80 ± 0.22	0.18 ± 0.06	0.018
Kidney	269.8 ± 64.93	85.86 ± 19.85	0.028	63.77 ± 17.77	3.58 ± 1.76	0.013

per 10E4 cells

Conclusion: Long-term anti-CD20 treatment significantly reduces ASCs in spleen and moderately reduces ASCs in bone marrow and kidney. Treatment also appears to alter antibody secretion in kidney. Therefore, longer term B cell depletion may have increased efficacy as a treatment for SLE.

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Mitochondrial Dysfunction in T Cells Precede Disease Development in Lupus-Prone Mice. Tiffany Telarico[4], David R. Fernandez[4], Ann F. Hofbauer[2], Gary S. Gilkeson[1], Jim C. Oates[3] and Andras Perl[5]. [1]Med Univ of South Carolina, Charleston, SC, [2]Medical University of South Carolina, [3]MUSC, Charleston, SC, [4]SUNY, [5]Upstate Medical Univ, Syracuse, NY

Purpose: T lymphocytes from patients with systemic lupus erythematosus (SLE) exhibit increased nitric oxide (NO) production, elevation of the mitochondrial transmembrane potential ($\Delta\Psi m$) or mitochondrial hyperpolarization (MHP), and ATP depletion which predispose to pro-inflammatory death via necrosis. T lymphocytes express the endothelial isoform of NO synthase (eNOS). Here, we examined whether mitochondrial dysfunction precedes the onset of disease in murine models of SLE.

Methods: Mitochondrial function, calcium flux, and the production of nitric oxide (NO) and underlying changes in gene expression were investigated in MRL/lpr, MRL/lpr/iNOS−/−, MRL/lpr/eNOS−/−, MRL, C57BL/6-lpr, C57BL/6, NZB × NZW F1, Balb-c/NZW, NZM2328, and NZM2328/R27 female mice that were matched for age and studied in parallel. $\Delta\Psi m$ (DiOC6 and TMRM), mitochondrial mass (MTG and NAO), NO production (DAF-FM and DAR-4M), reactive oxygen species (DCF-DA), intracellular reduced glutathione (GSH by MCB fluorescence) and cytosolic ([Ca2+]c) and mitochondrial calcium ([Ca2+]m) were measured by flow cytometry. Expression of the voltage-dependent anion channel 1 (VDAC1) and transaldolase that regulate GSH and $\Delta\Psi m$ was investigated in splenocytes and CD4+ T cells by western blotting. As disease development, glomerulonephritis was monitored by proteinuria and histopathology. P values < 0.05 calculated by GraphPad Prism version 5.0 using paired or unpaired two-tailed t-test were considered significant.

Results: MHP, increased mitochondrial mass, [Ca2+]m and ROI production and reduced GSH were found in CD3+ T cells from disease-free MRL/lpr but not from MRL or from C57BL/6-lpr mice relative to C57BL/6 control mice at 3 months of age. Consistent with these changes, expression of the VDAC1 (up to 7 –fold increase, $p=0.0008$) and transaldolase (67% increase, $p=0.034$), genes that influence $\Delta\Psi m$, were elevated in MRL/lpr splenocytes and CD4+ T cells. NO production, $\Delta\Psi m$ and mitochondrial mass were all increased in 11-month-old (NZB × NZW) F1 mice after disease onset, but these parameters were not consistently elevated prior to disease development at 6 months of age. However, increased expression of VDAC1 was detected at 6 months of age and preceded the onset of SLE (3.5-fold increase; $p=0.006$). NO production (DAF-FM fluorescence), $\Delta\Psi m$ (TMRM fluorescence), mitochondrial mass (NAO), [Ca2+]c and [Ca2+]m stores were reduced in CD3+ T cells from C57BL/6/eNOS−/− mice relative to C57BL/6 controls. NO production (DAF-FM fluorescence $p=0.001$) and mitochondrial and [Ca2+]c stores were reduced in CD3+ T cells from MRL/lpr eNOS−/− mice (Fluo-3 fluorescence; $p=0.03$) relative to MRL/lpr controls.

Conclusion: Mitochondrial dysfunction, characterized by MHP and increased [Ca2+]m as well as overexpression of VDAC1 and transaldolase, precede disease development in lupus-prone mice. Increased [Ca2+]m of MRL/lpr mice may be dependent on the expression of eNOS.

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Molecular Mechanisms of Lupus Dyslipidemia in Mice. Nilamadhab Mishra[1], Kailin Yan[3] and Qiang Cao[2]. [1]Wake Forest Univ Health Scienc, Winston-Salem, NC, [2]Wake Forest University Health Sciences, [3]Wake Forest University Unv Health Sciences

Introduction: Lupus dyslipidemia is characterized by increased total cholesterol, triglycerides, LDL, VLDL and decreased HDL. The molecular mechanisms of abnormal lipid profiles in lupus patients currently are not properly understood. In this study, we generated mice that has lupus dyslipidemia on chow diet and studied the pathways that are responsible for increased cholesterol and triglycerides in plasma.

Materials and Methods: $LDLr^{-/-}$ and $Fas^{-/-}$ (*lpr/lpr*) mice on the B6 background were purchased from the Jackson Laboratories (Bar Harbor, ME). These mice were interbred to produce mice homozygous for both LDLr−/− and *lpr* confirmed by PCR genotyping. $LDLr^{-/-}$(LDLr) and $LDLr^{-/-}lpr^{-/-}$ (LDLrLpr) mice were fed on chow diet. Thirteen female mice from each group were sacrificed at the age 24–28 weeks.

Results: LDLrLpr mice developed a lupus phenotype demonstrated by autoantibody production (ANA, anti-dsDNA, anti-sm, anti-cardiolipin antibodies), increased body weight, splenomegaly, hepatomegaly, and generalized lymphadenopathy compared to LDLr mice. LDLrLpr mice had a significantly increased proteinuria score (1.5 ± 0.2 vs. 1.1 ± 0.06; $p<0.02$) and renal histology score (1.8 ± 0.4 vs. 0.4 ± 0.1; $p<0.004$) compared to $LDLr^{-/-}$ mice. The lymphocyte population in the spleen measured by flow cytometry resulted in significantly increased CD4+Tcells (21% vs. 16%; $p<0.003$), double negative T cells (59% vs. 26%; $p<0.001$), and CD138+ plasma cells (12% vs. 0.4%; $p<0.001$) and decreased CD8+Tcells (6% vs. 14%; $p<0.001$) in LDLrLpr mice compared to LDLr mice similar to human lupus. Lipid analyses in LDLrLpr mice compared to LDLr mice on chow diet demonstrated significantly elevated total cholesterol (mg/dl) (347.0 ± 31.65 vs. 220.9 ± 8.235; $p<0.0008$), triglycerides (118.8 ± 18.51 vs. 42.85 ± 3.665; $p<0.0005$), VLDL (66.85 ± 17.54 vs. 3.385 ± 0.4875; $p<0.0014$) and LDL cholesterol (214.9 ± 22.22 vs. 148.1 ± 8.049; $p<0.0093$) without significant difference in HDL level. The increased level in triglycerides due to increased triglyceride secretion as measured by triton block experiment and decreased hepatic and lipoprotein lipase activity in LDLrLpr mice. The increased plasma cholesterol is due to increased cholesterol synthesis and decreased fatty oxidation in liver in LDLrlpr mice as measured by gene expression analysis.

Conclusion: Increased cholesterol synthesis, decreased fatty acid oxidation, increased triglyceride secretion and decreased lipase activity are the molecular mechanisms of dyslipidemia in lupus mice.

Disclosure: N. Mishra: None; **K. Yan:** None; **Q. Cao:** None.

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Nuclear Modifications during Apoptosis Are Required To Maintain Tolerance to Nuclear Antigens. Neelakshi R. Jog[1], Eline Luning-Prak[2] and Roberto Caricchio[1]. [1]Temple University, [2]University of Pennsylvania

Background: Our previous data show that in spontaneous models of lupus, the absence of caspase activated DNase (CAD)-generated nuclear modifications during apoptosis results in increased anti-nuclear antibody generation and severe nephritis. These data suggested that CAD generated apoptotic nuclei are a source of auto-antigens (autoAgs) that are involved in negative regulation of autoreactive B cell during development. In the present study we investigated the role of CAD in induction of tolerance in vivo. To this end we used 3H9 mice, an established model of anergy towards chromatin.

Methods: 3H9 mice carry a rearranged heavy chain reactive against dsDNA, and shows developmental arrest of autoreactive B cells. To determine whether absence of CAD, and therefore autoAgs, breaks tolerance in this anergic model, we generated CAD deficient 3H9 mice [3H9(−/−)]

Results: Contrary to 3H9+/+, 3H9−/− mice were able to break tolerance early in life and produce high titers of anti-dsDNA and anti-

chromatin antibodies. The antibodies made in 3H9−/− mice did not, however, differ in specificities as determined by immunofluorescent ANA. The autoreactive B cells in 3H9+/+ mice undergo stringent negative selection due to the presence of autoreactive heavy chain. Therefore we analyzed B cell development and maturation by flow cytometry. The developing B cells from bone marrow were divided into Hardy fractions D (L chain rearrangement), E (immature IgM+), and F (IgM+, recirculating B cells). Compared to wild type, both 3H9+/+ and 3H9−/− mice had increased numbers of fraction D cells, suggesting increased light chain rearrangements. In the periphery, both 3H9+/+ and 3H9−/− mice showed increased mature marginal zone B cells, and immature T2 transitional B cells, and increased lambda inclusion. These data show that absence of CAD does not alter the unique B cell development or maturation in 3H9 mice. The 3H9 heavy chain pairs with endogenous lamda1 light chain to generate anti-dsDNA antibody allowing to follow in vivo the fate of autoreactive B cells. In 3H9 mice lambda1+ cells are excluded from B cell follicles in secondary lymphoid organs and are not able to mature into autoantibody producing B cells. We therefore investigated the fate of lambda1 + cells in the absence of apoptotic nuclear modifications. We stained frozen spleen sections from 3H9+/+ and 3H9−/− mice with B220 to identify B cell follicles and lambda1 to identify the auto-reactive B cells. As expected, in 3H9+/+ mice the lambda1+ cells did not enter the B cell zone and accumulated at the T-B interface. In 3H9−/− mice, however, lambda1+ cells were not excluded from B cell follicles, and entered the B cell zone. These data show that in agreement with our hypothesis, auto-reactive B cells escape to the periphery in absence of CAD-dependent nuclear fragmentation.

Conclusions: Based on our data we conclude that in mice genetically predisposed to autoimmunity, the apoptotic nuclear modifications generated by CAD are necessary to maintain tolerance toward nuclear Ags.

Disclosure: N. R. Jog: None; **E. Luning-Prak:** None; **R. Caricchio:** None.

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PARP-1 Deficiency Leads to More Severe Glomerulonephritis and Increased Mortality in an Inducible Mouse Model of SLE. Maximilian F. Koenig[1], Serena M. Bagnasco[1], Janelle Montagne[1], Antony Rosen[2] and Thomas Grader-Beck[2]. [1]Johns Hopkins School of Medicine, [2]Johns Hopkins School of Medicine, Baltimore, MD

Purpose: PARP-1 regulates essential cellular functions, including cell death and DNA repair. Lower levels of PARP-1 activity have repeatedly been found in SLE patients. Functional PARP-1 deficiency may therefore play an important role in the pathophysiology of SLE. In this study we define the role of PARP-1 deficiency on the autoantibody response and end-organ disease phenotype in an inducible mouse model of SLE.

Methods: Lupus-like disease was induced in a chronic graft-versus-host disease (cGVHD) model of SLE by injecting B6 mice (wild-type or PARP-1−/−) with sex- and age-matched B6©-H2-Ab1bm12/KhEgJ (bm12) splenocytes. Proteinuria and serum autoantibody levels to ssDNA and histone H1 were measured serially over the course of the disease (14 weeks). At termination of the experiment, kidney sections were evaluated by hematoxylin/eosin staining as well as by immunofluorescence for IgG and C3 deposition in a blinded manner.

Results: Male B6 PARP-1−/− disease mice showed increased mortality compared to wild-type disease mice (4/6; 66% vs. 0/8; 0%; P= 0.015). This increase was gender-specific and not observed in female mice. PARP-1-deficient male mice developed higher levels of proteinuria associated with a nephrotic phenotype and wasting. Histological examination of renal tissue in PARP-1-deficient male mice showed abundance of hyaline, PAS-positive material within tubules as well as glomerular hyperplasia and marked sclerosis. These changes were not seen in wild-type and PARP-1−/− female mice. The burden of IgG deposition assessed by immunofluorescence intensity was comparable between wild-type and PARP-1 deficient mice. However, C3 deposition at the glomerular basement membrane (GBM) was more prevalent in PARP-1−/− male mice compared to wild-type male mice. This GBM deposition of C3 was closely correlated with the severity of proteinuria. Autoantibody levels of anti-ssDNA and anti-histone H1 over the course of the disease were similar in wild-type and PARP-1 deficient male disease mice.

Conclusion: PARP-1 deficiency is associated with more severe glomerulonephritis and increased mortality in an inducible cGVHD mouse model of SLE. This effect is specific for male mice and is not reflected by changes in the antibody response to commonly observed lupus autoantigens. The level of PARP-1 expression and activity in the target tissue may play an important role for disease phenotype and severity in SLE.

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Recombinant Chaperonin 10 Suppresses Cutaneous Lupus and Lupus Nephritis in MRL-(Fas)lpr Mice. Onkar P. Kulkarni[3], Mi Ryu[3], Claudia Kantner[3], Miklos Sardy[2], Dean Naylor[1], Richard Brown[1], Daina Vanags[1] and Hans-Joachim Anders[3]. [1]CBio Ltd, Eight Mile Plains, Queensland, Australia, [2]Department of Dermatology and Allergology, University of Munich, Munich, Germany, [3]Medizinische Poliklinik-Innenstadt, University of Munich, Munich, Germany

Purpose: Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder mostly affecting young females. The autoimmune disease manifestations are still treated with unspecific immunosuppressants such as steroids or cytotoxic drugs that cause serious toxicities. Since patients largely suffer from inflammatory tissue damage and not from autoimmunity per se, selective anti-inflammatory compounds may offer protection from tissue damage without causing immunosuppression.

Chaperonin 10 fulfills an essential role in mitochondrial protein folding and an extracellular role in immunomodulation suggesting potential therapeutic value for the treatment of inflammatory disorders1. Accordingly, in early phase II clinical studies in human patients the efficacy and safety of Cpn10 in treating signs and symptoms of rheumatoid arthritis2 and chronic plaque psoriasis (CPP)3 has been established. Here recombinant Cpn10 was examined for its' ability to additionally control the autoimmune manifestations of SLE.

Methods: Female MRLlpr/lpr mice with lupus-like autoimmunity were given either Cpn10 (100μg/mouse, 5mg/kg) or placebo (Tris-buffred saline) by intraperitoneal injection every alternate day from 10 to 22 weeks of age. Clinical signs were recorded over the study period, and mortality was recorded every week throughout the study. Plasma samples were collected prior to sacrifice after 11 weeks of treatment. Urine samples were collected in week 22 of age. Tissue samples for histology were immediately fixed in formalin prior to paraffin fixation.

Results: Cpn10 entirely prevented the lupus-like cutaneous lesions as compared to vehicle-treated MRLlpr/lpr mice as evident from macroscopy as well as from microscopical evaluation. Cpn10 also improved lupus nephritis as evident from serum creatinine levels, albuminuria, and the histomorpholocial scores of disease activity and chronicity ($p<0.05$). Autoimmune lung disease remained unaffected by Cpn10 treatment. However, Cpn10 prolonged overall survival of MRLlpr/lpr mice (90% survival vs. 65% for treated mice, $p<0.05$). The therapeutic potential of Cpn10 on skin and kidney disease was not associated with any significant effects on either T cell, dendritic cell or B cell counts in spleen, on plasma IFN-γ, TNF-α or IL-10 levels, plasma DNA autoantibody levels or on markers of lymphoproliferation.

Conclusion: Our study clearly demonstrates that Cpn10 prevents cutaneous lupus and suppresses lupus nephritis in MRLlpr/lpr mice without affecting the underlying autoimmune process or systemic inflammation. Hence, Cpn10 shows significant potential for the treatment of selective human SLE-related tissue pathologies, such as cutaneous lupus and lupus nephritis whilst possibly offering an improved safety profile by not blocking healthy immune responses. This work taken together with previously published data in human RA and CPP trials, provides evidence of Cpn10's utility beyond a single indication.

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TGF-β-Induced CD4+Foxp3+ Cells Suppress Lupus-Like Syndrome through Induction of Formation of Tolerogenic DC. Xiaohui Zhou[4], Julie Wang[4], David A. Horwitz[2], Huimin Fan[3], Hejian Zou[1], Zhongmin Liu[3] and Song Guo Zheng[4]. [1]Fudan University Medical School, [2]LAC/USC Medical Center, Los Angeles, CA, [3]Tongji University Medical School, [4]University of Southern California

Background: Regulatory T cells (Tregs) play vital roles in maintaining immune homeostasis and self tolerance. Recent studies revealed that dendritic cells (DCs) might be main target of Tregs and also induce immune tolerance. We have previously reported that adoptive transfer of TGF-β-induced Tregs (iTregs) prevents the appearance of lupus syndrome induced by injection of

DBA/2 mouse splenocytes to (DBA/2 × C57BL/6) F1 mice, we here ask if interaction between iTregs and DCs contributes to disease control.

Materials and Methods: DBA/2 naïve CD4+ cells were stimulated with anti-CD3/CD28 beads and IL-2 ± TGF-β (control or iTregs) for 5 days. 5×106 control or iTregs with 80×106 DBA/2 splenocytes were adoptively transferred to F1 mice. ALK-5 inhibitor and anti-IL-10R Ab were i.p injected twice a week for four weeks in some groups. On day 11 after transfer of control or iTregs, CD11c+ cells were selected from splenocytes in F1 mice and injected (1×106) with 80×106 DBA/2 splenocytes to F1 mice. Surface and intracellular staining included CD80, CD86, CD11c, IA-b, Foxp3, CD25, H-2Kd, H-2Kb. IgG and anti-DNA in sera was analyzed with ELISA and mice survival was monitored.

Results: A single injection of 5×106 iTregs markedly prevented increased IgG production, decreased anti-dsDNA autoantibodies, suppressed proteinuria and prolonged survival of these mice. The treatment with anti-TGF-b or ALK5 inhibitor completely, with anti-IL10R partially blocked the suppressive capacity of iTreg following injection in vivo. Moreover, iTreg suppressed CD80 and CD86 expression by DCs in vitro and in vivo. Adoptive transfer of these DCs in F1 mice received iTregs but not control cells to GVHD model can significantly prevent the development of lupus symptoms. The protective effect of these DCs was dependent on TGF-b/TbR signal but not IL-10/IL-10R signal. Thus, the protective effect of iTreg is dependent on TGF-b and/or IL-10 and formation of tolerogenic DCs that have developed TGF-b- but not IL-10-dependent suppression on lupus.

Conclusion: iTregs may suppress lupus-like syndrome through induction of formation of tolerogenic DC with TGF-b dependence pathway. iTregs may have therapeutic potential in treating autoimmune diseases.

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Widespread Upregulation of mEPCR in Kidney, Spleen and Liver of a Nephritic NZM B/W F1: Implications to Microvascular Disease. Sherry Xu[1] and Robert M. Clancy[2]. [1]NYU School of Medicine, [2]Tisch Hospital 4–407, New York, NY

Purpose: Membrane endothelial protein C receptor (mECPR), a cofactor for the anti-inflammatory activity and anti-coagulant activity of the Protein C pathway, is a prominent inducer of anti-apoptotic pathways in endothelial cells, and thus maintains vascular tone and normal blood flow in the microvasculature.

We previously found that mEPCR is highly expressed in the cortical peritubular capillaries of kidneys from patients with active lupus nephritis, as compared with normal human kidneys. This profound upregulation of mEPCR was observed even in areas absent tubulointerstitial damage; we therefore hypothesized that mEPCR may be an important anti-injury molecule in the cascade(s) leading to renal damage in Systemic Lupus Erythematosus.

Method: We used the autoimmune murine strain NZB/W F1 mice, and a nonautoimmune strain of mice with a podocyte-specific microRNA knockout of dicer (dicer k/o), which both display proteinuria. Healthy control mice were also utilized. Tissue was harvested from spleen, liver and kidney. Paraffin sections were stained using an anti-mEPCR antibody via avidin-biotin method. The isotope for mEPCR was used as a negative control. Intensity of immunostaining was scored from 0 to 3+, and staining was considered positive if >1+ and negative when 0 or trace (0.5+). The percent of tissue with positive staining for mEPCR was scored as focal or diffuse.

Results: At four months of age, anti-ds DNA and anti-ss DNA were evident in all NZB/W F1 mice. At early onset of proteinuria, the mEPCR immunostain of cortical peritubular capillaries (PTCs) was, in four cases, 2+ and diffuse, with an isotype control that stained appropriately negative. mEPCR was also negative in the cortical PTCs of 6 healthy control mice. Mice with dicer k/o develop proteinuria at 6 weeks; however, expression of mEPCR was negative in the cortical PTCs. In order to evaluate whether the changes in the microvasculature extend beyond the clinically targeted organ, paraffin sections of liver and spleen were evaluated for mEPCR. The liver of each NZB/W F1 mouse displayed, at the sinusoids, a 2+, diffuse profile of mEPCR expression. In addition, in the spleen of NZB/W F1 we observed a 3+ focal mEPCR staining at the vasculature which supports the white pulp. The expression of mEPCR was negative for liver and spleen in healthy mice and in nonautoimmune nephritic mice.

Conclusion: Consistent with the human studies, evaluation of the cortical peritubular capillaries from NZMB/W F1 mice, a classic murine model of lupus nephritis but not a murine model with nephritis secondary to a genetic podocytopathy, revealed an increase in mEPCR. These data are consistent with the notion that there is widespread activation of the microvasculature. The capacity of endothelial cells to utilize anticoagulation pathways is not restricted to the kidney, and expression of mEPCR in the microcirculation likely represents an attempt to limit microvascular inflammation in spleen, liver and kidney.

Disclosure: S. Xu: None; **R. M. Clancy:** None.

ACR Poster Session A
Systemic Lupus Enrythematosus - Clinical Aspects and Treatment I
Monday, November 8, 2010, 9:00 AM–6:00 PM

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Anti C1q Antibodies in Patients with Systemic Lupus Erythematosus and Cutaneous Vasculitis: A Controlled Study. Shirish R. Sangle[1], Loh Yet Lin[2], Esther Sanchez[2], Davies Rachel[2] and David P. D'Cruz[2]. [1]St Thomas' Hospital, London, United Kingdom, [2]St Thomas' Hospital, United Kingdom

Objective: To evaluate the prevalence of anti-C1q antibodies (aC1q) in patients with systemic lupus erythematous (SLE) as a possible marker for cutaneous vasculitis (CV).

Material and Methods: We prospectively enrolled 46 patients with SLE who fulfilled ACR classification criteria. Twenty three patients had clinically documented CV while 23 had no previous evidence of CV. The BILAG disease activity score was documented and active CV rashes were photographed. aC1q were measured by using ELISA and a aC1q titre above 15 units/ml was considered as positive. Statistics was by chi square test. This study was approved by the St Thomas' Hospital Ethics committee and all patients gave written informed consent.

Result: The median age of patients in the CV group was 37 years (27–46) and that of the non –CV patients was 44 (29 –66) years. In the CV group, 9 were Caucasian, 6 Asian and 8 Afro Caribbean and in the non-CV group 13 Caucasian, 5 Afro Caribbean and 5 Asian in origin. In the CV group the median BILAG score for vasculitis manifestations was 3 (3–4). In the CV group 22 had positive ANA, 18 ds DNA, 10 ENA, 13 Ro (SSA) and 6 had La (SSB) antibodies. In the non –vasculitis group 22 had positive ANA, 16 ds DNA, 10 ENA, 12 Ro and 6 had La antibodies. The median complement (C3) levels in the CV were 0.88 (0.24 – 1.49) and C4 0.16 (0.03–1.17) as compared to 1.31 (0.33 – 1.65) and 0.17 (0.02–0.34) in the non-CV groups respectively.

Eighteen of 46 (8 in the CV) patients had positive antiphospholipid antibodies (aPL). Six patients in the CV group had renal involvement with none in the non-CV group. aC1q were positive in 14 of 23 (52%) in the CV group compared to 3 (13%) in the non-CV group ($p < 0.0023$). The median titre of aC1q in the CV group was 35 (5–400) u/ml compared to 6 (5–53) in the non-CV group. All patients with positive aC1q had positive ANA and ds DNA antibodies, 13 had ENA positive, 8 had Ro antibodies, 3 La antibodies, 4 each had RNP and RNP with Smith antibodies. In the CV group 13 patients had low C3, C4 levels of which 10 were aC1q positive and in the non-CV group 1 aC1q positive patient had low C3 and C4 levels. The median C3 and C4 levels in aC1q positive patients in the CV group were 0.55 (0.24–0.64) and 0.08 (0.03-0.017) as compared to 0.7 (0.33–0.91) and 0.17 (0.02–0.08) in the non-CV group respectively. Hypocomplementemia was significantly more prevalent in the CV group ($p < 0.046$). Six patients with positive aC1q were positive for aPL. Three of 6 patients with renal involvement were positive for aC1q in the CV group. aC1q were significantly more prevalent ($p<0.024$) in the CV without previous renal disease compared to the non-CV non-renal group of patients. There was a statistically significant positive correlation between patients with positive C1q anti ds DNA, ANA antibodies and low C3 C4 levels.

Conclusion: Anti C1q antibodies may be a marker of activity in cutaneous vasculitis in patients with systemic lupus erythematosus even in the absence of lupus nephritis.

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Antimalarials May Attenuate the Risk of Metabolic Syndrome in SLE: Results from an International Imception Cohort Registry. M. H. X. Ting[2], R. P. Donn[3], M. Lunt[3], M. B. Urowitz[4], D. D. Gladman[1], D. Ibanez[1], C. Gordon[1], S. C. Bae[1], A. Clarke[1], S. Bernatsky[1], J. Hanly[1], D. Isenberg[1], A. Rahman[1], J. Sanchez-Guerrero[1], J. Romero-Diaz[1], P. R. Fortin[1], D. Wallace[1], E. Ginzler[1], A. Vasudevan[1], J. Merrill[1], G. S. Alarcon[1], B. Fessler[1], G. Sturfelt[1], O. Nived[1], K. Steinsson[1], M. Khamashta[1], M. Petri[1], S. Manzi[1], M. Dooley[1], R. Ramsey-Goldman[1], C. Aranow[1], R. Van Vollenhoven[1], M. Ramos[1], T. Stoll[1], K. Kalunian[1], A. Zoma[1], P. Maddison[1] and I. N. Bruce[3]. [1]Systemic Lupus International Collaborating Clinics, Toronto, ON, Canada, [2]The University of Manchester, Salford, Manchester, United Kingdom, [3]The University of Manchester, [4]Toronto Western Hospital, Toronto, ON, Canada

Background: The excess cardiovascular mortality in Systemic Lupus Erythematosus (SLE) is not completely accounted for by traditional risk factors. High waist circumference, high triglycerides, low HDL-cholesterol and impaired glucose homeostasis, the clustering of which constitutes the Metabolic Syndrome (MetS), may be implicated. Therapy related factors such as antimalarials and steroids, used widely in the management of SLE, may moderate these risks. We aimed to describe the baseline incidence of the MetS and its association with steroid and antimalarial use in an international prospective SLE cohort.

Method: Data was obtained from the SLE International Collaborating Clinics-Registry for Atherosclerosis (SLICC-RAS) cohort, collated from 30 centres worldwide. Information on 596 subjects, diagnosed with SLE within 1 year (baseline), was available. The International Diabetes Federation criteria was used to define the MetS, which included the presence of a high waist circumference plus two or more of elevated triglycerides or on specific therapy; reduced HDL-cholesterol or on specific therapy; raised blood pressure(BP) and raised fasting plasma glucose or known Type II diabetes mellitus.

Results: Of the 596 patients studied, 94 (15.8%) had MetS at their baseline visit. There was a significant difference in prevalence of MetS according to therapy with the highest prevalence being in the group taking steroids alone ($P < 0.014$) (Table). Similarly, the incidence of high triglycerides and glucose intolerance was also highest in the group on steroids alone ($P<0.00003$ and $P=0.010$ respectively). Compared to the steroid monotherapy group, the group on a combination of steroids and antimalarials were significantly less likely to fulfil the criteria for MetS ($P=0.002$), high BP ($P=0.005$) and high triglycerides ($P<0.0002$).

	Steroids alone (n = 160)	Antimalarials alone (n = 130)	Steroids and antimalarials (n = 253)	Neither steroids or antimalarials (n = 53)	P
Metabolic Syndrome	38 (23.8%)	18 (13.9%)	31 (12.3%)	7 (13.2%)	0.014
High waist circumference	69 (43.1%)	62 (47.7%)	106 (41.9%)	20 (27.7%)	0.639
High triglycerides or on specific therapy	77 (48.1%)	30 (23.1%)	75 (29.6%)	15 (28.3%)	0.00003
Low HDL-cholesterol or on specific therapy	32 (20%)	28 (21.5%)	54 (21.3%)	11 (20.8%)	0.985
High blood pressure	67 (41.9%)	35 (27.1%)	72 (28.5%)	17 (32.1%)	0.253
Raised fasting plasma glucose or Type 2 diabetes	40 (25%)	14 (10.8%)	55 (21.7%)	7 (13.2%)	0.010

Conclusion: In this early SLE cohort, steroid monotherapy was associated with the highest prevalence of MetS. The prevalence of MetS, increased blood pressure, increased triglycerides and glucose intolerance were all significantly lower with concomitant use of antimalarials. In addition to their anti-inflammatory effects, antimalarials likely have direct effects on vascular function and lipid metabolism that improves the overall metabolic and cardiovascular risk status of SLE patients.

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Arthritis in an Ethnically Diverse Systemic Lupus Erythematosus Population. Guada Respicio[1], Clare Cleveland[1], Kim Taylor[1] and Lindsey A. Criswell[2]. [1]Rosalind Russell Medical Research Center for Arthritis, University of California, San Francisco, San Francisco, CA, [2]UCSF-Box 0500, San Francisco, CA

Purpose: Arthritis is one of the most common manifestations of SLE with reported prevalence ranging from 70–95%. Previous research documents ethnic differences in risk and outcome, however ethnic differences in arthritis in SLE have not been well characterized. Further, clinical, laboratory and other correlates of arthritis in SLE have not been fully investigated. We studied the frequency of arthritis among a large and ethnically diverse lupus cohort, as well as factors associated with the presence of this specific disease manifestation.

Methods: SLE patients were recruited from various sources, including specialty clinics and practices, community sources and nationwide outreach. The presence of arthritis as well as other ACR classification criteria was documented by review of medical records. Information about ethnic background was based on self report information as well as genotyping results for a set of ancestry informative markers (AIMs, n = 384). Chi square testing was used to identify ethnic differences in presence of arthritis. Other factors associated with arthritis were examined using multivariate logistic regression. Correlation analysis was used to identify patterns of association between arthritis and other disease manifestations with results displayed visually as heat maps.

Results: 2129 SLE patients were studied, including 1201 (56%) Caucasians, 297 (14%) Hispanics, 259 (12%) Asian/Pacific Islanders, and 248 (12%) African Americans (AA). 91% of patients were female, the average age at SLE diagnosis was 33 years, and the average disease duration at study entry was 9 years. Analyses demonstrated statistically significant ethnic differences in arthritis ($p = 0.003$), with the highest prevalence of arthritis documented for AA patients (75%) and lowest prevalence among Asian patients (59%). Among AA patients, analysis of AIM data did not demonstrate a significant association between the percent African ancestry and risk of arthritis. Results of multivariate logistic regression analyses as well as heat maps representing the degree of correlation between arthritis and other clinical manifestations revealed differential clustering of disease features across ethnic groups. Table 1 summarizes clinical features significantly associated with arthritis based on multivariate analyses of individual ethnic groups. Independent variables in these models included disease duration, sex, and the other ACR classification criteria.

Table 1. Multivariate analyses of ACR Clinical Criteria Associated with Lupus Arthritis

Ethnic Group	Significant clinical criteria (OR, p value)
Caucasians	Malar rash (1.39, 0.021) Serositis (1.70, 0.001)
African-Americans	Discoid rash (0.355, 0.019) Oral ulcers (2.72, 0.042) Renal (0.681, 0.024)
Hispanics	Discoid rash (0.231, 0.003) Renal (0.711, 0.023)
Asians/Pacific Islanders	None significant

Conclusions: These results demonstrate ethnic differences in risk of arthritis among SLE patients, with Asian patients having relatively lower risks of arthritis and AA patients having the highest risk of arthritis. Additional research will be required to further define the basis for these ethnic differences in disease expression.

Disclosure: G. Respicio: None; **C. Cleveland:** None; **K. Taylor:** None; **L. A. Criswell:** None.

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Association of Low-Dose Pulsed Intravenous Cyclophosphamide Therapy and Amenorrhea in 62 Patients with Systemic Lupus Erythematosus: A Case-Control Study. Sayumi Baba[1], Yasuhiro Katsumata[4], Yasushi Kawaguchi[2], Kae Takagi[1], Takahisa Gono[1], Yuko Okamoto[1], Yuko Ota[1], Masako Hara[1] and Hisashi Yamanaka[3]. [1]Tokyo Women's Medical University, Tokyo, Japan, [2]Tokyo Women's Medical University, Tokyo, Japan, [3]Tokyo Women's Medical University, Shinjuku-ku, Tokyo, Japan, [4]Tokyo Women's Medical University

Purpose: Amenorrhea is a serious adverse effect associated with cyclophosphamide (CY). Although low-dose intravenous CY (IVCY) regimen has been proposed to reduce its various adverse effects in the treatment for major organ involvements in systemic lupus erythematosus (SLE), the beneficial effect of low-dose IVCY on amenorrhea has not been fully elucidated. We aimed to clarify the incidence of amenorrhea following low-dose IVCY and the association between amenorrhea and clinical parameters.

Methods: We performed a case-control study on women younger than 45 years who were treated with low-dose IVCY (500 mg/body/pulse) plus steroid or steroid alone (0.8–1.0 mg/kg/day of predonisolone) for active SLE in our university hospital from 2000 through 2009. Patients with pre-existing amenorrhea and patients who dropped out from our follow-up were also excluded. We conducted a questionnaire survey about secondary amenorrhea and reviewed

medical records from cases and controls. Amenorrhea was defined as lack of menses for at least 3 months. Sustained amenorrhea was defined as lack of menses for at least 12 months without resumption during the study period.

Results: Twenty-nine and 33 patients who were treated with low-dose IVCY (IVCY group) and steroid alone (steroid group) returned the questionnaire, respectively. The median cumulative dose of CY in the IVCY group was 1000 mg. All the patients in both groups were successfully treated and discharged. Amenorrhea developed more frequently in patients in the IVCY group than the steroid group (59% vs. 14%; $p = 0.02$; OR 3.5; 95% CI 1.3–11.0). The incidence of sustained amenorrhea was not statistically different between the groups (14% vs. 3%; $p = 0.18$). 'Age over 40 years at initiation of treatment' was the strongest risk factor for developing amenorrhea by the univariate analysis: Patients over 40 years of age had higher incidence of amenorrhea than younger patients ($p = 0.005$; OR 9.0; 95% CI 1.7–46.5) when both groups were analyzed as a whole. IVCY was also associated with amenorrhea ($p = 0.02$; OR 3.5; 95% CI 1.3–11.0). Sustained amenorrhea developed in 4 patients in the IVCY group and 1 patient in the steroid group and all these patients were in their forties. In contrast, menses resumed in all the patients younger than 40 years old irreverent to the treatment. The multivariate logistic regression demonstrated that 'age over 40 years at initiation of treatment' was significantly associated with amenorrhea ($p = 0.004$; OR 10.2; 95% CI 2.1–78.5). IVCY was weakly associated with amenorrhea without statistical significance ($p = 0.07$; OR 2.9; 95% CI 0.9–9.7).

Conclusions: Our data suggested that the strongest risk factor for developing amenorrhea in SLE patients treated with high-dose steroids with or without low-dose IVCY is 'age over 40 years at initiation of treatment.' In addition, even low-dose IVCY might also increase the risk for developing amenorrhea. Patients younger than 40 years old had minimum risk for sustained amenorrhea irreverent to treatment regimen. Higher risk of IVCY for sustained amenorrhea should be seriously pre-considered in patients over 40 years of age.

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Atherosclerotic Vascular Events in a Multinational Inception Cohort of SLE: Description and Attribution over an 8 Year Period. Murray B. Urowitz[33], Dafna D. Gladman[22], Dominique Ibanez[32], Caroline P. Gordon[29], Sang-Cheol Bae[6], Ann E. Clarke[15], Sasha R. Bernatsky[15], F. Jorge Sanchez-Guerrero[9], John G. Hanly[19], David A. Isenberg[24], Anisur Rahman[25], Paul R. Fortin[33], Daniel J. Wallace[1], Ellen M. Ginzler[20], Joan T. Merrill[18], Graciela S. Alarcón[28], Barri J. Fessler[23], Ian N. Bruce[13], Gunnar K. Sturfelt[27], Ola Nived[27], Kristjan Steinsson[12], Munther A. Khamashta[21], Michelle A. Petri[2], Rosalind Ramsey-Goldman[17], Susan Manzi[34], Mary Anne Dooley[31], Ronald V. Vollenhoven[11], Cynthia B. Aranow[4], Thomas Stoll[10], Manuel Ramos[7], Kenneth C. Kalunian[26], Asad A. Zoma[5], Guillermo Ruiz-Irastorza[8], Peter J. Maddison[16], Diane L. Kamen[14], S. Sam Lim[3] and Christine A. Peschken[30]. [1]West Hollywood, CA, [2]Timonium, MD, [3]Emory University, Atlanta, GA, [4]Feinstein Institute, Manhasset, NY, [5]Hairmyres Hospital, East Kilbride, United Kingdom, [6]Hanyang University Medical Center, Seoul, Korea, Republic of, [7]Hospital Clinico I Provincial, Spain, [8]Hospital de Cruces, Universidad del Pais Vasco, Spain, [9]Instituto Nacional Nutricion, Mexico City, DF, Mexico, [10]Kantonsspital Schaffhausen, Schaffhausen, Switzerland, [11]Karolinska University Hospital, Sweden, [12]Landspitalinn University Hospital, Iceland, [13]Manchester Royal Infirmary, Manchester, United Kingdom, [14]Medical University of South Carolina, Charleston, SC, [15]Montreal General Hospital, Montreal, QC, Canada, [16]North West Whales NHS Trust, Colwyn Bay, United Kingdom, [17]Northwestern University, Chicago, IL, [18]Oklahoma Med Research Foundation, Oklahoma City, OK, [19]Queen Elizabeth II Health Services Center, Halifax, NS, Canada, [20]SUNY-Downstate Medical Center, Brooklyn, NY, [21]The Rayne Institute, London, United Kingdom, [22]Toronto Western Hospital, Toronto, ON, Canada, [23]UAB Rheumatology, Birmingham, AL, [24]UCL Div of Medicine, London, United Kingdom, [25]UCL Div of Medicine, United Kingdom, [26]UCSD School of Medicine, La Jolla, CA, [27]University Hospital Lund, Lund, Sweden, [28]University of Alabama, Oakland, CA, [29]University of Birmingham, Birmingham, United Kingdom, [30]University of Manitoba, Winnipeg, MB, Canada, [31]University of North Carolina, Chapel Hill, NC, [32]University of Toronto Lupus Clinic, Toronto Western Hospital, [33]University of Toronto Lupus Clinic, Toronto Western Hospital, Toronto, ON, Canada, [34]West Penn Allegheny Health System, Pittsburgh, PA

A large mutlicentre multinational inception cohort was established to study risk factors for atherosclerosis (AS) in SLE. This study describes vascular events during 10 years of follow-up and their attribution to AS.

Methods: Patients enter the cohort within 15 months of SLE diagnosis (≥4 ACR criteria). Clinical and laboratory features of SLE and comorbidities are gathered in a standardized protocol at yearly intervals. Vascular events are described and attributed on a specialized form. Events recorded include myocardial infarction (MI), angina, congestive heart failure (CHF), intermittent claudication (PVD), stroke, transient ischemic attack (TIA). Diagnosis of an event was confirmed using standard clinical criteria, relevant laboratory data and imaging where appropriate. Attribution to AS was made on the basis of lupus disease being inactive at the time of the event, and/or the presence of typical AS changes on imaging or pathology and/or evidence of AS elsewhere. Factors associated with AVE were analysed using descriptive statistics, t-tests and χ^2.

Results: Since 2000, 1593 patients have been entered into the cohort (89%F, age at SLE 35y, mean followup of 3.7 years). Thus far there have been 134 vascular events in 96 patients. These include: MI (16), angina (17), CHF (32), PVD (10), TIA (21) stroke (33), pacemaker insertion (5). 70 of the events were attributed to active lupus and 20 to other causes and 4 were unknown. 40 events in 26 patients were attributed to AS including: MI (8), angina (14), CHF (6), PVD (6), TIA (3), pacemaker (2), stroke (1).

Ten patients in the AS group had more than one event. Lupus duration at AS event was 2.7 ± 2.4 years. Compared to patients followed for 3 years without vascular events (n=770), at enrolment, patients with AS events were more frequently male (42% vs. 11% $p < 0.0001$) were older at diagnosis (54 ± 13 vs. 34 ± 13, $p<0.0001$), more frequently had hypertension (65% vs. 32% $p=0.0003$), and were more often obese (52% vs 30% $p=0.02$). While hypercholesterolemia, diabetes, smoking and family history of CAD were more common among those with AS events than those without, the difference was not statistically significant. There was no difference in proportion of Caucasian versus other ethnicities in the two groups.

Conclusion: Over the follow-up of an inception cohort with SLE there were 134 vascular events but only 40 were attributable to AS. Patients with AS events were more likely to be male, older age at diagnosis, more frequently obese and more often had hypertension.

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Attention Deficit and Hyperactivity Disorder Scores Are Elevated and Associated with Disease Activity and Fatigue in Patients with Systemic Lupus Erythematosus. Ricardo J. Garcia, Lisa Francis, Maha Dawood, Irene Ramos, Stephen Faraone and Andras Perl. SUNY

Purpose: Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune inflammatory disease characterized by predisposition to pro-inflammatory T cell death by necrosis due to mitochondrial dysfunction, oxidative stress, and depletion of intracellular glutathione. The potential benefit of reversing glutathione depletion is being investigated in a double-blind placebo-controlled treatment trial of N-acetylcysteine in patients with stable disease (ClinicalTrials.gov Identifier: NCT00775476). Since disease activity in SLE may result in neuropsychiatric manifestations and N-acetylcysteine has been found to improve memory in animal models (Basic Clin Pharmacol Toxicol. 105:98–104, 2009), we investigated whether disease activity in patients with SLE is associated Attention Deficit Hyperactivity Disorder (ADHD) which may serve as a neuropsychiatric marker and target of treatment.

Patients and Methods: The validated ADHD Self-Report Scale (ASRS) Symptom Checklist (Psychol Med 35:245-56, 2005; Ann Clin Psychiatry 18:145–148, 2006) was used to evaluate 22 SLE patients at baseline. As a control for biochemical and immunological studies, a healthy donor matched for ethnicity, gender, and age of the SLE patient within 10 years was bled on the same morning and also asked to complete the ASRS checklist. In the SLE group, 20 of 22 patients were Caucasian, one was African American, and one was Asian. In the control group, 21 of the 22 donors were Caucasian and one was Asian. Mean age was 42.27 years (standard deviation, SD= 12.85, range= 21–64) in the SLE group. Mean age was 44.23 years (SD=10.86, range=23–62) in the control group. All patients were female. SLE disease activity was assessed by using the British Isles Lupus Assessment Group (BILAG) and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Fatigue was estimated using the Fatigue Assessment Scale (J Psychosom Res 54:345–352, 2003).

Results: The mean ± SD of part A, part B and total ASRS scores were 10.56 ± 5.75, 9.82 ± 6.01 and 20.36 ± 10.32, respectively, in the control

population. Using two-tailed t-test, the mean ± SD of part A, part B and total ASRS scores were increased at 17.23 ± 7.77 (p = 0.0001), 14.36 ± 5.89 (p = 0.004) and 31.59 ± 12.69 in the SLE group (p = 0.0004). Using Pearson's correlation, fatigue scores correlated with part A (r = 0.76, p<0.0001), part B (r = 0.44, p=0.04) and total ASRS scores (r=0.68, p=0.0005). SLEDAI correlated with part A (r = 0.50; p=0.02) and total ASRS scores (r=0.48, p=0.02). There was no correlation between BILAG and ASRS scores.

Conclusion: Elevated ASRS scores indicate the presence of previously unrecognized and clinically significant symptoms of ADHD in patients with SLE relative to healthy controls matched for age, gender, and ethnic background. ADHD symptoms may be a source of cognitive impairment in SLE, which could lead to functional disability. Longitudinal studies are needed to determine if ADHD symptoms predict the subsequent onset of severe neuropsychiatric disorders that frequently follow the onset of idiopathic ADHD in children (Am J Psychiatry 167:409 417, 2010).

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Autoantibody Response to Adjuvant and Non-Adjuvant H1N1 Vaccination in SLE. Murray B. Urowitz, Anoja Anton, Domonique Ibañez and Dafna D. Gladman. Toronto Western Hospital, Toronto, ON, Canada, Toronto Western Hospital, Toronto, ON, Canada

It has been reported that influenza vaccination increases autoantibody production and/or disease activity in a significant proportion of patients with SLE. A further concern would be whether adjuvant containing vaccinations might further enhance autoantibody production in these patients. During the recent H1N1 epidemic we investigated whether the use of adjuvant and nonadjuvant containing H1N1 vaccine induced increased authoantibody production in patients with SLE.

Methods: Patients with SLE who received H1N1 vaccination (with or without adjuvant) and had a battery of 9 autoantibodies tested before and 1 and 3 months after vaccination were included. Antibodies tested included rheumatoid factor (nephelometry), antinuclear antibody (immunofluorescence), anti-DNA (Farr), anti-RNP, anti-SM, anti-Ro, anti-La, anti-Scl70 and anti-Jo1 (ELISA). Patients were evaluated according to the standard protocol including items necessary to calculate SLEDAI-2K and SDI. Descriptive statistics and McNemar test were performed to evaluate change in antibodies positivity. These were repeated in the adjuvant and the non adjuvant groups separately.

Results: 103 patients (94F, 9M), with mean age at vaccination of 43.9 (±15.2) years, disease duration 14.2 (±11.0) years. Mean SLEDAI-2K was 4.38 (±4.28), SDI of 1.26 (±1.52). 64% were taking steroids and 62% on immunosuppressives. 51 patients received adjuvant and 52 nonadjuvant vaccines. Antibody testing was performed a mean of 1.9 months prior to the vaccination. First post-vaccination sample was taken a mean of one month and the second sample was taken a mean of 3.5 months after vaccination. The percent of patients with changes in antibodies following vaccination was not statistically significant for most antibodies. In rheumatoid factor 80% remained unchanged while 15% who were negative became positive while 5% who were positive became negative (p=0.07). This was more pronounced in the non adjuvant group then in the adjuvant group where 88% remained unchanged, 12% converted for positive and none converted to negative compared to 71% remaining unchanged, 18% converting to positive and 12% converting to negative (p=0.03 and p=0.53 respectively). In Anti-Ro 83% remained unchanged while 3% converted to positive and 14% converted to negative(p=0.03) but no difference was significant when looking at the vaccine type. No other antibodies changes significantly in either group. After adjusting for the number of tests performed none of the associations was significant.

Conclusion: H1N1 vaccination (both adjuvant and non adjuvant) did not increase the levels of autoantibodies in patients with SLE.

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Belimumab, a BLyS-Specific Inhibitor, Reduced Corticosteroid Use in Patients with Active SLE: Results from the Phase 3 BLISS-52 and -76 Studies. R. F. van Vollenhoven[9], A. Gallacher[3], S. Navarra[11], E. M. Ginzler[8], M. A. Dooley[10], R. Cervera[4], E. K. Li[2], R. A. Levy[5], R. Gúzman[7], Z. J. Zhong[6], S. Cooper[6], L. Pineda[6], D. Hough[6], D. J. Wallace[1] and for the BLISS-52 and -76 Study Groups. [1]Cedars-Sinai/UCLA, Los Angeles, CA, [2]Chinese University of Hong Kong, Hong Kong, China, [3]Hospital Británico de Buenos Aires, Argentina, [4]Hospital Clinic, Barcelona, Spain, [5]Hospital Universitário Pedro Ernesto, Rio de Janeiro, Brazil, [6]Human Genome Sciences, Inc, Rockville, MD, [7]SaludCoop, Bogotá, Colombia, [8]SUNY Downstate Medical Center, Brooklyn, NY, [9]The Karolinska Institute, Stockholm, Sweden, [10]University of North Carolina at Chapel Hill, Chapel Hill, NC, [11]University of Santo Tomas Hospital, Manila, Philippines

Purpose: To assess the corticosteroid-sparing activity of belimumab in patients on corticosteroids at baseline with seropositive SLE over 52 and 76 wk of treatment.

Methods: 1684 seropositive (ANA ≥1:80 and/or anti-dsDNA ≥30 IU/mL) SLE patients with SELENA-SLEDAI ≥6 were enrolled in the phase 3, 52-wk (BLISS-52; NCT00424476) and 76-wk (BLISS-76; NCT00410384) international trials and randomized to IV belimumab 1 or 10 mg/kg, or placebo, plus standard-of-care (SOC) therapy, on d 0, 14, and 28, and then q28d, for 48 or 72 wk. The use of corticosteroids and corticosteroid taper was according to clinical need; use beyond prespecified limits resulted in patient designation as a treatment failure.

Results: 1453 patients (86.3%) were taking corticosteroids at baseline. Mean baseline characteristics were similar across treatment groups: SLE disease duration 6.4 y; daily prednisone equivalent dose 12.5 ± 8.1 mg; 976 patients (67.2%) with prednisone ≥7.5 mg/d; 64.1% with antimalarials, 50.0% with immunosuppressants, 25.7% with nonsteroidal anti-inflammatory drugs. For the pooled dataset, of 976 patients taking prednisone >7.5 mg/d, SLE response index rates were 50.3% and 53.7% with belimumab 1 and 10 mg/kg, respectively (p<0.05 for both), vs 40.6% with placebo. Of patients taking prednisone >7.5 mg/d at baseline, 20.1% and 17.9% with belimumab 1 and 10 mg/kg, respectively (p<0.05 for both), vs 12.3% with placebo were able to reduce prednisone use by ≥25% from baseline to ≤7.5 mg/d during wk 40–52. Of 376 BLISS-76 patients taking prednisone >7.5 mg/d at baseline, 26.9% (p=0.07) and 24.2% (p=0.27) with belimumab 1 and 10 mg/kg, respectively, vs 17.5% with placebo were able to reduce prednisone use by ≥25% from baseline to ≤7.5 mg/d during wk 64–76. Mean steroid reductions in the pooled data set of patients with baseline prednisone >7.5 mg/d, were 4.0 mg/d (p=0.40) and 4.6 mg/d (p=0.15) with belimumab 1 and 10 mg/kg, respectively, vs 3.5 mg/d with placebo at wk 52. In the pooled dataset, of 708 patients (42.0%) taking prednisone ≤7.5 mg/d at baseline, 13.8% (p=0.28) and 10.9% (p=0.044) with belimumab 1 and 10 mg/kg, respectively, vs 18.0% with placebo required an increase in prednisone to >7.5 mg/d at wk 52. Of 443 BLISS-76 patients taking prednisone ≤7.5 mg/d at baseline, 13.5% (p=0.33) and 11.8% (p=0.17) with belimumab 1 and 10 mg/kg, respectively, vs 18.1% with placebo required an increase in prednisone to >7.5 mg/d during wk 64–76.

Table. Changes in Corticosteroid Dosages in BLISS Studies

	Corticosteroid Reduction[a]			Corticosteroid Increase[b]		
	SOC + Placebo	SOC + Belimumab 1 mg/kg	SOC + Belimumab 10 mg/kg	SOC + Placebo	SOC + Belimumab 1 mg/kg	SOC + Belimumab 10 mg/kg
BLISS-52 and -76	**n = 318**	**n = 334**	**n = 324**	**n = 244**	**n = 225**	**n = 239**
Mean baseline dose ± SE, mg/d	15.9 ± 0.4	15.7 ± 0.4	16.3 ± 0.5	3.9 ± 2.8	3.6 ± 2.8	3.5 ± 2.9
Wk 4	1.3%	0.9%	1.2%	7.8%	4.0%	8.8%
Wk 8	2.8%	4.2%	4.0%	11.5%	7.6%	9.6%
Wk 12	4.7%	5.4%	6.8%	14.8%	8.4%	12.1%
Wk 16	7.5%	9.9%	10.2%	16.0%	10.7%	12.6%
Wk 20	7.5%	9.6%	10.2%	18.0%	11.6%	13.0%
Wk 24	9.7%	14.1%	10.5%	16.8%	11.1%	11.3%
Wk 28	11.0%	16.8%*	14.2%	16.8%	12.9%	9.6%*
Wk 32	10.7%	17.4%*	14.8%	17.6%	11.6%	8.8%*
Wk 36	11.3%	18.3%*	16.7%*	16.8%	12.0%	8.8%*
Wk 40	12.6%	19.2%*	17.3%	16.4%	12.9%	8.4%*
Wk 44	12.9%	21.6%*	18.8%*	17.6%	12.9%	9.6%*
Wk 48	15.1%	21.9%*	19.1%	17.6%	13.8%	10.0%*
Wk 52	14.5%	21.6%*	21.9%*	18.0%	13.8%	10.9%*
	Corticosteroid Reduction[a]			**Corticosteroid Increase[b]**		
BLISS-76 only	**n = 126**	**n = 130**	**n = 120**	**n = 149**	**n = 141**	**n = 153**
Wk 52	15.9%	20.8%	24.2%	16.1%	13.5%	10.5%
Wk 56	15.9%	23.1%	25.0%	17.4%	12.8%	10.5%
Wk 60	17.5%	23.8%	26.7%	19.5%	13.5%	11.1%
Wk 64	17.5%	25.4%	27.5%	18.8%	12.8%	11.1%
Wk 68	18.3%	25.4%	24.2%	18.1%	13.5%	11.8%
Wk 72	18.3%	26.9%	25.8%	18.1%	13.5%	11.8%
Wk 76	17.5%	27.7%*	25.8%	18.1%	13.5%	11.8%

[a]% patients with average prednisone dose decrease to ≤7.5 mg/d from >7.5 mg/d at baseline (dropout = failure); [b]% patients with average prednisone dose increase to >7.5 mg/d from ≤7.5 mg/d at baseline (last observation carried forward); *p < 0.05
SE, standard error.

Conclusion: In patients with seropositive SLE on corticosteroids, belimumab significantly reduced SLE disease activity at wk 52 and permitted significantly more meaningful corticosteroid dosage reductions than placebo. These analyses suggest that treatment with belimumab may have corticosteroid-sparing activity.

Disclosure: R. F. van Vollenhoven: GlaxoSmithKline, 5, 8, Human Genome Sciences, Inc., 5, 9; **A. Gallacher:** Human Genome Sciences, Inc., 2, 5; **S. Navarra:** Human Genome Sciences, Inc., 2, 5, 9; **E. M. Ginzler:** Human Genome Sciences, Inc., 2, 9; **M. A. Dooley:** Human Genome Sciences, Inc., 9; **R. Cervera:** GlaxoSmithKline, 5, Human Genome Sciences, Inc., 5, 9; **E. K. Li:** Human Genome Sciences, Inc., 5, 9; **R. A. Levy:** GlaxoSmithKline, 8, Human Genome Sciences, Inc., 5, 8, 9; **R. Gúzman:** Human Genome Sciences, Inc., 9; **Z. J. Zhong:** Human Genome Sciences, Inc., 1, 3; **S. Cooper:** Human Genome Sciences, Inc., 1, 3; **L. Pineda:** Human Genome Sciences, Inc., 1, 3; **D. Hough:** Human Genome Sciences, Inc., 1, 3; **D. J. Wallace:** Human Genome Sciences, Inc., 9; **for the BLISS-52 and -76 Study Groups:** None.

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Belimumab, a BLyS-Specific Inhibitor, Reduced Disease Activity, Flares, and Prednisone Use in Patients with Seropositive SLE: Combined Efficacy Results from the Phase 3 BLISS-52 and -76 Studies. M. A. Petri[5], R. A. Levy[3], J. T. Merrill[7], S. Navarra[10], R. Cervera[2], R. F. van Vollenhoven[8], S. Manzi[11], D. Gladman[9], A. Gallacher[1], L. Pineda[4], Z. J. Zhong[4], D. Hough[4], W. Freimuth[4], R. A. Furie[6] and for the BLISS-52 and -76 Study Groups. [1]Hospital Británico de Buenos Aires, Argentina, [2]Hospital Clinic, Barcelona, Spain, [3]Hospital Universitário Pedro Ernesto, Rio de Janeiro, Brazil, [4]Human Genome Sciences, Inc, Rockville, MD, [5]Johns Hopkins University School of Medicine, Timonium, MD, [6]North Shore LIJ Health System, Lake Success, NY, [7]Oklahoma Medical Research Foundation, Oklahoma City, OK, [8]The Karolinska Institute, Stockholm, Sweden, [9]Toronto Western Hospital, Toronto, ON, Canada, [10]University of Santo Tomas Hospital, Manila, Philippines, [11]West Penn Allegheny Health System, Pittsburgh, PA

Purpose: To assess the efficacy of belimumab in patients with seropositive SLE over 52 wk of treatment by pooling the data from 2 large phase 3 clinical trials.

Methods: 1684 seropositive (ANA ≥1:80 and/or anti-dsDNA ≥30 IU/mL) SLE patients with SELENA-SLEDAI (SS) ≥6 on stable standard-of-care therapy for ≥30 d were enrolled in 2 phase 3, double-blind, placebo-controlled international trials of belimumab 1 or 10 mg/kg or placebo, plus standard-of-care (NCT00424476/NCT00410384). Patients were dosed on d 0, 14, and 28, and then q28d, for 48 or 72 wk. Efficacy analyses included SS, BILAG, and SS Flare Index (SFI). The primary endpoint in both trials was wk-52 SLE Responder Index (SRI): improvement in SS (≥4-pt decrease), no new BILAG A and no more than 1 B flare, and no worsening (<0.3-point increase) in Physician's Global Assessment (PGA) vs baseline at wk 52.

Results: Mean baseline characteristics were similar across treatment groups: age 37.8 y; female 94.1%; race: Caucasian 47.4%, Asian 21.1%, indigenous American 22.7%, African-American 8.8%; SLE disease duration 6.4 y; SS 9.7; BILAG 1A/2B 61%; anti-dsDNA+ 69.4%; low C4 56.1%; proteinuria (>0.5 g/24h) 20.1%; antimalarials 65.3%; prednisone ≥7.5 mg/d 58.0%; immunosuppressants 48.7%. SRI response rates were 46.2% (p=0.006) with belimumab 1 mg/kg and 50.6% (p<0.0001) with 10 mg/kg vs 38.8% with placebo (table). Significant improvement was seen with belimumab 10 mg/kg vs placebo for: SRI at wk 52; SS ≥4-point reduction; mean % reduction in PGA at wk 24; reduction in prednisone use; and new BILAG 1A/2B flares. Statistically significant improvement compared with placebo was seen in at least 1 belimumab treatment group for time to response, mean duration of response, time to first flare (all and severe) by SFI, and new BILAG 1A/2B organ domain scores.

Conclusion: Belimumab significantly reduced SLE disease activity and SLE flare rates; delayed time to first SLE flare; and reduced prednisone use in patients with seropositive SLE.

Table. Combined BLISS Efficacy Results

Parameter	SOC + Placebo (n = 562), n (%)	SOC + Belimumab 1 mg/kg (n = 559), n (%)	SOC + Belimumab 10 mg/kg (n = 563), n (%)
Primary endpoint			
SRI at wk 52	218 (38.8)	258 (46.2)**	285 (50.6)#
Mean response duration, d[a]	67.2 ± 4.9	90.3 ± 5.4***	103.3 ± 5.5#
Secondary endpoints			
≥4-point reduction in SS score[b]	230 (40.9)	269 (48.1)**	297 (52.8)*
No worsening in PGA (≤0.3 pts)	372 (66.2)	424 (75.8)***	420 (74.6)**
No new BILAG 1A/2B organ domain scores	389 (69.2)	429 (76.7)**	425 (75.5)*
Improvement in PGA, mean ± SE			
% change at wk 24	−24.3 ± 2.5%	−28.8 ± 2.1%	−32.3 ± 2.1%**
% change at wk 52	−27.1 ± 2.3	−36.7 ± 2.2**	−37.8 ± 2.4***
Prednisone reduction from >7.5 mg/d by 25% to ≤7.5 mg/d during wk 40–52, n (%)[b]	39 (12.3)	67 (20.1)**	58 (17.9)*
Prednisone increase from ≤7.5 mg/d baseline to >7.5 mg/d at wk 52, n (%)	82 (33.6)	58 (25.8)	62 (25.9)
SLE flares			
SFJ median time to first SLE flare (all) log-rank analysis, d	84	110**	110*
Flare rate, % (hazard ratio)	81.5	74.6 (0.82)**	74.6 (0.84)*
Flares per patient-y, mean ± SE			
D 0-wk 52	3.5 ± 0.1	2.9 ± 0.1***	2.9 ± 0.1***
Wk 24–52	3.4 ± 0.2	2.5 ± 0.1#	2.4 ± 0.1#
SFJ severe flare rate, % (hazard ratio) log-rank analysis	23.7	17.0 (0.71)*	15.6 (0.64)**
Severe flares per patient-y, mean ± SE			
D 0-wk 52	1.0 ± 0.1	0.9 ± 0.1	0.8 ± 0.1
Wk 24–52	1.0 ± 0.1	0.7 ± 0.1	0.6 ± 0.1*
New BILAG 1A/2B flare rate, % (hazard ratio) log-rank analysis	32.0	27.2 (0.83)	24.9 (0.75)*
New BILAG 1A flare rate, % (hazard ratio) log-rank analysis	23.1	19.0 (0.81)	16.2 (0.67)**

[a]Duration of response occurring at/before wk-52 visit and persisting to wk 52; [b]major secondary endpoint for both trials.
*p < 0.05; **p < 0.01; ***p < 0.001; *p < 0.0001.

Disclosure: M. A. Petri: GlaxoSmithKline, 5, Human Genome Sciences, Inc., 2, 5, 6, 9; **R. A. Levy:** GlaxoSmithKline, 8, Human Genome Sciences, Inc., 5, 8, 9; **J. T. Merrill:** Human Genome Sciences, Inc., 9; **S. Navarra:** Human Genome Sciences, Inc., 2, 5, 9; **R. Cervera:** GlaxoSmithKline, 5, Human Genome Sciences, Inc., 5, 9; **R. F. van Vollenhoven:** GlaxoSmithKline, 5, 8, Human Genome Sciences, Inc., 5, 9; **S. Manzi:** Human Genome Sciences, Inc., 9; **D. Gladman:** Human Genome Sciences, Inc., 9; **A. Gallacher:** Human Genome Sciences, Inc., 2, 5; **L. Pineda:** Human Genome Sciences, Inc., 1, 3; **Z. J. Zhong:** Human Genome Sciences, Inc., 1, 3; **D. Hough:** Human Genome Sciences, Inc., 1, 3; **W. Freimuth:** Human Genome Sciences, Inc., 1, 3; **R. A. Furie:** GlaxoSmithKline, 5, Human Genome Sciences, Inc., 2, 5, 9; **for the BLISS-52 and -76 Study Groups:** None.

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BILAG-Measured Improvement in Moderately and Severely Affected Body Systems in Patients with Systemic Lupus Erythematosus (SLE) by Epratuzumab: Results from EMBLEM™, a Phase IIb Study. Kenneth C. Kalunian[5], Daniel J. Wallace[1], Michelle A. Petri[2], Frederic A. Houssiau[6], Marilyn C. Pike[3], Brian Kilgallen[4], Lexy Kelley[4] and Caroline P. Gordon[7]. [1]West Hollywood, CA, [2]Timonium, MD, [3]Massachusetts General Hospital, Harvard Medical School, Boston, MA, [4]UCB, Smyrna, GA, [5]UCSD School of Medicine, La Jolla, CA, [6]Universite Catholique Louvain, Brussels, Belgium, [7]University of Birmingham, Birmingham, United Kingdom

Background: The efficacy of 2 epratuzumab doses was demonstrated in a 12-week, multi-center, randomized, double-blind, placebo-controlled, Phase IIb study in SLE (NCT00624351). Statistically or clinically significant efficacy was seen with epratuzumab 600 mg every week for 4 weeks and 1200 mg every other week (EOW) for 2 weeks, respectively, with responder rates twice those of placebo. The aim of this analysis was to assess improvement in BILAG 2004 index according to body systems in the epratuzumab 600 mg weekly and epratuzumab 1200 mg EOW dose groups (cumulative dose = 2400 mg).

Methods: A combined index of disease activity was used to assess efficacy (defined as BILAG improvement: reduction in all body systems of baseline BILAG A to B/C/D and BILAG B to C/D; no BILAG worsening in other organ systems; no deterioration in SLEDAI or physician's global disease activity assessment). Independent central readers determined BILAG grades for all 9 systems. Results for the BILAG improvement component of the combined index in body systems for which a sufficient number of patients per treatment group (≥5) had baseline disease activity to assess response are reported: musculoskeletal, mucocutaneous, cardiorespiratory, neuropsychiatric, constitutional and renal.

Results: Similar numbers of patients had BILAG A/B at baseline in all treatment arms in each system, apart from cardiorespiratory (where the placebo arm contained more patients) (Table). By Week 12, more patients in the epratuzumab 600 mg weekly group, compared with placebo, had an improvement from BILAG A/B to BILAG D in the 6 body systems, indicating no active disease. A higher percentage of patients receiving epratuzumab 1200 mg EOW, compared with placebo, had an improvement in baseline BILAG A/B scores to BILAG C or D in musculoskeletal, mucocutaneous, neuropsychiatric, and renal systems. Improvements were particularly prominent in the cardiorespiratory and neuropsychiatric systems. In the cardiorespiratory system, all 7 patients in the epratuzumab 600 mg weekly group had improved to a BILAG D at Week 12. Similarly, in the neuropsychiatric system, 5 out of 6 patients in the epratuzumab 600 mg weekly group improved from BILAG B at baseline to BILAG D at Week 12.

Table. Change in BILAG grade among subjects with flares at baseline

Body system	Treatment group	BILAG grade at baseline A/B (Severe/moderate disease) n	BILAG grade (shift) at Week 12 A/B (Severe/moderate disease) n (%)	C (Stable disease) n (%)	D (Inactive disease) n (%)
Musculoskeletal	Placebo	31	18 (58)	7 (23)	6 (19)
	Emab 600 mg weekly	35	13 (37)	12 (34)	10 (29)
	Emab 1200 mg EOW	34	13 (38)	10 (29)	11 (32)
Mucocutaneous	Placebo	31	18 (58)	9 (29)	4 (13)
	Emab 600 mg weekly	32	19 (59)	4 (13)	9 (28)
	Emab 1200 mg EOW	32	15 (47)	10 (31)	7 (22)
Cardiorespiratory	Placebo	17	10 (59)	2 (12)	5 (29)
	Emab 600 mg weekly	7	0 (0)	0 (0)	7 (100)
	Emab 1200 mg EOW	9	8 (89)	0 (0)	1 (11)
Neuropsychiatric	Placebo	11	6 (55)	3 (27)	2 (18)
	Emab 600 mg weekly	6	1 (17)	0 (0)	5 (83)
	Emab 1200 mg EOW	8	3 (38)	0 (0)	5 (63)
Constitutional	Placebo	9	1 (11)	1 (11)	7 (78)
	Emab 600 mg weekly	7	0 (0)	0 (0)	7 (100)
	Emab 1200 mg EOW	10	2 (20)	2 (20)	6 (60)
Renal	Placebo	5	3 (60)	2 (40)	0 (0)
	Emab 600 mg weekly	6	3 (50)	1 (17)	2 (33)
	Emab 1200 mg EOW	6	3 (50)	3 (50)	0 (0)

Emab, Epratuzumab.
Placebo, N = 38.
Emab 600 mg weekly, N = 37.
Emab 1200 mg EOW, N = 37.

Conclusions: Treatment with epratuzumab 600 mg weekly during a 12-week cycle provided greater BILAG improvement over placebo in disease activity in all affected body systems. Within specific body systems, most patients had symptom reduction or absence of active disease after treatment. Efficacy was particularly prominent in cardiorespiratory and neuropsychiatric systems in which symptom improvements are often difficult to achieve. Within specific body systems, the majority had symptom reduction or absence of active disease after treatment. This analysis supports the finding that epratuzumab may be an effective treatment for SLE.

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Biologics Use in SLE in 7 Centers—Data from the International Registry for Biologics in SLE (IRBIS). Ronald Van Vollenhoven[4], Søren Jacobsen[9], Daniel J. Wallace[1], John G. Hanly[8], Michelle A. Petri[2], David A. Isenberg[10], Ann E. Clarke[7], Julia F. Simard[3], Christian A. Pineau[6], Sasha R. Bernatsky[5] and for the SLICC Group. [1]West Hollywood, CA, [2]Timonium, MD, [3]Clinical Epidemiology Unit, Stockholm, Sweden, [4]Karolinska University Hospital, Stockholm, Sweden, [5]McGill UHC/RVH, Montreal, QC, Canada, [6]McGill Univ Health Center, Montreal, QC, Canada, [7]Montreal General Hospital, Montreal, QC, Canada, [8]Queen Elizabeth II Health Services Center, Halifax, NS, Canada, [9]Rigshospitalet-4242, Copenhagen, Denmark, [10]UCL Div of Medicine, London, United Kingdom

Background: No biologic agents are approved for use in SLE, but off-label use is possible in various settings. In order to obtain information regarding biologics use in SLE, members of the SLICC group recently initiated the International Registry for Biologics in SLE (IRBIS).

Methods: SLICC/IRBIS investigators were asked to provide retrospective data on all patients treated with a biologic for SLE at their center. Standardized case report forms (CRFs) were used to collect demographic, disease-specific, and treatment data at the time of biologic initiation and at yearly follow-up. A retrospective data collection is currently in progress, and data from the first 7 reporting centers were analyzed.

Results: 165 patients were treated off-label with a biologic agent, in all cases rituximab (RTX). Additional groups of patients were treated in open-label extensions of RCTs with belimumab (n=16) and epratuzumab (n=21) – these patients were not further analyzed here. Age (mean±SD) was 39.4±12.3 and 92% were female. 57% were Caucasian, and smaller proportions Southeast Asian, Asian/Indian subcontinent, African-American, Latino, or other (each <10%). Disease duration when the biologic was initiated was 11.2 ± 8.1 years. SLEDAI at biologic start was 10.5 ± 6.7, SLICC-damage index 1.45 ± 1.71, and glucocorticoid (GC) dosage (prednisone equivalent) 15.0 ± 13.8 mg. Two different dosing regimes for RTX were used: 375 mg/m2 × 4 (37%) and 1000 mg ×2 (63%). Concomitant cyclophosphamide (CYX) was used in 54% of patients. The major organ manifestations leading to biologic treatment were lupus nephritis (LN) in 46% of patients, skin disease in 20%, hematological in 10%, musculoskeletal in 9%, CNS in 8%, and other in 14% (some patients having more than one). Both disease-control and steroid-sparing were given as reasons for choosing a biologic. At 1-year follow-up (n=92) additional immunosuppressives (ISs) had been started in 13 patients. Both SLEDAI and GC dose had decreased (SLEDAI to 5.9±5.3; GC to 9.0±10.9 mg, p<0.0005 for both comparisons, and excluding patients on new IS). SLEDAI at baseline was higher in LN patients than in non-LN but similar at follow-up. The higher-dose RTX regime was employed more often in LN; baseline SLEDAI for these patients was higher, and the decrease greater, than for the lower-dose regimen. A similar pattern was seen for changes in SLEDAI when RTX was used with as compared to without concurrent CYX.

Conclusions: Off-label biologics use in this multi-center international cohort was limited to rituximab; additional groups of patients on other biologics are followed in open-label extensions of clinical trials. Biologics in SLE are used for LN as well as for a range of other SLE manifestations. Both disease control and a steroid-sparing effect are targeted. At 1-year follow-up, lupus activity and concomitant glucocorticoid dosage had decreased, and this could not be attributed to other IS treatment.

The complete retrospective dataset from all participating centers, and the initiation of the prospective IRBIS registry, will provide much-needed data on the use of and results achieved with biologics in SLE.

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Carotid Plaque Area Correlates Better Than Intima Media Thickness with Cardiovascular Risk Factors and Clinical Ischemic Heart Disease in Lupus Patients. Lihi Eder, Murray B. Urowitz, Dominique Ibanez and Dafna D. Gladman. Toronto Western Hospital, Toronto, ON, Canada

Aim: Patients with Systemic Lupus Erythematosus (SLE) have a significantly increased risk of accelerated atherosclerosis and cardiovascular disease (CVD). The extent of sub-clinical atherosclerosis can be assessed by an ultrasound (US) measurement of carotid intima-media thickness (c-IMT) and carotid plaque area (c-PA). In the general population, c-PA correlates with ischemic events better than c-IMT. The aim of this study was to investigate whether c-PA can serve as a preferred surrogate measure for sub-clinical atherosclerosis in SLE.

Methods: The study patients were recruited from a large single centre prospective cohort of SLE patients. Demographic, clinical and laboratory information was stored in a computerized database. The database was searched for subjects with a history of a documented ischemic heart event, including angina pectoris or myocardial infarction. Consecutive SLE patients without a history of CVD were recruited as controls. High resolution images were acquired with an optimized US system for carotid imaging. Each plaque was scanned in a longitudinal view until maximum area of the plaque was in the plane of view. The plaque area was measured by tracing the perimeter with a cursor. Total plaque area was recorded as the sum of all plaques in the right and left carotid arteries. Mean c-IMT was measured using a computerized software, in the left and right common carotid arteries. Correlation between c-PA and c-IMT were evaluated. Both measures were compared in patients with and without a history of CVD. To facilitate direct comparisons, c-IMT and c-PA were transformed into z scores. Logistic regressions were used to evaluate the Odds Ratio(OR) and 95% Confidence Interval (95% CI) of c-IMT and c-PA in their association with CVD, hypertension, cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL).

Results: 72 SLE patients participated in the study, of whom 19 had a history of ischemic heart event. Carotid IMT correlated only moderately with c-PA (r=0.46, p<0.001). Both c-IMT and c-PA were significantly higher in the group with ischemic heart event (712.7 ± 106.7 vs. 606.4 ± 96.0 mm, p<0.001 for c-IMT and 0.447 ± 0.577 vs. 0.048 ± 0.100 p=0.008 cm^2 for c-PA). After transforming c-IMT and c-PA into z scores, c-PA showed a stronger association with clinical ischemic event (OR 10.8 95% CI 2.5–46.9, p=0.001) than c-IMT (OR 2.8, 95% CI 1.5–5.2, p=0.001). Elevated c-PA was significantly associated with high LDL levels (OR 7.6, p=0.04) and with low HDL level (OR 4.78 p=0.02) however, no association was seen with hypertension or total cholesterol level. Carotid IMT did not correlate with any of the traditional cardiovascular risk factors. None of the measures correlated with SLE disease duration.

Conclusions: In SLE patients, c-IMT correlates moderately with c-PA suggesting that they measure different phenotypes of atherosclerosis. Carotid Plaque area correlated better than c-IMT with cardiovascular risk factors and ischemic heart events suggesting that it may serve as a better tool for investigation of atherosclerosis in SLE.

Disclosure: L. Eder: None; **M. B. Urowitz:** None; **D. Ibanez:** None; **D. D. Gladman:** None.

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Circulating Pro-Angiogenic Cells Are Reduced in Patients with SLE Independent of the Presence of Coronary Artery Calcification. Joshua Baker[1], Lifeng Zhang[2], Sotonye Imadojemu[2], Alexis Sharpe[2], Sarita Patil[2], Jonni Moore[2], Emile R. Mohler III[2] and Joan Marie Von Feldt[3]. [1]University of Pennsylvania, Philadelphia, PA, [2]University of Pennsylvania, [3]University of Pennsylvania-Philadelphia, Veterans Affairs Medical Center, Philadelphia, PA

Purpose: Circulating pro-angiogenic cells (PACs), often termed endothelial progenitor cells, are reduced in number in patients with SLE. A reduced number of PACs has been strongly associated with the presence of atherosclerosis and predicts cardiovascular events in other populations. We sought to determine if reduced PAC numbers in patients with SLE is dependent on the presence of advanced coronary artery calcification (CAC).

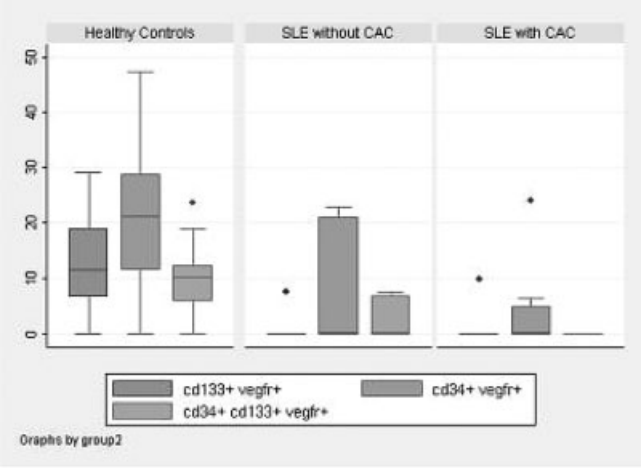
Methods: Patients were included if they met 4 criteria for the diagnosis of

SLE and had previous coronary calcium scores which placed them in either the >75th percentile or <25th percentile for their age. Exclusion criteria included a history of advanced renal disease, cardiovascular events, or current use of >10 mg of prednisone. 17 SLE patients and 13 healthy controls (HC) were included in the study. White blood cells from 30mL peripheral blood were stained for PAC and progenitor cell (PC) markers including CD34, CD133, and VEGFR and analyzed by flow cytometry as previously described (1). SLE patients had repeated coronary imaging with CT as well as carotid ultrasound to determine carotid intima-media thickness. Non-normal data were analyzed with non-parametric tests of significance.

Results: There was no difference in age betweeen HC and SLE. SLE patients were more likely to be hypertensive, and SLE patients with CAC were more likely to be hypertensive, smokers, and have longer disease duration than SLE patients without CAC. Patients with SLE had a significant decrease in PAC numbers when compared to HC. CD133+/CD34+/VEGFR+ cells were deficient in SLE patients (Median, IQR) 10.2 (5.8, 12.3) v. 0 (0, 0) (p<.0001). Compared to HC, SLE patients without evidence of CAC also had significantly lower numbers of PACs (Median, IQR) 10.2 (5.8, 12.3) v. 0 (0, 6.7) (p=0.02)). Total numbers of PCs (CD133+/CD34+) were not significantly decreased in patients with SLE ((Mean + SEM) 1007 + 154 v. 824 + 170 (p=0.2)). No significant difference was seen in PAC number between SLE patients without CAC and those with advanced CAC ((Median, IQR) 0 (0, 6.7) v. 0 (0, 0) (p=0.1). Increased carotid intima-media thickness did not correlate with CAC or decreased numbers of PACs in SLE patients.

Group	Healthy Controls	SLE patients without CAC	SLE patients with advanced CAC
CD133+, VEGFR+	11.5 (6.7, 18.9)	0 (0, 0) (p = 0.005)	0 (0, 0) (*p = 0.6)
CD34+, VEGFR+	21.2 (11.5,28.8)	0 (0, 20.9) (p = 0.05)	0 (0, 4.9) (*p = 0.9)
CD34+, CD133+, VEGFR+	10.2 (5.8, 12.3)	0 (0, 6.7) (p = 0.02)	0 (0, 0) (*p = 0.1)

* p value for comparison between SLE groups



Conclusions: Our study is the first to show that reduced numbers of PACs in SLE patients may be observed even in the absence of coronary calcification. Depletion of total circulating PCs does not appear to fully explain this difference.

1. Cherian S, et al. Cytometry B Clin Cytom. 2005; 64: 9–17.

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Effect of Belimumab, a B-Lymphocyte Stimulator–Specific Inhibitor, on Functional Antibodies to Pneumococcal, Tetanus, and Influenza Vaccines.

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Purpose: To evaluate the effect of belimumab plus standard of care (SOC) on antibodies against pneumonia, tetanus, and influenza in SLE patients with history of vaccination against these pathogens prior to study entry.

Methods: The phase 3, multicenter, randomized, double-blind, placebo-controlled, 76-wk BLISS-76 study evaluated the efficacy and safety of belimumab 1 or 10 mg/kg (IV infusion over 1 h on d 0, 14, and 28, and every 28 d thereafter through 72 wk) plus SOC vs placebo plus SOC in patients with seropositive SLE (ANA ≥1:80 and/or anti-dsDNA ≥30 IU/mL; NCT00410384). History of receiving pneumococcal, tetanus, and influenza vaccines was obtained at screening. Patients receiving a pneumococcal (n=73) or tetanus (n=81) vaccine within 5 y prior to d 0, or an influenza vaccine (n=146) within 1 y prior to d 0, were tested for vaccine antibody levels on d 0 and at wk 52. Immunoglobulin-G antibodies were measured for each vaccine (multi-analyte immune detection for pneumonia, enzyme-linked immunosorbent assay for tetanus, and hemagglutination inhibition test for influenza). Endpoints used to determine the impact of belimumab on vaccine responses included % change in antibody levels from baseline to wk 52 in patients with pre-existing antibodies, and proportion of patients with protective antibodies at baseline who maintained protective levels at wk 52.

Results: Consistent with the preservation of the memory B-cell compartment (CD20+/27+ B cells), belimumab did not cause a statistically significant decrease in pre-existing antibodies to pneumococcal and tetanus vaccines; most patients were able to maintain protective titers to these vaccines, and changes were similar across treatment groups (table). Pre-existing antibody responses to seasonal influenza vaccines were generally not affected by treatment with belimumab, although a statistical, but not clinically relevant, difference (<1-fold median change in titers) between treatment groups was observed for some antigens; the percentages of patients that maintained protective specific titers at the end of 52 wk were similar in the belimumab and placebo treatment groups.

Table. % Immunoglobulin-G Change in Response From Wk 0 to 52

		SOC + Placebo, n = 24	SOC + Belimumab 1 mg/kg, n = 27	SOC + Belimumab 10 mg/kg, n = 22
Antipneumococcal[a]				
9 (9N)	Mean ± SE	−10.3 ± 6.9	−1.5 ± 7.5	−11.9 ± 3.3
	Median	0.0	0.0	0.0
	% *Protective*[b]	100.0%	100.0%	92.3%
14 (14)	Mean ± SE	−8.3 ± 7.0	−1.2 ± 4.0	−10.1 ± 5.1
	Median	−8.6	0.0	−10.3
	% *Protective*[b]	100.0%	95.2%	94.7%
19 (19F)	Mean ± SE	−5.3 ± 7.2	−3.5 ± 5.8	−10.3 ± 5.1
	Median	−3.3	−2.6	−7.9
	% *Protective*[b]	100.0%	100.0%	93.8%
23 (23F)	Mean ± SE	−8.1 ± 8.5	−2.4 ± 6.4	−6.6 ± 3.9
	Median	−2.3	0.0	0.0
	% *Protective*[b]	94.4%	95.2%	100.0%
		SOC + Placebo, n = 29	**SOC + Belimumab 1 mg/kg, n = 29**	**SOC + Belimumab 10 mg/kg, n = 23**
Antitetanus				
	Mean ± SE	−12.0 ± 5.1	18.5 ± 36.2	−11.4 ± 7.1
	Median	−16.7	−17.5	−14.3
	% *Protective*[b]	81.8%	95.8%	78.6%
		SOC + Placebo, n = 15	**SOC + Belimumab 1 mg/kg, n = 22**	**SOC + Belimumab 10 mg/kg, n = 12**
Anti-influenza (2006–7)				
New Caledonia	Mean ± SE	38.9 ± 18.7	26.6 ± 21.2	1.2 ± 19.0
	Median	0.0	0.0	−18.3
	% *Protective*[b]	93.3%	95.2%	100.0%
Wisconsin	Mean ± SE	916.4 ± 842.4	3.8 ± 17.6	−11.4 ± 12.3
	Median	0.0	0.0	0.0
	% *Protective*[b]	100.0%	100.0%	100.0%
Malaysia	Mean ± SE	43.0 ± 18.5	−11.4 ± 7.8[a]	520.8 ± 525.6
	Median	0.0	0.0	0.0
	% *Protective*[b]	100.0%	100.0%	100.0%
		SOC + Placebo, n = 29	**SOC + Belimumab 1 mg/kg, n = 41**	**SOC + Belimumab 10 mg/kg, n = 27**
Anti-influenza (2007–8)				
Soloman Island 1_2_3	Mean ± SE	2.6 ± 26.3	−4.8 ± 11.2	−8.8 ± 16.5
	Median	−20.6	−10.0	−37.5
	% *Protective*[b]	100.0%	100.0%	100.0%
Wisconsin 1_2_3	Mean ± SE	63.1 ± 36.9	25.5 ± 19.8	−4.9 ± 15.1[c]
	Median	0.0	0.0	−20.6
	% *Protective*[b]	100.0%	100.0%	100.0%
Malaysia 1_2_3	Mean ± SE	−7.8 ± 11.3	−2.1 ± 7.8	−32.0 ± 5.5
	Median	0.0	0.0	−50.0
	% *Protective*[b]	100.0%	97.1%	92.6%

[a] Includes several representative antigen serotype results; [b]percentage of patients maintaining protective antibody level at wk 52; [c]1 patient did not have data available at wk 52 (n = 26).
* p < 0.05 for the comparison between active and placebo.
SE, standard error.

Conclusion: In this study, treatment with belimumab did not significantly affect the ability of SLE patients to maintain a protective immune response to prior immunizations.

Disclosure: W. W. Chatham: Human Genome Sciences, Inc., 2, 9; **D. J. Wallace:** Human Genome Sciences, Inc., 9; **W. Stohl:** Human Genome Sciences, Inc., 2, 9; **K. Latinis:** Human Genome Sciences, Inc., 9; **S. Manzi:** Human Genome Sciences, Inc., 9; **J. McCune:** Human Genome Sciences, Inc., 2, 9; **D. Tegzová:** Human Genome Sciences, Inc., 9; **J. McKay:** Human Genome Sciences, Inc., 9; **H. E. Avila-Armengol:** Human Genome Sciences, Inc., 9; **T. O. Utset:** Human Genome Sciences, Inc., 9; **Z. J. Zhong:** Human Genome Sciences, Inc., 1, 3; **D. Hough:** Human Genome Sciences, Inc., 1, 3; **W. Freimuth:** Human Genome Sciences, Inc., 1, 3; **T. S. Migone:** Human Genome Sciences, Inc., 1, 3; **for the BLISS-76 Study Group:** None.

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Effect of Systemic Lupus Erythematosus (SLE) on Pregnancy Outcome: An Analysis of 268 Pregnancies. Chi Chiu Mok and Ling Yin Ho. Tuen Mun Hospital

Objectives: To compare the maternal and fetal outcomes of pregnancies before and after the onset of SLE.

Methods: Female patients who fulfilled the ACR criteria for SLE and were ever pregnant were interviewed for the details of the maternal and fetal outcomes regarding their pregnancies. Comparison of the outcomes of pregnancies that occurred before and after the onset of SLE was made.

Results: 113 SLE patients with a history of pregnancy were studied. There were a total of 268 pregnancies: 216 pregnancies occurred before onset of SLE; 47 pregnancies occurred after SLE onset; and in 5 pregnancies, SLE was first diagnosed during conception. The maternal age was 28.7±5.6 and 26.4±5.0 years, respectively, in pregnancies that occurred after and before the onset of SLE. Induced abortion was significantly more common in pregnancies occurring after than before the onset of SLE (35% vs 18.1%; p=0.01). Spontaneous abortion also occurred at a higher frequency in pregnancies that occurred after SLE onset, but the difference was not statistically significant (12% vs 8.3%). Among 216 pregnancies that occurred before SLE onset, 158 (73%) ended up with live births and there was one (0.5%) intrauterine fetal death. The mean fetal birth weight was 2.98±0.51 kg. For pregnancies that occurred after SLE onset, only 55.3% ended up with liver births. The fetal birth weight was significantly lower than that in pregnancies that occurred before SLE onset (2.74±0.46 vs 2.98±0.51 kg; p=0.03). Low fetal birth weight (<2.5kg) was more common in pregnancies that occurred after SLE onset than those occurring before onset of SLE (14% vs 7%; p=0.19). The mean gestational age of fetus was also significantly lower in pregnancies that occurred after SLE diagnosis (36.1±2.7 vs 37.9±2.8 weeks; p=0.02). Preterm delivery was significantly more common in pregnancies after SLE onset (36% vs 7%; p<0.001). There were more maternal complications (eg. preeclampsia, proteinuria and lupus flares; 30.8% vs 3.8%; p<0.001) and fetal complications (eg. neonatal lupus, heart problems, infections, anemia; 3.8% vs 2.5%; p=0.75) in pregnancies that occurred after SLE diagnosis than before onset of SLE.

Conclusion: SLE increases the frequency of maternal complications and adversely affects fetal outcomes in terms of fetal loss, prematurity and low birth weight.

Disclosure: C. C. Mok: None; **L. Y. Ho:** None.

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Effects of Disease Activity and Use of Antimalarials on the Risk of Coronary-Artery Calcifications in SLE Patients. Juanita Romero-Díaz[3], Florencia Vargas-Worackova[1], Eric Kimura-Hayama[2], Carlos Aguilar-Salinas[3] and Jorge Sanchez-Guerrero[4]. [1]Instituto Nacional ce Ciencias Medicas y Nutricion Salvador Zubiran, [2]Instituto Nacional de Cardiologia Ignacio Chavez, [3]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, [4]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico

Traditional cardiovascular risk-factors do not fully explain premature atherosclerosis in SLE. We aimed to identify lupus-related factors associated with coronary-artery calcifications in an inception cohort for the study of atherosclerosis.

Methods: We included 139 patients (93% females) with SLE of recent-onset at enrollment, w/o preexisting coronary heart disease. At enrollment, a standardized medical evaluation was done assessing lupus characteristics, medications, cardiovascular risk-factors, and laboratory tests (lipid profile, homocystein, hsCRP, autoantibodies). Patients were seen every 3–6 months, and assessed for disease activity and medications. Every year, information was updated and a blood sample drawn.

At 5.5 ± 2.9 years of follow-up, all the 139 patients and 100 healthy subjects, matched for age and sex, were screened for coronary-artery calcifications using a 64-slice Multidetector Computed Tomography.

A nested analysis of lipids and inflammatory molecules was conducted among all lupus patients with calcifications and a random sample without calcifications (ratio 1:4), matched for age, sex and disease duration. Measurements were done in samples drawn at enrollment, mid follow-up, and at screening: total cholesterol, cHDL, cLDL, triglycerides, Lp(a) lipoprotein, and Apo B; CD40 ligand, IL-6, IP-10, MCP-1, sICAM-1, vCAM-1 (ELISA). Also, fasting levels of homocystein, and hsCRP were determined at enrollment and at screening.

Results: At enrollment, mean (SD) age of lupus patients was 27.2 (9.1) years, lupus duration 5.4 (3.8) months, and SLEDAI-2K score 6.9 (5.8). At screening for calcification, mean age of patients and controls was similar (31.8 ± 8.8 vs. 32.2 ± 9.8 years), as most cardiovascular risk-factors; however lupus patients had more often hypertension, higher levels of homocystein and hsCRP, wider waist, and females were more often post-menopausal, P<0.05.

Coronary-calcifications were detected in 10 patients (7.2%) and 1 control (OR 7.7, 95% CI 1.05–336.3, P = 0.02). Calcium scores in 9 patients ranged between >0–20, and in the remaining patient 402; in the positive control it was 239. Calcifications in lupus patients were detected since age 21–30 years and from 3 years of diagnosis.

In comparison to patients w/o calcifications, patients with calcifications were older, females more often postmenopausal, had higher Apo-B levels, IgG aPL antibodies, and the Framingham risk-scores were higher (p<0.05). Disease activity along the course of lupus was higher (SLEDAI-2K AUC 20.3±8.3 vs. 13.7±8.3, P=0.02), and the period of moderate/severe activity longer (SLEDAI-2K score ≥7, 20.0±18.3 vs. 8.0±12.5 months, P=0.006). Cumulative doses of prednisone and cyclophosphamide were higher (P<0.05), but use of antimalarials lower (20% vs 65%, P=0.006). Longitudinal analyses of lipids, cytokines and chemokines did not show differences. Logistic regression analysis showed an independent association of age, Apo-B, lupus activity (P=0.004), and use of antimalarials (P=0.008) with calcifications.

Conclusions: Lupus activity is an independent risk factor for coronary-artery calcifications, a risk that might be reduced using antimalarials.

Disclosure: J. Romero-Díaz: None; **F. Vargas-Worackova:** None; **E. Kimura-Hayama:** None; **C. Aguilar-Salinas:** None; **J. Sanchez-Guerrero:** None.

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Elevated Levels of Plasma Micro-Particles (PMPs) in Systemic Lupus Erythematosus (SLE) Are Associated with Higher Risk of Thrombosis. Aisha Lateef[3], Laurence S. Magder[4], Jayesh Jani[2], Thomas S. Kickler[2] and Michelle A. Petri[1]. [1]Timonium, MD, [2]Johns Hopkins University, [3]National University Health System, Singapore, Singapore, [4]University of Maryland Medical School

Objective: PMPs are sub-micron, membrane-bound vesicles, released during cell activation, apoptosis and exposure to shear stress. They are pro-thrombotic, expressing high levels of phosphatidylserine and tissue factor on outer membranes. PMPs modulate nitric oxide and prostacyclin production from endothelial cells, as well as monocyte chemotaxis and adherence to the endothelium.

Elevated levels of PMPs have been associated with pro-thrombotic disorders, including acute coronary syndromes, stroke, diabetes, hypertension, and hypertriglyceridemia. In addition, elevated PMP levels have been associated with inflammatory diseases such as SLE and cancer-associated thrombosis.

D-dimers are fibrin degradation products, reflecting activation of thrombosis and fibrinolysis. Elevated levels have been shown to predict risk of thrombosis in patients with atrial fibrillation on anticoagulation.

We evaluated the association of thrombotic events with PMP and d-dimer levels in a cohort of patients with SLE.

Methods We measured PMP and d-dimer levels in 894 SLE patients in a prospective cohort. The relationship between PMP and d-dimer levels and thrombotic events was evaluated using survival analysis.

Results: Of the 894 patients, 234 had at least one thrombotic event at some time in their life. The first event was DVT (108 patients), Stroke (70 patients), MI (23 patients), Other venous (19 patients), and Other arterial thrombosis (14 patients). Elevated levels of PMP (>5nM) were associated with higher risk of thrombotic events (RR=1.4, p=.05). We subdivided the group with elevated levels of PMP into different strata and the increased risk remained in all groups (Table). The risk was even higher if these patients were positive for lupus anti-coagulant or anticardiolipin antibodies (RR=1.5, p=.007). Elevated levels of d-dimer (>0.88 mg/L) were not predictive of higher risk of thrombosis in SLE.

Conclusion: We found that elevated PMP was associated with thrombosis in SLE. Elevated PMPs can affect the vasculature in many ways, leading to heightened inflammatory and thrombotic effects. They can induce adhesion molecules on endothelial cells, resulting in increased inflammation of atherosclerotic plaque. At the same time, their pro-thrombotic potential may favor thrombosis and clot formation.

We are now evaluating the effects of therapeutic intervention on PMP levels.

Group	Number of events	Number of person-years of follow-up	Rate per 1000 person years	Risk Ratio (95% Confidence Interval)	P-value	Adjusted[1] Risk Ratio (95% Confidence Interval)	P-value
Everyone	234	37,068	6.3				
Ddimer Group							
<0.88	156	24,076	6.5	1.00 (Ref. Group)	.12	1.00 (Ref. Group)	.22
0.88–1.0	13	3,059	4.3	0.64 (0.36, 1.12)	.95	0.70 (0.40, 1.24)	.65
1.0–1.5	36	5,639	6.4	0.99 (0.69, 1.42)	.86	0.92 (0.64, 1.32)	.94
1.5+	29	4,293	6.8	1.04 (0.70, 1.54)		1.02 (0.68, 1.51)	
Ddimer							
<.88	156	24,076	6.5	1.00 (Ref. Group)	.35	1.00 (Ref. Group)	.24
>.88	78	12,991	6.0	0.87 (0.66, 1.16)		0.84 (0.63, 1.12)	
PMP							
<5	65	12,458	5.2	1.00 (Ref. Group)	.080	1.00 (Ref. Group)	.023
5–10	96	14,156	6.8	1.33 (0.97, 1.82)	.15	1.44 (1.05, 1.98)	.012
10–20	41	6,102	6.7	1.33 (0.90, 1.97)	.21	1.67 (1.12, 2.48)	.22
20+	13	1,714	7.6	1.47 (0.81, 2.67)		1.46 (0.80, 2.64)	
PMP							
<5	65	12,458	5.2	1.00 (Ref. Group)	.050	1.00 (Ref. Group)	.0070
5+	150	21,971	6.8	1.34 (1.00, 1.79)		1.50 (1.12, 2.00)	

[1] Adjusting for ever having positive anticardiolipin antibodies or lupus anticoagulant.

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Evaluation of Cardiac Function and Myocardial Damage in Women with Systemic Lupus Erythematosus (SLE) by Cardiac MRI. Mala S. Kaul[2], Han Kim[2], E. William St Clair[2] and Megan E. B. Clowse[1]. [1]Duke Univ Med, Durham, NC, [2]Duke University, Durham, NC

Background: Cardiac magnetic resonance imaging (cMRI) can provide great detail about cardiac structure and function in a single session without harmful radiation. Very small areas of myocardial scar tissue can be identified using delayed gadolinium enhancement (DE) techniques. Additionally, impairments in coronary flow reserve may be measured by velocity-flow imaging, which identifies microvascular dysfunction. A recent study using cMRI found perfusion defects in 44% of asymptomatic SLE patients undergoing stress testing as well as areas of DE indicative of myocardial damage in 37% of patients.[1] Our objective was to take advantage of the sensitivity of cMRI to further evaluate the state of the myocardium in asymptomatic patients with SLE.

Methods: Consecutive patients meeting ACR Classification Criteria for SLE without history of cardiovascular disease or antiphospholipid syndrome were recruited from our university lupus clinic between January 2010 and May 2010. All patients underwent a comprehensive cMRI including adenosine stress perfusion imaging, and pre- and post- test electrocardiograms. Data collected included a chest pain history using the Rose chest pain questionnaire, SLEDAI scores, cardiovascular risk factors, disease duration and antiphospholipid antibody status.

Results: All 15 patients included in the study were women, with a mean age of 45 years (range 31–61 years); 60% were African American and the remainder were Caucasian. 27% patients had hyperlipidemia, and 47% had hypertension. 60% of patients were either obese (BMI >30) or overweight (BMI >25). The mean duration of SLE was 12 years (range 3 to 30 years) and average SLEDAI score was 3.5 (range 0 to 12). A previous history of chest pain was reported in 40% of patients. Only one patient tested positive for serum antiphospholipid antibodies.

No patient had evidence of prior myocardial infarction by ECG (Q-waves). By cMRI, left ventricular ejection fraction was normal. No patient had evidence of ischemia. The coronary flow reserve, a marker of coronary microvascular dysfunction, was normal in all patients. Delayed gadolinium enhancement of the myocardium, which is indicative of prior myocardial damage was identified in 3 (20%) of the patients. Additionally, 4 (27%) patients had evidence of delayed gadolinium enhancement of the papillary muscles and 1 patient had mild aortic regurgitation. An incidental thymoma was discovered in 1 patient. None of the subjects had pericardial effusion or thickening, or other valvular abnormalities.

Conclusion: In contrast to a previous study, asymptomatic patients with SLE were shown to have well preserved myocardial function, relatively normal cardiac structure, and no evidence of ischemia. Coronary flow reserve was not severely impaired. Small areas of myocardial and papillary muscle damage, however, were found in a minority of patients in our study, confirming that these abnormalities may be found in SLE despite a paucity of symptoms or other evidence of cardiovascular disease.

[1] Koyabashi H, et al. Cardiac magnetic resonance imaging abnormalities in patients with systemic lupus erythematosus. Mod Rheumatol. Jan 2010.

Disclosure: M. S. Kaul: None; **H. Kim:** None; **E. W. St Clair:** None; **M. E. B. Clowse:** None.

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Fulvestrant (Faslodex) an Estrogen Selective Receptor Down Regulator in the Therapy of Female SLE Patients, One to Two Year Following Faslodex Study Termination Revealed Mild Reactivation of the Serologic Parameters and Disease Activity. Nabih I. Abdou[1], Virginia Rider[3] and Cindy A. Greenwell[2]. [1]Center for Rheumatic Disease Allergy & Immunology, Kansas City, MO, [2]Center for Rheumatic Disease Allery & Immunology, Kansas City, MO, [3]University of Pittsburg, Pittsburg, KS

Background: Estrogen plays a role in upregulation of intracellular signals by binding to estrogen receptors. In SLE, the disease predominantly affects females. Faslodex (fulvestrant) competes for receptor binding in vitro and inhibits estrogen action in immune cells. This study investigated the role of the estrogen receptor blocker (Faslodex) given in a double blind protocol, monthly in vivo for one year with clinical and serological parameters. The bone density was measured pre-study and at the end of study. There was an observational visit one to two years after the completion of study.

Objective: We would like to examine the clinical status and immunologic parameters of female SLE patients at the end of the one-year study compared to the one-to-two year follow-up observation period after study completion.

Methods: Sixteen female SLE patients with moderate disease activity (SLEDAI 7.87+/− 3.7) were entered into the one-year double-blind placebo controlled Faslodex study. Eight patients received Faslodex IM monthly and eight received placebo IM monthly. Parameters checked pre-study and monthly as well as 3 months post study were SLEDAI, ANA, C3, C4, CH^{50}, urinalysis, anti-dsDNA, liver enzymes, creatinine, serum estrogen and Faslodex levels, and the bone density was done pre-study and at end-of-study. Two of these sixteen were lost to follow-up. At one to two years post study, 12 patients had SLEDAI, ANA, anti-dsDNA, C3 and C4 or CH^{50}, UA, liver enzymes, and creatinine measured.

Results: During the one-year study there was a significant drop in SLEDAI in the Faslodex group. SLEDAI pre-study of 8.25 dropped to 3.75 one to two years post Faslodex ($p < 0.02$). Antids-DNA in the same group dropped from 9.25 to 5.75 IU/ml ($p < 0.01$). The drop of anti-dsDNA persisted for one to two years after the study. There were no significant changes in any other parameter, including the estrogen levels and bone density.

Conclusion: Blocking estrogen receptors in vivo by an estrogen selective receptor down-regulator could be considered as a new therapeutic approach for moderately active female SLE. No untoward effects were seen in the patients studied by blocking the estrogen receptor without changes in estrogen levels or drop in the bone density. Only the anti-dsDNA was significantly decreased, but the complement leverls, ANA, and other measured parameters did not change. Faslodex is safe and could be a good alternative for the treatment of moderately active female SLE patients. We would like to extend this study for a longer duration and larger doses of Faslodex.

Disclosure: N. I. Abdou: None; **V. Rider:** None; **C. A. Greenwell:** None.

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Hydroxychloroquine Can Interfere with Flow Cytometric Analysis of Blood Cells from Patients Taking This Medication. Louise Fraser[1], Graham H. Mitchell[1], Shirish Sangle[2], Lee Meng Choong[2], Richard Ellis[1], Jo Spencer[1] and David P. D'Cruz[3]. [1]Department of Immunobiology, King's College London, [2]Lupus Research Unit, St Thomas' Hospital, [3]St Thomas Hospital, London, United Kingdom

Background: Immunological investigation of blood cells from patients with systemic lupus erythematosus (SLE) often involves flow cytometry. Quinoline ring-containing compounds are known to fluoresce. Therefore we asked whether the drug hydroxychloroquine (HCQ) might fluoresce and whether this might interfere with flow cytometric analysis of blood cells from patients taking this drug.

Methods: Blood cells from 13 patients with SLE were studied. They were all female, age range 19 to 71 years (average 45 years) with range of disease duration between 3 and 30 years (average 14 years). 9 patients were taking HCQ, and 5 taking steroids. In addition 3 disease controls and 10 healthy controls were studied. Peripheral blood lymphocytes were analysed by flow

cytometry, either with no stain or with a standard assay for expression of kappa and lambda light chains by B cells, which uses FITC, PE and APC channels. Data were analysed with Flowjo software. All the patients studied fulfilled the ACR classification criteria. The study was approved by the St Thomas Hospital Ethics committee and all subjects gave written informed consent.

Results: Blood cells from patients taking HCQ showed fluorescence on FITC, PE and APC channels when no fluorochrome conjugated antibodies were added to the assays. This was apparent when cells were sampled from any of the gates placed based on forward scatter and side scatter including the lymphocyte gate, and identified approximately 20% of cells as distinct populations (Figure).

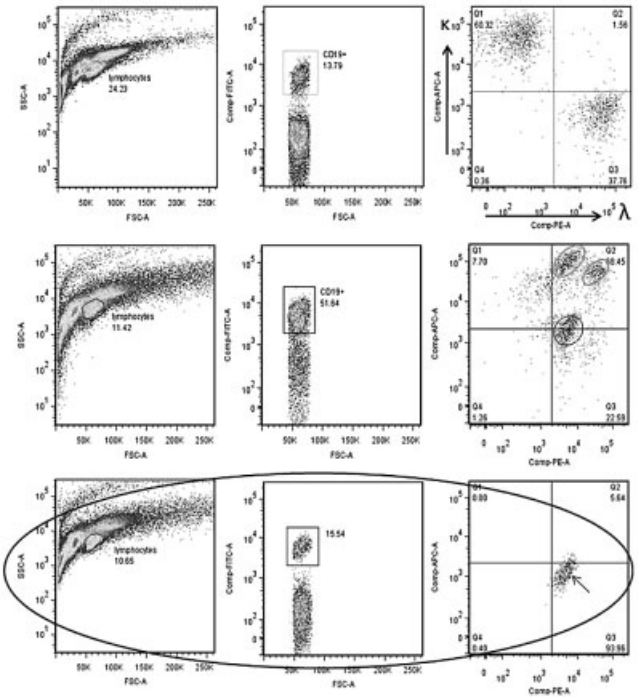

Figure. A. Analysis of healthy control blood. Lymphocytes (first column) were selected for expression of CD19 (second column) and the ratio of kappa: lambda light chain expression observed (third column).
B. When the process was repeated with blood from a SLE patient taking HCQ, the number of cells in the apparent CD19 gate increased. The profile of kappa and lambda expression was skewed (circles).
C. When cells from patients taking HCQ underwent the same procedure fluorescence in the FITC (second column), APC and PE channels was observed.

Blood cells from all individuals studied were assayed for kappa and lambda light chain expression on CD19 B cells by flow cytometry. The assays were standardized using blood from healthy control individuals and the percentage of B cells expressing each light chain determined accordingly. We observed that the fluorescence caused a shift so that cells appeared artifactually in the top right hand quadrant of the flow cytometric analysis of bloods from patients taking HCQ.

Conclusion: HCQ appears to have a broad spectrum of fluorescent excitation and emission which can interfere with flow cytometric analysis of blood cells from patients taking this medication. It is important when analyzing bloods from patients taking this drug that each sample is standardized according to its own isotype matched fluorescent control antibody.

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Immunogenicity of the Quadrivalent Recombinant HPV Vaccine in Female Systemic Lupus Erythematosus Patients Aged 9 to 26 Years. Arzu Soybilgic[2], Karen Onel[1], Tammy O. Utset[1], Kenneth A. Alexander[1] and Linda Wagner-Weiner[1]. [1]Univ of Chicago, Chicago, IL, [2]University of Illinois at Chicago, Chicago, IL

Background: Women with SLE have higher rates of persistent HPV infections than healthy women. HPV vaccine is safe and effective in healthy females aged 9–26 years. There are no data on the immunogenicity of HPV vaccine in females with SLE.

Objectives: To evaluate immunogenicity of recombinant quadrivalent HPV vaccine in female SLE patients aged 9–26 years.

Methods: Prospective, open-label, pre-post intervention study. All patients met ACR Criteria for SLE. Exclusion criteria: disease exacerbation within past 30 days resulting in ≥6 points increase in SLEDAI, increase in corticosteroid dose, initiation of new immunosuppressive medication or hospitalization; rituximab in the past 6 months; current cyclophosphamide treatment; previous HPV vaccination; pregnancy. HPV vaccine was given at months 0, 2, 6. Patients were monitored by physical examination, SLEDAI, lupus laboratories at months 0, 2, 4, 6 and 7. Each patient's SLEDAIs and laboratory profile in the year prior to vaccine administration were used as controls for that patient. Antiphospholipid, anti-ENA, HPV antibodies were measured at months 0 and 7. Primary outcome measures were change in SLEDAI and mean geometric HPV antibody titers. The secondary outcome measure was induction of autoantibodies.

Results: 26 patients, ages 12 to 26 years, were enrolled. 24 and 19 patients received two and three doses of HPV vaccine, respectively. Seven patients dropped out of the study: 2 pregnancies, 1 non-compliant, 2 moved out-of-state, 2 secondary to increased arthralgias. 19 patients completed the study.

Type-specific immunoassays with type-specific standards were used to assess immunogenicity to each vaccine HPV type. These assays measured antibodies against neutralizing epitopes for each HPV type. The immunogenicity analyses were conducted in a per-protocol immunogenicity (PPI) patient population. This population consisted of individuals who were seronegative to the relevant HPV type(s) at enrollment, received all three vaccinations, and did not deviate from the study protocol in ways that could interfere with the effects of the vaccine.

Immunogenicity was measured by (1)the percentage of individuals who were seropositive for antibodies against the relevant vaccine HPV type, and (2) the Geometric Mean Titer (GMT) (reported as Mmu/ml). GMTs were measured at month-7 because across all populations in previous clinical trials anti-HPV antibody titers peaked at month-7. HPV Antibody was determined by test kits, and cutoff values for seropositivity were titers at or above 20, 16, 20 and 24 mMU/mL for HPV 6, 11, 16 and 18 respectively.

Of the 19 patients who completed the study,16 had samples available at month-7 for analysis. Seropositivity rates after three doses of the vaccine were 90.9%, 100%, 100%, and 92.3%, and GMT were 641.4, 587.1, 28.44, 422.0 mMu/ml for HPV 6,11,16 and 18 respectively. One patient who received rituximab after the first vaccine dose had no antibody response at month 7.

Conclusion: The recombinant quadrivalent HPV vaccine was immunogenic in females aged 9–26. Only one patient who received rituximab after the first vaccine dose had no antibody response. Limitation of our study was the relatively small sample size.

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Immunoglobulin Levels as Potential Predictors of Response to B-Cell Depletion (BCD). Sara C. Croca[1] and David A. Isenberg[2]. [1]Hospital de Santa Maria, Department of Medicine 1, Lisbon, Portugal, [2]UCL Div of Medicine, Room 331, 3rd Floor, London, United Kingdom

Objectives: The use of BCD achieved by a combination of intra-venous methylprednisolone, cyclophosphamide and the anti-CD20 monoclonal antibody Rituximab has been reported to be an effective treatment for refractory systemic lupus erythemathosus (SLE) flares. The duration of the period of BCD is linked to the length of clinical improvement/ remission. Low C3 levels at the time of BCD predict a faster relapse but other predictors of the period of BCD are yet to be established. In this study we looked at the serum immunoglobulin levels (sIg) over time in order to assess whether they could provide an effective predictor of response to treatment.

Methods: Between July 2001 and December 2009, 78 lupus patients were treated with BCD at the University College Hospital London (UCLH). Patients were assessed at baseline and at 3 and 6 months after treatment with regards to the sIg levels (IgA, IgG, IgM). We selected patients with a minimum 12-month follow-up with consistent measurements of sIg over time (n= 44). The outcomes were defined as depletion status at 6 months (depleted: absolute CD 19 (CD19abs)≤ 0.005 ×109; non-depleted/ repopulated: CDabs> 0.005×109) and retreatment within 12 months of the first BCD treatment.

Results: Following the first BCD cycle, 86.4% (n= 38) were successfully depleted. However, six months after treatment, only 40.9% (n= 18) remained depleted. Depleted patients at 6 months had significantly lower baseline IgA

(p= 0.0003) and IgG levels (p< 0.001) with no differences with regards to the IgM levels. In addition, when comparing baseline and 6 months measurements, patients that remained depleted had a 40% reduction in the IgA levels whereas non-depleted patients had only a 10% reduction and this was statistically significant (p< 0.00001). No differences were found with respect to IgG and IgM reduction rates. A third of the patients (n= 14) were retreated within 12 months of BCD. Retreated patients showed significantly higher levels of IgA throughout follow-up (p= 0.002). No differences were found in terms of IgG and IgM between retreated and non-retreated patients.

Conclusions: We report that sIg levels, particularly IgA, may predict both duration of depletion following treatment with BCD and need to retreat. Recent data (DiLillo et al) suggest that the absence of a long term fall in antibody titres following BCD may be associated with the presence of long-lived plasma cells. Given the fact that serum IgA derives mainly from bone marrow plasma cells, the relation between higher levels of IgA could represent higher numbers of long-lived plasma cells that in turn could account, at least to some extend, for a poorer response to BCD. Further investigation of the potential role of long-lived plasma cells in the maintenance of an auto-immune memory after BCD is needed to confirm this hypothesis.

Disclosure: S. C. Croca: None; **D. A. Isenberg:** None.

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Influenza Humoral Immune Responses in Patients with Systemic Lupus Erythematosus. Evan Glenn Vista[3], Sherry Crowe[2], Linda Thompson[2], Gillian Air[4] and Judith A. James[1]. [1]Oklahoma Med Research Foundation, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]University of Oklahoma Health Science Center

Background: Annual seasonal flu vaccination has been the standard of care among the general population. Controversy still exists as to whether flu vaccination is effective among systemic lupus erythematosus (SLE) patients, who are identified by the United States Centers for Disease Control as a high risk group as part of the immunocompromised population. Select clinical and demographic factors may influence the response to influenza infection and vaccination among SLE patients. Flu vaccine is given at a particular period of the year in the clinical setting; however, nearly all previous studies have been limited in sample size, racial composition and focused on patients with relatively quiescent disease. This study assessed a large cadre of ethnically diverse SLE patients to identify clinical, demographic and therapeutic features associated with poor influenza vaccination responses.

Methods: A total of 201 SLE patients who fulfilled the American College of Rheumatology (ACR) criteria provided informed consent. Influenza antibody titers were tested at up to five-fold dilutions. A very low and a very high titer were defined as an endpoint titer of 1:200 and 1:10,000 respectively. Patient demographics and clinical profiles, including current medications, were collected. Antinuclear antibodies (ANA), anti-dsDNA, anti-Ro, anti-La, anti-Sm, anti-RNP, anti-Ribo P, anti-cardiolipin IgG were measured. Test for proportions and modified Wald method were used to compute for the 95% confidence interval of each influenza humoral immune endpoint titer.

Results: The sample population was comprised of 92 African Americans (45%), 98 Caucasians (48%) and 17 belongs to other or mixed races (7%). The median age of all subjects from this study is 43.5 years (range 17 to 87) and 87% are females. The mean influenza antibody endpoint titers were computed at 1:2146 (SD 2.48, CI 1802 to 2492), 17 subjects (8.5%, CI 0.05 to 0.13) were very low and 15 subjects (7.5%, CI 0.45 to 0.12) were very high. The majority (78 subjects) had an endpoint titer of 1:1000 (38.8%, CI 0.32 to 0.46). Endpoint titers for the others are as follows: 27 subjects (13.4%, CI 0.09 to 0.19) with 1:300 and 64 subjects (31.8%, 0.26 to 0.39) with 1:3000. Comparing the very low and very high endpoint titers, no significant differences in terms of sex, age and race were seen. In terms of their ACR criteria, patients with very high endpoint titers have higher incidence of discoid rash (30% vs 10%), photosensitivity (70% vs 50%) and serositis (60% vs 30%), while patients with very low endpoint titers fulfilled more immunologic criteria (80% vs 20%). Among the autoantibodies, no difference were seen in the ANA titers and the presence of anti-nRNP was significantly higher for those with very low endpoint titers (7/17 vs 1/15, OR 9.9 p <0.04). More patients with very low endpoint titers have concomitant prednisone medication than those with very high endpoint titers (12/17 vs 4/15, OR 6.6 p< 0.03).

Conclusions: Humoral immune responses to influenza were seen among patients with SLE. The variability of flu antibody titers could be influenced by factors that include current medications with steroids and select autoantibody production such as anti-RNP.

Disclosure: E. G. Vista: None; **S. Crowe:** None; **L. Thompson:** None; **G. Air:** None; **J. A. James:** None.

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Low-Dose Combination of Mycophenolate Mofetil and Tacrolimus for Refractory Lupus Nephritis: An Open-Labeled Trial. Chi Chiu Mok, Chi Hung To, Pak To Chan, Ka Lung Yu and Ling Yin Ho. Tuen Mun Hospital

Objectives: To evaluate the efficacy of low-dose combination of mycophenolate mofetil (MMF) and tacrolimus (Tac) for refractory lupus nephritis

Patients and Methods: Patients with refractory lupus nephritis were recruited. Inclusion criteria: (1) Active nephritis documented by renal biopsy within 24 months of entry; (2) Failure to respond to ≥ 2 immunosuppressive regimens which consist of high-dose corticosteroid combined with one other agent (eg. cyclophosphamide [CYC], azathioprine [AZA], MMF, cyclosporin A [CSA], Tac) together with ACE inhibitors ± angiotensin receptor blockers (ARB). Each regimen should be used for ≥6 months at the maximally tolerated dosage of the drugs; (3) Serum creatinine (Scr) ≤200umol/L. Exclusion criteria: (1) Previous intolerance to either MMF/Tac; (2) Scr >200umol/L; (3) Informed consent unavailable. Treatment failure to previous regimens was defined as any one of the following: (1) Failure of proteinuria to improve to <3g/day or urine protein-to-creatinine (uP/Cr) ratio to <3.0; or <50% of pre-treatment / baseline values; (2) Deteriorating Scr by ≥20% or loss in creatinine clearance (CrCl) by ≥30% compared to baseline not accounted by causes other than active nephritis; (3) Persistent active urinary sediments (RBC, active cellular casts ≥5/HPF). While prednisolone (≤10mg/day) and ACE inhibitors/ARB were continued, other immunosuppressive agents were discontinued and replaced by the current regimen, which consisted of MMF (1g/day) and Tac (4mg/day) in two divided doses. Patients were followed prospectively at least 2-monthly for the primary end-point (clinical response) at 12 months and adverse events.

Results: Up to May 2010, 11 patients were recruited. The mean age of these patients was 35.7±10 years and the mean SLE duration was 106±47 months at study entry. The distribution of the histological classes of lupus nephritis was as follows: ISN/RPS class IVG or III (36%), pure V (27%), V+III (36%). Previous treatment regimens received by these patients were: high-dose prednisolone (N=11), CYC (pulse/oral) (N=4), AZA (N=11), MMF (N=8), CSA (N=2) and Tac (N=7). All patients had been receiving the maximally tolerated doses of ACE inhibitor±ARB. The mean Scr, CrCl, uP/Cr, 24-hour proteinuria and serum albumin was 80.5±29umol/L, 85.3±32ml/min (8 patients [73%] had CrCl of <90ml/min), 2.85±1.4, 2.67±1.0g and 31.3±4.8g/L, respectively. Seven (64%) patients had active urinary sediments and 9(82%) patients had active lupus serology. Eight patients had completed 12 months' follow-up. Significant improvement in proteinuria and urinary sediments was observed in 7 (88%) patients and improvement started to occur at month 4–6. At month 12, a proteinuria of <1g/day and stabilization of CrCl was achieved in these patients. One patient was refractory to this regimen and withdrawn from the study. Treatment was well tolerated. The following adverse events were reported: minor infections (N=3), diarrhea (N=1), anorexia (N=1) and leg cramps (N=1).

Conclusions: Low-dose combination of MMF and Tac is a viable option for treating refractory lupus nephritis. A proper comparative trial with the novel biological agents is warranted.

Disclosure: C. C. Mok: None; **C. H. To:** None; **P. T. Chan:** None; **K. L. Yu:** None; **L. Y. Ho:** None.

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Lupus Disease Severity Is Not a Risk for Cervical Intraepithelial Neoplasia in SLE. J. Patricia Dhar[3], Lucie Gregoire[3], Wayne Lancaster[3], Azadeh Stark[1], Ann Schwartz[3], Daniel Schultz[2], Lynnette Essenmacher[3], Joel Ager[3], Lisa Chiodo[3], Mujitaba Husain[3] and Robert J. Sokol[3]. [1]Geisinger Health Systems, Danville, PA, [2]Hernry Ford Health Systems, Detroit, MI, [3]Wayne State University, Detroit, MI

Purpose: Women with systemic lupus erythematosus (SLE) are at increased risk for cervical intraepithelial neoplasia (CIN), possibly related to immunodysregulation. We hypothesized that women with SLE who developed CIN would be younger, have more severe disease and have received more immunosuppressive treatment.

Methods: In a case-control design, clinical characteristics of SLE women with CIN (cases) were compared to two groups of SLE women without CIN (controls). Diagnoses of cervical intraepithelial neoplasia (CIN) were confirmed from formalin fixed blocks of cervical tissue from 113 women with

SLE. Clinical data were obtained by chart review. Logistic regression was used to evaluate for any significant differences in clinical variables between the cases and the controls. Two sets of controls were used for comparison with a ~2:1 match for each control group to the cases group. For the first set, only the year of entry into our Lupus Clinic was controlled for ("unmatched" group, n=206); a second non-overlapping control group was matched for age, race, and year of entry into the clinic ("matched" group, n=212). The second matched control group was used to control for the three matching factors to allow smaller, but important effects of other factors, such as lupus severity, to emerge.

Results: For the cases, these predominantly African American (75.2%) women with SLE had a mean age at cervical biopsy of 38.5 years, with low grade CIN (CIN I/II) the most prevalent (80.5%) histology. Logistic regression showed that the cases differed from the both matched and unmatched controls only by being only one to two years younger (32.1 yrs. vs. 33.1 yrs. and 34.1 yrs., respectively) at lupus diagnosis. We did not combine the control groups because they were statistically significantly different from each other. Using the control group matched for age and race, logistic regression analysis showed no significant differences between cases and controls for any of the clinical variables. In particular, there were no significant differences for factors related to SLE (disease severity, use of immunosuppressive drugs, use of corticosteroids alone), chronic metabolic diseases (hypertension, diabetes), and HPV risk factors (marital status, smoking, gravidity, parity). Power analyses for both the unmatched and matched comparisons were similar for both lupus severity and immunosuppressive medications. At these sample sizes, with a two sided test, an alpha=.05 and 80% power, the difference in population proportions detectable was approximately 0.17, which is between a small and moderate difference. None of the described differences approached this magnitude of effect.

Conclusions: The key finding of this study is that SLE patients who develop CIN are not clinically different from SLE patients who do not develop CIN. In particular, worsened disease severity and immunosuppressive treatment do not appear to be susceptibility factors for CIN in SLE. All female SLE patients should be monitored closely for CIN, with at least annual PAP smears.

Disclosure: J. P. Dhar: Lupus Alliance of America- Michigan Indiana Chapter, 9; **L. Gregoire:** None; **W. Lancaster:** None; **A. Stark:** None; **A. Schwartz:** None; **D. Schultz:** None; **L. Essenmacher:** None; **J. Ager:** None; **L. Chiodo:** None; **M. Husain:** None; **R. J. Sokol:** None.

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Lupus Nephritis: Decrease in Proteinuria and Sustained Stabilization of Disease Activity in Patients under Prolonged Immunoadsorption (IAS). Georg H. Stummvoll[2], Peter Biesenbach[1], Sabine Schmaldienst[1], Josef Smolen[3] and Kurt Derfler[1]. [1]Dept. of Nephrology, Medical University of Vienna, Austria, [2]Dept. of Rheumatology, Medical University of Vienna, Vienna, Austria, [3]Dept. of Rheumatology, Medical University of Vienna, Austria

Introduction: SLE is characterized by pathogenic autoantibodies and immune complexes which can effectively be removed by extracorporeal procedures such as IAS. After up to one year of IAS, we had previously observed a reduction of proteinuria, disease activity and pre-treatment autoantibody levels in highly active SLE with renal involvement. Antibody removal, however, does not block the formation of new autoantibodies. Thus, a high percentage of these patients underwent prolonged IAS (>1 yr for up to 10yrs) and are the focus of this report. We evaluated patients under prolonged IAS for sustainability or further improvement of the primary response to IAS (proteinuria, disease activity, anti-dsDNA-Abs) and for the number of flares, infections, adverse events and tumors.

Patients and Methods: IAS therapy was started in highly active SLE patients with lupus nephritis (proteinuria 7.1±4.8 g/day, SIS 15±6, SLEDAI 20±8, anti-dsDNA 394±712 IU/ml) if i.v. CYC was contraindicated or ineffectual. 13 patients responding to initial IAS therapy were included into the prolonged IAS program, showing moderate disease activity at the start of the extension period (proteinuria 2.0±2.4, SIS 4±2, SLEDAI 3±2, anti-dsDNA 47±36 IU/ml). We defined the end of observation (EoO) upon either completion of 10 yrs of IAS therapy or by 1.1.2009.

During IAS, oral immunosuppression and ACE/ATII-inhibitors were kept constant, steroids were tapered as clinically feasible. IAS was performed with high affinity columns and the effective removal of serum Ig was monitored. Severe infections were defined as requiring i.v. therapy or hospitalization, flares according to the SELENA protocol.

Results: Under prolonged IAS (mean observation period of 6.7±3.5 years), proteinuria further decreased from 2.0±2.4 g/d to 0.9±1.7g/d ($p<0.05$) at the EoO and Creatinine clearence increased to normal ranges in all patients. Disease activity and anti-dsDNA levels could be stabilized at low levels (SIS3±3, SLEDAI 3±4, anti-dsDNA 26±24 IU/ml at EoO).

Complete remission (proteinuria <0.5g/d, SIS/SLEDAI ≤4, pre-treatment dsDNA <25 IU/ml) was achieved in 9 (69%) patients. One patient flared and was discontinued. Ten (77%) patients are still under IAS therapy at the EoO. In 2 patients, IAS was stopped because of a sustained response. Severe infections (0.1±0.3 per patient year) and severe flares (0.1±0.2 per patient year) were uncommon. There were no anaphylactic or orthostatic adverse events or tumors.

Conclusion: Prolonged IAS leads to stabilization of disease activity in moderately active SLE patients and can induce sustained remission in previously refractory SLE while showing an acceptable safety profile.

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Peripheral Vascular Disease in Systemic Lupus Patients. Rayford June[3], Robert C. Gilkeson[1], Shweta Bhatt[4] and Lisabeth Scalzi[2]. [1]Case Western Reserve University, [2]Penn State Univ Hershey Medical, Hershey, PA, [3]Penn State Univ Hershey Medical, [4]University of Rochester

Background: Systemic lupus erythematosus (SLE) is an independent risk for cardiovascular disease (CVD). Ankle brachial index (ABI), a simple measure of peripheral vascular disease (PVD), is known to be associated with CVD. We hypothesized that ABI would be lower in SLE subjects versus controls. In addition, we determined whether SLE-related, traditional, and/or non-traditional CVD risk factors help predict those SLE patients with PVD.

Methods: In a cross-sectional analysis of 134 SLE subjects and 77 age, sex, and racially-matched controls, SLE-related covariates and cardiovascular risk factors were measured. None of the participants had any history of known CVD. Measures of subclinical CVD were assessed including ABI, coronary artery calcification (CAC), and carotid intimal medial thickness (IMT). Covariates were compared between SLE and controls using chi-square testing for ordinal measures and a Student's t-test for continuous variables. In SLE patients, comparisons of the covariates were made between those patients in the lowest tertile (ABI ≤ 1.0) versus all others. A final logistic regression model was performed investigating correlations including all significant ($p \leq 0.10$) risk factors in the univariate analyses.

Results: When controlled for age, ABI was significantly lower between SLE and control subjects 1.05 vs. 1.09 ($p=0.003$). Significant covariates ($p \leq 0.05$) in the univariate analyses, examining those SLE patients in the lowest tertile versus those with higher ABI, included race (with Black SLE patients being more likely to have an ABI ≤ 1.0), a positive smoking history, and present or previous diagnosis of hypertension (HTN). In the final model, controlling for HTN, race, and homocysteine, only a smoking history ($p=0.02$) was significantly associated with having an ABI in the lowest tertile. There were no significant associations of CAC or carotid IMT with the lowest ABI tertile.

Conclusion: PVD, as measured by ABI, is more common in SLE patients as compared to non-SLE patients. Smoking is independently associated with PVD in SLE patients. SLE patients should be counseled of the increased risk of tobacco use and cardiovascular risk associated with their disease. Similar to other inflammatory diseases, an ABI of 1.0 (rather than 0.9 in the general population) is a more appropriate lower limit of normal when screening for PVD in SLE.

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PiHDL and High Plasma Leptin Levels Are Predictors of Longitudinal Progression of Subclincal Atherosclerosis in SLE. Maureen A. McMahon[5], Jennifer M. Grossman[7], Lori Sahakian[5], Brian Skaggs[5], John D. FitzGerald[6], Christina Charles-Schoeman[3], Alan H. Gorn[4], Michael H. Weisman[2], Daniel J. Wallace[1] and Bevra H. Hahn[8]. [1]West Hollywood, CA, [2]Cedars-Sinai Medical Center, Los Angeles, CA, [3]UCLA, Santa Monica, CA, [4]UCLA Medical Center, Los Angeles, CA, [5]UCLA School of Medicine, Los Angeles, CA, [6]UCLA School of Medicine Rehabilitation, Los Angeles, CA, [7]University of California Los Angeles, Sherman Oaks, CA, [8]University of California Los Angeles School of Medicine, Los Angeles, CA

Purpose: Women with SLE have an unexplained increase in atherosclerosis (ATH). We previously reported that 45% of SLE women vs. 5% of controls have pro-inflammatory HDL (piHDL), and that piHDL confers a 16-fold increased risk for the concurrent presence of carotid artery plaque. It is unknown, however, whether piHDL predicts future progression of atherosclerosis. Here we hypothesize that baseline presence of piHDL is associated with longitudinal accumulation of subclinical atherosclerosis.

Methods: Female SLE and healthy age-and gender- matched subjects not taking statins were studied. B-mode and Doppler scanning of carotid arteries was performed at baseline and at 24–36 months. Antioxidant function of HDL was measured as the change in fluorescence intensity caused by oxidation of DCFH by LDL in the presence or absence of test HDL. Fluorescence in the absence of HDL was normalized to 1.0. Values greater than 1.0 after the addition of HDL indicated piHDL. Plasma leptin was measured using ELISA (Biovendor).

Results: Follow-up carotid ultrasounds were completed on 185 SLE women and 84 controls. Overall, 21% (39) of SLE patients had accumulation of new plaques (defined as any new or accumulating plaque) vs. 15% (13) of controls. Among the 39 SLE patients in our cohort with plaque progression, 33 (85%) had piHDL, compared to 39% of SLE patients with no new plaques ($p<0.0001$). Follow-up intima media thickness (IMT) was also higher in patients with piHDL at baseline than in those without; 0.62 ± 0.14 vs. 0.52 ± 0.07 ($p<0.0001$). In addition, plasma leptin levels were also higher in SLE patients with plaque (28.3 ± 23.0 vs. 22.9 ± 26.8, $p=0.01$). After multivariate analysis, the only significant factors predictive of plaque progression in SLE were the baseline presence of piHDL, with an OR of 14.2 (95% C.I. 2.2 – 161.3, $p<0.001$), the baseline presence of plaque, OR 14.9, (95% C.I. 1.8 – 238.9, $p=0.02$), elevated leptin levels in the highest quartile (>34 ng/mL), OR 5.1, (95% C.I. 1.7 – 18.2, $p=0.03$) and increasing age, OR of 1.1; (95% C.I. 1.03 – 1.22, $p=0.004$).

Conclusions: piHDL and plasma leptin are strong predictors for the future progression of subclinical atherosclerosis in women with SLE.

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Positivity for Anti-RNP Antibody Is a Risk Factor for Adverse Effects by Trimethoprim-Sulphamethoxazole, a Prophylaxis Agent of *P. jiroveci* Pneumonia, in Patients with Collagen-Vasular Diseases. Reika Maezawa[1], Kazuhiro Kurasawa[2], Satoko Arai[2], Takayoshi Owada[2] and Takeshi Fukuda[2]. [1]Clinical Immunology, Dokkyo Medical University, Mibu, Tochigi, Japan, [2]Dokkyo Medical University, Mibu, Tochigi, Japan

Purpose: *Pneumocystis jiroveci* pneumonia (PCP) is a serious complication in patients with immunosuppressive therapy for collagen-vascular diseases (CVD). For prophylaxis of PCP, Trimethoprim-sulphamethoxazole (TMP-STX) is widely used. TMP-STX prevents the development of PCP, but often caused adverse effects (AEs) such as leucopenia, fever, and rash. However, risk factors for AEs by TMP-STX in CVD patients are unknown and also clinical features of AEs remain to be clarified. The aim of this study is to identify risk factors for AEs of TMP-STX, and to clarify clinical features of the AEs in CVD patients with immunosuppressive therapy.

Methods: We reviewed medical records of consecutive 541 patients who received TMP-STX as prophylaxis for PCP from 2003 to 2009 in our department. Subjects were 312 patients with CVD including 82 SLE, 60 myositis, 55 vasculitis, 26 SSc and 12 MCTD, and 229 patients with pulmonary diseases including 116 interstitial pneumonia and 56 lung cancer. These patients received corticosteroid (more than 30mg/day predonisolone) with/without immunosuppressants.

Results: AEs by TMP-STX were observed in 30 out of 541 patients (5.5%). Incidence of the AEs in CVD was 7.1%, significantly higher than that in pulmonary diseases (3.5%). In CVD, patients with SLE, MCTD and adult Still's disease frequently developed the AEs (11%, 33% and 13%, respectively), compared to those with myositis and vasculitis(4% and 5%). Particularly, incidence of the AEs in patients with anti-RNP antibody were significantly higher than those without the antibody (a-RNP(+) vs. (-); 21% vs 7%). High incidence of the AEs in RNP positive patients was observed in SLE. In addition, incidence of the AEs in CVD patients without anti-RNP antibody was similar to that in pulmonary diseases. Incidence of the AEs were similar between patients with and without antibodies such as anti-DNA, anti-SS-A, and anti-Sm antibodies.

Clinical features of the AEs in patients with CVD were different from those with pulmonary diseases. Fever was most frequent symptom in AEs in patients with CVDs, while no fever was observed as AEs in those with pulmonary diseases.

Conclusion: SLE and MCTD, and positively for anti-RNP antibody are risks factor for adverse effects by trimethoprim-sulphamethoxazole in collagen-vascular disease patients

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Potential Risk Factors for Lupus Nephritis. Mehrnaz Hojjati[3], Semi Ayub[4], Qi Wang[5], Timothy W. Behrens[2], Emily Gillespie[5] and Michelle A. Petri[1]. [1]Timonium, MD, [2]Genentech Inc, South San Francisco, CA, [3]Univ of Minnesota, Minneapolis, MN, [4]Univ of Minnesota, Little Canada, MN, [5]Univ of Minnesota

Introduction: Kidney involvement is a major clinical problem in systemic lupus erythematosus (SLE). Consideration of possible predictive factors for development of lupus nephritis (LN) may help to identify high-risk patients. The purpose of this study was to assess whether certain demographic, clinical and immunological variables can predict the occurrence of lupus nephritis (LN).

Methods: We studied 679 SLE patients enrolled from the Hopkins Lupus Cohort via the Autoimmune Biomarkers Collaborative Network. Patients were classified into 2 groups: (1) LN, defined as patients who had either a) renal biopsy, World Health Organization class II-V and/or b) met ACR criteria for LN (persistent proteinuria ≥3 or cellular casts attributable to SLE) and/or c) Lupus Activity Index renal subscore ≥1. (2) Non-LN (SLE patients with no history of LN and maintaining renal subscore=0, urine protein=0, urine RBC≤5 per high power field and serum creatinine ≤1.1mg/dl over the enrollment period. The variables assessed at the beginning of the study were from 2 domains, the demographic/clinical domain and the laboratory/immunologic domain. Chi-square tests were used to examine the association between LN and each variable, and we used t-tests to compare mean age and disease duration between LN and non-LN. Logistic regression was used for prediction of LN from knowledge of the person's demographic, clinical, laboratory and immunologic information at study entry. Stepwise multivariate regression was used to select the best set of predictors after adjusting for SLE disease duration.

Results: Of the 679 patients studied, there were 348 LN patients and 222 non-LN. The LN patients were significantly younger (mean age 40.82, SD=12) compared to non-LN patients (mean age 45.6, SD=12.7; $p<0.0001$). Mean SLE disease duration was 132 (SD=104) months in the LN group compared to 112.1 (SD=87) months in the non-LN group ($p=0.014$). Photosensitivity was negatively associated with LN (51.01% in LN group vs 61.3% in non-LN, $p=0.02$). Variables were included in the stepwise logistic regression model as significant predictors for LN are shown in Table 1.

Table 1. Variables included in stepwise multiple regression model for LN.

Variable	Adjusted odds ratio	p-value
Obesity	1.62	0.04
Hypertension	2.54	0.0001
High cholesterol	1.7	0.02
Male gender	3.3	0.003
Caucasian ethnicity	0.42	0.0001
Hispanic and Asian ethnicity	1.5	0.08
Age	0.95	<0.0001
Low C4	2.3	0.0009
dsDNA antibody	1.6	0.05
Anemia	2.45	<0.0001
Thrombocytopenia	1.9	0.02

Interestingly, when we included only demographic and clinical variables in the logistic regression model, smoking was negatively associated with LN (adjusted OR=0.65, $p=0.04$); however, disease duration (adjusted OR=1.003, $p=0.005$) and diabetes (adjusted OR=1.7, $p=0.02$) were positively associated with LN. Anti RNP (adjusted OR=2.1, $p=0.004$) and low C3 (adjusted OR=2.04, $p=0.0009$) were also positively associated with LN when we included only lab/immunologic parameters in the logistic regression model.

Conclusion: Our results suggest that certain demographic, clinical and laboratory/immunologic factors may be predictive of LN, including obesity, high cholesterol, diabetes, and disease duration.

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Predictors of Rate of Progression in Organ Damage in SLE. Sneha Purvey[2], Laurence S. Magder[3], Hong Fang[2] and Michelle A. Petri[1]. [1]Timonium, MD, [2]Johns Hopkins University School of Medicine, [3]University of Maryland School of Medicine

Purpose: The SLICC/ACR Damage Index (SDI) has become the accepted measure of permanent organ damage in SLE over time. Multiple cross-sectional and a few prospective studies have examined predictors or associates of damage. The damage may be due to lupus, its treatment or co morbid factors. We identified these in the largest on-going prospective study in SLE.

Methods: 2063 SLE patients (92.44% female, 56.27% Caucasian, 37% African-American, mean age 48.1years) were included. The SLICC/ACR Damage Index was calculated from diagnosis onwards in a prospective cohort. The analysis is based on the SDI at the last visit of the patients in the cohort using a linear regression model. Based on a scatter plot, the assumption of a linear relationship between the mean SDI and SLE duration appeared reasonable.

Results: The table shows the mean SDI at diagnosis and the mean rate of SDI progression in subgroups defined by predictors of interest.

Patient Characteristic		Mean SDI at Diagnosis	P-value	Mean Rate of Progression in SDI (per year)	P-value
Total		0.82		0.10	
Age at Diagnosis (years)	0–29	0.42	Ref gp	0.11	Ref gp
	30–44	0.61	.29	0.12	.51
	45–59	1.29	.0005	0.15	.097
	60+	2.40	.0001	0.13	.67
Gender	Males (n = 156)	1.27	Ref gp	0.11	Ref gp
	Females (n = 1907)	0.78	.10	0.10	.75
Ethnicity	Caucasian	0.81	Ref gp	0.09	Ref gp
	African-American	0.99	.29	0.11	.079
	Other	0.50	.37	0.09	.94
Income ($)	<30K	1.25	Ref gp	0.11	Ref gp
	30–65K	0.76	.02	0.09	.11
	>65K	0.71	.01	0.07	.006
Education (years)	0–12	0.04	Ref gp	0.11	Ref gp
	13–16	0.76	.13	0.09	.05
	17+	0.78	.31	0.09	.15
Mean SLEDAI	Lower tertial (<1.5)	0.87	Ref gp	.06	Ref gp
	Middle tertial (1.5–3.5)	0.81	.76	.11	.0003
	Upper tertial (3.5+)	1.01	.49	.09	.033
Number of ACR criteria satisfied at diagnosis	< = 5	0.69	Ref gp	.10	Ref gp
	>5	0.97	.098	.12	.057
SDI score at diagnosis	0	0.21	Ref gp	0.10	Ref gp
	1	1.43	<.0001	0.12	.071
	2+	4.24	<.0001	0.13	.043
Anti-dsDNA	Never	0.87	Ref gp	0.10	Ref gp
	Ever	0.81	.73	0.09	.43
Anticardiolipin	No	0.84	Ref gp	0.10	Ref gp
	Yes	0.80	.85	0.11	.60
Anti-Beta2-glycoprotein I	No	0.65	Ref gp	0.09	Ref gp
	Yes	0.54	.64	0.09	.70
Lupus Anticoagulant	No	0.80	Ref gp	0.10	Ref gp
	Yes	0.71	.72	0.18	.0004
Anti-Ro	No	0.88	Ref gp	0.10	Ref gp
	Yes	0.74	.43	0.10	.77
Hypertension	Never	0.51	Ref gp	0.07	Ref gp
	Ever	1.45	<.0001	0.09	.09
Proteinuria	Never	0.68	Ref gp	0.10	Ref gp
	Ever	1.23	.005	0.12	.11
Corticosteroid Use	Never	0.37	Ref gp	0.08	Ref gp
	Ever	0.96	.007	0.10	.472
Immunosuppressive Use	Never	0.75	Ref gp	0.09	Ref gp
	Ever	1.28	.009	0.11	.23
Hydroxychloroquine Use	Never	1.43	Ref gp	0.12	Ref gp
	Ever	0.68	.0004	0.10	.25

Conclusion: Surprisingly, some variables associated with damage at diagnosis (age, corticosteroid use, immunosuppressive use, less use of hydroxychloroquine) were not associated with damage progression. The most important demographic predictor of progression was income, not gender or ethnicity, in contrast to other studies. The most important serologic test of progression was the lupus anticoagulant, not anti-dsDNA or other antiphospholipid antibodies. Patients already damaged at diagnosis had a higher rate of progression. Disease activity clearly increased the rate of progression, as expected. These data clearly point to the need for effective prophylactic therapy for the lupus anticoagulant, and the need for tight control of disease activity.

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Pregnancy Outcomes among African American Patients with Systemic Lupus Erythematosus (SLE) Compared to Controls. April Barnado[1], Lee Wheless[4], Anna K. Meyer[4], Gary S. Gilkeson[2] and Diane L. Kamen[3]. [1]Duke University Medical Center, Durham, NC, [2]Med Univ of South Carolina, Charleston, SC, [3]Medical University of South Carolina, Charleston, SC, [4]Medical University of South Carolina

Purpose: SLE impacts women of childbearing age and the diagnosis is associated with adverse pregnancy outcomes. However, the question of whether there is a difference in outcome risk before and after diagnosis of SLE has not been well studied. Using data from a longitudinal study of Gullah African Americans, we compared pregnancy outcomes before and after SLE diagnosis to controls to test the hypothesis that there is a predisease state which negatively affects pregnancy outcomes.

Methods: Cases and controls reporting at least one pregnancy were drawn from a longitudinal observational cohort started in 2002. Controls were all Gullah African American females either related or unrelated to cases. We collected demographic, socioeconomic, and pregnancy data. Stillbirth was defined as pregnancy loss at or after 22 weeks and spontaneous abortion (SABs) as loss before 22 weeks. Low birth weight was defined as < 5 pounds, 8 ounces and preterm live birth as delivery before 37 weeks. Categorical variables were examined by chi-square tests. Differences in the means of continuous variables were tested using Student's t-test. We modeled pregnancy outcome associations with case status using multiple logistic regression to calculate odds ratios (OR) and 95% confidence intervals (CI). Two-sided p-values ≤ 0.05 were considered significant.

Results: Cases (n = 188) were younger (46 ± 12 vs 52 ± 13 years, $p<0.01$), less likely to have some form of insurance (83.4% vs 87.9%, $p=0.21$), and had similar years of education (13.2 vs. 13.1) compared to controls (n=205). Cases had fewer pregnancies (2.6 vs 3.2, $p < 0.01$) and fewer live births (2.3 vs. 2.8, $p < 0.01$) than controls. Overall, compared to controls, cases were more likely to have adverse outcomes including preeclampsia (OR 2.15, 95% CI 1.27–3.25), preterm live birth (OR 2.63, 95% CI 1.56 – 4.44), low birth weight (OR 2.30, 95% CI 1.35–3.90), SABs (OR 2.08, 95% CI 1.39–3.10), and stillbirths (OR 4.52, 95% CI 1.38–15.80), even after adjustment for age, education, insurance and pregnancy number. We found that the odds of adverse pregnancy outcomes increased after the diagnosis of SLE and, consistent with our hypothesis, that the risk was also higher prior to disease onset in women who later developed SLE compared to controls. (Table 1).

Table 1. Odds ratios and 95% confidence intervals for adverse pregnancy outcomes occurring before and after SLE diagnosis compared to controls in an African American population. All estimates are adjusted for age, education, insurance and number of the pregnancy.

	Stillbirth	Spontaneous abortion	Elective abortion	Preterm live birth	Low birth weight	Preeclampsia
Controls (660 pregnancies)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Cases before diagnosis (272 pregnancies)	4.01 (1.25–12.82)*	1.78 (1.16–2.72)*	1.36 (0.62–3.00)	2.26 (1.30–3.92)*	2.00 (1.14–3.50)*	1.99 (1.14–3.46)*
Cases after diagnosis (76 pregnancies)	4.31 (1.18–15.81)*	3.03 (1.91–4.82)*	1.88 (0.78–4.54)	3.26 (1.73–6.11)*	2.80 (1.47–5.34)*	2.45 (1.27–4.69)*

* = p-value <0.05.

Conclusions: Among a large cohort of African American women, we found significantly higher numbers of adverse pregnancy outcomes in cases, both before and after diagnosis of SLE, compared to controls. Our findings are consistent with a predisease state that predisposes to adverse pregnancy outcomes. Studies are underway to determine factors contributing to the predisease risk and to the increased risk following diagnosis of SLE.

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Prevalence and Persistence of Metabolic Syndrome in a Multicentre International Inception Cohort of Patients with SLE. Murray B. Urowitz[34], Dafna D. Gladman[22], Dominique Ibanez[33], Ian N. Bruce[13], Caroline P. Gordon[30], Sang-Cheol Bae[6], Ann E. Clarke[15], Sasha R. Bernatsky[15], F. Jorge Sanchez-Guerrero[9], John G. Hanly[19], David A. Isenberg[25], Anisur Rahman[24], Paul R. Fortin[27], Daniel J. Wallace[1], Ellen M. Ginzler[20], Joan T. Merrill[18], Graciela S. Alarcón[29], Barri J. Fessler[23], Gunnar K. Sturfelt[28], Ola Nived[28], Kristjan Steinsson[12], Munther A. Khamashta[21], Michelle A. Petri[2], Rosalind Ramsey-Goldman[17], Susan Manzi[35], Mary Anne Dooley[32], Ronald V. Vollenhoven[11], Cynthia B. Aranow[4], Thomas Stoll[10], Manuel Ramos[7], Kenneth C. Kalunian[26], Asad A. Zoma[5], Guillermo Ruiz-Irastorza[8], Peter J. Maddison[16], Diane L. Kamen[14], S. Sam Lim[3] and Christine A. Peschken[31]. [1]West Hollywood, CA, [2]Timonium, MD, [3]Emory University, Atlanta, GA, [4]Feinstein Institute, Manhasset, NY, [5]Hairmyres Hospital, East Kilbride, United Kingdom, [6]Hanyang University Medical Center, Seoul, Korea, Republic of, [7]Hospital Clinico I Provincial, [8]Hospital de Cruces, Universidad del Pais Vasco, [9]Instituto Nacional Nutricion, Mexico City, DF, Mexico, [10]Kantonsspital Schaffhausen, Schaffhausen, Switzerland, [11]Karolinska University Hospital, [12]Landspitalinn University Hospital, [13]Manchester Royal Infirmary, Manchester, United Kingdom, [14]Medical University of South Carolina, Charleston, SC, [15]Montreal General Hospital, Montreal, QC, Canada, [16]North West Wales NHS Trust, Colwyn Bay, United Kingdom, [17]Northwestern University, Chicago, IL, [18]Oklahoma Med Research Foundation, Oklahoma City, OK, [19]Queen Elizabeth II Health Services Center, Halifax, NS, Canada, [20]SUNY-Downstate Medical Center, Brooklyn, NY, [21]The Rayne Institute, London, United Kingdom, [22]Toronto Western Hospital, Toronto, ON, Canada, [23]UAB Rheumatology, Birmingham, AL, [24]UCL Div of Medicine, [25]UCL Div of Medicine, London, United Kingdom, [26]UCSD School of Medicine, La Jolla, CA, [27]Univerity of Toronto Lupus Clinic, Toronto Western Hospital, Toronto, ON, Canada, [28]University Hospital Lund, Lund, Sweden, [29]University of Alabama, Oakland, CA, [30]University of Birmingham, Birmingham, United Kingdom, [31]University of Manitoba, Winnipeg, MB, Canada, [32]University of North Carolina at Chapel Hill, Chapel Hill, NC, [33]University of Toronto Lupus Clinic, Toronto Western Hospital, [34]University of Toronto Lupus Clinic, Toronto Western Hospital, Toronto, ON, Canada, [35]West Penn Allegheny Health System, Pittsburgh, PA

Background: Metabolic Syndrome (MetSyn) is likely to be a significant predisposing factor to atherosclerotic vascular disease (ASVD) in Systemic Lupus Erythematosus (SLE). The purpose of this study is to determine the prevalence and persistence over two years of MetSyn in a multicentre, international inception cohort of patients with SLE.

Methods: An international inception cohort registry has enrolled 1593 recently diagnosed patients with SLE from 30 centres in 11 countries. All patients are assessed according to a standard protocol including clinical and laboratory variables, and SLEDAI-2K and SDI are calculated at enrollment and annual follow-up visits. The International Diabetes Federation definition for MetSyn was used and included the following criteria: increased waist circumference (≥ 94 cm for men, ≥ 80 cm for women) plus any two of raised triglycerides or specific treatment for this lipid abnormality and/or reduced HDL cholesterol or specific treatment for this lipid abnormality and/or raised blood pressure and/or increased fasting plasma glucose or previously diagnosed type II diabetes. A minimum of 2 of the latter 4 must be known for the definition to be valid.

Results: Of the inception cohort of SLE patients (89F, 48% Caucasian, age at diagnosis 35), 13.6% had MetSyn at baseline (Table 1).

Table 1. Presence of MetSyn criteria in inception cohort of 1593 patients.

	Present or Abnormal	Normal
Metabolic Syndrome	195 (13.6%)	1238
Waist Circumference	649 (47.6%)	715
BMI	265 (17.4%)	1259
Either Waist or BMI	700 (45.4%)	841
TG	374 (28.7%)	928
HDL	227 (31.4%)	495
BP	721 (45.9%)	851
BS	225 (16.9%)	1105

Although the prevalence of MetSyn is approximately 12% at any given time, the cumulative prevalence increases progressively to 25% by year 8. Most of the increased prevalence occurred within the first 3 years.

In total, 644 patients had at least two years of follow-up data available

The incidence of MetSyn over two years was 11.0% and in the subgroup of 88 with MetSyn at enrolment persistence of MetSyn was 17.0% (Table 2).

Table 2. Presence, incidence and persistence of MetSyn in 644 patients with two years of follow up.

Met Syn At enrol	Met Syn at Yr 1	Met Syn at Yr 2	# Patients	
556 without MetSyn at enrolment				
absent	absent	absent	495	Incidence 61/556 (11.0%)
absent	absent	present	23	
absent	present	absent	26	
absent	present	present	12	
88 with MetSyn at enrolment				
present	absent	absent	42	Persistence 15/88 = 17.0%
present	absent	present	12	
present	present	absent	19	
present	present	present	15	

Conclusion: MetSyn is present in 13.6% of newly diagnosed patients with SLE and persists in 17% of these patients over two years. Future work will determine the relationship between MetSyn prevalence and persistence with inflammatory disease activity and inflammation biomarkers as well as the effect of steroid exposure and lupus phenotype on the development and persistence of MetSyn.

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Risk of Renal Flares and Decline in Renal Function in Patients with Active Lupus Nephritis Treated with Mycophenolate Mofetil (MMF). Chi Chiu Mok[2], King Yee Ying[1], Cheuk Wan Yim[3] and Woon Leung Ng[3]. [1]Princess Margaret Hospital, [2]Tuen Mun Hospital, [3]United Christian Hospital

Purpose: To study the risk of renal flares and renal function deterioration in patients with active lupus nephritis treated initially with combined prednisolone and MMF.

Method: Data were extracted from an open randomized controlled trial of the efficacy of MMF vs tacrolimus for induction treatment of lupus nephritis. All patients recruited into the MMF arm were treated with prednisolone (0.6mg/kg/day for 6 weeks and tapered) and MMF (2–3g/day) for 6 months. Patients with good clinical response were shifted to azathioprine (AZA) (2mg/kg/day) and continued on low dose prednisolone (<10mg/day) for maintenance. Renal function and clinical outcome at last visit was assessed. Factors associated with decline of renal function were analyzed by Cox regression.

Results: Data from 56 patients who had completed the induction phase of the controlled trial were analyzed. The mean age was 36.0±12.8 years and SLE duration was 55.3±63 months. The histological classes of lupus nephritis (RPS/ISN) were IVG (32%), IVS (9%), III (21%) and V/V+III/IV (38%). The activity and chronicity scores were 7.4±3.6 and 2.8±1.6, respectively. 24(43%) patients were hypertensive and 27(48%) were nephrotic at presentation. The mean daily MMF dosage administered was 2.20±0.44g (2g in 75% and ≥2.5g in 25%). At 6 months, 33(59%) patients achieved good clinical response (urine P/Cr <1.0, improvement in lupus serology and urinary sediments, with no deterioration of creatinine clearance [CrCl] by ≥10%) and 13(23%) patients achieved good partial response (same criteria but urine P/Cr <2.0). These patients received AZA (86.4±23mg/day) for maintenance therapy. At last visit (median follow-up 36 months), 20 renal flares occurred in 17 patients (13 nephritic and 7 proteinuric). The cumulative risk of renal flare was 7.3% at 12 months and 31% at 36 months. Six (11%) patients had loss of CrCl by ≥30% at last visit, 5 of whom developed stage 4/5 chronic kidney disease (CrCl ≤30ml/min). The cumulative risk of loss of CrCl by ≥30% was 5.4% at 12 months and 7.5% at 36 months. Cox regression revealed that nephrotic syndrome, hypertension, CrCl <90ml/min

at baseline, failure to achieve good response at 6 months and the occurrence of renal flares were unfavorable factors for renal function loss.

Conclusions: Combined prednisolone and MMF is effective for the initial treatment of active lupus nephritis. However, patients with nephrotic syndrome, impaired renal function and hypertension at onset are associated with a higher risk of renal damage.

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Safety and Efficacy of a Pandemic 2009 Influenza A (H1N1) Monovalent, Unadjuvanted Vaccine in Systemic Lupus Erythematosus Patients. Alexis Mathian[3], Herve Devilliers[2], Anne Krivine[1], Nathalie Costedoat-Chalumeau[3], Julien Haroche[3], Du Boutin-Le Thi Huong[3], Bertrand Wechsler[3], Baptiste Hervier[3], Makoto Miyara[3], Nathalie Morel[3], Jean-Charles Piette[3], Brigitte Autran[3], Flore Rozenberg[1] and Zahir Amoura[3]. [1]Hôpital Cochin, [2]Hôpital Dijon, [3]Hôpital Pitié Salpêtrière

Objective: to assess the safety and efficacy of pandemic 2009 influenza A (H1N1) vaccination in patients with Systemic Lupus Erythematosus (SLE), and to evaluate factors influencing the immune response.

Methods: A hundred and eleven SLE patients were vaccinated with a pandemic 2009 influenza A (H1N1), monovalent, inactivated, unadjuvanted, split-virus vaccine in December 2009-January 2010 and received a second dose of vaccination three weeks after. Sera were obtained before each injection and three weeks after the last injection. Adverse events and SLE activity were recorded at each visit. The haemagglutination inhibition test was used to measure antibody titers. The antibody response was evaluated in three ways: the proportion of subjects with antibody titers $\geq$ 1:40 (seroprotection), the proportion of subjects with either a prevaccination HI titer $<$ 1:10 and a post-vaccination titer $\geq$ 40 or a prevaccination titer $\geq$ 10 and an increase in the titer by a factor of four or more (seroconversion) and the factor increase in the geometric mean antibody titers (GMTs) after vaccination (Geometric Mean Ratio (GMR)).

Results: According to international guidelines used to evaluate influenza vaccines, immunogenicity criteria were met, but not for all criteria, at day 21: seroprotection rate was 66.7% (95% CI 57.9–75.4) (below the required level of 70%), seroconversion rates was 60.4% (95% CI 51.3–69.5) (above the required level of 40%) and GMR was 8.5 (95% CI 3.2– 12.0) (above the required level of 2.5). The second vaccine administration did result in additional increased in humoral response. Indeed, immunogenicity criteria were fully met at day 42: seroprotection rate was 80.0% (95% CI 72.5–87.5) ($p = 0.0002$ versus day 21), seroconversion rate was 71.8% (95% CI 63.4–80.2) ($p = 0.003$ versus day 21) and GMR was 10.3 (95% CI 2.9–14.2) ($p < 0.0001$ versus day 21). None of SLE patients developed symptoms suggestive of influenza infection. Vaccine was well tolerated and did not increase disease activity. At day 21 and day 42, in the multivariate analysis, failure to obtain seroconversion was statistically associated with the use of an immunosuppressive treatment and lymphocytes count $<$ 1000/mm3. Failure to obtain seroprotection was statistically associated with the same parameters and a total serum IgM level $<$1 g/l at day 21. As expected, GMR values were significantly lower in SLE patients treated with an immunosuppressive drug. Vaccine was fully effective after one injection in patients with lymphocyte $>$ 1000/mm3 and not treated with immunosuppressive drugs.

Conclusions: pandemic 2009 influenza A (H1N1) unadjuvanted vaccination is safe and effective in SLE patients. Our study shows that SLE patients with normal lymphocyte count and not treated with immunosuppressive have a normal vaccine response.

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Serum Osteoprotegrin (OPG) in Systemic Lupus Erythematosus. Adnan N. Kiani[2], Pal Aukrust[3], Thor Ueland[3], Laurence S. Magder[4], Hollan Ivana[3] and Michelle A. Petri[1]. [1]Timonium, MD, [2]Johns Hopkins University School of Medicine, Baltimore, MD, [3]Oslo University Hospital, [4]University of Maryland

Purpose: Osteoprotegerin (OPG), is a member of the tumor necrosis factor (TNF) receptor family. It has recently been demonstrated that OPG is produced by a variety of tissues, including the cardiovascular system (heart, arteries, veins), lung, kidney, and immune tissues, as well as bone. OPG–RANKL signaling pathway is strongly related to vascular calcification. We determined the association of this biomarker with subclinical atherosclerosis in SLE at baseline and two years later.

Methods: 166 SLE patients (91% female, 64% Caucasian, 31% African-American, 5% others, mean age 45 yrs) had both measurement of subclinical atherosclerosis (coronary artery calcium CAC, carotid intima-media thickness (IMT) and OPG measurements.

Results: OPG was highly correlated with age ($p<.0001$) which is highly correlated with CAC and carotid IMT. However, once we adjusted for age, the relationship with atherosclerosis was diminished. We subdivided OPG levels into low, medium and high tertiles.

Table 1. Shows the association between OPG and the presence of coronary artery calcium

	Baseline Coronary Artery Calcium		New Coronary Artery Calcium at follow-up[1]	
	Odds Ratio	P-value	Odds Ratio	P-value
OPG level				
Low	1.0 (Ref Group)		1.0 (Ref Group)	
Medium	2.3 (1.0, 5.2)	.043	0.5 (0.4, 6.3)	.60
High	1.3 (0.6, 3.1)	.49	4.1 (0.7, 23.1)	.11

[1] Among those who did not have coronary artery calcium at baseline.

Table 2. Shows the association between OPG and the mean carotid IMT.

	Baseline IMT		Change in IMT	
OPG	Difference in Mean IMT	P-value	Difference in Mean change in IMT	P-value
OPG level				
Low	0.0 (Ref Group)		0.0 (Ref Group)	
Medium	0.02 (−0.01, 0.06)	.26	0.01 (−0.02, 0.06)	.49
High	0.02 (−0.01, 0.06)	.23	0.01 (−0.03, 0.05)	.61

The mean IMT among those with medium OPG was 0.02 points higher than for those with low OPG. This difference was not significant ($p=.26$).

Conclusion: OPG has been associated with atherosclerosis in the general population. In our 166 SLE patients OPG was strongly associated with age. Once we adjusted for age, there was no association of OPG with subclinical atherosclerosis nor with change in atherosclerosis two years later.

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Steroid Free Remission in Systemic Lupus Erythematosus. Akiko Suda[3], Haruko Ideguchi[1], Shigeru Ohno[1], Mitsuhiro Takeno[2], Shohei Nagaoka[4] and Yoshiaki Ishigatsubo[5]. [1]Center for Rheumatic Disease, Yokohama City University Medical Center, [2]Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, [3]Department of Rheumatology, Yokohama Minami Kyosai Hospital, Yokohama, Japan, [4]Department of Rheumatology, Yokohama Minami Kyosai Hospital, [5]Yokohama City Grad Sch of Med, Yokohama, Japan

Objectives: Although survival prognosis of SLE has been greatly improved by treatment with corticosteroids and immunosuppressants in some patients with SLE, some of the patients are suffering from adverse effects of long term corticosteroid therapy. Steroid free remission is an idealistic goal in management of SLE patients. We here examined the frequency of steroid free remission and analyzed clinical factors which are involved in achieving steroid-free remission in patients with SLE.

Methods: We retrospectively reviewed clinical charts of 288 patients (all Japanese, male 21, female 267, age 46.5 + 0.87 y.o., disease duration 15.0 + 0.58 years) who met 1997 ACR SLE Classification Criteria and received medical care in our hospitals. Therapeutic plans including steroid tapering in individual patients were determined by the attending physicians. The patients were divided into three groups based on steroid usage; concurrent user, never user, and steroid free remission that was defined as a 3-month consecutive period of no disease activity without corticosteroid. Clinical features and backgrounds were compared among the three groups.

Results: We found that 279 patients (96.9%) had received steroid at any time during the clinical course, whereas 9 (3.1%) patients had never received steroid (never users). Fifty two patients (18.0%) achieved steroid free remission. Of them, 45 patients (15.6%) maintained remission without steroid

(steroid free remission). Total 234 patients (81.3%) including 7 patients (2.4%) who experienced disease flare after cessation of corticosteroid were receiving corticosteroids at the study (concurrent users). Patients in steroid free remission were all female. They were older, and had longer disease duration than patients in concurrent user group. Renal involvement was less frequent (steroid free remission: 31.6% vs concurrent users: 50.9%, $P<0.05$), and negative anti-DNA angtiboydy was more frequent (26.3% vs 14.5%, $P<0.05$). Immunosupressants were more frequently used in concurrent users than patients in steroid free remission ($P<0.05$). The percentage of patients followed by practicing physician (S.O) were more frequently observed in steroid free patients (41.9% vs 16.3%, $p<0.01$). There was no difference in other factors including initial dose of steroid, initial disease activity, neurological disease and hematological disorders between the two groups.

Table. Factors associated with steroid free remission

	total (n = 288)	concurrent users (n = 234)	steroid free remission (n = 45)	p
age at study entry (y.o.)	46.5 ± 0.7	45.5 ± 0.9	51.2 ± 5.5	<0.05
disease duration at study entry (y.o.)	15.0 ± 0.6	14.4 ± 0.6	19.9 ± 1.6	<0.01
renal involvement (%)	48.8	50.9	26.7	<0.01
negative anti-DNA antibody (%)	82.3	85.5	64.4	<0.01
Immunosupressants use (%)	37.5	41.9	22.2	0.01
practicing physician (S.O.) (%)	23.1	16.3	41.9	<0.01

Conclusions: The present study shows that female, older age and absence of renal involvement, anti-DNA antibody and practicing physician (S.O) were associated with steroid free remission.

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The Novel Pandemic Influenza A (H1N1) 2009 Vaccine: Low Rate of Seroconversion after Vaccination in Systemic Lupus Erythematosus.

Eduardo F. Borba[4], Carla G. S. Saad[5], Ana Luisa G. Calich[5], Sandra G. Pasoto[5], Vilma S. T. Viana[5], Maria do Carmo S. T. Timenetsky[2], Alexander R. Precioso[3] and Eloisa Bonfa[1]. [1]Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [2]Instituto Adolpho Lutz, Brazil, [3]Instituto Butantan, Brazil, [4]Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [5]Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo, Brazil

Purpose: To evaluate efficacy and safety of a single vaccination with a novel split virion, inactivated, non-adjuvanted pandemic H1N1 influenza vaccine (A/California/7/2009/Instituto Butantan/Sanofi Pasteur S.A.) in systemic lupus erythematosus (SLE) patients.

Methods: 173 SLE patients (ACR criteria) of a single tertiary center and 159 healthy age-matched subjects were immunized with H1N1 influenza vaccine. Exclusion criteria were: fever, egg allergy, and autoimmune neurological diseases. At entry SLE patients and controls received a single dose of influenza vaccine containing A/California/7/2009 H1N1 strain. Patients and controls were evaluated at baseline (immunization day) and 21 days post-vaccination. Disease safety was monitored by SLEDAI. Antibody titers were evaluated by hemagglutination inhibition (HAI) assay. Seroconversion to vaccination was defined by either an antibody titer of 1:10 or less before and of at least 1:40 after or at least 1:10 before and at least four-fold increase in antibody titer 21 days after single vaccination. Vaccine adverse effects were also analyzed.

Results: Before vaccination, 8 (4.6%) patients and 20 (11.1%) controls ($p=0.01$) had a HAI titer of ≥1:40 and 21 days after vaccination 115 (66.4%) patients and 136 (85.5%) controls ($p=0.0001$) had a HAI titer of ≥1:40. Seroconversion rate for H1N1 was significantly lower in SLE patients compared to controls [108 (62.4%) vs. 123 (77.35%), $p=0.0041$]. Vaccine-related side-effects were only mild and transient with a similar frequency in both groups ($p>0.05$).The comparison of the 108 seroconverters patients with 65 nonresponders revealed a similar mean age, female predominance, mean disease duration, mean number of SLE criteria and mean SLEDAI score ($p>0.05$). In contrast, nonresponders were more often under mycophenolate mofetil than seroconverters (27.7 vs. 12.9%, $p=0.02$) with a tendency of higher frequency of immunomodulators (78.5 vs. 64.8%, $p=0.062$) and prednisone (64.6 vs. 50%, $p=0.082$) therapies. Regarding lupus safety at the time of immunization the mean SLEDAI was 3.5 ± 4.2 (0–24) and only 12 patients had an increased in SLEDAI scores (6.9%) whereas 133 remained stable (76.8%) and 28 had decreased (16.2%). Forty patients (23.1%) had SLEDAI ≥ 6 at baseline and none, except one, had an increase in SLEDAI.

Conclusions: The pandemic vaccine is safe in SLE patients regardless of disease activity but seroconversion is lower than in healthy subjects, particularly in patients under MMF therapy. Further studies are necessary to determine if a second dose will increase the seroconversion rate.ClinicalTrials.gov Identifier: NCT01151644

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The Presence of Renal Platelet Microthrombosis in Patients with Lupus Nephritis Correlates with the Degree of Macrophagic Infiltration.

Elena Gonzalo[4], María Paz Martinez-Vidal[2], Begoña Santiago[4], Natalia Redondo[4], Estibaliz Loza[1], José Luis Pablos[3] and María Galindo[3]. [1]Fundación Española de Reumatología, Sociedad Española de Reumatología, Madrid, Spain, [2]Servicio de Reumatología, Hospital 12 de Octubre, Madrid, Madrid, Spain, [3]Unidad de Investigación y Servicio de Reumatología, Hospital 12 de Octubre, Madrid, Madrid, Spain, [4]Unidad de Investigación, Hospital 12 de Octubre, Madrid, Madrid, Spain

Introduction: Intravascular CD61+ platelet microthrombi are found in the kidney of patients with lupus nephritis independently of the presence of antiphospholipid antibodies. Our objective was to analyze the correlation between CD61+ intravascular platelet microthrombi and intra or extraglomerular CD68+ macrophagic infiltration degree as a marker of active inflammation.

Methods: Seventy-two kidney biopsies from systemic lupus erythematosus (SLE) patients were immunohistochemically stained with CD68 (macrophage) and CD61 (platelet glycoprotein-IIIa). Intra or extraglomerular macrophagic infiltration was quantified using the image-processing program Image J. CD61+ microthrombi were identified as percentage of stained cells. Clinical data were retrospectively collected at the time of kidney biopsies, and during the follow-up for a mean time of 7.5 years after biopsies and were correlated to the immunohistochemical findings. The associations between categorical variables were tested using the chi-square or Fisher's exact test, where appropriate. The odds ratios with the corresponding 95% CIs were calculated. For continuous variables, the comparisons were carried out using the t-test for two independent samples. P-values <0.05 were considered significant.

Results: most of SLE kidneys showed glomerular (94%) and extraglomerular (87%) macrophagic infiltration. Both glomerular and extraglomerular CD68+ macrophagic infiltration were higher in patients with proliferative (WHO subtypes III and IV) nephritis ($p=0.001$). The CD68+ glomerular infiltration degree was increased in samples with CD61+ platelet aggregates ($p=0.03$), whereas CD68+ extraglomerular infiltration was higher in samples with histological thrombotic microangiopathy ($p=0,02$) and focal cortical atrophy ($p=0.02$). The CD68+ glomerular infiltration grade was also higher in patients with positive a-dsDNA ($p=0.009$), hypocomplementemia ($p=0.01$), microhematuria ($p=0.02$), the presence of cellular casts in urine sediment ($p=0.03$), and was significantly associated with SLE activity index (SLEDAI) at the time of kidney biopsy ($p=0.02$). Preliminary results have shown a potential correlation between CD68+ macrophagic infiltration and higher levels of complement factor C4d expression ($p=0.04$). Patients with kidney failure at biopsy presented higher mean extraglomerular macrophagic infiltration ($p=0.03$). However, the presence of CD61+ platelet aggregates and density of CD68+ macrophagic infiltration were not associated with response to treatment, renal function evolution or nephritis relapse rate.

Conclusions: In lupus proliferative nephritis, intra and extraglomerular macrophagic infiltration degree correlates with acute impairment of kidney function. Presence of acute microthrombi provides a good correlation with cellular infiltration grade. However, none of these parameters is a good

prognostic marker of the renal function evolution or response to treatment. Further studies are needed to better define correlation between the presence of renal thrombosis and inflammatory cells infiltration and activation of complement system in patients with lupus nephritis.

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The Relationship between N Terminal Pro Brain Natriuretic Peptide (NT-proBNP) and Atherosclerosis in SLE Patients. Diana Goldenberg[2], Emily Miller[2], Naveed Sattar[3], Paul Welsh[4], Mary Roman[5] and Jane E. Salmon[1]. [1]Hospital for Special Surgery, New York, NY, [2]Hospital for Special Surgery, New York, NY, [3]University of Glasgow, Glasgow, United Kingdom, [4]University of Glasgow, [5]Weill Cornell Medical College, New York, NY

Background: NT-proBNP is a biomarker of cardiovascular health in the general population that is independently associated with heart failure, coronary artery disease, stroke and death. It has been suggested that serum NT-proBNP levels are higher in SLE patients than controls, but its relationship with markers of atherosclerosis is still unclear. Because traditional cardiac risk factors do not adequately identify the SLE patients with increased risk for premature atherosclerosis, there is a need for a biomarker to improve risk stratification. The aim of this study was to investigate the relationship between NT-proBNP and atherosclerosis in SLE patients.

Methods: One hundred and twenty four patients meeting American College of Rheumatology diagnostic criteria for SLE who were participating in a longitudinal study of cardiovascular disease at the Hospital for Special Surgery were studied. Patients underwent clinical and laboratory assessment, echocardiography and carotid artery ultrasonography to detect plaque. Patients were defined as having atherosclerosis based on whether they had plaque (focal protrusion >50% of the thickness of the surrounding wall) on carotid ultrasonography. Echocardiography was performed and left ventricular ejection fraction, degree of mitral regurgitation and left atrial diameter were measured. SLEDAI was used to calculate SLE disease activity. Serum NT-proBNP levels were measured using a clinically validated electrochemiluminescence method (Roche Elecsys 2010). Group differences in NT-proBNP were compared using t-tests and independent correlates of NT-BNP and plaque were determined by multivariate regression analysis.

Results: The mean age of the124 SLE patients was 43.4 ± 13.7 years and 95.2% of the patients were female. Atherosclerotic plaque was present in 38.2 %. The mean SLEDAI score was 3.7± 4.8; range 0–22. Only 2.6% of the patients had diabetes and 12.7% were current smokers. Mean serum NT-proBNP was 346.1±1251 pg/ml (median 82.5 pg/ml, range 5–12905 pg/ml). As a reference, the baseline median NT-proBNP level measured using a similar electrochemiluminescence method in women in the general population was 66 pg/mL. Log transformed NT-proBNP was associated with higher left atrial diameter, lower body mass index and lower ejection fraction. SLE patients with atherosclerosis had higher NT-proBNP levels than SLE patients without atherosclerosis (615.4 pg/ml ± 286.5 vs 151.7 pg/ml ± 27.4; P = 0.044. However, in our regression models neither serum log NT-proBNP, gender, BMI nor SLEDAI predicted plaque. Age and lower ejection fraction were the only independent correlates of plaque.

Conclusions: In our analysis of 124 SLE patients with and without atherosclerosis, serum NT-proBNP levels correlated with plaque presence on carotid ultrasonography. As anticipated, it is likely that age and markers of cardiac function are in part mediating this relationship in our patient population. Prospective studies are now needed to determine the utility of NT-proBNP as a biomarker for predicting atherosclerosis in SLE patients.

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Underuse of Hydroxychloroquine among Patients with Systemic Lupus Erythematosus. Aimee O. Hersh[2], Daniel J. Shapiro[3], Edward H. Yelin[4] and Gabriela Schmajuk[1]. [1]Stanford University, Palo Alto, CA, [2]UCSF, San Francisco, CA, [3]UCSF, [4]University of California, San Francisco, CA

Purpose: Recent literature supports the routine use of hydroxychloroquine (HCQ) in the management of systemic lupus erythematosus (SLE), with evidence for reduced disease activity, lower rates of renal progression, better lipid profiles, and improved survival. The extent to which patients with SLE receive HCQ nationwide is unknown. The purpose of this study was to determine the frequency and factors associated with HCQ prescribing in a nationally representative sample of patients with SLE.

Methods: We examined HCQ use among ambulatory visits for patients with SLE (ICD-9-CM code 710.0) using the National Ambulatory and National Hospital Ambulatory Medical Care Surveys. These surveys record information about treatments provided among a nationally representative sample of patient visits to ambulatory settings. The primary outcome was HCQ use; this was defined as either new or continued HCQ prescription associated with each incident visit. Continued medications include those previously prescribed by other physicians (i.e. HCQ by a rheumatologist when the incident visit is to a primary care physician). Independent variables included patient demographics (age, gender, race/ethnicity), insurance status (private versus public), steroid use (as a marker of disease activity), physician specialty (rheumatologist versus other), and geographic region. Multivariable logistic regression was performed to identify factors independently associated with receipt of HCQ.

Results: Between 1998–2007, there was an average of 975,000 ambulatory visits for SLE per year. Hydroxychloroquine was prescribed for 32% (95% CI 24.1–40) of patients with SLE seen during these visits. Ninety percent of patients were female, 24% were non-white, mean age was 49 years, 54% had private insurance, and 39% received corticosteroids. In bivariate analyses, there were no differences in HCQ use based on patient age, race, gender, insurance status, steroid use or geographic region. HCQ prescribing was higher among visits to rheumatologists versus other physicians (51 vs. 17%, p= 0.0001). In a multivariable analysis, after adjusting for potential confounders, the only factor independently associated with HCQ use was a visit to a rheumatologist (OR 4.57, 95% CI 1.80–11.56).

Conclusion: Hydroxycholoroquine use was suboptimal in this national sample of SLE patients. Given recent evidence about the beneficial effects of HCQ on survival in SLE, interventions are needed to increase HCQ use, particularly among those patients seen by non-rheumatologists.

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Vitamin D Deficiency in Systemic Lupus Erythematosus (SLE) Is Not Associated with Coronary Artery Calcium (CAC) or Carotid Plaque. Adnan N. Kiani[2], Laurence S. Magder[3] and Michelle A. Petri[1]. [1]Timonium, MD, [2]Johns Hopkins University, School of Medicine, Baltimore, [3]University of Maryland

Purpose: Vitamin D deficiency is common in SLE. In the general population, vitamin D deficiency is associated with cardiovascular disease, diabetes mellitus and certain cancers. However, a recent study of vitamin D in African-Americans found that increased vitamin D levels were associated with more carotid and aortic plaque (1). We asked whether there was any similar relationship in SLE.

Methods: 167 SLE patients (93% female, 63% Caucasian, 32% African-American, mean age 45 yrs) had both measurement of subclinical atherosclerosis (coronary artery calcium, carotid intima-media thickness IMT (IMT), carotid plaque) and vitamin D.

Results: Vitamin D values ranged from 4 to 79 (mean 22.3, median 21). Among African-American Vitamin D values ranged from 4 to 55 (mean 15, median 11). Table1 shows the percentage with levels of CAC, by vitamin D status.

Vitamin D status	Coronary Artery Calcium Score		
All Patients	0	0.1 to 100	>100
Low (n = 133)	74 (56%)	45 (34%)	14 (11%)
Normal (n = 34)	22 (65%)	11 (32%)	1 (3%)
African-American			
Low (n = 47)	21 (45%)	21 (45%)	5 (11%)
Normal (n = 5)	4 (80%)	1 (20%)	0 (0%)

Of those with low Vitamin D, a higher proportion had a coronary calcium score >100 (11%), compared to among those with normal Vitamin D (1%). Among African-American patients this proportion was 11% and 0 respectively. However, these trends were not statistically significant (p=.17 and 1.0).

Table 2. Shows the mean coronary artery calcium score and carotid IMT, by vitamin D status.

Variable All Patients	Mean (SD) among those with low vitamin D	Mean (SD) among those with high vitamin D	P-value
Log-CAC score	1.17 (1.96)	1.04 (1.72)	.72
Carotid IMT	0.58 (.11)	0.57 (0.09)	.78
African-American			
Log-CAC score	1.38 (1.99)	0.87 (1.96)	.59
Carotid IMT	0.61 (.13)	0.61 (0.12)	.95

Table 3. Shows the association between vitamin D levels and presence of carotid plaque at baseline, for all patients and African-Americans.

	Vitamin D Level	Carotid Plaque Present	Carotid Plaque Absent	P-value
All Patients	Low (n = 130)	25 (19%)	105 (81%)	0.63
	Normal (n = 34)	5 (15%)	29 (85%)	
African-American	Low (n = 44)	11 (25%)	33 (75%)	0.57
	Normal (n = 5)	0 (0%)	5 (100%)	

Table 4. Mean Vitamin D (as a quantitative variable), in all patients and among African-American defined by presence or absence of high coronary artery calcium score, or carotid plaque.

All patients	Mean Vitamin D (SD)	P-value
Coronary Artery Calcium Score		
None (n = 96)	23.4 (13.8)	.26
.1–99 (n = 56)	21.6 (12.7)	
100+ (n = 15)	17.7 (9.6)	
Carotid Plaque		
Absent (30)	22.8 (13.0)	.41
Present (134)	20.6 (14.4)	
African-American Coronary Artery Calcium Score		
None (n = 25)	16.7 (12.7)	.51
.1–99 (n = 22)	13.7 (7.9)	
100+ (n = 5)	12.0 (7.8)	
Carotid Plaque		
Absent (38)	15.8 (11.6)	.31
Present (11)	12.1 (5.6)	

Conclusion: Vitamin D was not associated with any measure of subclinical atherosclerosis in SLE. In contrast to the study in African-Americans (1. J Clin Endocrinol Metab 95: 1076, 2010), higher vitamin D was not associated with MORE carotid plaque. In fact, in SLE, there was a suggestion that those with low vitamin D were more likely to have a coronary artery calcium score greater than 100 (11% vs. 1% and 11% vs. 0 among African-American).

Disclosure: A. N. Kiani: None; **L. S. Magder:** None; **M. A. Petri:** None.

ACR Poster Session A
Systemic Lupus Enrythematosus - Human Etiology and Pathogenesis:Genetics and Mechanisms
Monday, November 8, 2010, 9:00 AM–6:00 PM

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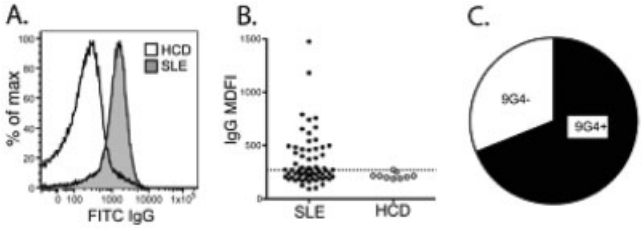
9G4 Autoantibodies Dominate the Anti-Apoptotic Cell Autoimmune Response in SLE. Scott A. Jenks[1], Elise Palmer[2], Elides Marin[2] and Ignacio Sanz[1]. [1]Univ of Rochester, Rochester, NY, [2]Univ of Rochester

Purpose: To understand the prevalence and characteristics of anti-apoptotic cell autoantibodies (APCA). These aspects of the autoimmune response in SLE remain poorly understood despite strong experimental evidence showing that impaired clearance of apoptotic cells in SLE provides an abundant source of immunogenic disease-related autoantigens and is likely to play a central role in disease pathogenesis. A flow cytometric assay for the quantification of serum APCA antibodies was applied to a cohort of SLE patients to ascertain the total amount of APCA. Given the high specificity of 9G4 autoantibodies for SLE and their association with disease activity we also determined the contribution of 9G4 autoantibodies to APCA reactivity. In this study we identify a high prevalence of IgG APCA that is heavily contributed to by 9G4+ antibodies.

Methods: Serum from 68 SLE patients with a spectrum of disease activity and 9 healthy volunteers, was used to assess 9G4+, IgG and IgM antibody binding to apoptotic Jurkat cells and to viable lymphocytes using multi-parameter flow cytometry (Fig A). Camptothecin was used to induce apoptosis in a CD45/B220-negative Jurkat cell line (J45.01). Viable lymphocytes were obtained from healthy control peripheral blood and identified as naïve B cells (CD19+IgD+CD27-). Positive binding to either naïve B cells or apoptotic cells was determined as an median fluorescence intensity ≥2 standard deviations of the mean median fluorescence intensity of healthy controls.

Results: After normalization of serum samples for total IgG quantity, 60% of patients displayed elevated levels of APCA. IgG APCA binding was prevalent as 53% of positive samples showed only IgG binding and 26% IgG and IgM (Fig B) whereas IgM only binding was 19%. APCA levels correlated with disease activity as measured by SLEDAI (p=0.014). 9G4 autoantibodies contributed substantially to APCA activity, 67% of APCA positive samples demonstrated strong 9G4 binding (Fig C). Moreover, initial depletion experiments indicate that up to 75% of all IgG APCA activity in SLE serum is contributed by 9G4+ antibodies. When the specificity of 9G4 binding was examined, the majority (55%) of the samples bound both naïve lymphocytes B and apoptotic cells, however, 35% bound only apoptotic cells and 10% bound just naïve B cells.



Conclusions: Our results demonstrate that APCA antibodies are common in SLE and their abundance correlates with disease activity. Moreover, our results indicate that the SLE-specific 9G4 antibody fraction represents the majority of APCA. These observations provide the basis for ongoing studies of the identity of apoptotic cell antigens responsible for the expansion of an SLE-specific autoreactivity. This work also illustrates the value of measuring APCA reactivity in future studies of B cell tolerance and suggests that these measurements may contribute to clinical studies and management of SLE.

Disclosure: S. A. Jenks: None; **E. Palmer:** None; **E. Marin:** None; **I. Sanz:** None.

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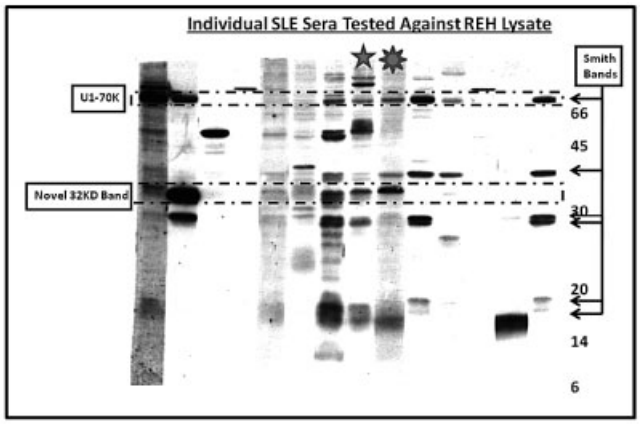
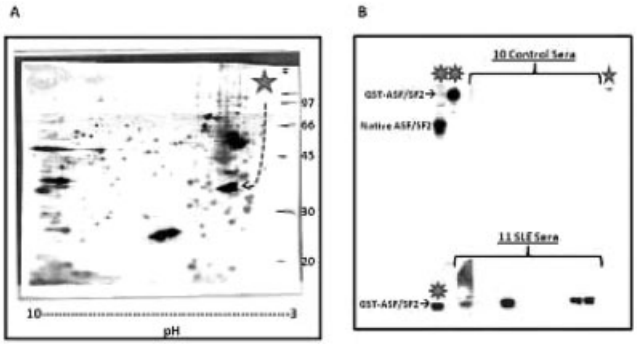
ASF/SF2, a Protein Involved in Multiple RNA and microRNA Processing Pathways, Is a Novel Autoantigen in SLE. Amit Golding[6], Ehtisham Akhter[4], Tonie Hines[3], Felipe Andrade[4], Ranjan Sen[5], Livia Casciola-Rosen[2], Antony Rosen[7] and Michelle A. Petri[1]. [1]Timonium, MD, [2]John Hopkins University, Baltimore, MD, [3]John Hopkins University, [4]Johns Hopkins University School of Medicine, Baltimore, MD, [5]NIA/National Institues of Health, [6]NIAID/National Institutes of Health, Bethesda, MD, [7]The Johns Hopkins University, Baltimore, MD

Purpose: In an attempt to discover novel lupus autoantigens, we sought to use lymphocytes as a source of antigen. Lymphocytes are likely to be a physiologic source of antigen due to the high frequency of lymphocyte cell death and their proximity to antigen receptors.

Methods: For our source of antigen, we used NP40-whole cell lysates of cultured REH cells. REH, is a non-EBV transformed, human ALL line with a combination of features of immature T and B cells. In our initial screen, SLE sera were used in standard Western Blots from 1D SDS-PAGE of REH lysates and a number of sera showed reactivity with a band of molecular weight range 32–34 kD (Figure 1).



This protein appeared to be unique from known lupus autoantigens such as anti-Smith bands and anti-Ku70/RNP. Subsequently, a large quantity of REH lysate was prepared in the appropriate buffer and resolved by 2D gel electrophoresis followed by transfer to membrane, scanning of the Ponceau stained blot and Western Blotting with one of the sera showing strong reactivity with the 32 kD band (Figure 2A).



A repeat 2D gel of REH lysate was coomassie-stained to visualize the proteins and, based on the alignment previously seen between the Western Blot and the 2D Ponceau Stain, the appropriate protein "dots" were sent for peptide sequencing by Mass spectrometry.

Results: The top non-keratin "hit" was SFRS1, also known as ASF/SF2, with 23% sequence coverage. In order to confirm that the SLE sera were in fact identifying ASF/SF2 as a novel autoantigen, the recombinant GST-fusion protein (MW 55kD) was purchased from ABNOVA and tested by immunoblotting using control and SLE patients' sera. We found that 12/57 (21%) of SLE patients' sera reacted with purified ASF/SF2 as compared to 0/25 of control normal sera. A representative blot is shown in [Figure 2B]. Studies to define antibody titers and correlation with disease activity are underway.

Conclusions/Discussion: ASF/SF2 is a member of the SR family of proteins that are involved in RNA splicing and are regulated by serine phosphorylation by SRPK1. More recently, ASF/SF2 has also been shown to be involved in processing microRNAs separate from its role in RNA splicing. Intriguingly, ASF/SF2, has also been implicated as a proto-oncogene in a number of malignancies. It will be interesting to look for anti-ASF/SF2 antibodies in individuals with certain malignancies and to attempt to correlate these with autoimmune manifestations versus protective immunity. We will also look for anti-ASF/SF2 antibodies in other rheumatologic conditions and investigate the role of phosphorylation and other protein modifications in the creation of autoantibodies.

Disclosure: A. Golding: None; **E. Akhter:** None; **T. Hines:** None; **F. Andrade:** None; **R. Sen:** None; **L. Casciola-Rosen:** None; **A. Rosen:** None; **M. A. Petri:** None.

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Association of adam33 Polymorphisms with Systemic Lupus Erythematosus. Seung-Cheol Shim, Mi-Kyoung Lim and Dong-Hyuk Sheen. Eulji University, Daejeon, Korea, Republic of

Background: A Disintegrin and Metalloprotease 33 (ADAM33) is a member of a family of genes that encode membrane-anchored proteins with a disintegrin and a metalloprotease domain, and is located on chromosome 20p13. Recently, the polymorphisms in Adam33 have been found to be associated with asthma. Among the rheumatic diseases, systemic lupus erythematosus (SLE) is a prototypic Th2-mediated autoimmune disease like allergic disorders.

Purpose: To assess whether genetic functional variants of ADAM33 are associated with susceptibility to SLE or development of specific phenotypes in patients with SLE.

Methods: We have identified 48 SNPs, and nine SNPs were selected with regard to the LD pattern. Genotyping for g.10918G>C, g.12433T>C and g.13506C>G in the ADAM33 gene was conducted with PCR–RFLP methods, and genotyping for g.-330C>T, g.517 A>G, g.8227 G>A, g.9511 G>T, g.12462 C>T, g.12988 C>A polymorphisms was performed by single-base extension (SBE), using the ABI Prism® SNaPshot™ Multiplex kit (Applied Biosystems). We conducted an association study for ADAM33 polymorphisms in 190 SLE patients, 469 healthy controls, and 390 rheumatoid arthritis (RA) patients as a disease control. Haplotype analyses of related variants were performed as well.

Results: Significant associations of ADAM33 polymorphisms with susceptibility to SLE were found at g.8227 G>A, g.12988 C>A, and g.13506 C>G (P value were all below 0.001). Polymorphisms at g.8227 G>A was associated with the ANA titers among SLE patients (P = 0.012). In addition, we analysed the haplotype, and found a positive association of susceptibility to SLE with the major haplotype CGCG (P = 3.5E-11). There was no association between ADAM33 polymorphisms and RA as expected.

Conclusion: ADAM33 polymorphisms were strongly associated with susceptibility to SLE and the development of specific clinical manifestations.

Disclosure: S.-C. Shim: None; **M.-K. Lim:** None; **D.-H. Sheen:** None.

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Binding of Apoptotic Fetal Cardiocytes by Anti-Ro/La Antibodies Stimulates uPA/uPAR-Dependent Activation of TGFbeta and Potentiates Fibrosis. Paraskevi Briassouli[2], Daniel Rifkin[1], Jill P. Buyon[1] and Robert M. Clancy[1]. [1]New York University School of Medicine, [2]New York Univesity Medical Center, New York, NY

Purpose: Organ injury induced by antibodies characteristic of Sjogren Syndrome and Systemic Lupus Erythematosus, while varied in the adult and fetus, may share in common a link between apoptosis and ultimate fibrosis. In congenital heart block (CHB), binding of maternal anti-Ro/La antibodies to apoptotic cardiocytes impairs their removal by healthy cardiocytes and increases uPA/uPAR-dependent plasmin activation. Immunological staining of CHB hearts reveals AV node TGFb staining and TGFb activation promotes fibroblast transdifferentiation, a scarring phenotype. Since the uPA/uPAR system plays a role in TGFb activation, this study evaluated whether anti-Ro/La binding to apoptotic cardiocytes via plasmin activation stimulates TGFb and promotes a profibrosing phenotype.

Methods and Results: Initial analysis showed increased TGFb in supernatants from co-cultures of healthy cards and apoptotic cards incubated with IgG fractions from mothers whose sera contain anti-Ro/La antibodies and who had a child with CHB (apo-CHB-IgG) compared to co-cultures of healthy cards and apoptotic cards incubated with control IgG (apo-nl-IgG). Using a luciferase bioassay of active TGFb, supernatants from co-cultures of healthy cards and apo-CHB-IgG cards exhibited increased levels of active TGFb compared to those cocultured with apo-nl-IgG cards (511pg/ml CHB-IgG RLU vs 217 nl-IgG RLU; p=0.007; n=7). Abrogation of RLU via anti-TGFb antibody or TGFb inhibitor (SB431542) confirmed TGFb activation was solely due to TGFb. Significantly increased uPA levels (903 pg/ml vs 508 pg/ml; p =0.01; n=5) and uPA activity (0.8 units vs 0.04 units; p=0.005; n=3) were demonstrated in supernatants generated from coculture of healthy cards and apo CHB-IgG cards compared to healthy cards and apo nl-IgG, respectively. To determine whether uPA activity was responsible for TGFb activation, coculture experiments were conducted in which the apo-CHB-IgG cards were treated with anti-uPAR or anti-uPA antibodies or the plasmin inhibitor aprotinin prior to coculturing with healthy cards. In all instances treatments attenuated TGFb activation and uPA activity. To evaluate the profibrotic role of the observed TGFb activation, supernatants from either apo -CHB-IgG or apo-nl-IgG cocultures with healthy cards were applied to serum deprived cardiac fibroblasts. Only supernatants derived from cocultures of healthy cards and apo -CHB-IgG cardiocytes promoted transdifferentiation as evidenced by increased SMAc staining, an effect that was decreased when fibroblasts were treated with supernatants where cocultures were pretreated with uPAR antibodies. Supporting the hypothesis that increased uPA activity is causally related to the pathogenesis of CHB, cord

blood samples from 12 of 18 children with CHB exhibited increased uPA activity and uPAR cleavage compared to 4 of 14 non CHB children exposed to maternal anti-Ro antibodies.

Conclusions: These data suggest that binding of anti-Ro/La antibodies to apoptotic cardiocytes by virtue of increased uPAR-dependent uPA activity trigger TGFb activation thus initiating and amplifying a cascade of events that promote myofibroblast transdifferentiation and scar.

Disclosure: P. Briassouli: None; **D. Rifkin:** None; **J. P. Buyon:** NIAMS-NIH, 2, NIH, 2; **R. M. Clancy:** None.

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Binding Target for C-Reactive Protein Is Released from Secondary Necrotic Cells. Christina Janko[1], Christine Schorn[1], Luis Munoz[1], Manfred Rauh[3], Kirsten Lauber[2], Georg Schett[1] and Martin Herrmann[1]. [1]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]Department of Internal Medicine I, University of Tuebingen, Tuebingen, Germany, [3]Department of Paediatrics and Adolescent Medicine, University of Erlangen-Nuremberg, Erlangen, Germany

Background: The C-reactive Protein (CRP) is an acute-phase protein whose serum concentration massively increases in response to tissue injury or inflammation. Beside opsonizing of bacteria CRP is known to bind calcium dependent to altered mammalian membranes (e.g. occurring in cell death) via phosphocholine, the polar headgroup of phosphatidylcholine and its derivates. CRP also opsonizes intracellular components leaking from necrotic cells.

This study was performed to analyse whether CRP differentially binds to primary and secondary necrotic cells. Primary necrosis is defined as immediate cell death appearing after severe cell death stimuli, whereas secondary necrosis follows after an apoptotic stadium.

Methods: We prepared Fitc-labelled CRP to determine the binding of CRP to primary and secondary necrotic cells by flow cytometry and confocal microscopy. The release of a CRP target from dying cells was detected in the supernatant by inhibition assays. The released CRP antagonist was identified by enzymatic cleavage and by mass spectrometry.

Results: The binding of CRP to primary necrotic cells was significantly stronger compared to secondary necrotic ones. We detected a CRP antagonistic activity in supernatants of secondary necrotic cells, which was identified as glycerophosphocholine (GlyceroPC). Actually, CRP binding to necrotic cells was blocked by synthetic GlyceroPC. The release of the CRP antagonist was significantly reduced by inhibitors of Phospholipase A2 and Caspases.

Conclusion(s): Secondary necrotic cells show a weaker binding of CRP resulting from the release of the CRP target during late apoptosis. That may have implications for opsonisation with CRP of dying and dead cells and for CRP-mediated effects in clearance. Secondary necrotic cells, for example in SLE patients, may release high amounts of the CRP antagonist with the following consequences (1) missing CRP binding targets on the dead cells and (2) neutralizing of circulating CRP, both possibly contributing to clearance failure.

Disclosure: C. Janko: None; **C. Schorn:** None; **L. Munoz:** None; **M. Rauh:** None; **K. Lauber:** None; **G. Schett:** None; **M. Herrmann:** None.

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C1q and Complement Proteins Induce a Non-Caspase-Dependent, Non–Necrotic, Cell Death, That Protects from Autoimmunity. Mizhir Atallah, Amir Grau and Dror Mevorach. Hadassah-Hebrew University

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease of unknown etiology characterized by the presence of pathogenic high-titer autoantibodies to a diverse group of autoantigens. Eearly complement proteins are important in protecting humans against the development of SLE and the protective role of C1q and complement in SLE is mainly related to their role in clearance of dying cells. Since there are few other mechanism available for apoptotic cell clearance we were questioning whether C1q has unknown additional role that may lead to increased necrotic debris found in patients with SLE. Using spontaneous human neutrophil apoptosis in the presence of complement deficient sera we show that by 12h incubation with C1q-deficient serum there were 61.28% ± 14.51% viable cells compared with 46.1% ± 14.88% in autologous serum. Furthermore, there were more than three-fold higher rate of necrotic cells ($p<0.001$) when cells were incubated in autologous serum in comparison with C1q-deficient serum. We further characterized complement induced cell death by electron microscopy and caspase inhibitors to concluded that complement induced apoptotic, non-necrotic, non-caspase-dependent neutrophil death.

We further injected dying cells in the presence and absence of C1q and were able to show that in the absence of C1q, a lupus-like disease was developed whereas in the presence of C1q lupus-like disease was much milder (0.001) as judged by the development of immunoglobulins, autoantibodies, and kidney disease. Taken together, we conclude that C1q induced a non caspase-dependent cell death that is protected from necrosis and avoids autoimmunity. This is a novel role for C1q that was thus far suggested to have a role only in clearance of apoptotic cells. This observation and may add a new explanation for the presence of elevated necrotic debris in SLE patients.

Disclosure: M. Atallah: None; **A. Grau:** None; **D. Mevorach:** None.

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Characterisation of Ex Vivo Leukocyte Rolling and Adhesion Responses in SLE. Eric F. Morand[1], Qiang Cheng[2], Alberta Hoi[2] and Michael J. Hickey[2]. [1]Monash University, Melbourne, Australia, [2]Monash University

Purpose: Systemic lupus erythematosus (SLE) is characterised by the presence of autoimmunity and inflammatory injury mediated by effector leukocytes recruited from the circulation. Mechanisms of increased leukocyte recruitment into affected tissues may include increased endothelial expression of chemokines and endothelial adhesion molecules, or disease-related alterations in leukocyte adhesive behaviour. The latter has not previously been investigated.

Aim: To determine whether SLE is associated with intrinsic alterations in blood leukocyte adhesive responses.

Methods: Rolling and adhesion interactions were quantified under flow conditions using fresh unstimulated whole peripheral blood (PB) leukocytes. PB was obtained from MRL/lpr lupus-prone mice and MRL+/+ control mice, and from healthy subjects (n=33) and patients with SLE (>4 ACR criteria) (n=57). Adhesive substrates used were platelet monolayers and/or recombinant VCAM-1.

Results: Compared to control mice, PB leukocytes from MRL/lpr mice exhibited markedly and significantly increased rolling and adhesion interactions on platelet monolayers. After adjustment for increased PB leukocyte counts in MRL/lpr mice, increases in leukocyte rolling and adhesion remained significant, at time points prior to the onset of clinical disease. This suggested an intrinsic alteration in leukocyte behaviour in a model of SLE. Therefore, we next studied this phenomenon in humans. Unstimulated PB leukocytes from SLE patients demonstrated significant increases in neutrophil rolling on platelet monolayers compared to healthy subject PB. Neutrophil rolling was P-selectin- and PSGL1-dependent. However, after correction for the increased PB neutrophil counts associated with steroid therapy in SLE patients, differences between SLE and healthy PB were non-significant. To investigate mononuclear cell interactions, recombinant VCAM-1 was used as an adhesive substrate. Lymphocytes formed the dominant PB leukocyte subset adherent to VCAM-1 in both SLE and control blood, and these interactions were alpha-4 integrin-dependent. After correction for SLE-related lymphopenia, no increase in PB lymphocyte adhesion interactions was present in SLE. However, a significantly increased proportion of SLE patient lymphocytes adherent to VCAM-1 underwent spreading, a motility response which precedes lymphocyte emigration. Significantly higher spreading responses were seen both in patients with active SLE (SLEDAI>4) and inactive SLE.

Conclusions: We describe a novel method for investigation of leukocyte recruitment events ex vivo in SLE. Increased PB leukocyte rolling and adhesion interactions were observed in MRL/lpr mice, prior to the onset of clinical disease. In contrast, neutrophil interactions with P selectin and lymphocyte interactions with VCAM-1 were normal in human SLE, but lymphocyte spreading responses on VCAM-1 were significantly increased in SLE PB. Further exploration of blood lymphocyte intrinsic migratory behaviour in SLE is justified, and may represent a novel therapeutic target.

Disclosure: E. F. Morand: None; **Q. Cheng:** None; **A. Hoi:** None; **M. J. Hickey:** None.

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Inhibition of Cytosolic Nucleic Acid Receptor Pathways Using the Small Molecule IKKε/TBK1 Kinase Inhibitor MPI-0485520. Burt Richards, Ju-Fen Zhu, Nathan Seager, Monica Cronin, Harry Austin, Thomas Douce, Daniel Cimbora, Ryan Holcomb, Daniel Wettstein and Paul Bartel. Myrexis, Inc., Salt Lake City, UT

Response to infection by bacterial and viral pathogens includes recognition of foreign nucleic acids. Several cytosolic nucleic acid receptors have been characterized, including the dsRNA receptors MDA5 and RIG-I and the dsDNA receptor DAI. Activation of cytosolic nucleic acid receptors leads to production of type I interferons and proinflammatory proteins through phosphorylation of IRF3 transcription factor by the IKK-related kinase TBK1.

We have developed a small molecule kinase inhibitor, MPI-0485520, that potently and selectively inhibits the IKK-related kinases IKKϵ and TBK1. MPI-0485520 also exhibits high oral bioavailability, favorable ADME/PK properties, and efficacy in a pharmacodynamic mouse model. To examine cytosolic nucleic acid receptor signaling through IKKϵ and TBK1, we activated receptors by introduction of dsRNA and dsDNA mimetics into the cytosol of mouse RAW264.7 and human THP-1 monocytic cell lines. Cells were subsequently dosed with MPI-0485520 and mRNA and protein levels of proinflammatory cytokines (IFNα/β, IP-10, IFIT1, MX1, RANTES, and IL-6) were monitored using qRT-PCR and ELISA. Both RAW264.7 and THP-1 cells exhibit robust induction of specific proinflammatory cytokines after cytosolic introduction of the RIG-I and MDA5 agonists, using low and high molecular weight poly(I:C), respectively. This induction was potently inhibited with MPI-0485520 for several of the induced cytokines. Treatment of mouse RAW264.7 cells with the dsDNA receptor agonist poly(dA:dT) also resulted in potent induction of proinflammatory cytokines that was inhibited by MPI-0485520 in a dose-dependent manner. THP-1 cells were not responsive to poly(dA:dT) suggesting that a dsDNA receptor is not present or is poorly induced in this cell line.

In addition to foreign nucleic acids, recent studies have demonstrated that accumulation of endogenous nucleic acids, due to improper disposal of retroelements, can generate a type I interferon response. Patients with mutations in TREX1, RNASEH2A/B/C, or SAMHD1 have a genetic predisposition to autoimmune diseases, including systemic lupus erythematosus, Sjögren's syndrome, and Aicardi-Goutieres syndrome (AGS). Trex1-knockout mouse studies support a model in which accumulated retroelements induce a cytosolic nucleic acid receptor that leads to type I interferon production via an IRF3-dependent pathway. We have demonstrated that production of type I interferons following activation of cytosolic nucleic acid receptors is potently blocked by MPI-0485520. These studies suggest that MPI-0485520 and other IKKϵ/TBK1 inhibitors may be efficacious in the treatment of forms of lupus, AGS, and Sjögren's syndrome caused by cytosolic nucleic acid receptor activation.

Disclosure: B. Richards: Myrexis, Inc., 3; **J.-F. Zhu:** Myrexis, Inc., 3; **N. Seager:** Myrexis, Inc., 3; **M. Cronin:** Myrexis, Inc., 3; **H. Austin:** Myrexis, Inc., 3; **T. Douce:** Myrexis, Inc., 3; **D. Cimbora:** Myrexis, Inc., 3; **R. Holcomb:** Myrexis, Inc., 3; **D. Wettstein:** Myrexis, Inc., 3; **P. Bartel:** Myrexis, Inc., 3.

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Inhibition of Interferon-Alpha by Sialylated IgG in Response to TLR7 and TLR9 Activation Is Mediated by a Soluble Factor Produced by Monocytes. Alice E. Wiedeman[2], Deanna M. Santer[2], Fabian Käsermann[1], Sylvia Miescher[1] and Keith B. Elkon[2]. [1]CSL Behring, [2]University of Washington

Objective: IgG in the form of intravenous immunoglobulin (IVIg) has been used as an anti-inflammatory agent in multiple autoimmune diseases. Recent studies reported that it is the small fraction of sialylated IgG (SA+) in human IVIg preparations that attenuates arthritis or immune thrombocytopenia. However, these studies were performed across species (human IgG injected into mouse models of disease). Our goal was to study the importance of the sialylated subset of IVIg in the inhibition of the inflammatory responses of *human* cells stimulated with TLR7 and 9 agonists that induce type 1 IFN.

Methods: Human IVIg preparations were enriched (SA+, 7- to 10-fold) or depleted (SA-, 2- to 5-fold) of the sialylated subset by lectin affinity chromatography. PBMC were isolated from whole blood of healthy individuals, cultured overnight in the presence of TLR7 (Loxoribine, CL097) or TLR9 (CpG) agonists with or without SA+ or SA- IgG at two doses (0.5 and 5 mg/mL). Antibodies to DC-SIGN, Fc receptors, as well as isotype controls (1ug/mL) were also used. In certain experiments, monocytes, B cells or NK cells were depleted or isolated from PBMC using magnetic beads. Some cultures were treated with TNF-α, IL-10, IL-6, and IL-8 or with antibodies to these same cytokines. Supernatants were collected 20 hours post-treatment and analyzed by ELISA for IFN-α, TNF-α, IL-10, IL-8, and IL-6.

Results: In response to the TLR agonists tested, SA+ IgG inhibited IFN-α production significantly more than SA- IgG ($p<0.05$), and the inhibition by SA+ IgG increased with higher doses ($p<0.05$). Blocking DC-SIGN or FcRs did not abrogate the inhibition by SA+ IgG. Inhibition of IFN-α by SA+ IgG was decreased by the depletion of CD14+ monocytes, but not depletion of CD19+ B cells or CD56+ NK/NKT cells. Supernatants from isolated monocyte cultures treated with SA+ IgG could transfer inhibition to fresh cultures of TLR agonist-stimulated PBMC or isolated pDC. Surprisingly, levels of TNF-α, IL-10, IL-6, and IL-8 were not inhibited by SA+ or SA- IgG, and in fact the production of TNF-α was modestly enhanced in cultures treated with SA+ compared to SA- IgG ($p<0.05$). Neutralization of TNF-α or IL-10 did not abrogate IFN-α inhibition by SA+ IgG.

Conclusions: SA+ IgG is more potent at inhibiting IFN-α production in response to TLR agonist stimulation compared to SA- IgG. Results suggest that SA+ mediated inhibition is not mediated through an Fc gamma receptor nor the human homolog of SIGN-R1, DC-SIGN. Soluble factor(s) produced by CD14+ monocytes mediate this inhibition by acting directly on pDC. Cytokine blocking studies indicate that cytokines TNF-α and IL-10, that are produced by monocytes and known to inhibit IFN-α, are not responsible. The greater potency of SA+ IgG has therapeutic implications for SLE because our results suggest that a lower dose of IVIG enriched for the active, sialylated subset may dampen IFN-α responses to TLR stimuli. Also, identification of the SA+ binding receptor and soluble factor(s) released from monocytes in response to SA+ IgG could reveal new targets for immune modulation of type 1 IFN in SLE.

Disclosure: A. E. Wiedeman: None; **D. M. Santer:** None; **F. Käsermann:** CSL Behring, 3; **S. Miescher:** CSL Behring, 3; **K. B. Elkon:** None.

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IRF5 SLE-Risk Haplotype Is Strongly Enriched in Anti-Ro Positive Mothers of Neonatal Lupus Patients with Diverse Diagnoses. Timothy B. Niewold[2], Silvia N. Kariuki[2], Beverly S. Franek[2], Jill P. Buyon[1] and Robert M. Clancy[1]. [1]Division of Rheumatology, New York University School of Medicine, [2]Section of Rheumatology and Gwen Knapp Center for Lupus and Immunology Research, University of Chicago

Objective: In patients with systemic lupus erythematosus (SLE), IRF5 genotype is associated with anti-Ro autoantibodies. It is not clear whether this association with autoantibody profile is specific to SLE disease status. To examine this question, we assessed IRF5 genotypes in a large cohort of individuals who all had high titer anti-Ro autoantibodies and carried a variety of diagnoses including healthy/asymptomatic, Sjogren's syndrome (SS), and SLE.

Methods: We studied 85 European-ancestry individuals recruited to the Research Registry for Neonatal Lupus who all had high titer anti-Ro autoantibodies and a child with neonatal lupus. The diagnoses of these subjects were as follows: 15 healthy/asymptomatic, 10 SLE, 19 SLE/SS, 20 SS, and 21 undifferentiated autoimmune disease (UAS). IRF5 SNPs were genotyped using Taqman primer-probe sets to define previously reported European-derived SLE risk and protective haplotypes.

Results: The IRF5 SLE-risk haplotype defined by the rs10488631 C allele was enriched in subjects of all diagnoses except SS when compared to large published data sets of European-American controls [OR=2.30 (1.50–3.32), $p=8.4\times10^{-5}$]. Each of the asymptomatic, SLE, SLE/SS, and UAS mothers showed a very similar increase in rs10488631 allele frequency when examined individually (ORs range from 2.00 to 3.15, no significant differences between the asymptomatic, SLE, SLE/SS and UAS groups). The rs10488631 C allele frequency in the subjects diagnosed with SS was essentially the same as controls (OR=1.05). Interestingly, the rs3807306 C allele was significantly increased in the SS patients as compared to subjects from the other 4 diagnostic categories [OR=2.34 (1.14–4.79), p=0.026].

Conclusions: There was a significant increase in the frequency of the IRF5 SLE-risk haplotype in subjects with anti-Ro antibodies with varying diagnoses which was of comparable magnitude to the anti-Ro/IRF5 association observed in SLE (OR>2). Interestingly, the SS cohort was distinct from the other neonatal lupus mothers with respect to IRF5 genotype, and a different SNP was associated with SS status. These data suggest that the genetic association of IRF5 with autoimmunity is strongly influenced by serologic profile, and that the anti-Ro association with IRF5 genotype extends beyond the SLE disease state to some degree.

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IRF8 Allele Associated with Susceptibility to Multiple Sclerosis Is Associated with Serum Interferon Alpha and Serologic Profile in Systemic Lupus Erythematosus. Beverly S. Franek[2], Silvia N. Kariuki[2], Jasmine Arrington[2], Rachel A. Mikolaitis[3], Meenakshi Jolly[3], Tammy O. Utset[2], Dimitrios T. Boumpas[1], George Goulielmos[1] and Timothy B. Niewold[2]. [1]Internal Medicine and Rheumatology, Clinical Immunology and Allergy, University of Crete Medical School, Heraklion, Greece, [2]Section of Rheumatology and Gwen Knapp Center for Lupus and Immunology Research, University of Chicago, [3]Section of Rheumatology, Rush University Medical Center

Objective: Alleles of IRF8 have been associated with susceptibility to both systemic lupus erythematosus (SLE) and multiple sclerosis (MS). While interferon alpha (IFN-α) is thought to be causal in SLE, recombinant human IFN-α is used as a therapy in MS. We investigated whether the IRF8 alleles associated with these two diseases were associated with differences in serum IFN-α or serologic profile in a multi-ancestral cohort of SLE patients.

Methods: The rs12444486 and rs17445836 single nucleotide polymorphisms (SNPs) in IRF8 (associated with SLE and MS respectively) were genotyped with Taqman primer-probe sets in 244 African-American and 137 European ancestry SLE patients. All patients had serum IFN-α and serology data available, and had been previously genotyped at SLE-risk SNPs in the IRF5 and IRF7 loci. Data from each ancestral background was analyzed separately initially, and combined in meta-analysis when associations were not significantly heterogeneous between ancestral backgrounds. Principal component analysis was used to control for proportional ancestry at the individual level.

Results: The MS-associated rs17445836 G allele was associated with the presence of anti-dsDNA autoantibodies in SLE patients of both ancestral backgrounds [meta-analysis OR=2.01 (1.09–3.68), p=0.024]. The same allele was also associated with increased serum IFN-α activity in both ancestral backgrounds (meta-analysis p=0.017). There was no evidence for statistical interaction between rs17445836 G and SNPs in IRF5 and IRF7 which have been previously associated with anti-dsDNA in SLE patients. No significant associations were observed between the SLE-associated rs12444486 SNP and serum IFN-α or serologic profile.

Conclusions: The rs17445836 G allele associated with susceptibility to MS was associated with anti-dsDNA antibodies and serum IFN-α in SLE patients of both African-American and European ancestry. This is interesting, given the therapeutic effect of IFN-α in MS patients, and the pathogenic effect of this same cytokine in SLE. Further exploration of the impact of the IRF8 locus upon in vivo IFN-α levels could provide insight into both diseases.

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Leptin Promotes T Cell Autoimmunity through Modulation of the PKB/Akt/mTOR Pathway in Systemic Lupus Erythematosus (SLE) Patients. Elaine V. Lourenco, Bevra H. Hahn, Noriko Iikuni, Sarah J. Kim, Maida Wong, Ram P. Singh, Jennifer Grossman and Antonio La Cava. UCLA

Leptin is a pro-inflammatory (adipo)cytokine that promotes the onset and progression of organ-specific autoimmunity by facilitating pro-inflammatory immune responses. We investigated the possibility that leptin could modulate autoimmune T cell reactivity in systemic lupus erythematosus (SLE) patients, and found that the elevation of leptin in plasma from SLE patients (n=164) - as compared to matched controls (n=124)($p<0.0001$) - facilitated the proliferation and release of pro-inflammatory cytokines in peripheral autoreactive SLE $CD4^+$ T cells. These effects were abrogated if leptin was blocked by antibodies anti-leptin, anti-leptin receptor, or leptin receptor chimera. Interestingly, the effects of leptin were different on the $CD4^+CD25^-FoxP3^-$ effector T cells (T_{Eff}) and $CD4^+CD25^+FoxP3^+$ regulatory T cells (T_{Reg}). In particular, leptin promoted the proliferation and release of pro-inflammatory cytokines in T_{Eff} and it constrained the activity of T_{Reg}, with a net result of unabated autoreactive T_{Eff} responses. These effects associated with leptin-induced differential activation of the protein kinase B (PKB)/Akt/mTOR signaling pathway in autoreactive T_{Eff} versus T_{Reg}, and this action could be reversed by pharmacologic intervention. These findings identify a new mechanism through which leptin can concomitantly promote T cell autoreactivity and inhibit immune suppression in SLE, suggesting the possibility of targeted leptin-based intervention for the control of unbalanced T cell autoimmune reactivity in the disease.

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Low C4A Gene Copy Number in Systemic Lupus Erythematosus. Kaline M. C. Pereira[4], Atila G. A. Faria[4], Eloisa S. Moreira[1], Viviane C. Santos[3], Marcelle Grecco[3], Neusa P. Silva[3] and Luis Eduardo C. Andrade[2]. [1]Hospital Sirio Libanes, Brazil, [2]Universidade Federal de São Paulo, Sao Paulo, Brazil, [3]Universidade Federal de Sao Paulo - UNIFESP, Brazil, [4]Universidade Federal de Sao Paulo - UNIFESP, Sao Paulo, SP, Brazil

Introduction: C4 is an important component of Complement system and plays an essential role in the activation cascades of the classical Complement pathway. Complete deficiency of C4 is among the strongest genetic risk factors for systemic lupus erythematosus (SLE). There are two C4 circulating isoforms (C4A and C4B) encoded by C4A and C4B genes, respectively, that differ by only five nucleotides. C4A protein is involved in immune complex and apoptotic debris clearance while C4B protein is relevant in the defense against microbes. C4A and C4B genes are located at a gene cassette within the MHC class III region and depict gene copy-number variation (CNV). The number of C4A copies may be related to susceptibility to SLE.

Objective: To investigate the C4A and C4B gene CNV in patients with SLE.

Methods: One hundred SLE patients (meeting SLE ACR criteria) were sequentially retrieved from the rheumatology outpatient clinic and 100 healthy individuals (HI) without evidence of autoimmune diseases were retrieved among blood bank donors. Peripheral blood leukocyte DNA was amplified by quantitative real-time PCR (qPCR) technique using sequence specific TaqMan® probes with minor groove binding (MGB) non-fluorescent quencher. Gene copy number (GCN) was determined by the delta-delta cycle threshold (DDCT) method. Samples with known C4A and C4B GCN were kindly provided by Dr. Szilagyi (Hungary).

Results: Gene copy number (GCN) varied from 2 to 8 for total C4 and from 0 to 5 for C4A and C4B. Patients with SLE had lower total C4 (C4A + C4B) and C4A GCN than HI. GCN for total C4 was lower in SLE patients (3.7 ± 1.2; 95% CI=3.5 – 3.9) in comparison with HI (4.3 ± 1.3; 95% CI= 4.0 – 4.5; p=0.003). This difference was due to C4A GCN variation that was lower in SLE (1.9 ± 1.0; 95% CI= 1.7 – 2.1) than in HI (2.3 ± 1.1; 95% CI=2.1 – 2.6; p=0.015). In contrast there was no difference in C4B GCN in both groups [(SLE = 1.8 ± 0.8; 95% CI= 1.6 – 1.9) and (HI = 1.9 ± 1.1; 95% CI=1.7 – 2.1) p=0.320]. The frequency of patients with only two C4 copies (C4A and/or C4B) was significantly higher in SLE (16%) than in HI (5%; p=0.028). The same was observed for subjects with only one C4A copy (SLE = 30%; controls = 16%; p=0.020). The frequency of patients with low C4 GCN (less than 4 copies) was significantly higher in SLE than in HI (40% versus 25%; p=0.022). The same was observed for low C4A gene dosage (less than 2 copies) (SLE = 35%; HI = 17%; p=0.009).

Conclusion: Patients with SLE presented lower C4A GCN as compared to control healthy individuals. This finding suggests that the ensuing relative deficiency in circulating C4A protein in individuals with low C4A GCN is one relevant risk factor for susceptibility to the development of systemic lupus erythematosus.

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Lupus Immune Complex Gene Expression Arrays Reveal Divergent Pro- and Anti-Inflammatory Pathways Induced Depending on the Presence of Plasmacytoid Dendritic Cells and C1q. Deanna M. Santer and Keith B. Elkon. University of Washington, Seattle, WA

Background: Patients with Systemic Lupus Erythematosus (SLE) have an 'IFN-signature' that correlates with disease severity. RNA-containing immune complexes (ICs) stimulate IFN-alpha (IFN-a) production by plasmacytoid dendritic cells (pDCs) through activation of TLR7. We recently demonstrated that normal human serum contains potent inhibitors of IFN-a including IgG and the classical complement protein C1q. We showed that C1q inhibition of IFN-a required monocytes to indirectly inhibit pDCs, but thus far we only knew that the inhibition was soluble factor *independent*. The

purpose of this study was 2-fold: 1) To determine what genes are induced by C1q-containing ICs that could explain the mechanism by which C1q regulates IFN-a induction, and 2) To identify what other pathways, in addition to type I IFNs, are induced by SLE ICs.

Methods: SLE ICs were formed with diluted SLE serum (1:2000) or purified IgG and necrotic cell extract. ICs were added to normal donor peripheral blood mononuclear cells (PBMCs) or purified monocytes (>97% pure) in the absence (IC) or presence of C1q (C1q-IC) for 6 hours (microarray) or 40 hours (ELISA and flow cytometry). Controls included unstimulated and C1q alone treated cells. IFN-a and other pro-inflammatory cytokines were quantified by ELISA in culture supernatants and the expression of the activation markers CD86 and CD40 were determined by flow cytometry. Gene expression was quantified using Illumina Ref 8 beadchips and the results were confirmed by qRT-PCR with a total of 4 donors. ICs and necrotic extracts contained <0.06EU/ml endotoxin contamination.

Results: We found that SLE ICs altered the expression of 105 genes greater than 2-fold for PBMCs and only 7 genes for purified monocytes. Surprisingly, none of the ICs tested, whether formed with purified IgG or diluted serum, induced a typical pro-inflammatory response (e.g. TNF-a and IL-6) by PBMCs or monocytes. Rather, 40 of the top 50 genes induced in PBMCs were known type I IFN stimulated genes (ISGs). These ISGs were not induced in our monocyte microarrays. Upon addition of C1q to ICs, we observed a striking downmodulation of the expression of the 40 ISGs. In agreement with our findings that C1q is anti-inflammatory, we found that C1q-ICs specifically induced inhibitors of the NFkB, MAPK and Syk signaling pathways >1.5 fold compared to ICs alone. SLE ICs also upregulated the activation markers CD86 and CD40 on CD14+ monocytes within PBMC cultures, but upon depletion of pDCs or when using purified monocytes, ICs were significantly less stimulatory ($P<0.01$) despite the fact that C1q strongly promoted binding to, and endocytosis of ICs, by monocytes.

Conclusions: (1) In the absence of pDCs, SLE ICs are remarkably inefficient at stimulating PBMCs or isolated monocytes. (2) The presence of C1q in SLE ICs significantly downregulates the expression of 40 ISGs in both PBMCs and monocytes. (3) The presence of C1q in SLE ICs also alters the expression of genes that may impact inflammation through modulation of the NFkB, MAPK and Syk signaling pathways.

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Meta-Analysis of Autoimmune Variants Shared between Systemic Lupus Erythematosus (SLE) and 16 Other Diseases Identifies Novel SLE Loci. Paula S. Ramos[3], Patrick M. Gaffney[1], Lindsey A. Criswell[12], Mary E. Comeau[3], Adrienne H. Williams[3], Robert R. Graham[8], Sharon A. Chung[10], Raphael Zidovetzki[5], Jennifer A. Kelly[2], Kenneth M. Kaufman[2], Chaim O. Jacob[9], Robert P. Kimberly[4], Betty P. Tsao[11], Marta E. Alarcon-Riquelme[6], Timothy J. Vyse[7], John B. Harley[13], Kathy L. Moser[1], Carl D. Langefeld[3] and SLEGEN Consortium. [1]Arthritis and Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Arthritis and Immunology Program, Oklahoma Medical Research Foundation, [3]Dept Biostatistical Sciences, Wake Forest University Health Sciences, [4]Dept Medicine, University of Alabama at Birmingham, Birmingham, AL, [5]Dept of Cell Biology and Neuroscience, University of California, Riverside, [6]Dept of Genetics and Pathology, Uppsala University, Uppsala, Sweden, [7]Faculty of Medicine, Imperial College, London, UK, [8]Immunology Biomarkers Group, Genentech, [9]Keck School of Medicine, University of Southern California, Los Angeles, Los Angeles, CA, [10]Rosalind Russell Medical Research Center for Arthritis, University of California, San Francisco, San Francisco, CA, [11]UCLA School of Medicine, Los Angeles, CA, [12]UCSF-Box 0500, San Francisco, CA, [13]Univ of OK Hlth Sci Ctr, Oklahoma City, OK

The clustering of multiple autoimmune disorders (ADs) in families is well known. Nevertheless, evidence of specific shared variants is sparse, and consequently the genetic mechanisms that may explain the patterns of disease aggregation remain unclear. This study is aimed at assessing which variants are common and different between SLE and other ADs. As such, we compared the variants reported as associated in genome-wide association studies (GWAS) of ADs to those identified in our large-scale analysis of SLE. We compiled a list with 381 non-MHC variants identified as significant in 49 GWAS of 16 ADs, available at the GWAS catalog (www.genome.gov/gwastudies). We combined the genotypic and imputed data from three published Caucasian cohorts (total of 1500 cases and 5706 controls)(Seligman et al, 2001; Remmers et al, 2007; Graham et al, 2008; Harley et al, 2008) and performed a joint- and a meta-analysis. When available, we used data from a previously described independent replication cohort of 2085 SLE cases and 2854 controls (Harley et al, 2008). All analyses were adjusted for admixture. Of the 213 SNPs that met quality control criteria, 44 survived a multiple comparisons adjustment with $P<0.05$ in the joint-analysis. Interestingly, the loci most shared between GWAS of ADs include IL23R, TNFAIP3, PTPN22, IL12B, IL12RA and PFKFB3-PRKCQ. Based on the number of genome-wide significant loci, we observe that SLE shares the most loci with Crohn's disease (TNFAIP3, ATG5, and 7p12.2), followed by both rheumatoid arthritis (TNFAIP3, BLK) and psoriasis (TNFAIP3, TNIP1), reflecting the number of published GWAS and associated SNPs available from the GWAS catalog. Several autoimmune variants were herein confirmed to be associated with SLE. These include SNPs in the TNFAIP3 (rs2230926, P=1.39×10–20; rs5029939, P=1.51×10–14; rs6920220, P=5.34×10-06), BLK (rs2736340, P=3.59×10-07; rs2618476, P=1.10×10-07), IL10 (rs3024505, P=6.45×10-05; rs3024493, P=4.38×10-05), and TYK2 (rs2304256, P=2.44×10-08) regions. Novel SLE loci include the VTCN1 (rs12046117, P=2.02×10-06), CD40 (rs1569723 P=1.26×10-03), IRGM (rs11747270, P=1.12×10-03) and IL12A (rs4680534, P=1.78×10-03) regions. This study expands the number of candidate loci associated with SLE and further dissects the extent of genetic overlap between SLE and other ADs.

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MicroRNA miR-146a, Type I Interferon, and Race in Systemic Lupus Erythematosus. Paul R. Dominguez[1], Minoru Satoh[2], Angela R. Ceribelli[1], Eric S. Sobel[2], Yi Li[2], Westley H. Reeves[2] and Edward K. L. Chan[2]. [1]Department of Oral Biology, University of Florida, Gainesville, FL, [2]University of Florida, Gainesville, FL

Background: A few microRNAs (miRNA) have known gene expression regulatory roles in innate immunity. miR-146, a NFκB regulated transcript, is activated during lipopolysaccharide stimulation of monocytes and is critical in endotoxin tolerance to prevent cellular overstimulation when in excess of the TLR4 ligand. Interestingly, miR-146a has been reported to be upregulated in PBMCs and synovial tissue in rheumatoid arthritis patients but reported downregulated in PBMCs of SLE patients. The aim of the study is to determine whether the repressed expression of miR-146a reported in Chinese SLE can be observed in our US SLE cohort with more diversity in ethnic background.

Methods: Blood samples were collected from 124 SLE patients (European Americans (EA) 48 F, 10 M; African Americans (AA) 41 F, 2 M; Latin Americans (LA) 11 F, 6 M; others 6 F)) fulfilling ACR criteria and this included 35 patients with 2 or more collections from multiple visits to our autoimmune center. Total RNA, isolated from leukocytes, was analyzed by Taqman qPCR. miRNA copy number was determined using a standard curve. Expression of Type I interferon (IFN) signature genes (ISGs) and other cytokine/chemokine including TNFα, CCL2, CCL19, and CxCL10 was determined by ΔΔCT method. IFN score was calculated from ISGs (Mx1, OAS1, and Ly6e). Results were correlated with clinical data and analyzed by Wilcoxon/Kruskal-Wallis Test.

Results: Comparing CCL2, ISGs, and IFN score levels by race, AA had significantly higher levels compared to EA (p=0.016) and LA (p0.004), but LA had significantly lower levels than EA (p=0.038). miR-146a appeared to be higher in EA than AA or LA but did not reach significance. Reduced miR-146a expression was also observed in SLE patients with nephritis but did not reach significance. Correlation of miR-146a level with other clinical parameters including arthritis, pleritius, pericarditis, lymphopenia etc. did not show statistical significance. When 35 returning patients divided based on changes in miR-146a level comparing the first and the last visit, 11 had increased in miR-146a vs. 17 reduced. In the miR-146a reduced group (p=0.001), Mx1 (p=0.03), Ly6e (p=0.04), OAS1 (p=0.02), IFN score (p=0.02) reduced significantly whereas no significance were found for TNFα, CCL2, and CXCL10. The miR-146a increased group (p=0.0003) was more heterogeneous and none of the markers had statistically significant difference.

Conclusions: Comparison in race demonstrates with statistical significance that LA has the lowest level of IFN while AA has the highest. The data show potentially two groups: a miR-146a responsive group where miR-146a maybe regulating IFN production and a miR-146a resistant group where IFN production appears independent of miR-146a. For SLE patients with decreas-

ing levels of miR-146a in subsequent visit correlating with decreasing IFN score, this may represent the transition from active to remission state. In more active SLE, miR-146a levels most likely represent a balance in continuous IFN stimulation and innate controls as represented by patients with both high IFN score and miR-146a levels.

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Multiple Independent Major Histocompatibility Complex Associations with Nephritis and Autoantibody Production in Systemic Lupus Erythematosus. Sharon A. Chung[7], Kimberly E. Taylor[7], Suzanne L. May[fo], Patricia P. Ramsay[9], Hong L. Quach[9], Julie A. Lane[2], Joanne Nititham[8], Janelle A. Noble[2], Diana L. Quach[9], Jennifer A. Kelly[3], Kathy L. Moser[4], Timothy W. Behrens[3], Michael F. Seldin[11], John B. Harley[r], Patrick M. Gaffney[4], Lisa F. Barcellos[9] and Lindsey A. Criswell[6]. [1]Children's Hospital Cincinnati Medical Center, Cincinnati, OH, [2]Children's Hospital Oakland Research Institute, Oakland, CA, [3]Genentech, Inc., South San Francisco, CA, [4]Oklahoma Medical Research Foundation, Oklahoma City, OK, [5]Oklahoma Medical Research Foundation, Oklahoma City, OK, [6]Rosalind Russell Medical Research Center for Arthritis, University of California, San Francisco, San Francisco, CA, [7]Rosalind Russell Medical Research Center for Arthritis, University of California, San Francisco, [8]Rosalind Russell Medical Research Center for Arthritis, University of California, San Francisco, CA, [9]University of California, Berkeley, CA, [10]University of California, Berkely, CA, [11]University of California, Davis, CA

Background: The most significant genetic associations with systemic lupus erythematosus (SLE) have been with the major histocompatibility complex (MHC), a gene dense region on chr6p21 spanning >5Mb. Prior attempts to identify MHC associations independent of *HLA-DRB1* (the most consistently associated MHC locus) were limited, in part, by the region's extensive linkage disequilibrium. In addition, MHC associations with SLE manifestations such as nephritis and autoantibody production have not been fully explored. Therefore, we performed high-density single nucleotide polymorphism (SNP) genotyping to identify MHC associations with lupus nephritis, anti-dsDNA, and anti-Ro/La (SSA/SSB) autoantibody production among SLE patients.

Methods: Using the Illumina Combined MHC panel, we genotyped 1,610 SLE cases of European descent for 2,360 MHC SNPs. SLE cases were also genotyped for *HLA-DRB1* and 384 ancestry informative markers. Lupus nephritis and autoantibody status was obtained from medical record review. We identified associations with *HLA-DRB1* alleles using a relative predispositional effects (RPE) method. Forward selection with conditional logistic regression (CLR) based on haplotypes was used to identify SNPs associated with particular SLE manifestations that were independent of each other and *HLA-DRB1*.

Results: After applying stringent quality control criteria (including removal of SLE cases with <90% northern European ancestry), we analyzed 1,974 SNPs in 1,125 SLE cases. Thirty-two percent (32%) had lupus nephritis, 50% had anti-dsDNA autoantibodies, and 27% had anti-Ro/La (SSA/SSB) autoantibodies. RPE analysis showed that different *HLA-DRB1* alleles were associated with lupus nephritis as compared to anti-Ro/La (SSA/SSB) autoantibody production (**1501* and **1302* for nephritis vs. **0301*, **0401*, **0404*, **1301*, and **0101* for anti-Ro/La). No *HLA-DRB1* alleles were significantly associated with anti-dsDNA autoantibody production (global χ^2 $p>0.05$). CLR analysis identified associations independent of *HLA-DRB1* in the *HLA-DOB*, *HLA-A/HCG9*, and *LEMD2* regions with lupus nephritis (OR for the most associated haplotype [OR_{hs}] 3.04, haplotype-specific p [p_{hs}]=3.1E-04). *HLA-DRB1*-independent associations were observed in the *HLA-DPA1/HLA-DOA*, *C6orf205*, and *OR2H2* regions with anti-Ro/La (SSA/SSB) autoantibody production (OR_{hs} 3.23, p_{hs}=1.6E-08). SNPs in or near *TAP2*, *C6orf10*, and *TRIM40/TRIM15* were associated with anti-dsDNA autoantibody production (OR_{hs} 2.82, p_{hs}=1.5E-08).

Conclusions: We have identified several significant MHC associations with lupus nephritis and autoantibody production that are independent of *HLA-DRB1*. Of interest, different genes/genetic regions were associated with these specific SLE manifestations. These results indicate that MHC genetic variation contributes significantly to disease heterogeneity in SLE.

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NK Cells Regulate the IFN-α Production by Plasmacytoid Dendritic Cells Via Soluble Factors and Cell-Cell Contact. Niklas Hagberg[2], Olof Berggren[2], Gunnar V. Alm[1], Maija-Leena Eloranta[2] and Lars Rönnblom[2]. [1]Department of Biomedical Sciences and Veterinary Public Health, Swedish University of Agricultural Sciences, Uppsala, Sweden, [2]Department of Medical Sciences, Uppsala University, Uppsala, Sweden

Background: Overactivation of the type I IFN system has been demonstrated in patients with SLE and several other autoimmune diseases. We previously showed that the IFN-α production by pDCs stimulated with RNA-containing immune complex (RNA-IC) was regulated by NK cells and monocytes. NK cells enhanced the IFN-α production, while monocytes inhibited the NK cell stimulation of pDCs. The suppressive effect of monocytes was largely due to ROS, PGE2 and TNF-α, while the mechanisms for NK cell enhancement were hitherto unknown.

Objective: This study was performed to investigate the mechanisms whereby NK cells promote the IFN-α production by RNA-IC-stimulated pDCs. Furthermore, NK cells from SLE patients were also investigated for their capacity to enhance the IFN-α production.

Methods: pDCs and NK cells were isolated from PBMCs of healthy blood donors or SLE patients and stimulated with RNA-IC consisting of purified U1 snRNP and IgG from an SLE patient. Concentrations of IFN-α and 16 other cytokines in cell culture supernatants from pDCs, NK cells or cocultivations of pDCs and NK cells were determined using single or multiplex immunoassays.

Results: Soluble factors which could enhance the IFN-α production from RNA-IC stimulated pDCs were produced after FcγRIII-ligation or IL-12/IL-18 stimulation of NK cells. MIP-1α(CCL3), MIP-1β(CCL4), RANTES (CCL5), IFN-γ and TNF-α were found in the cell culture supernatants from FcγR-stimulated NK cells and MIP-1β was identified as partially responsible for the NK cell-mediated increase in IFN-α production. In addition, cell-cell contact via LFA-1 also contributed to the NK cell enhancement of IFN-α production by pDCs. When NK cells and pDCs were co-cultivated, the production of several other cytokines implicated in the pathogenesis of SLE, e.g. IL-6, IFN-γ and TNF-α, were also increased. NK cells from SLE patients and healthy blood donors were compared for their ability to promote the RNA-IC induced IFN-α production by pDCs. SLE NK cells were less stimulatory compared to NK cells from healthy blood donors when co-cultivated with pDCs and RNA-IC (p=0,004). However, addition of IL-12/IL-18 made the SLE NK cells as efficient as NK cells from healthy blood donors in enhancing the IFN-α production by pDCs.

Conclusions: This study describes novel mechanisms involved in the cross-talk between NK cells and pDCs which regulates the production of IFN-α. Both soluble factors such as MIP-1β and cell-cell-contact between NK cells and pDCs via LFA-1 were found to promote the IFN-α production. In addition, the regulatory function that NK cells exert on pDCs is altered in SLE patients. These results are of importance for understanding molecular mechanisms behind the increased IFN-α production in several autoimmune diseases and also indicate new potential therapeutic targets.

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Novel Fc gamma Receptor 3B Gene (FCGR3B) Allele Variants and Polymorphism Distribution in Brazilian Systemic Lupus Erythematosus Patients and Blood Bank Donors. Viviane C. Santos[2], Marcelle Grecco[2], Kaline M. C. Pereira[2], Luis E. C. Andrade[2] and Neusa P. Silva[1]. [1]Universidade Federal de São Paulo, São Paulo, Brazil, [2]Universidade Federal de São Paulo, Brazil

Background: Immunecomplex (IC) deposition is a characteristic feature of systemic lupus erythematosus (SLE) and several pieces of evidence point towards an inefficient IC clearance in SLE. Fc gamma receptors (FcγR) are involved in the uptake and degradation of ICs by a variety of cells. FcγRIIa, FcγRIIb, FcγRIIIa and FcγRIIIb are polymorphic in humans and some alleles have been associated with SLE susceptibility. The FcγRIIIb gene (FCGR3B) presents three alleles, HNA-1a, HNA-1b and HNA-1c, characterized by specific nucleotides at six different positions in the 3rd exon.

Objectives: to determine FCGR3B polymorphic distribution and describe novel allelic variants present in SLE patients and blood bank donors, in Sao Paulo, Brazil.

Patient and Methods: peripheral blood was obtained from 260 consec-

utive SLE patients, attending the outpatient clinic of the Rheumatology Division at Universidade Federal de Sao Paulo, and from 246 ethnic-matched blood bank donors in Sao Paulo, Brazil. All individuals signed the informed consent approved by the Institutional Ethics Board. DNA was extracted by salting out and a 243bp sequence containing the polymorphic region of interest of the 3rd exon of FCGR3B was amplified by PCR. All samples were sequenced and processed in capillary gel electrophoresis (ABI 3130xl).

Results: Among SLE patients we found 52 homozygous for HNA-1a, and 208 heterozygous (188 HNA-1a/HNA-1b and 20 HNA-1a/HNA-1c). Among blood donors, HNA-1a homozygosis was found in 56, and heterozygosis in 190 (170 HNA-1a/HNA-1b and 20 HNA-1a/HNA-1c). Novel allelic variants (one HNA-1a and three HNA-1b) were also found. Point mutations, previously described in nucleotides not related to allelic discrimination (G230T, A249G, and G330T) were observed in both SLE (57) and blood bank donors (60). In addition we also identified 22 new point mutations in 76 SLE patients and 66 blood bank donors. There was no statistical difference between groups regarding genotype or phenotype distribution. Interestingly, homozygous individuals for the HNA-1b allele were not found in the population under study.

Conclusion: There was no association of FCGR3B gene polymorphism and SLE. Our results indicate that FCGR3B is a highly polymorphic gene possibly due to the existence of either somatic recombination or hyper mutation within this gene segment.

Disclosure: V. C. Santos: None; **M. Grecco:** None; **K. M. C. Pereira:** None; **L. E. C. Andrade:** None; **N. P. Silva:** None.

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Numerical and Functional Deficiencies of Natural Killer T Cells in Systemic Lupus Erythematosus: Their Dysfunction Related to Up-Regulation of *Cbl-b*. Young-Nan Cho[2], Sung-Ji Lee[3], Seong-Rye Seo[3], Seung-Jung Kee[1], Tae-Jong Kim[3], Shin-Seok Lee[3] and Yong-Wook Park[2]. [1]Department of Laboratory Medicine, Chonnam National University Medical School and Hospita, [2]Department of Rheumatology, Chonnam National University Medical School and Hospital, Gwangju, Republic of Korea, [3]Department of Rheumatology, Chonnam National University Medical School and Hospital

Purpose: This study was designed to examine the frequency of natural killer T (NKT) cells and the response to α-galactosylceramide (α-GalCer) in systemic lupus erythematosus (SLE) and to investigate the clinical relevance of NKT cell levels.

Methods: Patients with SLE (n = 128) and age- and sex-matched healthy controls (n = 92) were enrolled in the study. NKT cell and CD1d levels were measured by flow cytometry. Gene expression was determined by reverse transcription-polymerase chain reaction, and cytokine secretion by multiple cytokine assay. Peripheral blood mononuclear cells (PBMCs) were cultured in vitro with α-GalCer. Proliferation indices of NKT cells were estimated by flow cytometry.

Results: Percentages and absolute numbers of NKT cells were significantly lower in the peripheral blood of SLE patients than in that of healthy controls, whereas CD1d levels in PBMCs were comparable between these two groups. Notably, this NKT cell deficiency was found to be correlated with SLE Disease Activity Index. NKT cell proliferation was found to be impaired in SLE patients, and cytokine production by NKT cells in response to α-GalCer was diminished. This poor responsiveness to α-GalCer was found to be due to a NKT cell dysfunction rather than to an abnormality in CD1d-expressing cells. Furthermore, this dysfunction was found to be related to the up-regulation of Cbl-b.

Conclusions: Our data show that NKT cell levels and functions are defective in SLE patients. Furthermore, these deficiencies were found to reflect disease activity. It would appear that these NKT cell abnormalities could contribute to immune system dysregulation in SLE.

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Paucity of PD-L1 Expression on Monocytes during Active Systemic Lupus Erythematosus Is Regulated by IL-10, TNF-α and TGF-β. Anne M. Stevens[3], Jing-Ni Ou[1] and Alice Wiedeman[2]. [1]Center for Immunity and Immunotherapies, Seattle Children's Research Institute, Seattle, WA, [2]Department of Immunology, University of Washington, Seattle, WA, [3]Pediatrics, U. of Washington, Seattle, WA

Purpose: Programmed death ligand 1 (PD-L1) plays an important role in controlling autoreactive and follicular T helper lymphocytes, thus preventing autoimmune disease. Induced by inflammatory cytokines, PD-L1 is reportedly elevated on monocytes from patients with infections and rheumatoid arthritis, but is poorly expressed on Mo from SLE patients with active disease. Our goal was to define the mechanism for PD-L1 dysregulation in pediatric patients with SLE, and to clinically characterize those patients with loss of PD-L1.

Methods: Serial samples were obtained from 23 pediatric controls and patients with SLE (20 samples during active disease, SELENA-SLEDAI score >4, and 37 during remission). PD-L1 expression on $CD11c^+$ $CD14^{high}$ monocytes was assayed in cultured peripheral blood cells by flow cytometry. Cytokines in culture supernatants were assayed by multiplex ELISA. Area under the curve (AUC) measurements of non-parametric receiver operating characteristic (ROC) curves were used to compare the ability of PD-L1 expression to distinguish between subject groups.

Results: PD-L1 expression on healthy control monocytes was 2.7-fold higher than patients with active disease (mean induction $\pm$SD 27.8$\pm$20.4, 95% confidence interval (CI) 20.4–35.3 versus 10.5$\pm$11.4, 95% CI= 5.2–15.8, $p<0.005$). SLE patients in remission expressed normal levels of PD-L1 on monocytes (mean 24.2$\pm$16.5, 95% CI= 16.5–31.8, $p<0.0005$ versus active SLE). PD-L1 surface expression was induced on a mean of 80% of healthy Mo, whereas fewer Mo from patients with active SLE expressed PD-L1 (mean 52%, $p=0.00003$). ROC curves demonstrated how well PD-L1 expression distinguished between active and inactive disease (AUC 0.75) and between active SLE and healthy controls (AUC 0.79). Patients with renal SLEDAI criteria had a two-fold increase in PD-L1 expression on Mo compared to those without renal disease ($p=0.01$), but no correlation was detected with other clinical characteristics. PD-L1 expression on active SLE Mo could be restored by normal T cells or by supernatant from healthy cells producing IL-10 and/or TNF-α. Both IL-10 and TNF-α secretion correlated with PD-L1 expression, and either cytokine could restore PD-L1 expression on SLE Mo. Conversely, SLE cells over-produced TGF-β, and PD-L1 expression on healthy Mo was suppressed by TGF-β.

Conclusions: During an inflammatory response patients with SLE may be lacking a key step to limit autoreactive lymphocyte activity: the local, cytokine-mediated induction of PD-L1 expression on antigen presenting cells. Moreover, therapeutic agents that inhibit TNF-α may induce autoantibodies in part by preventing PD-L1 induction, thereby impeding an important mechanism of T and B lymphocyte regulation. Infection and other autoimmune diseases may potentially be distinguished from active SLE on the basis of monocyte PD-L1 expression.

Disclosure: A. M. Stevens: None; **J.-N. Ou:** None; **A. Wiedeman:** None.

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RFX1 Regulates CD70 and CD11a Expression by Recruiting the Histone Methyltransferase SUV39H1 in Lupus T Cells. Ming Zhao, Xiaoyan Wu, Fei Gao, Qing Zhang, Heng Yin and Qianjin Lu. Second Xiangya Hospital, Central South University, Changsha, China

Background: Methylation of histone H3 lysine 9 (H3K9) represses gene expression. H3K9 is hypomethylated in $CD4^+$ T cells from systemic lupus erythematosus (SLE) patients, resulting in de-repression of genes involved in promoting auto-immune responses. However, the mechanism leading to H3K9 hypomethylation is unclear. The transcription factor RFX1 normally recruits DNMT1 and HDAC1 in $CD4^+$ T cells but is down-regulated in SLE $CD4^+$ T cells, reducing DNA methylation and histone acetylation and leading to the overexpression of the auto-immune related genes CD70 and CD11a. In this study we measured the methylation of H3K9 at the CD70 and CD11a loci in SLE $CD4^+$ T cells and investigated the involvement of RFX1 in H3K9 hypomethylation.

Methods: Peripheral blood monocytes (PBMCs) from 20 patients with SLE and 20 healthy controls were isolated by Ficoll-Hypaque density gradient centrifugation. $CD4^+$ T cells were isolated by positive selection using CD4 beads (Miltenyi, Bergisch Gladbach, Germany; purity was generally higher than 95%), and cultured in human T cell culture medium (Lonza, Walkersville, MD, USA). H3K9 tri-methylation levels at the CD70 and CD11a promoters were detected by chromatin immunoprecipitation (ChIP) and realtime PCR. SUV39H1 expression level was assessed by Western blot. Interactions of RFX1 with SUV39H1 and G9a were examined

by immunoprecipitation (IP). RFX1 expression and shRNA constructs were transfected into $CD4^+$ T cells using Human T cell Nucleofector kits (Lonza, Walkersville, MD, USA).

Results: Compared with healthy controls, the tri-methylation levels of H3K9 at the CD70 and CD11a promoters were lower in SLE $CD4^+$ T cells ($p < 0.05$). The protein level of the histone methyltransferase SUV39H1 was not different between SLE patients and healthy controls ($p > 0.05$). However, SUV39H1 was found to bind to the promoters of CD70 and CD11a. RFX1 immunoprecipitated with SUV39H1, but not G9a, in $CD4^+$ T cells and lupus $CD4^+$ T cells transfected with RFX1 exhibited an increase of H3K9 tri-methylation levels and decreased expression of CD70 and CD11a. In contrast, knocking down RFX1 expression by using RNAi down-regulated H3K9 tri-methylation levels at the CD70 and CD11a loci and activated their transcription in normal $CD4^+$ T cells.

Conclusions: RFX1 recruits SUV39H1 to the promoters of the autoimmune related genes CD70 and CD11a in $CD4^+$ T cells, and down-regulation RFX1 contributes to H3K9 hypomethylation leading to CD70 and CD11a overexpression in SLE $CD4^+$ T cells.

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The HLA Haplotype DQA1+, DQB1+, DR4- Identifies Lupus Patients in Whom Anti-dsDNA Titers Correlate with Disease Activity. Mikhail Olferiev[1], Kyriakos A. Kirou[1], Dorthe Lundsgaard[4], Klaus S. Frederiksen[3], Jan Fleckner[2] and Mary K. Crow[1]. [1]Hospital for Special Surgery, New York, NY, [2]Novo Nordisk, [3]Novo Nordisk, Denmark, [4]Novo Nordisk, Copenhagen, Denmark

Objective: Anti-dsDNA titers are used by rheumatologists to assist in disease activity assessment of SLE patients. However, anti-dsDNA titers do not always correlate with disease activity. In this study we explored whether SLE patients with anti-dsDNA titers that parallel disease activity [based on SELENA SLEDAI (SS) score] differ in their PBMC transcriptional profile compared to other SLE patients.

Methods: Longitudinal PBMC and plasma samples were obtained over an average 6 visits (2–12) from 23 SLE patients and 5 healthy donors (HD). The duration of study follow-up for individual patients varied from 197 to 812 days. Plasma levels of autoantibodies were evaluated using the Multi-Analyte Profiling (MAP) technology (Rules-Based Medicine, Austin, TX). PBMC transcriptional profiles for each visit were established using Human Genome U133 Plus 2.0 Arrays.

Results: Microarray data analysis revealed 566 differentially expressed transcripts comparing HD samples versus samples of SLE patients during mild/moderate or severe SELENA SLEDAI flares, or those without a flare (ANOVA FC<2.0, $p<0.05$). From 44 tested autoantibodies 14 were significantly upregulated in SLE patients (T TEST and fold change (FC) = $p<0.05$ and >1.5). Eight autoantibodies, including anti-dsDNA, correlated weakly with disease activity based on SS. Nine patients showed high levels of anti-dsDNA autoantibody. Comparative analysis of transcripts between anti-dsDNA positive and negative patients identified 136 differentially regulated transcripts (FC>1.5 and $p<0.05$). Comparative analysis of those transcripts and autoantibody titer showed that anti-dsDNA autoantibodies correlated with multiple interferon signature genes and granulocyte markers (LTF, CEACAM6, MPO, and MMP9). Five SLE patients (22%) showed a strong correlation of anti-dsDNA titer and SS score ($R=0.9$; $p<0.001$). Comparative analysis of transcripts in those individuals compared with the other lupus patients identified 38 transcripts (FC>1.5; $p<0.05$). Of interest, the anti-dsDNA patients were all positive for HLA alleles DQA1, DQB1 and negative for DR4, in contrast to variable alleles for the rest of the patients (Fisher's test $p<0.01$).

Conclusion: SLE patients showing strong correlation of anti-dsDNA titers and disease activity have a distinct MHC class II haplotype. This observation, if confirmed, may help to identify SLE patients in whom anti-dsDNA titers are helpful in management of disease. This genetic background may favor skewing of the autoimmune response toward certain dsDNA epitopes that are particularly pathogenic.

Disclosure: M. Olferiev: None; **K. A. Kirou:** Novo Nordisk, 2; **D. Lundsgaard:** Novo Nordisk, 3; **K. S. Frederiksen:** Novo Nordisk, 3; **J. Fleckner:** Novo Nordisk, 3; **M. K. Crow:** Biogen Idec, 5, Bristol-Myers Squibb, 5, Idera, 2, 5, MedImmune, 2, 5, Novo Nordisk, 2, 5, Roche, 5.

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The Integrity of Double Strand Break Repair in Pediatric Systemic Lupus Erythematosus Cells. Robert C. Davies[2], Kelly Pettijohn[2], Francesca Fike[2], Jiexi Wang[2], Shareef A. Nahas[2], Richard A. Gatti[3] and Deborah K. McCurdy[1]. [1]Mattel Children's UCLA-Rheumatology, Los Angeles, CA, [2]UCLA-Pathology and Laboratory Medicine, [3]UCLA-Pathology and Laboratory Medicine; Human Genetics

Introduction: Our laboratory previously demonstrated a delay in single strand break (SSB) processing in cells from pediatric patients with systemic lupus erythematosus (SLE). Because SSBs are often converted to double strand breaks (DSBs) at the replication fork and some DSB repair proteins are immnunogenic in SLE, i.e., DNA ligase IV, Ku 70/80, DNAPKcs, and XRCC4, we assessed the integrity of DSB recognition, signaling, and repair mechanisms in B-lymphoblastoid cell lines (LCLs) derived from pediatric and adolescent patients with SLE. This study assesses the integrity of DSB recognition, signaling, and repair mechanisms in LCLs derived from 16 pediatric and adolescent patients with SLE (pSLE).

Methods: Lymphoblastoid cells lines (LCLs) were established from the whole blood of 16 pSLE patients. Eight assays were used to assess four major pathways of repair of DSBs in pSLE LCLs. The assays included: (i) γ-H2AX and (ii) 53BP1 IR-induced nuclear foci (IRIF); (iii) immunoblot analysis of the kinetics of IR-induced phosphorylation of Structural Maintenance of Chromosomes 1 (SMC1); (iv) a DNA ligation assay to evaluate the NHEJ (v) neutral comet assay (vi) monoubiquitination of FANCD2 (vii) flow cytometry to assess the S-phase checkpoint; and (viii) colony survival assay as a measure of general radiosensitivity.

Results: Three of eight assays showed abnormal patterns of response to IR-induced DNA damage in some patients: 1) pSMC1 kinetics were intermediate in four patients, suggests defective repair, 2) the neutral comet assay was abnormal in half of the cells, showing delayed DSB repair, 3) colony survival assay showed radiosensitivity in half of the cell lines tested. We also observed reduced DNAPKcs, Ku70 and Ku80 proteins in one pSLE patient.

Conclusion: Our data suggest that DSB repair is compromised in pSLE LCLs as shown in the broad-based DSB repair assays (neutral comet assay, colony survival assay). This contrasts with results from our functional assays (γ-H2AX, 53BP1, NHEJ, FANCD2 monoubiquitination, S-phase checkpoint), which all appear normal. Although the majority of SLE cell lines exhibited DSB repair defects, the etiology of this remains unclear.

Disclosure: R. C. Davies: None; **K. Pettijohn:** None; **F. Fike:** None; **J. Wang:** None; **S. A. Nahas:** None; **R. A. Gatti:** None; **D. K. McCurdy:** None.

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The Lupus Africa to US Gradient Revisited—Genetic Versus Environmental Factors in Lupus. Gary S. Gilkeson[1], Diane L. Kamen[4], Natasha M. Ruth[3], Anna Meyer[2] and Darrius Maggi[5]. [1]Med Univ of South Carolina, Charleston, SC, [2]MUSC, [3]MUSC, Charleston, SC, [4]MUSC PO Box 250637, Charleston, SC, [5]West Africa Fistula Foundation

Background: The Africa to US Lupus Gradient is a widely held belief that lupus is rare in west Africa while common in African Americans. This belief is based on limited assessments in Africa. If true, this gradient would provide novel insight into the genetic versus environmental causation of lupus. Assessing true lupus prevalence in west Africa is impossible at present, we therefore sought to assess prevalence of "autoimmunity", i.e. positive autoantibodies, in lupus unaffecteds.

Methods: Two unique cohorts were utilized for this study: the Gullah population in South Carolina and comparator patients of the West Africa Fistula Foundation in Sierra Leone. Sierra Leone is the ancestral home of the Gullah. All individuals were screened by history and exam to exclude lupus and SLE in a family member. The cohorts are all female and matched for age. Serum was obtained and autoantibody prevalence, viral seropositivity and vitamin D levels tested to assess autoimmunity prevalence and potential environmental factors implicated in lupus. ANA was done by Hep2 IFA, ACL by ELISA, anti-DNA by Crithidia and ENA by Ochterlony. Viral seroconversion was tested by standard ELISAs.

Results: A trend towards decreased ANA positivity that was not significant in the Sierra Leoneans was found (Table). A marked increase in APL positivity was found in the Sierra Leoneans, with no difference in antibodies against dsDNA, Sm, or RNP. Sierra Leoneans had significant increased seropositivity for EBV, CMV, HSV1 and HSV2. In addition there was a significant difference in serum 25OH vit D with a mean of 11ng/ml in the Gullah and 36ng/ml in the Sierra Leoneans. There was a trend towards lower

vitamin D levels in the Sierra Leoneans who were ANA+ >1/120 (mean 32 for ANA+ and 37 for ANA-). There were only three Sierra Leoneans that were seronegative for CMV/EBV and they were ANA-.

	SLEIGH Female Unrelated Controls (N = 122)	Sierra Leone Females (N = 70)	Age Adjusted p-value
ANA Positivity ≥1:40	35.2%	28.5%	NS
ANA Positivity ≥1:120	19.7%	15.7%	NS
ANA Titer >1:1000	3.3%	4.2%	NS
Cardiolipin IgG >20	4.9%	37.1%	<0.01
Cardiolipin IgM >20	0.0%	10.0%	<0.01
dsDNA or Sm positive	0.0%	0.0%	NS
RNP positive	0.8%	0.0%	NS
Ro (SSA) or La (SSB) positive	0.0%	2.8%	NS

Conclusions: Overall, there is a trend towards higher ANA reactivity in the Gullah, while ACL positivity is markedly higher in the Africans, possibly related to infections. Thus, autoimmunity is not significantly less common in Africans; differences in the prevalence of clinical lupus remain to be determined. There is a significant difference in environmental factors implicated in lupus including viral seropositivity and vitamin D levels. Further studies are needed to assess the lupus gradient hypothesis and the potential role of environmental factors in disease development.

Disclosure: G. S. Gilkeson: None; **D. L. Kamen:** None; **N. M. Ruth:** None; **A. Meyer:** None; **D. Maggi:** None.

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The Variant of MHC Class I Polypeptide-Related Sequence (*MICA*) Is a Genetic Risk Factor for SLE Independent of *HLA-DRB1* and Modulates the Behavior of NK Cell *Via* NKG2D Receptor. Kohsuke Yoshida[1], Koichiro Komai[2], Kazuko Shiozawa[7], Aya Mashida[2], Takahiko Horiuchi[6], Yuki Tanaka[4], Masato Nose[5], Akira Hashiramoto[3] and Shunichi Shiozawa[3]. [1]Dept. of Biophysics, Kobe Univ. Graduate School of Health Sciences, Kobe, Hyogo, Japan, [2]Dept. of Biophysics, Kobe Univ. Graduate School of Health Sciences, Kobe, Japan, [3]Dept. of Biophysics, Kobe Univ. Graduate School of Health Sciences/Department of Medicine, Kobe University Graduate School of Medicine/The Center for Rheumatic Diseases, Kobe University Hosp., Kobe, Japan, [4]Dept. of Clinical Immunology, Rheumatology, and Infectious Diseases, Kyushu Univ., Fukuoka, Japan, [5]Dept. of Pathogenomics, Ehime Univ. Graduate School of Medicine, Ehime, Japan, [6]Div. of Genome Analysis, Medicine Institute of Bioregulation, Kyushu Univ., Fukuoka, Japan, [7]Rheumatic Diseases Center, Konan-Kakogawa Hosp., Kakogawa, Japan

Purpose: MIC (MHC class I polypeptide-related sequence) molecules interacts with NKG2D (natural-killer group 2, member D) and stimulates NK cells to release cytokines such as IFNγ and to exert cytotoxicity against its cellular targets. The expression of MICA is normally restricted to the intestinal and thymic epithelium, but is often aberrantly expressed on rheumatoid synovial cells or peripheral blood $CD14^+$ monocytes in patients with SLE. The *MICA* gene is located within the human leukocyte antigen (HLA) locus, and its exon5 coding transmembrane (TM) region contains a polymorphic microsatellite, which is classified according to the number of alanine-encoding GCT repeats as A4, A5, A5.1, A6 and A9. A single nucleotide polymorphism (SNP) at codon 129 in exon 3 of the *MICA* gene, Val129Met (rs1051792), has been shown to modulate the affinity of MICA to the NKG2D receptor. We previously showed that MICA 129Met and A9 alleles are genetically associated with the Japanese patients with SLE (Arthritis Rheum. 58: suppl (9). S815, 2008), but the genetic linkage between *MICA* 129, TM polymorphism and *HLA-DRB1* in patients with SLE and the effect of MICA polymorphism on the function of NK cell remain unclear. Here, we show that *MICA* 129Met/A9 is a genetic risk factor for Japanese patients with SLE independent of *HLA-DRB1* and modulates the behavior of NK cell *via* NKG2D receptor.

Methods: Japanese patients with SLE (n = 677) or controls (n = 350) were genotyped for *MICA* Val129Met (rs1051792), TM polymorphism and *HLA-DRB1*. The recombinant MICA-GST fusion proteins 129Val/A5 or 129Met/A9, which combine polymorphisms at 129Val and TMA5 or 129Met and TMA9, respectively, were tested on NK cell line NK92MI for the expression of NKG2D receptor, NK cell-mediated cytotoxicity against K562 target cells and IFNγ production.

Results: The *MICA* 129Met/A9 allele was significantly increased in the patients with SLE as compared with control: 178/647 (27.5%) vs. 56/321 (17.4%) ($P < 0.001$; OR = 1.6). Importantly, the frequency of *MICA* 129Met/A9 allele was also significantly increased in the patients with SLE: 24/100 (24.0%) vs. 31/234 (13.2%) ($P = 0.01$; OR = 2.2) as in the case with the population negative for the *HLA-DRB1 *1501* previously indicated as the risk allele for SLE in the Japanese population. When the disease-associated MICA 129Met/A9 protein was incubated with NK92MI cells, it significantly suppressed both the expression of cell surface NKG2D on NK92MI cells and the NK cell-mediated cytotoxicity against K562 cells more strongly than those with the most prevalent non-disease-associated MICA 129Val/A5 ($P < 0.05$ and $P < 0.01$, respectively). These findings are consistent with previous findings showing that NK cell cytotoxicity is significantly decreased in SLE. Interestingly, we also observed that the 129Met/A9 protein enhanced the release of IFNγ from NK92MI cells as compared with 129Val/A5 protein ($P < 0.01$), possibly because *MICA* 129Met variant has been shown to be higher affinity to the NKG2D receptor than the 129Val variant.

Conclusion: The MICA polymorphism is genetically associated with SLE independent of *HLA-DRB1**1501, and MICA appears to contribute to the pathogenesis of SLE by modulating NK cell function.

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ACR Poster Session A
Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment I
Monday, November 8, 2010, 9:00 AM–6:00 PM

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Acute Anterior Uveitis in Ankylosing Spondylitis: Clinical Characteristics and Impact of Biologic Therapy. Nai Lee Lui[1], Finbar (Barry) D. O'Shea[3], Hua Shen[2], Richard J. Cook[2] and Robert D. Inman[4]. [1]Department of Rheumatology and Immunology, Singapore General Hospital, Singapore, [2]Department of Statistics and Actuarial Science, University of Waterloo, Canada, [3]St James's Hospital, Dublin, Ireland, [4]Toronto Western Hospital, Toronto, ON, Canada

Objective: To describe the characteristics of acute anterior uveitis (AAU), impact of biologic therapy on the incidence of AAU and to indentify predictors of AAU flare in an ankylosing spondylitis (AS) prospective longitudinal cohort.

Methods: We conducted a retrospective study of all AS patients developing AAU in a longitudinal AS cohort. All patients met the modified New York criteria for AS. Demographics and clinical characteristics (age of AS and AAU onset, HLA-B27 status) were recorded. Recurrence rates and impact of anti-TNF therapy were evaluated. Logistic regression analysis was used to determine predictors of AAU flare.

Results: Among the 464 AS patients, 132 patients with history of AAU were evaluated (28.4%). The mean age at onset of AAU is 31.7 years, higher than the age of AS onset (22.5) and diagnosis of AS (30.2) respectively. 10.2% (N=9) of patients developed AAU prior to the onset of AS symptoms, with a mean of 2.9 ± 2.4 years; while 77.3% (N=68) developed AAU after a mean of 11.5 ± 6.4 years following the onset of AS symptoms. There was no difference in the occurrence of AAU in male or female patients (p=0.19). 88.6% (N=109) of patients with AAU were associated with the HLA-B27 gene (OR 2.39, p=0.01). AS patients with history of AAU had more frequent enthesitis (p=0.024) but did not appear to require more anti-TNF therapy compared to AS patients without AAU (54.9% versus 45.1%; p=0.47). Following the commencement of anti-TNF, the AAU flare rate was 3.69 flares per 100 patient-yr compared to 15.72 flares per 100 patient-yr in AS patients who were treated with non-steroidal anti-inflammatory drugs (NSAIDs). There was no differential association with any particular biologic agent in 12 patients who developed AAU while on anti-TNF therapy. There was no correlation of indicators of higher AS disease activity (ESR, CRP, BASDAI or BASFI scores) at the time of AAU flares.

Conclusion: HLA-B27 is a strong predictor of AAU in AS patients. Higher incidence of enthesitis in AAU patients may suggest a potential similarity in the underlying pathogenic process between the two sites. Biologic therapy reduced the incidence of AAU. The incidence of AAU flare while on anti-TNF therapy is low and did not correlate with AS disease activity.

Disclosure: N. L. Lui: None; **F. D. O'Shea:** None; **H. Shen:** None; **R. J. Cook:** None; **R. D. Inman:** None.

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Ankylosing Spondylitis: High Frequency of Varicocele Associated with Teratozoospermia. Lucia A. Nukumizu[5], Carla G. S. Saad[5], Breno P. de Almeida[5], Jozélio F. Carvalho[5], Marcello Cocuzza[2], Celio R. Goncalves[5], Osmar Saito[1], Eloisa Bonfa[3] and Clovis A. A. Silva[4]. [1]Department of Radiology - Faculdade de Medicina da Universidade de São Paulo, Brazil, [2]Department of Urology - Faculdade de Medicina da Universidade de São Paulo, Brazil, [3]Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [4]Pediatric Reumatology Unit, Faculdade de Medicina da Universidade de São Paulo, Brazil, [5]Rheumatology Division - Faculdade de Medicina da Universidade de São Paulo, Brazil

Purpose: To assess testicular function in male ankylosing spondylitis (AS) patients and controls.

Methods: 20 consecutive post-pubertal AS patients (modified New York criteria) were prospectively assessed for demographic data, urologic examination, testicular Döppler ultrasound (US), standardized semen analysis according to World Health Organization (WHO) guidelines and Kruger strict criteria, and anti-sperm antibodies. Selection criteria never under biological agents were included; sulfasalazine and methotrexate wash-out period of at least 3 months and no restriction to the use of non-steroidal anti-inflammatory drugs and/or low dose prednisone (≤ 10mg/day). The evaluation of AS included: clinical features, laboratory exams, treatment and scores (BASDAI, BASFI, BASMI and BASRIt). The control group consisted of 24 male healthy subjects.

Results: The median of current age was similar in AS and controls (31.5(23–44) vs. 34(17–53)yrs, p=0.353). The frequencies of left or bilateral varicoceles by clinical examination and by US were significantly higher in AS patients compared to controls (30% vs. 4%, p=0.035; 40% vs. 8%, p=0.027). Likewise, the median of vein diameters of pampiniform plexus in left testicles were significantly higher in AS patients *versus* controls (0.25(0.16–0.49) vs. 0.2(0.2–0.37)cm, p=0.009). Of note, the median of normal sperm forms by Kruger strict criteria was significantly lower in AS patients *versus* controls [3.25(0–14.5) vs. 6.75(0–18), p=0.035) and the frequency of teratozoospermia (abnormal sperm morphology) was significantly higher (55% vs. 8% p=0.0001). Reinforcing these findings, the median of normal sperm morphology by WHO guidelines was significantly lower in AS patients with ultrasonographic varicoceles compared to patients without varicoceles [13.5(2–27) vs. 22(10–32.5)%, p=0.049]. In addition, the median of normal sperm morphology by WHO guidelines and by Kruger strict criteria were alike in AS patients *versus* controls without ultrasonographic varicoceles (p>0.05). No differences were observed in penis median length and circumference in AS patients and controls, and testicular (left and right) by way of US in both groups (p>0.05). The median and frequencies of other parameters of sperm analysis and anti-sperm antibodies were comparable (p>0.05) in AS patients and controls. The demographic data, clinical findings and laboratory exams were also similar in AS patients with ultrasonographic varicoceles compared to patients without varicoceles (p>0.05), likewise tem median of BASDAI (4.21(1.66–6) vs. 3.95(1.04–8.68), p=0.899), BASFI (4.06(1.4–7.79) vs. 3.77(0–8.41), p=0.819), BASMI (4.5(0–7) vs. 6(0–8), p=0.486) and BASRIt (9(6–16) vs. 10(5–16), p=0.463).

Conclusions: This is the first demonstration that AS patients have a high frequency of varicoceles associated with isolated teratozoospermia. Further studies are necessary to determine if oxidative stress may underlie this testicular dysfunction in AS, since high levels of reactive oxygen species were reported to have a harmful effect in sperm quality of men with varicocele.

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Application of Composite Disease Activity Scores in Psoriatic Arthritis to the PRESTA Dataset. Oliver M. FitzGerald[3], Philip Helliwell[5], Aizad Mumtaz[4], Laure Coates[5], Ronald Pedersen[2] and Charles T. Molta[1]. [1]Pfizer, Inc., Paoli, PA, [2]Pfizer, Inc., Collegeville, PA, [3]University College Dublin, Ranelagh Dublin, Ireland, [4]University College Dublin, Dublin, Ireland, [5]University of Leeds, Leeds, United Kingdom

Objectives: A number of rheumatoid arthritis composite disease activity indices have been used in clinical trials in psoriatic arthritis (PsA). Two composite disease activity measures have recently been proposed for PsA, but further validation is required. The purpose of this study is to compare the performance of the Composite Psoriatic Disease Activity Index (CPDAI) and the Disease Activity Index for Psoriatic Arthritis (DAPSA) in the PRESTA dataset, a large (N=752) randomised, double-blind, two-period study which evaluated the safety and efficacy of 2 doses of etanercept in the first study period on skin and joint disease in psoriasis subjects with active PsA.

Methods: Using the data obtained from the PRESTA study, the components of the CPDAI (4 domains, including joints [66 swollen/68 tender joint counts; HAQ]; skin [PASI; DLQI]; dactylitis [each digit rated 0 to 3]; and enthesitis [number of tendons showing enthesitis, 0–4, based on Achilles tendons and plantar fasciae bilaterally] and the DAPSA (patient global; pain assessment; 66/68 swollen and tender joint counts; and C-reactive protein [CRP]) were extracted. The performance of the scores at baseline and follow-up (weeks 12 and 24) was compared and also between the 2 treatment schedules (etanercept 50 mg QW v 50 mg BIW). Spearman correlations and both univariate and stepwise regression analyses were also used.

Results: Both CPDAI and DAPSA could distinguish response to treatment comparing baseline and 12- or 24-week values (<0.0001). CPDAI, and not DAPSA, could distinguish response in the 2 treatment groups at 12 weeks (p=0.0492) but not at 24 weeks. All domains contributed to the data variability of the CPDAI, with dactylitis (r=0.64) and enthesitis (r=0.60) the most significant. Joint scores (SJC: r=0.8; TJC: r=0.91) contributed most to the variability in DAPSA. For change in CPDAI from baseline, stepwise regression revealed that change in enthesitis, DAS28, HAQ, dactylitis and DLQI were most significantly associated. For change in DAPSA, change in all of the 5 components were significantly associated.

Conclusions: Both CPDAI and DAPSA are effective in determining treatment response in patients treated with etanercept for active psoriasis and psoriatic arthritis. Joint responses were equally reflected by both composite scores but CPDAI, which better reflects other domains such as skin, enthesitis and dactylitis, is the only composite score which can distinguish global treatment response between the 2 etanercept doses.

Disclosure: O. M. FitzGerald: Abbott Laboratories, 8, Pfizer Inc, 2, 8; **P. Helliwell:** Pfizer Inc, 2, 8; **A. Mumtaz:** None; **L. Coates:** Pfizer Inc, 2, 8; **R. Pedersen:** Pfizer Inc, 1, 3; **C. T. Molta:** Pfizer Inc, 1, 3.

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Association of BMI and Psoriatic Arthritis Disease Activity. Elena Eberle[2], Eric Knight[2], Donald A. Raddatz[2], Susan Messing[5], George Reed[4], Jeffrey D. Greenberg[1] and Joel M. Kremer[3]. [1]Millburn, NJ, [2]Bassett Healthcare, Cooperstown, NY, [3]The Center for Rheumatology, Albany, NY, [4]University of Massachusetts, Worchester, MA, [5]University of Rochester, Rochester, NY

Background: Obesity may induce a low-grade chronic inflammatory state. Adipocytes are involved in the recruitment and activation of macrophages, which produce TNF-alpha, IL-6, and IL-12. Studies have also shown an association between body mass index (BMI) and gouty arthritis and osteoarthritis of the hand joints. Psoriatic arthritis (PsA) patients have a significantly higher mean BMI and prevalence of obesity compared to population-based means. Therefore, we hypothesized that there may be an association between BMI and PsA disease activity.

Methods: We selected patients with PsA from the CORRONA database for a cross-sectional study. BMI was presented as a categorical and continuous variable. Patients were categorized into quartiles by weight including "Normal Weight" (BMI>=18.5, <25), "Overweight" (BMI>=25, <30), "Obese" (BMI>=30, <40), and "Morbidly Obese" (BMI>=40). Our primary outcomes were 28 tender joint count (TJC) and 28 swollen joint count (SJC). The secondary outcomes were physician global assessment of disease activity (PGDA), physician global assessment of skin involvement (PGSI), mHAQ, ESR, and CRP. We used Poisson regression models to investigate associations as relative risks between BMI categories and tender and swollen joint counts. Generalized estimating equations, employing a robust sandwich estimator for the variance of the beta weights, were used to assess the associations expressed as beta weights for secondary outcomes of interest.

Results: 1980 patients with PsA were identified from the CORRONA registry. 781 participants had ESR values and 593 individuals had CRP values. The majority of the patients had between 1 and 5 tender joints (80%) and between 1 and 5 swollen joints (82%). ESR in the obese quartile was 6 mm/h higher than the normal weight quartile and almost 10 mm/h higher in the morbidly obese quartile.

Table 1. Association between weight quartiles and tender joint count (TJC) and swollen joint count (SJC). Data are presented as relative risk (RR) per 1 joint increase with 95% confidence interval (CI). Normal Weight quartile (n = 344) serves as the reference group.

Primary Outcomes	Overweight (n = 636)	Obese (n = 702)	Morbidly Obese (n = 298)
TJC	1.00 (CI 0.81–1.24)	1.35 (CI 1.10–1.65)	1.53 (CI 1.22–1.93)
SJC	1.01 (CI 0.82–1.26)	1.30 (CI 1.06–1.60)	1.59 (CI 1.26–2.00)

Table 2. Association between weight quartiles and physician global assessment of disease activity (PGDA), physician global assessment of skin involvement (PGSI), mHAQ, ESR, and CRP. Normal Weight quartile (n = 344) serves as the reference group.*

Secondary Outcomes	Overweight (n = 636)	Obese (n = 702)	Morbidly Obese (n = 298)
PGDA	2.1339 (SE 1.2690) *p = 0.09*	4.2249 (SE 1.2570) *p = 0.0008*	5.9451 (SE 1.5377) *p = 0.0001*
PGSI	0.1544 (SE 0.0632) *p = 0.0147*	0.3077 (SE 0.0638) *p < 0.0001*	0.3103 (SE 0.0778) *p < 0.0001*
mHAQ	0.0218 (SE 0.0235) *p = 0.35*	0.1230 (SE 0.0244) *p < 0.0001*	0.2020 (SE 0.0327) *p < 0.0001*
ESR	0.2730 (SE 1.6003) *p = 0.86*	6.0946 (SE 1.7701) *p = 0.0006*	9.6867 (SE 2.1573) *p < 0.0001*
CRP	0.8044 (SE 1.0156) *p = 0.42*	0.7853 (SE 0.7853) *p = 0.39*	2.1585 (SE 1.5958) *p = 0.17*

* The beta weight expresses the rate of change in the outcome for the column BMI quartile vs. the Normal Weight quartile.

Conclusion: BMI>=30 was strongly associated with a higher disease activity in patients with PsA. This association may be the result of the induction of inflammation by adipose tissue as we found a positive relationship between ESR and obesity. There is presently limited recognition of this relationship amongst clinicians. Expanded investigations of the biologic factors associated with obesity and disease activity are needed in patients with Psoriatic arthritis.

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Can We Discontinue Anti-TNF Therapy in Patients with Ankylosing Spondylitis and Remission? A Systematic Literature Review. Miguel A. Abad[3], Ana M. Ortiz[2], Estibaliz Loza[1], Juan A. Martinez Lopez[1], Maria P. Rosario[1] and Loreto Carmona[1]. [1]Fundación Española de Reumatología, Madrid, Spain, [2]Hospital Universitario de la Princesa, Madrid, Spain, Spain, [3]Rheumatology Unit, Hospital Virgen del Puerto, Plasencia, Spain, Spain

Background: The introduction of anti-TNF agents has changed the management of patients with Ankylosing spondylitis (AS). At present there is no doubt about the efficacy of anti-TNF agents: Infliximab (IFX), etanercept (ETN) and Adalimumab (ADA) in controlling symptoms of AS. However, it is unclear which should be the attitude once patients have achieved remission.

Objectives: To analyze the effect of discontinuing anti-TNF therapy in AS patients who achieved complete remission, and to assess whether the readministration would be effective and safe in case of relapse.

Methods: We conducted a systematic literature search for studies published up tol January 2009 on the efficacy of IFX, ETN and ADA in AS in Medline, Embase and the Cochrane Central databases. Selection criteria were: a)Type of study: clinical trials with any quality level (according to Jadad scale), b)Participants: patients with AS; c)Intervention: IFX, ETN or ADA d) Outcome: clinical relapse (according to ASAS criteria), time to relapse, effectiveness and safety after readministration of anti-TNFs. Two reviewers screened the titles and abstracts of the retrieved articles for selection criteria independently and collected the data by using ad hoc standard forms. One of them also graded the quality of the selected studies using a modification of the Oxford Centre for Evidence-based Medicine Levels of Evidence in its May 2001 update. A hand search was completed by reviewing the references of the included studies.

Results: We identified a total of 406 titles, of which 390 were excluded after reading the title and abstract. The final number of selected studies for a detailed review was 16. Finally 9 were excluded and 6 included (1 was a randomized controlled trial, 1 an open trial and the other 4 were follow-up studies) 2 evaluated ETN, 4 IFX. We did not found studies regarding ADA.

After the discontinuation of IFX in AS patients who achieved remission, almost 100% relapsed. The mean time to relapse was 17.5 weeks ± 7.9 weeks (range 7–45). Patients who were in partial remission and those with normal C-reactive protein levels at the time point of withdrawal had longer times to relapse. Retreatment with IFX was safe and the clinical improvement was similar to that before the treatment was stopped.

All of AS patients on ETN relapsed after treatment cessation. The median time to recurrence after discontinuation was 6.2 weeks ± 3 weeks, with relapse at 3 months 75% and 100% 9 months. Retreatment with ETN was efficacious and safe after readministration over 1 year in patients with active AS.

Conclusion: The discontinuation of IFX leads to a relapse in almost all of AS patients who achieved remission within weeks or few months (level of evidence 1b, grade of recommendation A). The reinfusion of IFX in AS patients is safe, and the clinical improvement is comparable to the observed before the discontinuation (level of evidence 4, grade of recommendation C).

The discontinuation of ETN leads to a relapse in almost all of AS patients who achieved remission within weeks or few months (level of evidence 1b, grade of recommendation A). The reintroduction of ETN achieved similar clinical response to that observed previously (evidence level 4, recommendation grade C).

Disclosure: M. A. Abad: Abbott Laboratories, 9; **A. M. Ortiz:** Abbott Laboratories, 9; **E. Loza:** Abbott Laboratories, 9; **J. A. Martinez Lopez:** Abbott Laboratories, 9; **M. P. Rosario:** Abbott Laboratories, 9; **L. Carmona:** Abbott Laboratories, 9.

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Clinical and Demographic Characterization of a Colombian Cohort of Patients with Diagnosis of Spondylarthritis. Wilson A. Bautista[1], John Londoño[3], Marlon Porras[3] and Rafael R. Valle[2]. [1]Military Hospital, Division of Rheumatology, Bogota, Colombia, [2]Military Hospital, Division of Rheumatology, Bogota, Colombia, [3]Military Hospital, Division of Rheumatology, Bogota, Colombia

Purpose: The Spondyloarthropaties are a heterogeneous group of diseases characterized by axial as well as peripheral enthesitis and arthritis. Their presentation and clinical course is influenced by ethnicity, age at onset and sex; and share certain clinical features and laboratory findings, according to the population group. Given genetic susceptibility, environmental and socio cultural characteristics in our region, the clinical manifestations are different. Our objective is to describe clinical and demographic characteristics of a cohort of patients with spondyloarthropaties in our country.

Method: Data was collected from a database of Rheumatology Service; which includes the clinical and paraclinical information related to the disease. The patients were evaluated following the ASAS recommendations. Patient demographics, disease duration, family and personal history, clinical pattern (axial, peripherical), and HLA status were recorded. Questionnaires were administered for functional status (Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI). All analyses were performed using SPSS software.

Results: 282 patients with spondyloarthropaties were identified. 69.6% were men with a mean age of 35.9 years. The main characteristics are as follows: 99 (35.1%) with Ankylosing Spondylitis, 111 (39.4%) with Undifferentiated Spondyloarthritis, 51 (18.1%) with Reactive Arthritis, 10 (3.5%) with Psoriatic Arthritis and 1 (0.4%) with Inflammatory Bowel Disease associated to Spondyloarthritis. 9 patients (3.2%) did not have a specific diagnostic. In 244 (86.5%) patients who had HLA report, 146 (51.8%) were negative and 98 (34.8%) positive. 77 patients were B15 positive.

According to the form of disease onset, 92 patients (32%) had axial involvement, 98 (34.8%) had peripheral and 79 (28%) mixed onset. When we analyzed the data according to initial symptoms, we found that arthritis was the initial manifestation in 80 (28.4%) patients, enthesopathy in 17 (6%), back pain in 98 (34.8%), uveitis in 4 (1.4%) and buttock pain in 2 (0.7%) patients. In 70 patients (24.8%) several initial symptoms were presented to the onset of the disease. Inflammatory back pain was present in 215 (76.2%) patients. The average age of onset of symptoms was 28 with a minimum of 11 and maximum of 71. In addition, we found a history of infection in 30.1% of patients mainly acute diarrheal disease. Only 6.1% of the patients had known family history of spondiloarthritis. Also we evaluate the functional status and level of activity of the disease, using the BASFI and BASDAI questionnaires at the time of examination. The main BASDAI score was 5.53 and main BASFI score was 5.26.

Conclusion: The clinical and demographic presentation of Spondylarthri-

tis in our region compared to other pupulation groups is different. The subgroup of undifferentiated form is the more frequent clinical presentation and the history of infection is remarkable. Enrollment continues to increase the cohort and characterize the population.

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Comparison of ASAS Partial Remission and Low ASDAS as Indicators of Remission-Like States in Ankylosing Spondylitis. Desiree van der Heijde[4], Joachim Sieper[3], Steve Brown[2], Frederic Lavie[1] and Aileen Pangan[2]. [1]Abbott Laboratories, Rungis, France, [2]Abbott Laboratories, Abbott Park, IL, [3]Charité Universitätsmedizin Berlin, Berlin, Germany, [4]Leiden University Medical Center, Leiden, The Netherlands

Introduction: Definition of remission in patients with Ankylosing Spondylitis (AS) has previously been based on the ASAS partial remission (ASAS PR) criteria. More recently, the AS Disease Activity Score (ASDAS) was developed and cut-offs validated, including low ASDAS (<1.3) as indicator of a remission-like state.

Objective: To compare the performance of ASAS PR and low ASDAS in identifying patients in remission in the 5-year ATLAS (Adalimumab Trial Evaluating Long-Term Efficacy and Safety for AS) clinical trial and to determine potential causes of observed differences in response rates.

Methods: Patients were randomized to receive adalimumab (ADA) 40 mg every other week (wk) or placebo (PBO) during a 24-wk double-blind period, followed by an open-label extension of up to 236 wks (total of 5 years). Efficacy and safety were assessed throughout the study. We evaluated the proportion of patients achieving ASAS PR, low ASDAS, ASDAS clinically important improvement (CII, decrease of at least 1.10 from baseline) and ASDAS major improvement (MI, decrease of at least 2.00 from baseline) at weeks 12 and 24 using a non-responder imputation analysis; and at weeks 52, 104 and 260 using observed analysis. Because ASDAS is calculated using the same components as the ASAS PR except for BASFI, plus the addition of CRP and peripheral pain/swelling (BASDAI Question 3), we also determined if baseline BASFI and mSASSS scores contributed to the observed differences in ASAS PR and low ASDAS response rates.

Results: ATLAS enrolled 315 patients (208 ADA, 107 PBO). Only patients in the ADA arm could have received 5 years of ADA therapy. At week 12 there were more subjects in the ADA arm compared with PBO who achieved ASAS PR (20.7% vs. 3.7%, $P<0.001$), low ASDAS (36.5% vs. 2.8%, $P<0.001$), CII (61.5% vs 17.8%, $P<0.0001$) and MI (39.9% vs. 3.7%, $P<0.0001$). At 1, 2, and 5 years of ADA exposure, the response rates (%) were higher for the 3 ASDAS-based response criteria compared with ASAS PR: (N, low ASDAS, CII, MI, ASAS PR) – 1 year (N=282, 42%, 69%, 47%, 33%); 2 years (N=261, 53%, 77%, 53%, 38%); 5 years (N=124, 61%, 87%, 65%, 51%). Higher baseline BASFI and mSASSS were noted for subjects who achieved low ASDAS but not ASAS PR, compared with those who achieved both low ASDAS and ASAS PR (Table 1). Even higher baseline BASFI and mSASSS were noted for those who did not fulfill either criteria. BASFI was the most frequently observed ASAS component to have not met the required value of <20 in the sub-group "low ASDAS +/ASAS PR -."

Duration of Adalimumab Exposure	*low ASDAS*	*ASAS PR*	*Mean (SD) Baseline BASFI*	*Mean (SD) Baseline mSASSS*
1 Year				
Any ADA (N = 79)	+	+	42.85 (19.93)	12.75 (14.52)
Any ADA (N = 39)	+	−	51.84 (20.78)	20.55 (20.04)
Any ADA (N = 149)	−	−	61.53 (20.88)	25.67 (21.68)
Any ADA (N = 15)	−	+	48.52 (19.20)	15.64 (19.74)
2 Years				
Any ADA (N = 90)	+	+	44.03 (19.09)	12.25 (14.16)
Any ADA (N = 47)	+	−	55.79 (20.80)	24.76 (22.11)
Any ADA (N = 114)	−	−	61.06 (21.70)	25.77 (22.54)
Any ADA (N = 10)	−	+	62.49 (20.56)	17.50 (15.58)
5 Years				
Any ADA (N = 55)	+	+	42.23 (17.55)	12.77 (14.49)
Any ADA (N = 20)	+	−	54.27 (25.61)	25.19 (23.77)
Any ADA (N = 41)	−	−	62.44 (18.80)	27.60 (24.33)
Any ADA (N = 8)	−	+	62.35 (16.23)	24.29 (18.33)

Conclusion: Low ASDAS detects more subjects in a remission-like state and allows for better differentiation between active treatment (ADA) and placebo than ASAS PR. This is likely due to the inclusion of BASFI in ASAS PR criteria, which may not reflect response to effective therapies if irreversible damage and functional disability are present.

Disclosure: D. van der Heijde: Abbott Laboratories, 5, Amgen Inc., 5, Bristol-Myers Squibb, 5, Centocor, Inc., 5, Chugai, 5, Merck Pharmaceuticals, 5, Novartis Pharmaceuticals Corporation, 5, Pfizer Inc, 5, Roche, 5, sanofi-aventis, 5, Schering-Plough; **J. Sieper:** Abbott Laboratories, 2, 5, 8, Bristol-Myers Squibb, 2, 5, 8, Centocor, Inc., 2, 5, 8, Merck Pharmaceuticals, 5, 8, Novartis Pharmaceuticals Corporation, 5, 8, Pfizer Inc, 2, 5, 8, Roche, 2, 5, 8, sanofi-aventis, 5, 8, Schering-Pl; **S. Brown:** Abbott Laboratories, 1, 3; **F. Lavie:** Abbott Laboratories, 1, 3; **A. Pangan:** Abbott Laboratories, 1, 3.

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Complex Assessment of Subclinical Vascular Disease Associated with Ankylosing Spondylitis. Nóra Bodnár[3], György Kerekes[2], Zoltan Szekanecz[1], Ildiko Seres[4], György Paragh[4], Pál Soltész[2], Gabriella Szücs[3] and Sándor Szántó[3]. [1]University of Debrecen Med Ctr, Debrecen, Hungary, [2]University of Debrecen Medical and Health Sciences Center, Department of Medicine, [3]University of Debrecen Medical and Health Sciences Center, Department of Rheumatology, [4]University of Debrecen Medical and Health Sciences Center, First Department of Medicine

Background: There have been recent studies indicating that ankylosing spondylitis (AS), as well as rheumatoid arthritis, may be associated with accelerated atherosclerosis and vascular disease.

Objectives: Here we assessed endothelial dysfunction, carotid atherosclerosis and aortic stiffness in AS in context with several clinical and laboratory parameters.

Methods: Forty-three AS patients and 40 matched healthy controls were studied. We assessed common carotid intima-media thickness (ccIMT), flow-mediated vasodilation (FMD) and pulse-wave velocity (PWV) in association with age, disease duration, smoking habits, body mass index, patient's assessment of pain and disease activity, BASDAI, BASFI, metric parameters, ESR, CRP and HLA-B27 status.

Results: We found impaired FMD (6.85±2.98 versus 8.30±3.96 %; p=0.005), increased ccIMT (0.65±0.15 versus 0.54±0.15 mm; p=0.01) and higher PWV (8.64± 2.44 versus 8.00±1.46 m/s; p=0.03) in AS patients compared to controls. ccIMT negatively correlated with FMD (r=−0.563; p=0.0001) and positively correlated with PWV (r=0.374; p=0.018). In addition, both ccIMT and PWV correlated with disease duration (r=0.559; p=0.013 and r=0.520; p=0.022, respectively), BASFI (r=0.691; p=0.003 and r=0.654; p=0.006, respectively), decreased lumbar spine mobility (r=−0.656; p=0.006 and r=−0.604; p=0.013, respectively) and chest expansion (r=−0.502; p=0.047 and r=−0.613; p=0.012, respectively) and increased wall-occiput distance (r=0.509; p=0.044 and r=0.614; p=0.011, respectively).

Conclusion: In this well-characterized AS population, impaired FMD, increased ccIMT and PWV indicate abnormal endothelial function, increased atherosclerosis and aortic stiffness, respectively. The early determination of FMD, ccIMT and PWV may be useful to assess and treat AS patients with high cardiovascular risk.

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Correlates of Physical Function in Axial Spondylarthropathy: Fear of Movement as an Independent Contributor. Thijs Swinnen[3], Johan Vlaeyen[4], Wim Dankaerts[1], Rene Westhovens[5] and Kurt de Vlam[2]. [1]Department of Rehabilitation Sciences, Catholic University of Leuven, Leuven, Belgium, [2]Department of Rheumatology, University Hospitals Leuven, Sint Martens Leerne, Belgium, [3]Department of Rheumatology, University Hospitals Leuven, Department of Rehabilitation Sciences, Catholic University of Leuven, Leuven, Belgium, [4]Research Group on Health Psychology, Catholic University of Leuven, Department of Clinical Psychological Science, Maastricht University, Leuven, Belgium, [5]University Hospitals Leuven, Department of Rehabilitation Sciences, Catholic University of Leuven, Leuven, Belgium

Purpose: To establish the independent contribution of the psychological attribute "fear of movement and (re)injury" in explaining physical function in a large cohort of patients with axial Spondylarthropathy (aSpA).

Methods: We collected measures of anthropometrics (Body Mass Index), gender, disease duration, the use of medication (Biologicals and NSAIDs), physical function (Bath Ankylosing Spondylitis Functional Index), stiffness

(averaged items 5 and 6 of the Bath Ankylosing Spondylitis Disease Activity Index), pain (Numerical Rating Scale), spinal mobility (Bath Ankylosing Spondylitis Metrology Index) and fear of movement and (re)injury (Tampa Scale for Kinesiophobia[1]) in 126 patients with aSpA. We used a stepwise multiple linear regression modeling approach with physical function as the dependent variable. Because the assessment of fear of movement in aSpA is new, we checked for the Tampa Scale for Kinesiophobia's normal distribution and internal consistency with the Shapiro-Wilk and Cronbach's Alpha tests respectively. The level of significance was set at.05 for all analyses.

Results: Spinal mobility (mean=3.3;stβ=.409;p=.000), pain (mean=3.6;stβ=.347;p=.000), stiffness (mean=3.8;stβ=.277;p=.000), fear of movement and (re)injury (mean=25.6;stβ=.175;p=.000), the use of biologicals (no=0/yes=1:61/65;stβ=.118;p=.011) and gender (male=0/female=1:80/46;stβ=.103;p=.032) contributed significantly to physical function (mean=3.9). Disease duration (13.3years;p=.517), anthropometrics (mean=26.3;p=.273) and the use of NSAIDs (no=0/yes=1:52/74;p=.632) were not entered during the stepwise analysis. Pain partially mediated the effect of fear of movement on physical function as evidenced by simple mediation (Sobel test;p=.000) and after controlling for all other modeled variables in our mediation model (bootstrapping procedure;95% confidence interval=.0103-.0503). Our potent model on correlates of physical function explained as much as 76% of the variance (adjusted R^2) without violating any assumption of regression modeling. The Tampa Scale for Kinesiophobia scores were normally distributed (p=.348) and showed a good internal consistency (α=.81).

Conclusion: Fear of movement and (re)injury is an important contributor to physical function beyond traditional disease-specific outcome measures in patients with aSpA. The Tampa Scale for Kinesiophobia appears to be an appropriate instrument to assess fearful beliefs related to movement and (re)injury. Further exploration in this area is both justified and needed.

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DC-STAMP (Dendritic Cell-Specific Transmembrane protein), a Potential Biomarker To Predict the Risk of Psoriasis Patients in Developing Psoriatic Arthritis. Yahui Grace Chiu[1], Sutha Shanmugarajah[3], Ben Panepento[1], Lihi Eder[2], Vinod Chandran[2], Dafna Gladman[2], Sharon Moorehead[1], Rick Barrett[1] and Christopher T. Ritchlin[1]. [1]AIR Unit, University of Rochester, Rochester, NY, [2]UHN-Toronto Western Hospital, Toronto, ON, Canada, [3]UHN-Toronto Western Hospital, Toronoto, ON, Canada

Purpose: 20% of psoriasis (Ps) patients (pts) develop psoriatic arthritis (PsA) within 10 years of Ps onset. Identification of an arthritis biomarker in Ps pts would facilitate early intervention and possibly delay and/or prevent onset of PsA. Previously, we reported an increased frequency of circulating osteoclast precursors (OCP) in one third of Ps pts without arthritis. We hypothesized that DC-STAMP (Dendritic Cell-Specific Transmembrane protein), a transmembrane protein that is required for the fusion of monocytes during osteoclast (OC) formation, may serve as an arthritis susceptibility biomarker in Ps.

Methods: We previously identified 4 major DC-STAMP expression patterns in human PBMC with an anti-DC-STAMP antibody by flow cytometry. Most healthy controls have low OCP and show DC-STAMP pattern I, whereas PsA pts demonstrate elevated OCP and are more likely to manifest DC-STAMP pattern IV. We analyzed DC-STAMP expression patterns by flow cytometry and OCP frequency in cultured monocytes in a longitudinal cohort of 24 Ps pts. They were assessed by rheumatologists based on standard criteria and did not have PsA. They have been followed for 3 years on average.

Results: Table 1 summarizes the baseline clinical features, DC-STAMP patterns and frequency of OC in 24 pts. Two, 6, 10, 6 Ps pts manifested DC-STAMP pattern I, II, III, and IV, respectively (column (a) & (b)). The OCP frequency (mean±standard deviation) is shown in column (c). Within 3 years, 2 pts developed PsA by the CASPAR criteria (column (f)). Their demographics and clinical variables are depicted in Table 2.

Table 1.

(a) DC-STAMP Pattern	(b) # of subjects	(c) OCP frequency (per 10^6 monocytes)	(d) Average of age	(e) PASI score	(f) # of pts develop PsA
I	2	47 ± 25	62	4.6	0
II	6	279 ± 365	57	2.9	0
III	10	380 ± 398	49	8.2	1
IV	6	1063 ± 954	36	4.1	1

Table 2.

Subject	Gender	Age	DC-STAMP pattern	OC frequency (per 10^6 monocytes)	PASI score 3 years ago	PASI score after arthritis onset	Years from Ps to PsA
#1	Female	58	III	580	3.5	3.1	5.7
#2	Female	48	IV	1185	6.6	12.2	4.7

Conclusions: Data from this longitudinal cohort registry suggest that DC-STAMP is a potential marker to predict development of PsA in Ps pts. Two pts who developed PsA have DC-STAMP pattern III and pattern IV, the most common patterns seen in PsA pts. Additional studies are required to further define the potential of DC-STAMP as an arthritis susceptibility biomarker.

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Development and Validation of a Questionnaire for Evaluation of Spondyloarthritis Related Manifestations in the First Degree Relatives of Patients with Ankylosing Spondylitis. Roozbeh Sharif[4], John D. Reveille[6], Michael H. Weisman[1], Michael M. Ward[2], Laura A. Diekman[4], Mamatha Hanumanthaiah[5] and Shervin Assassi[3]. [1]Cedars-Sinai Medical Center, Los Angeles, CA, [2]NIH, NIAMS, IRP, Bethesda, MD, [3]Univ of Texas Health Science, Houston, TX, [4]Univ of Texas Health Science Center Houston, Houston, TX, [5]Univ of Texas Health Science Center Houston, [6]Univ Texas Health Sci Ctr, Houston, TX

Background: Previous studies have shown increased frequency of spondyloarthritis (SpA) related phenotypes in the first-degree relatives (FDR) of patients with Ankylosing Spondylitis (AS). However, large scale familial aggregation studies have been hampered by difficulties in screening and diagnosis confirmation. Our goal was to develop and validate a self-administered tool to evaluate the presence of SpA manifestations in the FDRs of AS patients.

Methods: A multidisciplinary team of rheumatologists, ophthalmologists, epidemiologists, and patient focus groups were involved in the design of the questionnaire. The low back pain questions were developed in close collaboration with the CDC/NHANES 2009 group and modified for utilization as a self-administered instrument. In the validation step, family members of AS patients completed the questionnaire and were subsequently examined by a rheumatologist at the study sites. A pelvic X-ray was obtained if inflammatory back pain (IBP) symptoms were present. We compared the questionnaire (method 1) to the physician evaluation (method 2) for each SpA manifestation and for the IBP criteria by Rudwaleit. IBP was defined as presence of at least 2/4 IBP criteria in conjunction with chronic lower back pain ($>$ 3 months) and age at symptom onset $\leq$ 50 years. The agreement and equivalency between the questionnaire and study site assessments were examined by Kappa statistics and Nam's equivalency test.

Results: Ninety one FDRs of AS patients with mean age of 50.7 (±16.6) years were enrolled, consisting of 36 parents, 28 siblings, and 27 children. Overall, 56% of study subjects were female and 87% were Caucasians. We confirmed IBP in 27, AS in 10, Achilles' tendonitis in 25, peripheral arthropathies due to SpA in 7, uveitis in 6, psoriasis in 4, reactive arthritis (ReA) in 2 study subjects. No case of inflammatory bowel disease was reported. As shown in Table, the agreement rates ranged from 76.9% to 98.9% between two modes of acquisition. The assessment for inflammatory back pain, Achilles' tendonitis, uveitis, psoriasis and reactive arthritis showed good to very good agreement between the questionnaire and site visit results. Furthermore, the questionnaire had adequate sensitivity and specificity for all SpA manifestations except for peripheral arthritis secondary to SpA. Particularly, the sensitivity and specificity of the instrument for capturing IBP according to Rudwaleit criteria was 81.8% and 88.4%, respectively. More

importantly, IBP per questionnaire had a sensitivity of 80% and specificity of 77% for AS as confirmed at the site visit.

Conclusion: These findings suggest that the developed questionnaire captures the SpA manifestations including AS with adequate diagnostic accuracy. This raises the possibility of utilization of this instrument for screening the FDR's of AS patients for SpA manifestations.

	Agreement	Expected agreement	Kappa	Nam's test of equivalence	Sensitivity	Specificity
Inflammatory back pain	86.81%	61.07%	0.6613	0.085	81.8%	88.4%
Achilles' tendonitis/ Plantar Fasciitis	85.71%	60.64%	0.6370	0.021	72%	90.9%
Peripheral Arthritis 2nd to SpA	93.26%	87.40%	0.4649	0.016	42.9%	97.6%
Uveitis	97.80%	87.68%	0.8216	0.001	83.3%	98.8%
Psoriasis	97.80%	89.59%	0.7889	0.007	100%	97.7%
Reactive Arthritis	98.90%	94.56%	0.7946	0.002	100%	98.9%
Low back pain screen question	79.12%	50.31%	0.5798	0.314		
Morning stiffness more than 30 Minutes	89.01%	59.09%	0.7314	0.073		
Improvement with Exercise but not Rest	76.92%	61.68%	0.3977	0.043		
Awakening in only in 2nd Half of the Night	86.81%	72.44%	0.5215	0.032		
Alternating Buttock pain	90.11%	76.30%	0.5828	0.012		

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Differences in Body Mass Index among Individuals with Psoriatic Arthritis, Psoriasis, Rheumatoid Arthritis, and the General Population. Vidula M. Bhole[1], Hyon K. Choi[5], Lindsay C. Burns[1], Cristián Vera Kellet[2], Diane V. Lacaille[1], Dafna D. Gladman[3] and Jan P. Dutz[4]. [1]Arthritis Research Centre of Canada, Vancouver, BC, Canada, [2]Department of Dermatology, Pontificia Universidad Católica de Chile, Santiago, [3]Toronto Western Hospital, Toronto, ON, Canada, [4]Univ of BC, Vancouver, BC, Canada, [5]Univ of British Columbia, Vancouver, BC, Canada

Purpose: To compare the adiposity among individuals with psoriatic arthritis (PsA), psoriasis (Ps), rheumatoid arthritis (RA), and general population (N), as well as identify correlates of adiposity among individuals with Ps and PsA.

Method: We included: 1) 448 dermatologist-diagnosed Ps patients and 2) 644 rheumatologist-diagnosed PsA patients from the International Psoriasis and Arthritis Research Team (IPART) database; 3) 350 RA patients who participated in a longitudinal study of RA care; and 4) the general population from Canadian Community Health Survey 3.1. All PsA cases met the Classification of Psoriatic Arthritis (CASPAR) criteria. We compared the body mass index (BMI) among the four groups (PsA, Ps, RA, N) using analysis of variance (ANOVA) and performed all pairwise comparisons using Tukey's test. We performed age-and-sex adjusted linear regression analyses using BMI as a continuous outcome, as well as logistic regression analyses using obesity ($\geq$30 kg/m^2) as a dichotomous outcome. We conducted multivariate analyses limited to Ps and PsA groups to determine the independent correlates of increased adiposity in these patients.

Results: The mean BMI (kg/m^2) for individuals with PsA, Ps, RA, and the general population were 29.6, 27.9, 27.3, and 26.1, respectively.

Table 1. Demographics and Body Mass Index (BMI) of the Study Population

	PsA	Ps	RA	N
N	644	448	350	115787
Age	50	47	65	50
Sex, female	41%	42%	68%	53%
BMI, mean (SD)	29.6 (7.3)	27.9 (5.7)	27.3 (6.0)	26.1 (5.0)

The differences in BMI were significant for all the categories (ANOVA p <0.0001, Tukey test p<0.05) except those between Ps and RA. Adjustments for age and sex using linear and logistic regressions did not change the results materially (all p values <0.0001). In the multivariate linear regression analysis limited to Ps and PsA groups, after adjustments for age, sex, smoking, Ps duration, Psoriasis Area Severity Index (PASI) score, DMARDs, glucocorticoids and biologics; BMI of PsA remained higher than that of Ps by 1.54 kg/m^2 (95% CI: 0.63–2.56). In similar multivariate logistic regression analyses, the odds ratio of obesity increased by 50% in those with PsA compared to those with Ps (95% CI: 1.09 – 2.05). Age, smoking, PASI score, glucocorticoid use, and female gender were significantly associated with a higher BMI or increased odds of obesity in patients with Ps or PsA.

Conclusion: BMI is higher in PsA (skin and joint disease) than that in Ps (skin disease), RA (joint disease) or the normal population. Furthermore, our results suggest that the BMI difference between PsA and Ps is independent of other risk factors of obesity. Other significant correlates of increased BMI or obesity among individuals Ps or PsA were age, smoking, PASI score, glucocorticoid use, and female gender.

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Disease Activity Assessment by ASDAS Doesn't Predict Sacroiliac Inflammation with MRI in Axial SpA. Sibel Z. Aydin[2], Alex Bennett[1], Paul Emery[2], Dennis McGonagle[2] and Helena Marzo-Ortega[2]. [1]Defence Medical Rehabilitation Centre, Headley Court, Epsom, Surrey, [2]Section of Musculoskeletal Diseases, The Leeds Institute of Molecular Medicine. University of Leeds, UK

Objective: The ASDAS (Ankylosing spondylitis disease activity score) is a newly developed composite index to measure disease activity in AS. It incorporates items of back pain, morning stiffness, patient global assessment of disease activity, pain/swelling of the peripheral joints and the CRP using a weighted formula. In the present study we aimed to test the construct validity of ASDAS comparing it with active inflammation of the sacroiliac joints (SIJs) as shown by MRI.

Methods: Twenty-three patients (n=23) with axial SpA according to the ASAS criteria were included. All patients were questioned for the parameters included in ASDAS and had an MRI scan of the SIJs. ASDAS values were categorized according to the different cut-off levels recently presented at OMERACT 10 and compared to the MRI findings according to the guidance of ASAS proposals. Further scoring to identify patients with severe MRI sacroiliitis (grade 3 according to the Leeds MRI SIJ Scoring System) and total MRI scores (sum of scores at all quadrants with a maximum score of 24) were also available.

Results: All patients had active disease according to ASDAS (scores >1.3).

Table 1. Distribution of ASDAS according MRI findings

Disease activity according to ASDAS	ASDAS cut off levels	Positive MRI (n)		Severe sacriolitis by MRI (n)		MRI scores median (range)
		+ n = 18	− n = 5	+ n = 4	− n = 19	
inactive disease	<1.3	0	0	0	0	NA
moderate activity	1.3–2.1	2	1	1	2	5 (0–16)
high activity	2.1–3.5	7	2	1	8	1 (0–18)
very high activity	>3.5	9	2	2	9	2 (0–12)
		p = NS		p = NS		p = NS

Moderate disease was found in 13%, 39 % had active and 48 % had very active disease. No relationship was found between the different states of disease activity according to ASDAS and MRI findings, including severity of the MRI. Similarly, ASDAS levels were found comparable in groups with/without sacroiliitis by MRI (3.5 ±1.1 vs 3.1±0.9, p=0.5, respectively) and severe sacroiliitis by MRI (3.5 ±1.8 vs 3.4±0.9, p=0.8, respectively). MRI scores were also independent from ASDAS categories.

Conclusion: Besides the clinical benefits of ASDAS, there does not appear to be a relationship between ASDAS and the presence of bone marrow oedema on MRI at the SIJ of axial SpA patients.

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Estimation of Optimal Cutt-Off Point of Ankylosing Spondylitis Disease Activity Score (ASDAS), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Mini-BASDAI. Ruxandra Schiotis[7], Eliza Muñoz Gomariz[3], Juan Mulero[5], Xavier Juanola[4], Janitzia Vazquez-Mellado[1], Percival D. Sampaio-Barros[2] and Eduardo Collantes[6]. [1]Department of Rheumatology, General Hospital of México, México City, [2]Division of Rheumatology, University of São Paulo, [3]Instituto Maimónides de Investigación Biomédica/Hospital Universitario Reina Sofia, Cordoba, Spain, [4]Rheumatology Department, H. U. Bellvitge, Barcelona, [5]Rheumatology Department, Hospital Puerta de Hierro Majadahonda. Madrid, Spain, [6]Rheumatology Department, Hospital Reina Sofía. Córdoba, Spain, [7]University of Medicine and Pharmacy Iuliu Hatieganu, Cluj-Napoca, Romania

Objective: To estimate the best optimal cut-off point of Ankylosing Spondylitis Disease Activity Score (ASDAS), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and modified BASDAI (mini-BASDAI) in a large population of patients with ankylosing spondylitis (AS)

Methods: The analysis was performed in two large cohorts of patients from two registries of spondylarthropaties patients: REGISPONSER (Spain) and RESPONDIA (Latin-America). For performing further analyzes patients were divided in two subgroups with and without peripheral arthritis: (1) AS peripheral and (2) AS axial. The optimal cut-off point of the three activity disease indexes was estimated with the ROC curves. The discrimination between active and inactive disease was performed with the area under the curve ROC. The "gold standard" used in our analysis was the physician global assessment obtained on a numerical rating scale (NRS).

Results: The optimal cut-off point for ASDAS, BASDAI and mini-BASDAI were as follows: 2.68; 4.24 and 5.14 respectively. ASDAS cut-off point statistical significantly discriminated active disease compared to BASDAI (P=0.015) and mini- BASDAI (P=0.002). The same tendency of ASDAS cut-off in discriminating active disease was found in both "AS peripheral" and in "AS axial" although, significant statistical difference was encountered only in the "AS axial group"(ASDAS vs BASDAI, P=0.027 and ASDAS vs mini-BASDAI, P=0.040). Higher activity scores were found in "AS peripheral group" for all three studied indexes.

Conclusion: ASDAS is a validated instrument that offers a high discriminatory capacity of active disease when compared with BASDAI and mini-BASDAI, for all presenting AS forms. ASAS should be the preferred score in assessing AS patients in daily practice.

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Evaluation of the New ASAS Instrument To Assess Disease Activity, the ASDAS, in Patients with Ankylosing Spondylitis Treated with TNF Blockers over 8 Years. Xenofon Baraliakos[4], Claudia Fritz[2], Joachim Listing[2], Joachim Sieper[1] and Juergen Braun[3]. [1]Charite Campus Benjamin Frankl, Berlin, Germany, [2]German Rheumatism Research Center, [3]Rheumazentrum Ruhrgebiet, Herne, Germany, [4]Rheumazentrum Ruhrgebiet Herne

Background: Currently used clinical parameters for assessment of disease activity (BASDAI) or response to therapy (BASDAI50%, ASAS20% and 40%) in patients with AS mainly rely on patient′s opinion. The Spondyloarthritis International Society (ASAS) has recently developed a new disease activity score, the ASDAS, which includes clinical measures and CRP and has a high discriminatory capacity for assessing disease activity in AS.

Objective: To compare the performance of established tools with the new instrument, the ASDAS, in a longterm clinical of continuous anti-TNF therapy with infliximab in patients with active AS (n=33) after 3, 5 and 8 years.

Methods: According to recent data, an ASDAS <1.3 was considered as 'inactive', 1.3–2.1 as 'moderate', 2.1–3.5 as 'high' and > 3.5 as very high disease activity. An ASDAS change >1.1 was defined as 'minimally important improvement' and ≥2 as 'major improvement', as recently proposed.

Results: The mean BASDAI decreased from 6.4±1.9 at baseline to 2.3±2.0 at 3y (64% decrease), to 2.4±2.0 at 5y (63% decrease), and to 2.6±1.9 (59% decrease) at 8y (all p<0.05). In comparison, the ASDAS decreased from 4.3±0.8 at BL to 1.5±1.0 (65% improved) at 3y, to 1.6±1.0 at 5y and to 1.6±0.9 at 8y (63% decrease).

Overall, a BASDAI < 3 was achieved by 22/33 patients (66.7%) at 3y and by 21/33 patients (63.6%) at 5y and 8y years. In comparison, at 3y, 5y and 8y, an ASDAS<1.3 was found in 15 (46%), in 13 (39%), and in 17 (52%) patients, respectively. An ASDAS between 1.3–2.1 was seen in 11 (33%), in 13 (39%) and 6 (19%) patients after 3y, 5y and 8y, respectively. An ASDAS between 2.1–3.5 was found in 6 (18%), in 9 (27%) and in 9 (27%) after 3y, 5y and 8y, respectively and an ASDAS ≥3.5 was seen in only 1 (3%) patient at all time points. The comparison of different outcome parameters for change is shown in Table 1.

Conclusions: The ASDAS, a new composite disease activity score for AS proposed by the ASAS, was more sensitive than the conventional scores for disease activity and change, confirming recent data on short-term outcomes. More studies are needed to establish the ASDAS as a standard tool for assessment of disease activity in patients with AS in clinical practice.

Response parameter	3 years (n = 33 Pat.)	5 years (n = 33 Pat.)	8 years (n = 33 Pat.)
ASAS 20%	93.9% (31)	81.8% (27)	84.8% (28)
ASAS 40%	72.7% (24)	66.7% (22)	63.6% (21)
BASDAI 50%	66.7% (22)	69.7% (23)	63.6% (21)
ASAS Part. Remission	39.4% (13)	36.4% (12)	24.2% (8)
ASDAS impr. > 1.1	97.7% (32)	90.9% (30)	93.9% (31)
ASDAS impr. ≥ 2.0	72.7% (24)	66.7% (22)	69.7% (23)

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Evolution of Familial Spondyloarthritis (SPA) without Radiographic Sacroiliitis over Time: Results of a Prospective Follow Up Study. Nadine Zeboulon-Ktorza[3], Roula Said-Nahal[1], Maria-Antonietta D'Agostino[3] and Maxime Breban[2]. [1]Hôpital Ambroise Paré, Assistance Publique Hôpitaux de Paris, Boulogne-Billancourt, France, [2]Hôpital Ambroise Paré, Assistance Publique Hôpitaux de Paris, Boulogne-Billancourt, France; INSERM Unité 1016; Université Versailles Saint Quentin en Yvelines, F-78000, Versailles, France, [3]Hôpital Ambroise Paré, Assistance Publique Hôpitaux de Paris, Boulogne-Billancourt, France; Université Versailles Saint Quentin en Yvelines, F-78000, Versailles, France

Background: Transversal study of familial SPA shows that all subtypes of SPA, (i.e. ankylosing spondylitis (AS), SPA associated with psoriasis or inflammatory bowel disease (IBD), with or without radiographic sacroiliitis, and undifferentiated SPA (uSPA)) coexist in families, and that longer disease duration correlates with higher frequency of radiographic sacroiliitis (Arthritis Rheum. 2000;3:1356). It was previously suggested that the various subtypes of familial SPA may correspond to different stages of the same disease but this remains as yet unproven. Only longitudinal study could properly address this question.

Material and Methods: The study population consisted of an adult (≥ 16 years) cohort of familial SPA fulfilling Amor's criteria and/or European Spondylarthropathy Study Group criteria, without definite radiographic sacroiliitis at inclusion (i.e. ≥ grade 2 bilateral or ≥grade 3 unilateral, according to the New York modified criteria). Patients underwent thorough clinical evaluation, and a pelvic radiograph at the inclusion and at the end of follow up, which lasted 5 to 15 years. Blinded films were read by 2 expert examinators. Univariate and multivariate logistic regression were performed to identify factors present at inclusion which could predict the evolution of SPA without definite sacroiliitis and evolution of uSPA to a differentiated form, and notably to AS.

Results: Of the initial cohort consisting of 150 non-radiographic SPA followed more than 5 years, analysis were performed on 83 patients (68.7% of females; 93.7% HLA-B27+; 71.1% of uSPA, 25.3% with psoriasis, 3.6% with IBD) with available pelvic radiograph at the end of follow up. At inclusion, age (mean ± SD) was 43.1 ± 13.5 years and disease duration was 14.8 ± 12.1 years. The mean duration of follow up was 8.3 ± 2.2 yrs. At the end of follow-up, definite radiographic sacroiliitis (i.e. AS) was detected in 21.7% of the patients (7.2% with psoriasis). Of the remaining patients, 21.7% had psoriasis, 9.6% IBD and 47.0% had uSPA. Of 59 initial uSPA, 20 (33.4%) developed a differentiated form of SPA: 13 (65.0%) AS (1 with psoriasis), 4 (20.0%) non-radiographic SPA with psoriasis, 3 (15.0%) non-radiographic SPA with IBD. The only factor at inclusion that was moderately but significantly associated with a higher risk to develop radiographic sacroiliitis was a disease duration < 10 years: Odds Ratio = 0.26 (95% Confidence Interval 0.09–0.77).

Conclusion: This prospective study conducted on familial SPA without definite radiographic sacroliiitis at inclusion shows for the first time that a

substantial proportion of them develop AS and that uSPA tends to evolve to differentiated form over time. This validates the hypothesis that distinct subtypes of familial SPA correspond to different stages of the same disorder.

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Frequency of Iridocyclitis at Onset in a Large Series of Patients with Early Psoriatic Arthritis. Fabrizio Cantini[2], Carlotta Nannini[2], Emanuele Cassarà[2], Olga Kaloudi[2], Massimo Susini[1] and Laura Niccoli[2]. [1]Ophthalmology Unit, Hospital of Prato, Prato, Tuscany, Italy, [2]Rheumatology Unit, Hospital of Prato, Prato, Tuscany, Italy

Background: The occurrence of iridocyclitis (IC) in early psoriatic arthritis (PsA) has been rarely assessed [1,2].

Objective: Primary end-point was to evaluate the frequency of IC at onset in a large cohort of p. with early PsA.

Methods: We evaluated the frequency of IC in a clinical series of consecutive, new outpatients with early PsA observed between January 2000 and December 2009. All p. met the CASPAR criteria for PsA and had a disease duration ≤12 months. The demographic and clinical information were stored in a computed database. At baseline sex, age at diagnosis, date of diagnosis, articular and extra-articular manifestations, laboratory assessments [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), HLA B27], radiological evaluation (sacro-iliac joints X-ray, and MRI), were assembled. The following clinical patterns were considered: peripheral PsA (oligoarthritis ≤4 and polyarthritis ≥5 involved joints), axial PsA (Calin's criteria for inflammatory spinal pain, radiographic or MRI evidence of sacroiliitis), mixed (concomitant axial and peripheral features). IC diagnosis was accepted in presence of typical ocular signs/symptoms and ophthalmology examination. Therapy was standardized as previously reported[3]. P. were followed by the same rheumatologist, and follow-up visits were scheduled at baseline and every 4 months. Control visit intervals were shortened in the case of urgent clinical problems, and all p. were instructed to call the centre in presence of worsening of previous arthritis, additional joint involvement, extra-articular manifestations onset, adverse events (AEs).

Results: 242 p., 137 (57%) women and 105 (43%) men with a mean age of 50.33±11.7 ys and a mean duration of symptoms of 9.38±3.1 months were studied. Peripheral pattern was observed 132 (51%) p., axial in 41 (17%) and mixed in 69 (28%). Mean ESR and CRP were 31±18 mm/h and 1.83±2.28 mg/dl respectively. A total number of 26 episodes of IC were recorded at diagnosis in 22 (9%) p., 17 (77.3%) females and 5 (22.7%) males; 11 (50%) p. had peripheral PsA, 2 (9.1%) axial and 9 (40.9%) mixed; 5/22 (22.7%) p. were B27 positive. IC recurred in 2/22 (9%) p. over the follow up. Mean follow-up duration was 4.6±3.5 years. Multiple logistic regression analysis did not disclose any significant association with IC for all demographic, clinical, and laboratory variables.

Conclusion: IC occurred in 9% of 242 p. with early PsA. This frequency is higher than previously reported. IC was not associated with the PsA clinical pattern and B27 positivity.

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Hip Involvement Concerns 18% of Spondyloarthritis Patients, Is Often Bilateral and Total Joint Replacement Leads to Good Functional Results in These Patients. Vincent Burki, Simon Paternotte, Muriel Elhai, Isabelle Fabreguet, Eugenie Koumakis, Magali Meyer, Judith Payet, Fanny Roure, Laure Gossec and Maxime Dougados. Paris Descartes University, Cochin Hospital, Paris, France

Background: Hip involvement is a common but little studied feature of spondyloarthritis (SpA).

Objective: To study the prevalence and clinical features of hip involvement, in a cohort of patients with spondylarthritis (SpA) in a tertiary care center.

Methods: *Study design*: retrolective single center observational study in 2010 (COSPA). *Patients*: definite SpA (Amor's criteria). Each patient underwent direct interview by a physician. *Data collection*: prevalence of hip involvement, and if present, the date of appearance, the localization and nature of the pain, treatments performed (intra-articular injections, surgery) and outcomes of total joint replacement (TJR). *Analysis*: descriptive analysis.

Results: To date, 148 consecutive SpA patients were assessed: 26/148 patients (18%) suffered from SpA-associated hip involvement; median age 44.2 (range 25.9–69.4) years, median symptom duration 23.5 (5–51) years, 22 (85%) were men, 22/24 (92%) were B27 positive. 22/26 (85%) of patients with hip involvement had been treated by anti TNF at data collection versus 65/120 (54%) of other patients. Hip involvement appeared during the first 5 years of disease duration in 68% and during the first 10 years in 81%. Prevalence varied according to SpA predominant manifestation: more frequent in axial patients (20%, 22/110), than in peripheral disease (14%, 4/29). Hip involvement was bilateral in 46% (12/26) and unilateral in 54% (14/26); 11 patients (46%) received intra articular corticoid injections (of which, 23% were triamcinolone hexacetonide). In all, 9 patients (6% of the whole group and 36% of patients with hip involvement) had a TJR; the median delay between first hip symptoms and TJR was 36 months (range 0–27 years). After a median follow-up of TJR of 101 months (range 2– 27 years), TJR was considered as having a good function in 100% and only 22% (2/9) patients had TJR complications with a second TJR of the hip for both of them.

Conclusion: Hip involvement occurs in 18% of our SpA patients; hip involvement seems to start usually in the first 10 years of the disease (81% of our patients) with almost equal bilateral or unilateral involvement. TJR is still the best treatment at the moment for serious destruction, with good results even if corticoid intra articular injections are used to retard it.

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HLA-Cw*06 Allele Increases the Duration of Time between the Onset of Psoriasis and Psoriatic Arthritis. Lihi Eder[2], Vinod Chandran[2], Fawnda Pellett[2], Sutha Shanmugarajah[2], Hua Shen[3], Richard Cook[3] and Dafna D. Gladman[1]. [1]Toronto Western Hospital, Toronto, ON, Canada, [2]University of Toronto Psoriatic Arthritis Clinic, Toronto Western Hospital, [3]University of Waterloo

Aim: Most of the patients with psoriatic arthritis (PsA) develop arthritis following the onset of the skin disease, with a mean duration of approximately 7 years. It was suggested recently that the risk of developing PsA remains constant after the diagnosis of psoriasis. We aimed to investigate whether the rate of PsA after the onset on psoriasis is constant and whether it is affected by clinical and genetic factors.

Methods: We performed a retrospective cohort analysis of patients with PsA and psoriasis without arthritis. The PsA patients were part of a large single centre longitudinal cohort. The psoriasis patients were recruited from a recently established prospective cohort of psoriasis without arthritis. They were assessed annually by a rheumatologist to rule out PsA. Only patients that developed arthritis after the onset of psoriasis were included. We analyzed the rate of PsA cases per year from the onset of psoriasis. Patients with psoriasis alone were censored at their last visit to the clinic. Parametric survival analysis was used to determine the probability model that predicts the risk of developing PsA after the onset of psoriasis. The following variables were tested for their effect on the interval of time from psoriasis to PsA: HLA-C*06, HLA-B*27, gender, type I vs. II psoriasis.

Results: 438 patients with psoriasis and 769 patients with PsA were included in the study. The mean age at onset of psoriasis and PsA were 26.8±14.7 and 37.3±13.3 years. The sex ratio was 1.3:1 (male: female). The proportion of type I psoriasis was 82.8%. 36% of the participants were carriers of HLA-Cw*06 allele and 11% of the participants were carriers of HLA-B*27 allele. The mean time from the onset of psoriasis to development of PsA was 12.2±10.7 years. The estimated annual probability of PsA was fit with an exponential probability model, suggesting that the risk of developing PsA over time was constant. Tests for trend did not suggest any evidence of departure from a constant hazard. HLA-Cw*06 carriers were associated with longer intervals of time between psoriasis and development of PsA (Relative Risk 0.54, 95% Confidence Interval 0.37–0.78, p=0.001). HLA-B*27, type of psoriasis and gender were not found to affect the time interval between psoriasis and PsA.

Conclusions: The risk of developing PsA over time among psoriasis patients is constant. HLA-Cw*06 allele doubles the duration of time between the onset of psoriasis and PsA.

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Hypertension and Diabetes Significantly Enhance the Risk for Cardiovascular Disease in Patients with Psoriasic Arthritis (PsA). Maria Helena Sampaio Favarato[1], Carla Gonçalves Saad[2], Célio Roberto Gonçalves[2], Percival Degrava Sampaio-Barros[2] and Claudia Goldenstein-Schainberg[2]. [1]Rheumatology, HC-FMUSP, São Paulo, Brazil, [2]Rheumatology, HC-FMUSP

New evidence has lightened the linkage between psoriatic arthritis (PsA) and the development of atherosclerosis and cardiovascular disease (CVD) events.

Objective: To describe the prevalence of cardiovascular events and associated risk factors among patients with PsA from a tertiary hospital.

Methods: Retrospective evaluation of medical records from all current patients who fulfilled the CASPAR criteria for PsA attending a specialized spondyloarthritis clinic at a universitary tertiary hospital.

Results: 158 PsA patients, 48.73% females and 51.27% males, aged 53.67 ± 13.89 yrs (52.61± 14.96yrs for women and 54.69 ± 12.80yrs for men, p= 0.34). Mean joint disease duration was 13.7 ± 8,92yrs. Cutaneous psoriasis preceded articular involvement in 53%, was concomitant in 38% and followed joint disease in 9%. Polyarticular subtype was the most common presentation accounting for 42% of PsA patients, while peripheral olygoarticular involvement occured in 20%, axial + peripheral polyarticular in 18%; pure axial disease in 12% and axial + peripheral olygoarticular in 8% of cases. According to drug therapy, 32 (20%) were under the action of anti-TNFagents, 94 (60%) were taking metothrexate, 18 (11%) leflunomide, 13 (8%) sulfasalazine, 5 (3%) other immunossupressors and 4 (2.5%) chloroquine; 85 (54%) were using NSAIDs and 21 (13%) were on low-dose prednisone. Over half patients (87patients, 55%) had arterial hypertension (AH) and 23% (36) had diabetes mellitus (DM). Statins were being used by 32% (51) cases. Lipid profile was similar for men and women revealing total cholesterol mean levels of 186.5±38.6mg/dl, LDL=112.3±30.6mg/dl, HDL= 47, 89 ± 14,6 and total triglycerides = 127.4±65.6mg/dl. Mean CRP levels was 9,13 ± 16,25. Remarkably, 14% (n=XX) PsA patients have had CVD, namely cerebrovascular or coronary heart disease. Sex, age, disease duration, joint involvement subtype, CRP and lipids levels were similar among patients with and without CVD. Notably, the prevalences of AH and DM were significantly higher ($p<0.001$) in the group of PsA patients who have had CVD, conferring an odds ratio of 5.44 for AH, of 3.27 for DM and of 8,32 for both.

Conclusion: We have shown for the first time that despite psoriasis has recently been recognized as an independent CV risk factor, traditional risk factors such as AH and DM are important in the enhancement of the incidence of CVD in PsA patients. Therefore, early recognition and specific treatment of AH and/or DM is mandatory in order to prevent CVD in PsA patients

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Identification of the Clinical Features That Can Distinguish between Psoriatic Polyenthesitis and Fibromyalgia. Antonio Marchesoni[6], Valentina Varisco[6], Fabiola Atzeni[7], Antonio Spadaro[3], Ennio Lubrano[5], Salvatore D'Angelo[10], Alberto Cauli[4], Carlo Salvarani[8], Giuseppe Provenzano[2], Raffaele Scarpa[9], Daniela Melchiorre[1], Piercarlo Sarzi Puttini[7], Ignazio Olivieri[10], Mariangela Atteno[9], Monica Montepane[3], Gabriele De Marco[6], Laura Rotunno[6] and Maria Manara[6]. [1]AOUC University of Florence, Italy, [2]CTO Hospital, Palermo, Italy, [3]Department of Clinical and Medical Therapy, Sapienza-University of Rome, Italy, [4]Department of Medical Sciences, University of Cagliari, Italy, [5]Fondazione Maugeri, IRCCS, Telese Terme, Italy, [6]G.Pini Orthopedic Institute, Milan, Italy, [7]L. Sacco University Hospital, Milan, Italy, [8]Reggio Emilia Hospital, Italy, [9]Rheumatology Research Unit, University Federico II Naples, Italy, [10]San Carlo Hospital of Potenza, Italy

Background and Purpose: As polyenthesitic psoriatic arthritis (PsA) is sometimes hard to distinguish from fibromyalgia (FM), secondary FM in PsA patients and PsA in FM patients can be misdiagnosed. The purpose of this study was to identify which clinical features can help distinguish between polyenthesitic PsA and FM.

Materials and Methods: This was a multicentre cross-sectional study carried out by 10 Italian tertiary Rheumatologic (8 recruiting PsA patients and 2 FM patients) centres from January 2009 to September 2009. All of the consecutives patients with PsA (CASPAR criteria) and FM (ACR criteria) who accepted to participate to the study were enrolled in it. For each patient all of the standard clinical and laboratory data, including the questionnaires for PsA and FM, were collected. For the statistical analysis, Student's t test, χ^2 test, Fisher's exact test, univariate and multivariate logistic regression, and Receiving Operating Characteristic (ROC) curves, were used as appropriate.

Results: Two-hundred-sixty-two PsA patients (122 females and 140 males, mean age 51.9±12.8, mean disease duration 10.1±9.2 years) and 96 FM patients (89 females and 7 males, mean age 50.6±1.8, mean disease duration 5.4±4.1 years) were enrolled in this study. Eighteen (6.9%) PsA patients met the classification criteria for FM. Tender and swollen joint counts, dactylitis count, ESR and CRP, and response to NSAIDs were significantly higher in the PsA group. Inflammatory back pain, HAQ values, and PtGA scores were comparable in the two groups. Enthesitis score, tender point count, morning stiffness, VAS pain by patient, and all of the typical symptoms of FM (headache, irritable bowel syndrome, sleep disturbances, paresthesias, anxiety, depression, Raynaud's phenomenon) were significantly associated with FM. However, using the univariate logistic regression, the ORs of morning stiffness, anxiety, and depression were not statistically different between the two groups. The ROC curves showed that 6 or more FM-associated symptoms (sens. 93%, spec. 86%) and 8 ore more tender points (sens. 93%, SPEC 82%) had the best performance in identifying FM patients. The multivariate logistic regression (table 1) showed that 6 or more FM-associated symptoms, 8 or more tender points, and no response to NSAIDs were significantly predictive of FM.

Table 1. Multivariate logistic regression of the main features associated with FM

Feature	OR	95% IC	p
Female gender	0.88	0.23–3.40	0.853
FIQ	1.01	0.98–1.03	0.624
VAS pain	1.00	0.97–1.02	0.798
FM symptoms ≥6	20.05	7.15–56.23	0.000
Enthesitis score ≥3	0.53	0.20–1.44	0.212
Tender points ≥8	16.49	4.62–58.86	0.000
No response to NSAIDs	6.37	1.52–26.71	0.011

Conclusions: Number of FM-associated symptoms, number of tender points, and response to NSAID can help distinguish between polyenthesitic PsA and FM.

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Impact of Environmental Factors on Disease Activity in Spondyloarthritis (SPA): Results of the Prospective Co-Env Cohort. Nadine Zeboulon-Ktorza[9], Pierre-Yves Boelle[6], Roula Said-Nahal[1], Maria Antonietta D'Agostino[7], Jean-Francois Vibert[6], Emmanuelle Durand[1], Homa Madrakian[1], Odile Launay[3], Alfred Mahr[2], Antoine Flahault[4], Thomas Hanslik[8] and Maxime Breban[5]. [1]Assistance Publique Hôpitaux de Paris, Hôpital Ambroise Paré, F-92100, Boulogne Billancourt, France, [2]Assistance Publique Hôpitaux de Paris, Hôpital Cochin, F-75014, Paris, France, [3]Assistance Publique Hôpitaux de Paris, Hôpital Cochin, F-75014, Paris, France; Universite Paris Descartes, Faculte de Médecine; INSERM (Institut National de la Santé et de la Recherche Medicale, [4]EHESP School of Public Health, F-35200, Rennes, France, [5]Hôpital Ambroise Paré, Assistance Publique Hôpitaux de Paris, Boulogne-Billancourt, France, INSERM Unité 1016, Université Versailles Saint Quentin en Yvelines, F-78000, Versailles, France, [6]INSERM, UMR S 707, F-75012, Paris, France; UPMC Université Paris 06, UMR S707, F-75012, Paris, France; APHP Hopital Saint Antoine F-75 012 Paris France, [7]Université Versailles Saint Quentin en Yvelines, F-78000, Versailles, France; Assistance Publique Hôpitaux de Paris, Hôpital Ambroise Paré, F-92100, Boulogne Billancourt, France; [8]Universite Versailles Saint Quentin en Yvelines, F-78000, Versailles, France; Assistance Publique H[pitaux de Paris, Hopital Ambroise Pare, F-92100, Boulogne Billancourt, France; INSERM, UMR S707, F-75012, Paris, France; UPMC Universite Paris, [9]UNIVERSITY of Versailles Saint Quentin en Yvelines, F-78000, Versailles, France; APHP Hopital Ambroise Paré F-92100 Boulogne Billancourt, France; Inserm UMR-S 707 F-75012, Paris, France

Background: Susceptibility to SPA has been shown to be largely genetically determined but the contribution of environmental factors to

disease evolution has not yet been elucidated. The objective of this study was to prospectively investigate the impact of several environmental factors on disease activity.

Methods: The study population consisted of a dedicated cohort of adult (age ≥ 18 years) SPA patients fulfilling Amor's criteria. The follow up period extended over 3 years (December 2005 to October 2008). Patients were asked to log on a secured website every 3 months and to complete a standardized auto-questionnaire. They notified if they were exposed since the previous connexion to environmental factors suspected of being non-specific stimulants of inflammatory response, such as infections (respiratory tract infection, gastroenteritis, urinary tract infection), stressful or traumatic life events and vaccinations. Outcome variables included the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the patient global assessment (PGA), and the Bath Ankylosing Functional Index (BASFI) (rated each from 0 to 10). Univariate and multivariate analysis were performed using a standard generalized estimating equation approach for repeated measures adjusting on the outcome measurement collected at the previous connexion. This model assesses the variation of the outcome following the exposure to environmental factors.

Results: Two hundred and sixty two patients (57% of females) were included in the analysis (2078 patient-connexions). Mean Age (± SD) was 43.6 ± 10.5 years and disease duration was 16.8 ± 11.3 years. The mean total number of connexions per patient was 8.0 ± 2.0. The mean time between two connexions was 4,1 ± 2,4 months. Occurrence of life events were followed by an average increase of 0.4 points (95% confidence interval [CI] 0.3–0.6) on the BASDAI score ($p<0.0001$) (consecutive to an increase of the score of each question), of 0.6 points (95% CI 0.4–0.8) of the PGA ($p<0.0001$) and of 0.4 points (95% CI 0.2–0.6) on the BASFI score ($p<0.0001$). A moderately significant link between vaccination and disease activity was found with the BASDAI rising by 0.3 points (95% CI 0.0–0.6) ($p=0.028$). There was no relationship with disease activity for any of the other investigated events.

Conclusion: This prospective study conducted in a large cohort of SPA patients shows for the first time a link between stressful events and disease activity. This may offer insights into pathogenesis and approaches to disease management.

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Increased Risk of Cardiovascular Disease in Patients with Active Ankylosing Spondylitis. Inger J. Berg, Anne G. Semb, Hanne Dagfinrud, Camilla Fongen, Sella A. Provan and Tore K. Kvien. Dep of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway

Background: Several inflammatory rheumatic diseases are associated with an increased risk of cardiovascular disease (CVD). There are also some studies suggesting a higher risk of CVD in patients with ankylosing spondylitis (AS).

The aim of this study was to compare prevalence of CVD and levels of Augmentation index (AIx), a surrogate markers for CVD risk, between a cohort of AS patients and a population control group. Comparisons were made between patients with high and low disease activity.

Methods: 161 patients with AS and 134 controls were examined in 2008–2010. The AS patients derived from the 5-year longitudinal follow-up of a cohort of hospital-recruited patients diagnosed according to the New York classification criteria. The control population was randomly selected by Statistics Norway. AIx estimation was performed using the Sphygmocor apparatus. BASDAI score was calculated from the standard questionnaire. Statistical analyses were preformed in SPSS ver 14.0 using bivariate tests as appropriate. The risk of CVD and levels of CVD risk markers were explored across levels of BASDAI (dichotomized at the median) and compared to controls in logistical and linear regression models adjusted for age, sex and smoking habit.

Results: The groups were comparable regarding demographic data (AS vs controls): age (51.2 vs 53.1 $p=0.18$), gender/male (62.7% vs 57.9% $p=0.41$) and smoking (56.4% vs 60.2% $p=0.52$), but as expected there were significant differences regarding ESR (17 vs 8 $p<0.001$). Total cholesterol was significant lower in the AS group (5.43 vs 5.75 $p=0.01$).The subgroup analyses are presented in Figure 1.

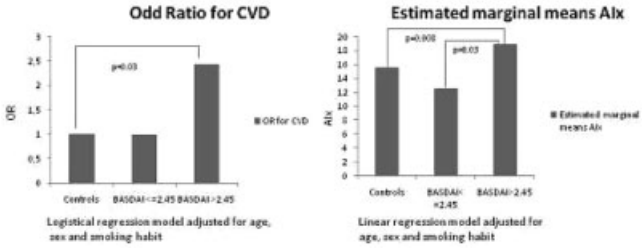

Figure 1. OR for CVD and levels of AIx compared across AS disease activity and population controls.

Conclusion: We found significantly higher OR for established CVD among patients with active AS despite the total AS group having significantly lower total cholesterol. The increased risk of CVD was further confirmed by a significantly increased AIx in patients with high BASDAI. The results indicate that there might be a higher risk of CVD in the AS patient with the most active disease. These findings will be investigated in further analysis.

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Increased Risk of Gastrointestinal Complications among Persons with Ankylosing Spondylitis: A Population-Based Study from Québec, Canada. Adrian R. Levy[3], Shelagh M. Szabo[3], Walter P. Maksymowych[4], Sumati Rao[1], Diane V. Lacaille[2] and Mary Cifaldi[1]. [1]Abbott, [2]Arthritis Research Ctr Canada, Vancouver, BC, Canada, [3]Oxford Outcomes, [4]University of Alberta, Edmonton, AB, Canada

Purpose: Individuals with ankylosing spondylitis (AS) may be at increased risk of developing gastrointestinal (GI) complications as a result of at least two pathways. First, both subclinical and manifest GI inflammation is frequently observed in persons with AS. Second, the symptoms of AS are often treated with non-steroidal anti-inflammatory drugs; an unintended consequence of these medications is increased risk of GI ulcers. However, the magnitude of increased risk of GI complications in AS and the demographics of patients at more pronounced risk is not well-characterized. Published studies of the excess risks of GI disorders among persons with AS have been clinic-, and not population-, based. The objective was to estimate the age- and sex-specific risk of GI disorders in a population-based cohort of persons with AS compared to a cohort of persons without AS.

Methods: A retrospective cohort study was conducted using the population-based administrative physician-billing database maintained by the Régie de l'Assurance Maladie du Québec. The cohort included individuals with at least one International Classification of Diseases 9th Revision, (ICD-9) billing code for AS between 1996 and 2006. The comparison cohort was a 1% random sample of individuals without AS. GI complications were defined according to ICD code, and included: ulcer-related GI complications (hemorrhage, ulcer, esophagitis, gastritis, or duodenitis); inflammatory GI diseases (Crohn's or colitis); and other GI complications (irritable bowel or diverticulitis). We calculated incidence rates per person-year and age- and sex-adjusted incidence rate ratios (IRRs) with 95% confidence intervals (CIs) compared to the comparison cohort.

Results: Among 8,616 persons with AS, 55% were male and median age at diagnosis was 42.5 years. Age-specific incidence of GI complications increased with age from 43 to 59 per 1000 person-years among males aged 20–39, and >60 years, respectively; and from 52 to 58 per 1000 person-years among females aged 20–39, and >60 years, respectively. There seemed to be a trend of decreasing IRRs (95% CI) with increasing age; among men, from 1.7 (1.6–1.8) for those 20–39 years, to 1.5 (1.4–1.6) for those >60 years; and, among women, from 1.7 (1.6–1.8) for those 20–39 years to 1.3 (1.2–1.4) for those >60 years. Ulcer-related GI events were the most frequent complication (incidence rate, 32 per 1000 person-years) followed by other GI events (27 per 1000 person-years), and inflammatory GI diagnoses (25 per 1000 person-years). Age- and sex-adjusted IRRS were: hemorrhage: 1.9 (1.7–2.2); ulcer: 2.0 (1.9–2.2); esophagitis: 1.7 (1.6–1.8); gastritis: 1.8 (1.7–1.9); Crohn's: 4.6(4.1–5.0); Colitis: 1.8 (1.7–1.9); irritable bowel: 2.3 (2.1–2.5); and diverticulitis: 1.6 (1.5–1.8).

Conclusions: Individuals with AS are at increased risk for many types of GI complications. The excess risk may be more pronounced among younger

individuals. Ulcer-related GI complications were the most common and the increased risk among persons with AS was highest for inflammatory GI diseases. These data support a policy of routine assessment of GI disorder among patients with AS.

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Inflammation in an Individual Joint Predicts Damage to That Joint in Psoriatic Arthritis. Vinod Chandran[3], Lynne Creswell[1], Vernon T. Farewell[1] and Dafna D. Gladman[2]. [1]MRC Biostatistics Unit, Cambridge, UK, [2]Toronto Western Hospital, Toronto, ON, Canada, [3]University of Toronto Psoriatic Arthritis Clinic, Toronto Western Hospital

Background: Psoriatic arthritis (PsA) leads to progressive joint damage and disability. Predictors for joint damage progression have been identified. However, these analyses were based on total joint counts in the individual patient and not on the presence of swelling, tenderness or damage at the individual joint level. We aimed to identify predictors of damage to individual joints in the hands and feet of patients with PsA, in particular those that capture previous activity.

Methods: Data from 705 patients followed prospectively at a large PsA clinic between 1978 and 2006 were available for analysis. Data from 511 patients who had no clinical damage in their hand joints [wrists, MCP, PIP and DIP (total 30)] at clinic entry were included in the analysis of the hand joints; data from 552 patients who had no clinical damage observed in the joints of the feet [ankles, MTP, IP (total 22)] at clinic entry contributed data to the analysis of the foot joints. An active joint was defined as a joint with either tenderness or swelling. Clinical damage was determined by the presence of a limitation of range of movement of >20% of the range not related to the presence of joint effusion, the presence of joint deformities, subluxation, flail joints or ankylosis. Logistic regression was used to relate the probability of a joint developing damage, within a specified time interval after the most recent clinic visit, to potential predictor variables. The predictor variables considered encompassed the history of disease activity of the joint and elsewhere, previous damage and the timing of clinical assessments.

Results: 511 patients (286 males, median age 41 years, PsA duration 3 years, active joint count in hands 2) with no hand damage at clinic entry and 552 patients (310 males, median age 41 years, PsA duration 3 years, active joint count in feet 2) with no foot damage at clinic entry were included in the analysis of the hand and foot joints, respectively. The results of the multivariate analyses are given in tables 1 and 2.

Table 1. Results for the Final Multivariate Model for Damage to Hand Joints

	Explanatory Variable	Odds Ratio (95% CI)	P
Joint specific activity variables	EWMA	1.40 (1.25, 1.56)[1]	<0.001
	PROP	1.33 (1.20, 1.48)[1]	<0.001
	Swelling at any visit	1.63 (1.35, 1.97)	<0.001
Global activity variable	Swelling in the same hand at any of most recent 3 visits	1.55 (1.30, 1.84)	<0.001
Damage variables	Damage in the symmetric joint	2.24 (1.79, 2.80)	<0.001
	Damage in an adjacent joint	1.53 (1.22, 1.91)	<0.001

EWMA = Exponentially Weighted Moving Average; PROP = proportion of visits with activity observed in the joint
Symmetric joint = equivalent joint on the opposite hand/foot
Adjacent joint = a joint of the same type (MCP, PIP or DIP) of an adjacent finger
[1] The odds ratio for the EWMA and PROP are presented in a form that describes the multiplicative effect on the odds of damage developing caused by an increase of 0.25.

Table 2. Results for the Final Multivariate Model for Damage to Foot Joints

	Explanatory Variable	Odds Ratio (95% CI)	p
Joint specific activity variables	Activity at any visit	1.48 (1.27, 1.72)	<0.001
	Swelling at any visit	1.44 (1.17, 1.78)	0.001
Global activity variables	Activity in the feet at any of the three most recent visits	1.56 (1.32, 1.78)	<0.001
	Activity in the other toe joint at any visit	2.14 (1.85, 2.46)	<0.001
Damage variable	Damage in the symmetric joint	1.53 (1.14, 2.06)	0.005

The analyses of the hand and foot joints demonstrated that the activity (tenderness and/or swelling) history of the specific joint is associated with subsequent damage. For the joints of the feet, activity observations elsewhere, in particular in the same toe, were also shown to be associated with subsequent damage. Moreover, the longer the patient is in clinic and longer the time between visits, the more likely that joint damage is observed.

Conclusions: Both joint tenderness and swelling are important predictors of joint damage in PsA. Frequent and regular follow-up assessments may contribute to the prevention of joint damage.

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Inflammatory Bowel Disease Markers in the Stool of Patients with Ankylosing Spondylitis Compared to Healthy Controls. Franziska Matzkies[1], Dermot McGovern[2], Stephen Targan[2] and Michael H. Weisman[3]. [1]Cedars Sinai, San Bruno, CA, [2]Cedars Sinai, Los Angeles, CA, [3]Cedars-Sinai Medical Center, Los Angeles, CA

Background: Past and current research continues to uncover relationships between Ankylosing Spondylitis (AS) and inflammatory bowel disease (IBD). AS patients have a high frequency of asymptomatic chronic gut inflammation. IBD and AS share key genetic and pathogenetic features. In both diseases the mucosal integrity is disrupted, leading to increased permeability, exposure to dietary/infectious antigens, and subsequent loss of tolerance to bowel flora and priming of inflammatory T-cells. Since T cells reactive to bacterial antigens have also been detected in the joints of AS patients, it is tempting to hypothesize the gut might play an important role in the pathogenesis of AS.

Advances in IBD research have identified fecal Calprotectin (fCAL), a neutrophil-derived protein that can be quantified in the feces, as a marker of bowel inflammation that correlates with the histological degree of inflammation. We propose that patients with AS will have increased levels of fecal calprotectin in their stool compared to healthy controls (HC) even in the absence of any clinical symptoms.

Methods: 41 consecutive patients with established AS were selected from our cohort and 42 HC were recruited. AS patients or HC that used NSAIDS within 2 days of the collection and AS patients currently on humira or infliximab or with a prior diagnosis of IBD were excluded. Stool samples were sent to Genova diagnostics; fCAL was measured by ELISA and a cut of 50μg/ml was used for a sample to be called positive.

Results: 17 AS patient (40%) and 3 HC (7%) had positive fCAL levels in their stool. Average fCAL level in AS was 112μgr/ml vs 26μgr/ml in HC. Results were statistically significant with p less than 0.001. When fCAl positive and negative AS patients were compared no statistical significant differences were found in regards to age, gender, disease duration, NSAIDs use, HLA-B27 positivity, prior uveitis or peripheral arthritis. More Enbrel use (58% vs 36%), higher BASDAI (3.4 vs 2.9), BASFI (35 vs 24) and BASRI (6.6 vs 5.6) scores were observed in the fCAL positive AS group compared to the negative AS group. However none of these parameters were statistically significantly different between the two groups.

Conclusion: fCAL was found at significant higher levels in patients with AS compared to HC. These AS patients did not possess typical symptoms or had a prior diagnosis of IBD and were not treated with medications that would influence bowel inflammation. Increased levels of fCAL therefore truly represent subclinical inflammation of the bowel in this cohort of AS patients. fCAL is a noninvasive, stable, reliable, and reproducible test for IBD inflammation. It therefore can be studied to evaluate subclinical bowel inflammation in large cohort of patients. Currently, there are no serologic or other biological markers in AS that are associated with clinical phenotypes, genetic associations, or treatment response. Further studies utilizing fCAL might prove to have pathophysiological significance with regard to genetic associations and environmental triggers.

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Influence of Fc-Gamma Receptor IIA (CD32) and IIIA (CD16) Polymorphisms on the EULAR Response to Anti-Tumor Necrosis Factor-alpha Therapy in Psoriatic Arthritis: A Longitudinal Study with 2 Years Follow-Up. Julio Ramirez[7], José Luis Fernández-Sueiro[6], Raquel López-Mejías[1], Carlos Montilla[5], Belen Suarez[2], Raimon Sanmartí[4], Concepción Moll[3], Francisco Blanco[6], Francisco Lozano[1] and Juan D. Cañete[3]. [1]Servicio de Inmunología, Hospital Clínic y Universidad de Barcelona, Barcelona, Spain, [2]Servicio de Inmunología, Hospital Clínic y Universidad de Barcelona, Barcelona, Spain, [3]Servicio de Reumatología, Hospital Clínic e IDIBAPS, Barcelona, Spain, [4]Servicio de Reumatología, Hospital Clinic e IDIBAPS, Barcelona, Spain, [5]Servicio de Reumatología, Hospital Clinico de Salamanca, Salamanca, Spain, [6]Servicio de Reumatología, Hospital Juan Canalejo, La Coruña, Spain, [7]Servicio Reumatología, Hospital Clinic e IDIBAPS, Barcelona, Spain

Introduction: Therapies targeting tumor necrosis factor (TNF)-alpha have shown to be very efficacious in psoriatic arthritis (PsA). However, around 40% of patients do not achieve a satisfactory response to treatment. This heterogeneity in the response might be partly due to the high/low affinity polymorphisms of the Fc-IgG receptors, which are expressed on the cell membrane of platelets and myeloid cells and might produce differences in the rate of clearance of TNF-blockers and therefore in their clinical effects.

Objective: To assess the influence of FCGR2A-R131H and FCGR3A-F158V polymorphisms on the clinical response to anti-TNF-alpha therapy in patients with PsA.

Methods: Patients fulfilling the CASPAR criteria for PsA, non-responsive to methotrexate (≥15 mg/week) and starting anti-TNF-alpha therapy were included. The efficacy of therapy was evaluated according to EULAR response criteria at 3,6,9,12 and 24 months. FCGR2A-R131H and FCGR3A-F158V polymorphisms were genotyped by allele-specific PCR and PCR sequence-based typing, respectively. Differences in the clinical response with respect to the FCGR2A-R131H and FCGR3A-F158V polymorphisms were calculated using the chi^2 test.

Results: 111 PsA patients were included and treated with the following TNF-blockers: 53.2% etanercept, 33.3% infliximab and 13.5% adalimumab. Fifty- one percent were male (median age at inclusion 46.3 years, disease duration 13.3 years, PCR 2.48 mg/dl and DAS 4.67).

More than 85% of patients achieved a EULAR response during the 24 month follow-up. Globally, more than 60% of patients achieved a good EULAR response (63.1% at 3 and 6 months, 60.7% at 9 months, 61% at 12 months and 73.8% at 24 months). Significantly-more patients with high affinity FCGRIIA polymorphisms (HH and HR) achieved a EULAR response at month 6 compared with patients with low affinity polymorphism (RR).

No other significant differences were found in EULAR responses at any time during follow-up between patients with high (HH and HR for CD32, VV and VF for CD16) and low (RR for CD 32 and FF for CD 16) affinity polymorphisms.

Conclusions: The effect of FCGR2A-R131H and FCGR3A-F158V polymorphisms on the response to TNF-blockers in PsA is mild and seems to be contrary to that previously found in patients with rheumatoid arthritis (RA).

Possible explanations for these findings might be the different pathogenesis of PsA and RA and the complexity of the interactions between Fc-Ig receptors and TNF-blockers over time. However, given that therapeutic responses to anti-TNF-alpha agents are substantially higher and better sustained over time in PsA compared with RA, the effect of polymorphisms on response to this therapy might be lower in PsA than in RA.

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Intestinal Microsporidiosis: High Risk in Rheumatic Diseases Patients under Anti-TNF Therapy Combined with Methotrexate. Nadia E. Aikawa[3], Aline O. Twardowsky[5], Jozelio Carvalho[5], Clovis Silva[4], Ivan Silva[2], Ana Medeiros[5], Carla Gonçalves[5], Julio Moraes[5] and Eloisa Bonfa[1]. [1]Faculdade Medicina, Sao Paulo, Brazil, [2]Rheumatology Division (CEDMAC) and Infectology Division, Faculdade de Medicina da Universidade de Sao Paulo, [3]Rheumatology Division (CEDMAC) and Pediatric Rheumatology Unit, Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil, [4]Rheumatology Division (CEDMAC) and Pediatric Rheumatology Unit, Faculdade de Medicina da Universidade de Sao Paulo, [5]Rheumatology Division (CEDMAC), Faculdade de Medicina da Universidade de Sao Paulo

Background: Microsporidiosis are among the most frequent opportunistic intestinal diseases in immunocompromised subjects. However, there are scarce studies regarding the relevance of microsporidia and other intestinal parasites in high risk rheumatic diseases patients.

Purpose: To evaluate microsporidiosis and other intestinal pathogenic parasites in patients with rheumatic diseases under disease modifying anti-rheumatic drugs (DMARDs) and biological agents therapies and to investigate possible associations between these parasitoses, disease activity and drugs.

Methods: 98 consecutive rheumatic diseases patients [47 rheumatoid arthritis (RA), 31 ankylosing spondylitis (AS), 11 psoriatic arthritis (PsA) and 9 juvenile idiopathic arthritis (JIA)] and 92 socio-economic-matched healthy controls were enrolled. Stool parasitological analysis and culture were performed in all participants. Three stool samples from each subject were collected in different days. Stools were evaluated using microscopic examination for detection of pathogenic protozoan oocysts, cysts, helminthic eggs and larvae. GRAM-Chromotrope for Microsporidium and intestinal Coccidia, Leishman staining for *Blastocystis hominis and* fecal leukocytes, Kinyoun procedure and capture-ELISA for *Cryptosporidium sp*., *Cyclospora cayetanensis* and *Isospora belli*, and Kato-Katz for *Schistosoma mansoni* were also performed. Clinical manifestations, disease activity data and treatments were also analyzed.

Results: The mean of current age (44.2±14.3 vs. 43.75±14.29 years, $p=0.8155$), frequencies of Caucasian race and socio-economic classes were comparable in patients and controls ($p>0.05$). Of note, the frequency of microsporidia was significantly higher in rheumatic diseases compared to controls (36% vs. 4%, $p<0.0001$), as well as in RA (32% vs. 4.4%, $p<0.0001$), EA (45% vs. 4%, $p<0.0001$), PsA (40% vs. 4%, $p<0.0001$) and JIA patients (56% vs. 4%, $p=0.0002$). Regarding the other pathogenic parasites, only *Giardia lamblia* was more often observed in EA patients *versus* controls (9.7% vs. 0%, $p=0.0149$). The frequency of methotrexate/anti-TNF therapy was higher in patients with pathogenic parasites compared to those without these parasitosis (77% vs. 54%, $p=0.0249$), in spite of similar mean duration of anti-TNF therapy in both groups (12.3 ± 9.9 vs. 15 ± 11.1months, $p= 0.2231$) and disease activity parameters ($p>0.05$). Gastrointestinal symptoms occurred in a similar frequency in patients with and without pathogenic parasitosis ($p>0.05$) and none had disseminated disease. All patients and controls were treated with albendazole for microsporidia infection and metronidazole for giardiasis.

Conclusion: We have identified that microsporidiosis is a frequent opportunistic infection in rheumatic diseases patients under concomitant methotrexate and anti-TNF treatment regardless of the gastrointestinal symptoms and therefore investigation for microsporidia is highly recommended for early diagnosis. This drug combination seems to play an important role in host defense probably by inhibiting inflammatory mediators.

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Involvement of the Anterior Chest Wall in Patients with Spondyloarthritis: Relationships between Clinical Symptoms and Imaging Features. Roberta Ramonda[2], Alessandro Lo Nigro[2], Mariagrazia Lorenzin[2], Valentina Modesti[2], Federico Angelini[1], Carla Campana[2], Paola Frallonardo[2] and Leonardo Punzi[2]. [1]Radiology Unit, University of Padova, [2]Rheumatology Unit, University of Padova

Background: The anterior chest wall (ACW) is frequently affected in spondylarthritis (SpA), although its involvement is underestimated. The wide range of disorders found in this anatomic region renders the conventional radiology frequently inadequate for the diagnosis. Plain radiography appears of limited value, due to the difficulty of multiplanar evaluation of ACW joints and a poor sensitivity in revealing the first pathological changes. Bone scintigraphy (BS) is sensitive in showing the articular involvement pattern, but its specificity is considered low. New diagnostic methods, such as magnetic resonance imaging (MRI), appear potentially more effective to study the initially changes found in early SpA.

Objectives: The aim of this study was to compare the reliability of two different sensitive methods, such as BS and MRI, in assessing the involvement of ACW in patients with early SpA.

Methods: Out of 105 consecutive patients (pts) with early (≤ 1 year) SpA attending the Rheumatology Unit of the Padova University, from January 2008 to April 2010, 31 (29.5%, 17 F, mean age 46.2±12.6 yrs) complained of symptoms (pain and/or tenderness) in the ACW and so were submitted to BS and targeted MRI. Eighteen pts (58.1%) were affected with psoriatic

arthritis (PsA), 5 (16.1 %) with ankylosing spondylitis (AS) and 8 (25.8%) with undifferented SpA (USpA).

Results: At clinical examination, the right sternocostoclavicular (SCCJ) was involved in 28 pts (90.3%), the left SCCJ in 25 pts (80.7 %) and the sternum in 4 pts (12.9%). Out of the 31 pts with clinical symptoms BS was positive in 26 (83.8%) and MRI in 18 (58.1%). At BS, the most frequently involved joints were the left and right SCCJ, respectively in 16 pts (51.6%); and in 19 pts (61.2%), followed by the sternum, found in 12 pts (38.7 %). MRI too showed a more frequent involvement of SCCJ, found in 17 pts (54.8%), while the sternum was involved only in 6 pts (19.4%). Main changes reflecting early signs of active disease such as bone edema with synovial hyperaemia were observed in 11 pts (35.5%), endoarticular swelling in 1 (3%), increase of thickness of capsular structure in 12 pts (38.7%) and erosions in 5 (16.1%); among other signs, marginal bone irregularities were found in 5 pts (16.1%), osteoproductive processes in 6 (19.4%), and osteophytes in 2 (6.5%). The concordance between symptoms and imaging was more evident for BS (26 pts, 83.8 %) than for MRI (18 pts, 58.1 %).

Conclusions: The ACW involvement in early SpA is not so rare and it is mainly found in female pts. Both two imaging methods seem useful to investigate ACW symptoms. The BS confirms its higher sensitivity and, although less specific, it can reveal a subclinical involvement. MRI may give information useful for the therapeutic approach, revealing type and extent of articular involvement, in particular the presence of bone erosions.

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Long Term Profile of Cytokine, Metalloproteinase and Cartilage Biomarkers in Psoriatic Arthritis Patients Treated with Biologic Therapy. Jose Luis Fernandez-Sueiro, J. C. Fernández-Lopez, N. Oreiro-Villar, S. Pertega-Diaz, J. A. Pinto and FJ Blanco. Complejo Hospitalario Universitario La Coruña, La Coruña, Spain

Objective: to assess the cytokine, metalloproteinase (MMP) and cartilage biomarkers (CB) profile in long term psoriatic arthritis (PsA) patients treated with biologic therapy.

Patients and Methods: PsA patients met CASPAR criteria. Biologic therapy was started following the recommendations of the Spanish Society of Rheumatology. Patients were evaluated just before starting therapy and then every 12 weeks until last evaluation. In each visit SJC, TJC, VAS patient, physician, total pain, morning stiffness, HAQ, ESR and CRP was performed. Serum and blood was taken just before starting therapy and then every 12 weeks. For this study we analysed serum samples before starting therapy and at the last evaluation. We determined by ELISA the following: IL-1b, IL-6, IL-10, TNFa, MMP-1, MMP-3, C2C and CPII. All determinations were performed with commercial kits following the manufacturer's instructions. For the statistical analysis, Mann-Whitney test and Wilcoxon signed-rank tests were used.

Results: 38 PsA patients started the study, 19 were females. The mean age was 43.1±10.6 years; mean time of evolution was 8.2±4.8 years, mean time of follow up 47.6±15.2 months. 16 patients (42.1%) were treated with infliximab (INFx) and 22 (57.9%) were treated with etanercept (ETA) at start, in the last visit 9 patients were on INFX, 21 with ETA and 4 with adalimumab. 28 patients (73.7%) had peripheral disease and 10 patients (26,3%) had "mixed" disease. Basal clinical features were as follows: TJC 11.7±7.4, SJC 5.6±4.1, morning stiffness 39.9±24.2 minutes, VAS pain 63.5±18.0mm, VAS patient 64.8±17.6mm, VAS physician 52.0±10.7mm, HAQ 1.4±0.7, ESR 29.0±23.9 mm1/h, CRP 3.0±6.7 mg/dl.

With respect to the first visit, at last visit there was a significant monthly decrease in IL-6, MMP3 (ng/ml) and C2C and an increase in CPII/C2C.

Table I. Average monthly change of Cytokine, metalloproteinase and cartilage biomarkers from basal to last visit.

	Last visit-Basal visit		
	Mean	SD	p*
IL-1β*	0.0004	0.0263	0.923
IL-6*	−0.1639	0.2292	**<0.001**
IL-10*	0.023	0.075	0.111
TNFα*	−0.433	2.814	0.423
MMP-1†	−0.018	0.061	0.091
MMP-3†	−0.450	0.655	**<0.001**
C2C†	−0.230	0.256	**<0.001**
CPII†	0.318	2.583	0.478
CPII/C2C	0.086	0.134	**0.001**
ESR‡	−0.05	0.41	0.456
CRP#	−0.05	0.20	0.161

* pg/ml, †ng/ml, ‡mml [a]hour, # mg/dl

22 (64.7%) patients reached an ACR20, in these patients there was a significant decrease in IL-6, MMP-3 and C2C and an increase in CPII/C2C values with regard to basal levels.

Table II. Average monthly change of Cytokine, metalloproteinase and cartilage biomarkers from basal to last visit according to ACR20 response.

	ACR20 responders (n = 22)			ACR20 non responders (n = 12)		
	Last visit-Basal visit			Last visit-Basal visit		
	Mean	SD	p	Mean	SD	p
IL-1β*	0.003	0.029	0.583	−0.005	0.020	0.408
IL-6*	−0.212	0.255	**0.001**	−0.068	0.128	0.107
IL-10*	0.028	0.092	0.165	0.014	0.022	**0.043**
TNFα*	−0.837	3.255	0.264	0.577	0.409	0.005
MMP-1†	−0.025	0.064	**0.083**	−0.006	0.056	0.715
MMP-3†	−0.566	0.605	**<0.001**	−0.239	0.717	0.273
C2C†	−0.232	0.246	**<0.001**	−0.227	0.285	**0.019**
CPII†	−0.054	1.721	0.884	0.999	3.685	0.368
CPII/C2C	0.074	0.129	**0.014**	0.109	0.145	**0.025**
ESR‡	−0.075	0.481	0.473	−0.014	0.264	0.856
CRP#	−0.075	0.248	0.173	−0.003	0.013	0.405

*pg/ml, †ng/ml, ‡mm1 [a]hour, # mg/dl

In non responders (n=12), there were differences but not at the same level of significance. According to the pattern of joint involvement, there were basal differences in the levels of MMP-3 (peripheral 6.10±3.68 vs "mixed" 3.34±2.04, p=0.031).

Conclusion: In the long term follow up of PsA patients treated with biologic therapy, IL-6, MMP-3 and C2C decrease whereas CPII/C2C increases, however these changes are more profound if patients clinically respond to therapy as assessed by ACR20. In this long term follow up study, IL-6, MMP-3 as well as CPII/C2C seems good markers of synovial inflammation and cartilage metabolism.

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Myocardial Infarction and Cardiovascular Risk Profile in Ankylosing Spondylitis. A Systematic Review and Meta-Analysis. Sylvain Mathieu[3], Laure Gossec[2], Maxime Dougados[1] and Martin Soubrier[3]. [1]Hospital Cochin, Paris, France, [2]Rhumatologie B, Hôpital Cochin, Paris, France, Paris, France, [3]Rhumatologie, CHU Gabriel Montpied, Clermont-Ferrand, France

Background: Rheumatoid arthritis (RA) is associated with increased cardiovascular risk. In ankylosing spondylitis (AS) there is little information on cardiovascular risks, especially that of myocardial infarction (MI) risk.

Objectives: To assess the incidence of MI and the cardiovascular risk profile in AS patients.

Methods: A literature review of publications up to August 2009 was performed using Pubmed, Embase, the Cochrane Collaboration and congress abstracts. All observational studies reporting MI and all case/control studies assessing traditional (blood pressure, glycemia, metabolic syndrome, body mass index (BMI), lipid profile) and newer cardiovascular risk factors (intima-media thickness (IMT)) in AS patients and healthy controls were included. Myocardial infarction risks were calculated by metaproportion (inverse of the variance method) and for 100 patient-years (pyrs) of exposure. To assess the MI risk in AS, a meta-analysis was performed using Mantel-Haenszel's method. For continuous variables, the differences between AS patients and controls were expressed by standardized mean difference using inverse of variance method.

Results: Eight longitudinal studies were included (N patients=3279). In control groups (N=82735), 1318 MI were observed (4.6 % (95%CI [0.01, 0.10])). A total of 224 MI were reported in the 3279 AS patients during a mean follow-up of 22 years. In AS patients, the incidence of MI was about 7.0 % (95% CI [0.05, 0.10]) i.e, 0.35/100 pyrs. Meta-analysis of the three longitudinal studies comparing occurrence of MI in AS patients (146/2266) and healthy controls (1318/82745) showed no significant increase in MI in AS patients: risk ratio = 1.88 (0.83–4.28). Fifteen case/control studies and nine abstracts were included (N patients=1214 and N controls=1000). AS patients were characterized by a higher weighted mean intima-media thickness (0.61±0.12 vs. 0.54±0.10 mm; p=0.008), a significant decrease in levels of triglycerides, of total cholesterol and of HDL cholesterol compared with healthy controls. The risk of metabolic syndrome was higher in AS

patients: RR= 2.13 (95% CI [1.46, 3.06]), but without differences in level of glycemia or in BMI. No difference was evidenced in blood pressure, levels of homocysteinemia, of LDL cholesterol and atherogenic index (total cholesterol/HDL cholesterol).

Conclusion: AS patients appear at higher risk of MI compared to controls. This could be due to an atherogenic lipid profile or to systemic inflammation. Management of cardiovascular risk factors and control of systemic inflammation should be taken into account in AS.

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National Survey of Patients with Psoriatic Arthritis in Spain: Disease Activity, Pharmacological Therapy and Impact on Quality of Life. Juan D. Cañete[1], Julio Ramírez[2] and Rosario Rodríguez[3]. [1]Arthritis Unit, Rheumatology Dpt. Hospital Clinic and IDIBAPS, Barcelona, Spain, [2]IDIBAPS, Barcelona, Spain, [3]Medical Dept, Sanofi-Aventis Spain, Barcelona, Spain

Objective: To evaluate disease activity, pharmacological treatment and the impact on functional capacity and quality of life of psoriatic arthritis in Spain.

Methods: Cross-sectional, multicenter, national survey. The following data were collected: age, sex, type of psoriasis, swollen and tender joint counts (SJ 44/TJ 46), ESR (mm/1hour), CRP (mg/dL), DAS28, Psoriasis Global Assessment (PGA), Physician Global Assessment (PhyGA), Patient Global Assessment (PatGA), pharmacological therapy (AINEs, glucocorticoids, DAMARDs, and anti-TNFalfa therapy), Visual Analogue Scale (VAS) of pain, Disease impact as measured by VAS in the personal, occupational and social spheres, Health Assessment Questionary (HAQ) and Dermatology Life Quality Index (DLQI).

Results: 214 patients with psoriatic arthritis fulfilling CASPAR criteria from 54 Spanish rheumatology outpatient clinics were included. Fifty-six per cent were male and the mean age was 52 years (mean (95%CI:50.1;53.8)). Seventy-eight percent of patients had type I and 22% type II psoriasis. Patient had the following clinical and functional parameters: TJC:3.2 (2.6;3.7); SJC:2.4 (2;2.9) ESR:20.6 mm/1h (18.4–22.8); CRP:5.3 mg/dL (3.7;6.8); DAS28 3.1 (2.9;3.3); PhyGA:24.7(21.4; 27.9); PatGA:29.2 (25.3;33.2); VAS of global pain:29.7(25.5;33.8). 24% of patients had a moderate-severe extent of PsA as measured by PGA.

Disease impact as measured by VAS in the personal, occupational and social spheres, were 26.2(22.1;30.3), 27.9(23;32.8) and 23.2(19.1:27.3), respectively, with females reporting more significant involvement than males in the personal sphere (31.2(25;37.4) vs 22.1 (16.7;27.5); $p<0.03$). The global HAQ was 0.61 (0.52;0.7), being significantly higher en females than in males (0.84 (0.71;0.97) vs 0.42 (0.31–0.54), respectively; $p<0.00001$). Global DLQ was 3.5 (2.8;4.2), with youngest patients (18–29 years) reporting greater involvement (27% marked moderate to very severe affectation; $p<0.05$, Fisher test).

Regarding pharmacological therapies, 98.6% of patients were taken drugs for treatment of psoriatic arthritis; 58% AINE; 21% oral glucocorticoids (≤5 mg of prednisolone), 86.2% DMARDs (96% methotrexate and/or leflunomide, and 10% these drugs in combination) and 26.2% TNFalfa blockers. Of 173 patients from whom DAS28 was avalaible, 38% were en remission (DAS28<2.6); 23% had low disease activity (DAS28>2.6<3.2) and 39% had moderate or high activity (DAS28>3.2).

Conclusions: This observational national survey on psoriatic arthritis is the first trying to reflect treatment, clinical activity of disease and quality of life of patients with psoriatic arthritis in Spain. Globally it suggests that despite most patients are treated with DMARDs and one quarter with TNFalfa blockers, almost 40% of patients still exhibit moderate-high disease activity and 25% had moderate-high skin involvement. Furthermore, although the impact of the disease on functional capacity and psoriasis-related quality of life is globally mild-moderate, the group constituted by females and people of <30 years suffered a greater impact, suggesting we need to intensify the treatment of their joint and skin involvement.

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Performance of Different Criteria Sets for Inflammatory Back Pain in Patients with Axial Spondyloarthritis with and without Radiographic Sacroiliitis. Dilek Solmaz[3], Servet Akar[3], Ozgul Gunduz[3], Feride Yuksel[1], Gercek Can[3], Vedat Gerdan[3], Yesim Akkoc[2], Merih Birlik[3], Fatos Onen[3] and Nurullah Akkoc[3]. [1]Internal Medicine, Dokuz Eylul University Faculty of Medicine, [2]Physical Therapy and Rehabilitation, Ege University Faculty of Medicine, [3]Rheumatology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey

Background: The most prominent clinical feature of axial spondyloarthritis (SpA), is inflammatory back pain (IBP). Therefore it is of crucial impaortance to recognize inflammatory back pain for an early diagnosis of axial SpA, including ankylosing spondylitis (AS). Up to now several criteria sets have been proposed to define inflammatory back pain (IBP). Assessment of SpondyloArthritis International Society (ASAS) has just recently published new criteria set for diagnosing IBP. In the present study we evaluated the performance of the new ASAS criteria for IBP in comparison to Calin and Berlin criteria in patients with axial SpA using a control group of patients with chronic mechanical low back pain (MLBP).

Patients and Methods: The study sample included a total of 214 patients [117 male (54,7%); mean age42,6±12,2] with a diagnosis axial SpA based on clinical and radiologic findings and 44 patients with a diagnosis of chronic (>3 moths) MLBP based upon the treating physician's clinical judgment (MLBP group). Among patients with axial SpA, 70 patients had active sacroiliitis (SI) on MRI as defined by ASAS (SI on MRI group) and 144 patients had radiographic SI as defined by the modified New York criteria (AS group). A face to face interview by using a standardized questionnaire addressing all the components of inflammatory back pain included in Calin, Berlin and new ASAS criteria sets was performed by the same trained physicain. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) were measured. Data about HLA B27 status, erythrocyte sedimentation rate and C reactive protein (CRP) levels were obtained from the patients charts if available.

Results: There were significantly more male patients ($p<0,001$) in the AS group (%66) than in the SI on MR (%31,4) and also than in the MLBP group (%36,4). Some demographic and clinical features in the patient groups are shown in Table 1.

Table 1. Demographic and clinical features in the study groups

	AS group (n = 144)	SI on MRI group (n = 70)	MLBP group (n = 44)
Males, n (%)	95 (66)	22 (31)	16 (36,4)
Age, mean ± SD	42,3 ± 11,6	43,1 ± 12,7	43,6 ± 11,6
Age at onset of back pain, mean ± SD	24,7 ± 7,4	27,8 ± 7,4	29,7 ± 9,6
Education Level, mean ± SD (years)	9,5 ± 3,8	10,4 ± 4,2	9,0 ± 4,2
BASDAI, mean ± SD	3,4 ± 2,2	4,8 ± 2,6	3,2 ± 2,4
BASFI, mean ± SD	2,7 ± 2,6	3,1 ± 2,4	2,2 ± 2,0
CRP, mean ± SD	12,9 ± 14,5	8,2 ± 14,3	3,6 ± 3,7
HLA-B27 positivity	72%	36%	7–11%*

*HLA-B27 positivity reported in the general Turkish population in previous publications.

Among the criteria sets, Calin criteria showed the best sensitivity (92%), and Berlin criteria showed the best specificity (84%) in the differentiation of inflammatory back pain from chronic mechanical back pain. If the morning stiffness component of Calin's criteria set was defined as longer than30 minutes, the specificity improved (75%), but at a price of loss in sensitivity (84,5%). The performance of different criteria sets in different patient groups are shown in Table 2.

Table 2. Performance of different criteria sets in different patient groups

	Calin		Calin 30		Berlin		ASAS	
	AS	SI on MRI	AS	SI on MRI	AS	SI on MRI	AS	SI on MRI
Sensitivity (%)	95,1	88,5	88,0	75,7	74,3	78,5	77,0	72,8
Specificity (%)	50,0	50,0	75,0	75,0	84,0	84,0	72,7	72,7
+LR (%)	1,9	1,7	3,5	3,0	4,6	4,9	2,8	2,6
−LR (%)	0,09	0,2	0,1	0,2	0,3	0,2	0,3	0,3
Odds Ratio	19,5	7,7	24	9,3	15,2	19,3	8,9	7,1

Conclusion: New ASAS criteria for IBP did not seem to perform better in differentiating IBP from chronic mechanical back pain, than the existing criteria sets in patients followed at a rheumatology outpatient clinic.

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Pregnancy in Ankylosing Spondylitis Is Associated with Fluctuation in Back Pain but Return to Baseline Postpartum: A Case Control Study. Nai Lee Lui[1], Adele Carty[4], Nigil Haroon[3], Sutha Shanmugarajah[4], Hua Shen[2], Richard J. Cook[2], Dafna D. Gladman[5] and Robert D. Inman[6]. [1]Department of Rheumatology and Immunology, Singapore General Hospital, Singapore, [2]Department of Statistics and Actuarial Science, University of Waterloo, Canada, [3]Division of Rheumatology, Toronto Western Hospital, Toronto, ON, Canada, [4]Division of Rheumatology, Toronto Western Hospital, Toronto, Canada, [5]Toronto Western Hospital, Toronto, ON, Canada, [6]Toronto Western Hospital, Toronto, ON, Canada

Objective: Previous studies of pregnancy in ankylosing spondylitis (AS) have not included a control group in order to control for pregnancy-related effects on back pain in general. We performed a case control study to evaluate the impact of pregnancy in patients with AS.

Methods: A questionnaire was developed and mailed to female AS patients in a longitudinal AS clinic and to a group of female psoriasis patients as controls. Patients with psoriatic arthritis were excluded. The questionnaire consisted of clinical data on AS (age of symptom onset and diagnosis of AS, analgesics use), numerical rating scale (NRS) for pain and stiffness for the periods pre-, during and post-pregnancy, and the Roland-Morris questionnaire, a disease-specific validated questionnaire with 24 items inquiring about the severity of symptoms and functional impairment due to back pain.

Results: Nineteen female AS patients (with 35 pregnancies) and 33 psoriasis controls (with 77 pregnancies) completed the questionnaire. AS patients experienced significantly more back pain compared to controls in all three trimesters based on the Roland-Morris questionnaire (mean values for 1st, 2nd, 3rd trimesters; 6.4, 9.7, 11.7 for AS *vs* 0.4, 1.4, 4.5 for controls; $p<0.001$ for the 1st and 2nd trimesters and $p=0.001$ for the 3rd trimester).

In the 1st trimester, there was a significant improvement in pain and stiffness in the AS patients ($p= 0.002$ and 0.016 respectively) compared to baseline pre-pregnancy levels. However, in the 2nd and 3rd trimesters, AS patients experienced significantly more pain and stiffness. The first month postpartum showed trend towards less pain ($p=0.072$) and stiffness ($p=0.108$) in the AS patients, but worsening of symptoms ensued from the second to the sixth month post partum. At six months postpartum the level of pain and stiffness had returned to baseline pre-pregnancy levels.

No increase in flares of psoriasis, uveitis, peripheral arthritis or inflammatory bowel disease was reported during pregnancy. Most AS patients who performed stretching exercises prior to their pregnancies continued with their exercise regime during their pregnancies ($p=0.005$). Seven patients did not perform stretching exercises due to fear of complication to pregnancy ($p=0.023$). Most AS patients refrained from analgesic medications during their pregnancies ($p=0.028$) for fear of adverse effects on the fetus ($p<0.001$). Back pain did not hinder breast feeding.

Conclusion: The improvement in back pain and stiffness in the 1st trimester could be related to the high levels of human chorionic gonadotropin (HCG) hormone in the 1st trimester of pregnancy. Previous hormonal reports have found HCG to possess significant analgesic effects. The worsening of symptoms in the 2nd and 3rd trimesters was seen both in AS and controls and likely reflects biomechanical loading of the low back with later stages of pregnancy. AS patients appear to return to baseline levels of back pain and stiffness post partum, suggesting that pregnancy does not substantially aggravate disease activity in AS.

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Prevalence and Characteristics of Uveitis in US Veterans with Seronegative Spondyloarthropathy. Hashem Monshie-Vahabzadeh[4], Saloomeh Vahadat[4], J. Steuart S. Richards[4], Andreas Reimold[1], Jessica Walsh[2] and Gail S. Kerr[3]. [1]Dallas VA Medical Center, Dallas, TX, [2]Salt Lake City VA Medical Center, Salt Lake City, UT, [3]VA Medical Center Washington DC, Washington, DC, [4]VA Medical Center Washington, DC, Washington, DC

Purpose: Acute anterior uveitis (AAU) is recognized as the most common extra-articular manifestation of ankylosing spondylitis (AS) occuring in up to 41% of cases but is less frequently in other spondyloarthopathies (SpA), and is more prevalent in SpA patients who are HLA-B27 positive. Herein we describe the frequency, demographic and clinical associations of AAU in a cohort of US veterans enrolled in the PULSAR registry (Program to Understand the Long Term Outcomes of SpA).

Method: Patients > 18 years old, with EULAR Criteria for SpA were enrolled in PULSAR from 4 VA Medical Centers. SpAs included were AS, Psoriatic arthritis (PsA), Reactive arthritis (ReA), SpA due to inflammatory bowel disease (IBD), and undifferentiated SpA (USpA). All participating sites received IRB approval and all subjects gave written informed consent. Data collected included demographic data, clinical and laboratory features of SpA, HLA-B27, DMARD/biologic agents, comorbid diseases, and extra-articular manifestations. AAU was defined as painful photophobia, with ophthalmologic confirmation of uveal tract inflammation, and visual acuity (va) and intra-occular pressure (IOP) data obtained.

Results: There were 265 SpA patients enrolled in PULSAR, the majority were male (95.5%), with a mean age of 57.13 years, and mean disease duration of 20.5 years and 57.9% were HLA-B27 positive. Seventy-six had AS, 137 had PsA, 27 ReA, and 22 had USpA or IBD arthritis. AAU was present in 28 (10.6%), with a mean disease duration of 10.9 years. One hundred and ninety-five (73.6%) were Caucasian, 34 (12.8%) were African American (AA). Patients with AS had the highest prevalence of AAU, [14/76 (18.4%)] and frequencies in other SpA were: PsA, [5/137 (3.7%)], ReA [5/27 (18.5.%)], and USpA/IBD [4 of 22 (18.2%)]. The ethnic distribution of AAU was similar to that of SpA: Caucasians 72.7% and AA 11.8%. Most were HLA-B27 positive [89/150 (59.3%)]. AAU was more common in HLA-B27 positive versus HLA-B27 negative patients, (19/105 patients; 18.1% vs 3/87; 3.5%, respectively). The majority (16/22), had chronic or recurrent episodes of AAU. Thirteen of 20 had arthritis concurrent with uveitis flares. Two patients were ineligible for drivers licenses (va 20/50 – 20/70), while only one was legally blind (va < 20/200). Glaucoma (IOP > 21) was present in only 4 of 19 subjects and approximately one third (7/20) developed cataracts. In addition to topical steroids, 30% received oral prednisone,46% were on traditional DMARDS, while 18 of 26 (67%) received an anti-Tumor Necrosis Factor alpha (anti-TNF) agent.

Conclusion: In a cohort of male US Veterans, AAU was more common in HLA-B27 positive individuals, occurred half as frequently as reported in the literature, but oral prednisone and/or steroid sparing agents were required in as many as a third. Therapy for concomitant active SpA with DMARDs and/or anti-TNF agents may have accounted for the infrequent occurrence of AAU in our cohort.

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Prevalence of Metabolic Syndrome in Patients with Seronegative Spondyloarthritis. Marwin Gutierrez[1], Andrea Becciolini[1], Emilio Filippucci[1], Fausto Salaffi[1], Rossella De Angelis[1], Bernd Raffeiner[4], Marco Canzoni[2], Viviana Ravagnani[3], Chiara Bertolazzi[1], Maria L. Sorgi[2], Domenico Biasi[3], Leonardo Punzi[4] and Walter Grassi[1]. [1]Clinica Reumatologica, Università Politecnica delle Marche, Jesi, Ancona, Italy, [2]Dipartimento di Clinica e Terapia Medica, Sapienza Università di Roma, Italy, [3]Unità Semplice di Reumatologia, Università degli Studi di Verona, Italy, [4]UOC Reumatologia, Clinica Medica e Sperimentale, Politecnico Universitario, Padova, Italy

Background: Seronegative spondyloarthritis (SpA), may be associated with an increased risk of cardiovascular disease (1). Metabolic syndrome (MetS) clusters risk factors for atherosclerotic cardiovascular disease including: insuline resistance, central obesity, low levels of high density lipoprotein, high triglyceride levels and elevated blood pressure. To date, different studies demonstrating a high prevalence of MetS in patients with rheumatic diseases have been published (2). However, little is still known about its prevalence among patients with SpA.

Objective: To investigate the prevalence of MetS in patients with SpA.

Methods: 119 consecutive patients (72 men and 42 women; disease duration 116.42 months, 95% CI 85–137.7; median of age 51.37, range 22–79) affected by SpA (73 with psoriatic arthritis, 20 with ankylosing spondylitis, 15 with undifferentiated spondyloarthritis, 6 with enteropathic spondyloarthritis and 5 with reactive arthritis), attending the out-patient and in-patient clinic of the Rheumatology Departments involved in this multicenter cross-sectional study were enrolled. The diagnoses were made according to European Spondyloarthritis Study Group criteria (3). The following

items for each patient were taken: waist circumference, triglycerides, high density lipoprotein, fasting glucose and blood pressure. The presence of MetS was determined according to the modified National Cholesterol Education Program 2004 (NCEP 2004) criteria (4).

Results: The overall prevalence of the MetS among SpA patients was 36.9% (44/119). The patients who did not satisfy at least one item for MetS was 21.8% (26/119). The group with the highest prevalence of MetS was enteropathic spondyloarthritis (50%), followed by psoriatic arthritis (41%), ankylosing spondylitis (35%), undifferentiated spondyloarthritis (26.6%) and reactive arthritis (0%). MetS resulted more prevalent in patients with more than 60 years (58.3%) respect to 35.4%, 34.4% and 8.6%, in patients between 50–59 years, 40–49 years and less of 40 years respectively. We found more frequently MetS in male patients (43%) compared with female patients (27.6%).

Conclusion: The MetS is a common finding in patients with SpA to increases cardiovascular risk. NCEP 2004 criteria are a fast and easy screening tool that should be adopted in the management of patients with SpA.

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Prospective Serum Levels Assessment of DKK-1 and SOST in Patients with Ankylosing Spondylitis and Treated with Anti-TNFa Treatments. Corinne Miceli-Richard[1], Stéphanie Malbos[1], Stephan Pavy[1], Sami Kolta[3], Karine Briot[3], Jérémie Sellam[5], Xavier Mariette[2], Christian Roux[3] and Maxime Dougados[4]. [1]Bicêtre Hospital, Université Paris XI Sud, [2]Bicetre Hospital/Paris Univ, Le Kremlin Bicetre, France, [3]Cochin Hospital, Université Paris-Descartes, [4]Hospital Cochin, Paris, France, [5]Saint-Antoine Hospital, Paris

Background: Sclerostin (SOST) and Dickkopf-1 (DKK-1) are two inhibitory proteins of Wnt signalling pathway which is involved in osteoblastogenesis. Studies assessing serum levels of DKK-1 and SOST in ankylosing spondylitis (AS) are scarce and have provided conflicting results. DKK-1 and SOST could rationally be involved either in AS osteoporosis or in osteoblastogenesis associated with syndesmophyte construction.

Objective: To investigate the role of DKK-1 and SOST among AS patients and to assess the effect of anti-TNF treatments on DKK-1 and SOST serum levels.

Methods: We assessed 28 AS patients (17 males/11 females, age 39 ± 11 years, disease duration 17 ± 13 years, mean± SD), and 25 controls (11 males/14 females, age 57 ±17 years, mean+/− SD) without any inflammatory condition. AS patients were prospectively studied for DKK-1 and SOST serum levels by sandwich enzyme-linked immunosorbent assay (ELISA) before, and 3 months (N=24) or 6 months (N=5) after the initiation of an anti-TNFa treatment. All AS patients were naive of any TNF blockers at inclusion in the study. All but 3 patients were treated with NSAIDs at inclusion in the study (89%).

Results: Serum DKK-1 levels were significantly increased in AS patients (mean; SEM 54.28 ± 4.82 pg/mL) compared with controls (11.13 ± 0.61pg/mL) ($p<0.0001$). Serum SOST levels were not different between AS patients and controls. Neither SOST nor DKK-1 serum levels were significantly modified by anti-TNFa treatment ($P=0.68$ and $P=0.77$, respectively). A trend for a negative correlation between DKK-1 serum levels and lumbar spine T-score was observed (P=0.056; r=−0.12) but such correlation was not observed with femoral T-score. SOST was not correlated with any of the studied BMD parameters. SOST (but not DKK-1) was significantly correlated with disease duration (P=0.0009; r=0.58). None of the other studied parameters were significantly associated with DKK-1 or SOST serum levels (BASFI, BASDAI, C-reactive protein, ESR, gender).

Conclusions: These results suggest an up-regulation of DKK-1 in AS, neither explained by patient's demographic characteristics nor by parameters related to disease activity (BASDAI, or biological markers of inflammation). DKK-1 serum level tends to be negatively correlated with lumbar spine T-score and SOST was highly correlated with disease duration, suggesting that both factors could contribute to osteopenia and/or osteoporosis described in AS patients. The respective role of DKK-1 and/or SOST in the structural progression of the disease has not been assessed in this study but high basal levels for DKK-1 and increased levels of SOST according to disease duration are unlikely to explain syndesmophyte formation in AS. The lack of significant variation of DKK-1 and SOST under anti-TNF treatment is in accordance with the absence of structural effect reported for these treatments, at least after a short time follow-up. Conversely, NSAIDs daily intake for most patients (89%) at inclusion in the study may partially account for such DKK-1 serum level increase, a hypothesis that could suggest a potential structural effect of NSAIDs in AS.

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Radiographic Progression Is Influenced by *ERAP1* Polymorphisms with Gender and Age Being Cofactors. Nigil Haroon[2], Walter P. Maksymowych[4], Proton Rahman[1], Florence W. Tsui[3] and Robert D. Inman[2]. [1]St Claires Mercy Hospital, St Johns, NL, Canada, [2]Toronto Western Hospital, Toronto, ON, Canada, [3]Toronto Western Research Institute and University of Toornto, [4]University of Alberta, Edmonton, AB, Canada

Introduction: Endoplasmic reticulum aminopeptidase 1 (ERAP1) polymorphisms have recently been identified to be associated with ankylosing spondylitis (AS). It is not however known if ERAP1 variants influence radiographic severity in AS.

Methods: Caucasian patients with AS (by the modified New York Criteria) from two centers were included in the study. X-rays of the lumbar and cervical spine were scored by the modified Stoke AS spine score (mSASSS). Patients had to have at least two mSASSS scores for inclusion. Genotyping for 14 AS-associated ERAP1 single nucleotide polymorphisms (SNPs) were done using the MassARRAY system. SNPs were excluded from analysis if the minor allele frequency (MAF) was <0.05. Linear regression analysis was done to examine the influence of the SNPs on the baseline mSASSS. For logistic regression, the patients were classified as progressors (any progression in mSASSS) and moderate or faster progressors if they had ≥1 or ≥2 mSASSS unit change/year respectively. Chi-square test was used to further analyze individual SNPS with significance in the regression analysis.

Results: A total of 334 patients (19% female, 137 and 197 from the respective centers) with a mean age of 41.8 ± 13 yrs were included in the study. The mean (± SD) BASDAI, ESR and CRP were 4.8 ± 2.4, 18 ± 23 mm/hr and 13 ± 16 g/L respectively. The mean mSASSS score at baseline was 19.8 ± 22.6 with 40% showing some progression at a mean rate of 0.8 ± 1.5 units/year. The SNPs rs17587(LMP2), rs26618, rs26653, rs27044, rs30187 (ERAP1) and rs241447 (TAP2) were included in the analysis while the MAF of the SNPS rs1057141, rs1800454, rs2071543, rs2228396, rs3734016, rs4148876 and rs10050860 were too low and excluded.

In binary logistic regression by forward stepwise conditional method, a model with rs17587 (p=0.01) predicted patients with high baseline mSASSS (defined as >50% of maximum = 36). Gender significantly improved the model (p=0.004) with males being more likely to have higher scores (OR=3.6; p=0.01). The addition of ESR, CRP or BASDAI did not improve the model. Chi-square test across the different genotypic groups for high baseline mSASSS scores were significant for rs17587 ($\chi^2=8.4$, p=0.01) and there was a trend in rs30187 (p=0.054). The mean baseline mSASSS in patients with change in mSASSS of < 4 units was significantly lower than those with >4 mSASSS units change (15 vs 25; p=0.0005).

There were significant baseline differences between the two cohorts with patients in one center being younger (38±13 vs 43±13 years; p=0.0003), and tended to have lower baseline mSASSS (20±21 vs 16±21) and more progression (2±3.1 vs 1.6±3.2). As baseline mSASSS is a strong predictor of progression, and the radiographic progression can vary between early and late disease, the cohorts were analyzed separately. Logistic regression model predictive of progression included rs30187 in patients from centre 1 and these patients were more likely to progress with the rs30187CC genotype compared to rs30187TT (OR 13.5; p=0.006), with this effect being further enhanced in males.

Conclusions: Genetic variants of ERAP1 and LMP2 are associated with radiographic severity in AS. Gender, age and disease duration are important cofactors influencing this interaction.

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Recently Diagnosed Ankylosing Spondylitis: Gender Differences and Factors Related to Delay in the Diagnosis. The North Israeli Study of ANkylosing Spondylitis (NISAN). Gleb Slobodin[1], Iris Reychan[7], Nina Avshovich[5], Alexandra Balbir-Gurman[6], Nina Boulman[2], Mona Elias[3], Joy Feld[3], Reuven Mader[4], Doron Markovitz[6], Doron Rimar[2], Itzhak Rosner[2], Michael Rozenbaum[2], Devy Zisman[3] and Majed Odeh[2]. [1]Bnai Zion Medical Center, Haifa, Israel, [2]Bnai Zion Medical Center, [3]Carmel Medical Center, [4]Haemek Medical Center, Afula, Israel, [5]Hillel Yaffe Mecial Center, [6]Rambam Medical Center, [7]Technion

Background: Gender differences have been demonstrated in patients with advanced ankylosing spondylitis (AS). There are no studies evaluating this in patients with recently diagnosed disease. The aim of the study was to characterize a cohort of patients with recently diagnosed AS, both preradiographic and established, with emphasis on gender differences and factors leading to delay in diagnosis.

Methods: All consecutive patients diagnosed with AS in 2004–2009 were recruited over a 6 month period by participating rheumatologists. Clinical, laboratory and imaging data was collected during the screening visit and/or retrospectively for all patients enrolled.

Results: Seventy-nine men and 72 women with AS were enrolled.

Table 1. Gender-dependent features of AS

Variable	Men (79)	Women (72)	p
Age at diagnosis (years)	35.6 ± 11.7	38.5 ± 12.3	0.13
Delay time to diagnosis (years)	5.9 ± 6.4	5.7 ± 6.0	0.87
Follow-up time (years)	2.1 ± 1.5	1.9 ± 1.2	0.3
Frequency of anti-TNFα usage (%)	37/79 (47%)	33/72 (46%)	1
Presenting symptom (%)			
Inflammatory low back pain	70 (89%)	52 (73%)	0.02
Neck pain	4 (5%)	8 (11%)	0.23
Arthritis			
knee	11 (14%)	8 (11%)	0.6
hip	4 (5%)	1 (1.4%)	0.36
Heel pain	1 (1.3%)	5 (7%)	0.23
Uveitis	4 (5%)	5 (7%)	0.74
Symptoms at the time of diagnosis			
Inflammatory low back pain	74 (94%)	70 (97%)	0.45
Radiation:			
Non radiating	20	7	0.016
Buttocks	37	41	0.16
Legs	17	19	0.56
Lower abdomen or pelvis	3	14	0.0032
Musculoskeletal chest/rib pain	5 (6.3%)	12 (17%)	0.07
Neck pain	21 (26%)	27 (37%)	0.16
Arthritis or arthralgia	40 (51%)	42 (58%)	0.4
Heel pain	18 (23%)	33 (46%)	0.003
Dactylitis	2 (2.5%)	3 (4.2%)	0.67
Uveitis	9 (12%)	8 (11%)	0.8
Widespread pain	5 (6.3%)	28 (39%)	<0.0001
Diarrhea/Crohn's disease	4/2	9/1	0.14
Physical examination [N]*:			
Schober test (cm)	3.4 ± 1.5 [64]	3.4 ± 1.5 [50]	0.87
Finger-to-floor distance (cm)	19.5 ± 15.6 [59]	17.2 ± 13.3 [42]	0.42
Occiput-to-wall distance (cm)	3.0 ± 5.9 [62]	0.2 ± 0.8 [40]	0.0032
Chest expansion (cm)	3.4 ± 1.8 [59]	4.4 ± 2.1 [38]	0.012
Elevated ESR	31 (48%) [65]	42 (62%) [62]	0.19
Elevated CRP	51 (69%) [74]	43 (65%) [65]	0.72
CT/MRI studies of SIJ	43 (54%)	53 (74%)	0.018

*[N] - number of subjects with available measurements

Both groups (men versus women) had similar age of onset of disease-related symptoms, as well as similar delay time to diagnosis, follow-up duration and frequency of anti-TNF treatment. Typical inflammatory back pain as a first symptom related to AS was reported more often by men (p=0.02). Women reported significantly more frequent lower abdominal or pelvic pain (p=0.0032), heel pain (p=0.003) and widespread pain (WP) (p=0.0001) during the course of AS. There was no gender-related difference in the incidence of uveitis, dactylitis or peripheral joint involvement. At the time of diagnosis, men were more limited in chest expansion (p=0.012) and showed increased occiput-to-wall distance compared to women (p=0.0032). At diagnosis, elevated erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) were detected in a similar proportion of men and women. X-ray films were more often diagnostic for AS in males, with more females undergoing CT or MRI studies to confirm the presence of sacroiliitis (p=0.018). In the subgroup analysis, women with WP had longer delay to diagnosis (p=0.0073) and more frequently elevated ESR/CRP levels (p=0.0068) compared to women without WP. No other statistically significant differences in disease presentation or burden, laboratory findings, or imaging characteristics were demonstrated to correlate with delay to diagnosis.

Conclusions: Women constituted almost 50% of all recently diagnosed patients with AS, with CT or MRI studies more frequently utilized in their diagnosis. Gender-related differences were demonstrated in both disease presentations and burden. WP in women was frequently reported, being related to significant delay in the diagnosis. As no other disease-related features were found responsible for delay in AS diagnosis, the physician's high level of suspicion may be the dominant factor in the early diagnosis of AS.

Table 2. Disease features in AS women with and without widespread pain (WP) #

Variable	With WP (28)	Without WP (41)	p
Age at diagnosis (years)	43.3 ± 11.7	35.4 ± 12.1	0.0091
Delay time to diagnosis (years)	8.3 ± 7.2	4.3 ± 4.8	0.0073
Follow-up time (years)	1.8 ± 1.1	2.0 ± 1.3	0.35
Frequency of anti-TNFα usage (%)	15/28 (54%)	17/41 (41%)	0.34
Symptoms of the disease:			
Inflammatory low back pain	28 (100%)	39 (95%)	0.51
Musculoskeletal chest/rib pain	9 (32%)	2 (5%)	0.005
Neck pain	18 (64%)	8 (20%)	0.0003
Joint involvement	15 (54%)	26 (63%)	0.46
Heel pain	16 (57%)	16 (39%)	0.15
Dactylitis	0 (0%)	3 (7%)	0.27
Uveitis	3 (11%)	4 (10%)	1
Diarrhea	3 (11%)	5 (12%)	1
Lower abdominal or pelvic pain	6 (21%)	5 (12%)	0.33
Physical examination [N]*:			
Schober test (cm)	3.2 ± 1.3 [20]	3.6 ± 1.6 [29]	0.4
Finger-to-floor distance (cm)	19.6 ± 14.9 [21]	15.1 ± 11.9 [24]	0.26
Chest expansion (cm)	4.1 ± 2.3 [17]	4.6 ± 1.9 [21]	0.42
Elevated ESR or CRP	25 (63%)	24 (59%)	0.0068
CT/MRI studies of SIJ	18 (64%)	33 (80%)	0.16

#only 69 of 72 women were included to this subgroup analysis due to absence of data regarding WP in 3 women
*[N] - number of subjects with available measurements

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The ECHOSPA MRI Module for Diagnosis of Early Spondyloarthritis (SpA): Preliminary Validation and Assessment of Diagnostic Utility. Walter P. Maksymowych[4], Damien Loeuille[2], Alexandra Desvignes-Engelbert[2], Olivia Judet[3], Isabelle Chary-Valckenaere[2], Robert Lambert[4], Maxime A. Breban[1] and Maria-Antonietta D'Agostino[3]. [1]Courbevoie, France, [2]Faculté de Médecine de Nancy, Vandoeuvre les Nancy, France, [3]Université Versailles Saint Quentin en Yvelines, Boulogne-Billancourt, France, [4]University of Alberta, Edmonton, AB, Canada

Purpose: MRI is now accepted as an imaging criterion for the classification of axial SpA but its diagnostic utility using conventional sequences in early pre-radiographic SpA requires further study. In particular, it is unclear which features on MRI of the sacroiliac joints (SIJ) have greatest diagnostic utility.

Methods: We developed an atlas of reference MRI images depicting the entire range of abnormalities observed in the SIJ. This included various patterns of bone marrow edema (linear, subchondral, capsular, posterior ligamentous, extra-articular, transitional vertebra), entheseal (capsulitis, ligamentary) and joint space inflammation, and structural lesions. These were

incorporated into an online data entry module that displays schematics of the SIJ allowing the recording of lesions in each SIJ quadrant of each slice. Three readers blinded to patient and diagnosis, independently assessed MRI scans (T1-weighted (TIW), short tau inversion recovery (STIR), and post-gadolinium fat-saturated T1W sequences) from the following subjects: 24 patients with AS, 20 age and sex-matched patients with mechanical causes of low back pain (NSBP), and 20 patients followed in the French multi-center ECHOSPA pre-radiographic SpA prospective cohort, in which patients were included for symptoms suggestive of SpA (i.e. IBP, arthritis, enthesitis or dactylitis, B27+ uveitis and family history of SpA). Semi-coronal slices through the synovial portion of the SIJ were read systematically from anterior to posterior as described in a standardized online training module developed by the Spondyloarthritis Research Consortium of Canada (SPARCC). Readers answered the following question dichotomously (yes/no): This SIJ scan confirms the presence of SpA? Sensitivity, specificity were calculated according to clinical diagnosis and reliability of detection of individual lesions was assessed using intra-class correlation coefficient (ICC).

Results: Sensitivity/specificity of MRI for the diagnosis of SpA in confirmed AS patients was 87.5/100, 95.8/80, and 83.3/83.3 for the 3 readers, respectively. The specific inflammatory lesions seen by all 3 readers in >30% of AS patients were capsular edema, ligamentous edema, and capsulitis, and each was reliably detected (κ = 0.76, 0.70, and 0.85, respectively). Sensitivity of MRI for the diagnosis of SpA in the pre-radiographic cohort was 5%, 20%, and 55% for the 3 readers respectively. There was no significant difference between readers in the detection of either specific inflammatory lesions or in the mean number of SIJ quadrants with bone edema. However, reliability for detection of erosions (ICC = 0.65) was less than for edema (ICC = 0.75) and fat infiltration (ICC = 0.75). Moreover, the reader who had the highest sensitivity (55%) rated abnormalities on T1W MRI as contributory to the diagnosis of SpA in 72.7% of patients diagnosed with SpA as compared to only one patient by either of the two other readers.

Conclusion: Our data shows that although various inflammatory features on MRI can be reliably detected, further improvement in diagnostic utility of MRI for early SpA may depend on further training of readers to recognize structural lesions on T1W MRI.

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The New ASAS Classification Criteria for Axial and Peripheral Spondylarthritis: Valid in the Latin American Patients, but. . . . John D. Londono[1], Marlon B. Porras[2], Enrique Calvo[4], Pedro Santos[3], Wilson Bautista[3], Consuelo Romero-Sánchez[3], Mabel Avila[3], Ana María Santos[3] and Rafael Valle-Oñate[3]. [1]Spondylarthropathies Group/Rheumatology Division, Hospital Militar Central/Universidad de La Sabana, Chía, Cundinamarca, Colombia, [2]Spondylarthropathies Group/Rheumatology Division, Hospital Militar Central/Universidad de La Sabana, Bogotá, Cundinamarca, Colombia, [3]Spondylarthropathies Group/Rheumatology Division, Hospital Militar Central/Universidad de La Sabana, Bogotá, Colombia, [4]Universidad Nacional de Colombia, Bogotá, Colombia

Background: Different Spondylarthritis (SpA) presentation pattern have been described in Latin American countries. The Undiferentiated Spondylarthritis (uSpA) and Reactive Arthritis (ReA) forms are frequent (about 75%), whereas Ankylosing Spondylitis (AS) is near to 25%. Mixtures of axial and peripheral manifestations are common at onset and during evolution of the disease. We assess the new ASAS classification criteria for axial and peripheral SpA in a cohort of Colombian patients with established diagnostic of the disease.

Methods: Two hundred and eighty-one consecutive patients were evaluated in the last 10 years following the ASAS recommendations. Seventy four, with established diagnostic (by experts) were selected. All of them had complete clinical and laboratory information (including HLA-B27 screening), X-ray and magnetic resonance imaging of sacroiliac joints and were under 45 years old at the beginning of the disease. We also collected a control group: patients referred to our clinic in the same period of time with chronic back pain in which the diagnostic of SpA was ruled out, after following the same protocol.

Summary of the Results: A total of 74 patients (58 males, 16 females) with definite SpA (15 AS, 39 uSpA and 20 ReA), and 48 controls (34 males, 14 females) were analyzed. Mean disease duration in SpA patients was 1,4±1,1 vs. 4,5±4,3 years; mean age at disease onset was: 25,2±7,3 vs. 30,5±7,6 years. The key clinical findings were: arthritis and enthesitis in 75,7% (vs. 4,2% in controls), and inflammatory back pain (IBP) in 56,8% of the patients (vs. 4,2%). The other differences between the groups were: twenty-seven (36,5%) HLA-B27 positive patients (vs. 4,2%); buttock pain present in 32,4% of the patients and only 8,3% of the controls. Dactylitis was present in 24,7% of the patients vs. 0% in the controls. Uveitis was documented in 10,8% of the patients but not in controls. The family history of SpA was present in 4,2% of the patients (0% in the controls). The new Axial SpA classification criteria had a sensitivity and specificity of 66,2 and 91,7%; and the peripheral SpA classification criteria had a sensitivity and specificity of 90,5 and 87,5% respectively. When we decided to test them combined, we obtained a sensitivity of 93,2% and specificity of 87,5%. The European Spondylarthritis Study Group (ESSG) criteria had a sensitivity and specificity of 91,9 and 100%.

Conclusions: Although, the new ASAS classification criteria for axial and peripheral SpA show a good performance in our cohort, the predominant mixed form of the disease in the Latin American patients and low prevalence of HLA-B27 positivity should make us keep in mind the ESSG criteria. These results should be validated in a large group of patients.

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The New ASAS Criteria for Axial SpA Does Not Predict the Development of mNYC AS at 8 Years in a Cohort of Very Early IBP Patients. Sibel Z. Aydin[2], Alex Bennett[1], Paul Emery[2], Dennis McGonagle[2] and Helena Marzo-Ortega[2]. [1]Defence Medical Rehabilitation Centre, Headley Court, Epsom, Surrey, United Kingdom, [2]Section of Musculoskeletal Diseases, The Leeds Institute of Molecular Medicine. University of Leeds, Leeds, United Kingdom

Objective: Axial SpA can be identified by using the new ASAS criteria. We aimed to test the predictive value of the imaging (MRI) and HLA-B27 arms of these criteria for the future development of Ankylosing Spondylitis (AS).

Method: An inception cohort of 33 patients with early inflammatory back pain (IBP) (median symptom duration 24 weeks) were retrospectively evaluated against both arms (imaging and HLA-B27) of the criteria. Plain radiographs and MRIs of the SIJs at baseline and radiographs after a mean duration of 8-years were assessed. MRIs were scored according to the ASAS definition of a "positive MRI" and the predictive value of both arms was compared. Further scoring to identify patients with severe MRI sacroiliitis (grade 3 according to the Leeds MRI SIJ Scoring System) was also available.

Results: All patients could be classified as axial SpA with more patients fulfilling the imaging (85%, n=28/33) than the clinical arm (58%, n=19/33) of the criteria. Eight patients with baseline evidence of radiographic sacroiliitis fulfilling the mNYC were excluded from the predictive analysis. Of the rest (25/33), n=4 patients developed AS at follow-up (all had a positive baseline MRI and 2 were HLA-B27+ve) and 11/33 had an increase in the radiographic sacroiliitis scores at 8 years. For prediction of new AS the MRI arm showed 100% sensitivity and 19% specificity whereas the HLA-B27 arm had 50% sensitivity and 43% specificity. No differences were seen between both arms for developing new AS or for progression of sacroiliitis when applying the ASAS definition of a positive MRI.

Table 1. New AS or worsening of sacroiliitis by X-rays according to the MRI findings and HLA-B27 positivity

		Positive MRI (ASAS definition)			Severe MRI (Leeds Scoring System)			HLA-B27		
		+	−	p	+	−	p	+	−	p
New AS (mNYC) n = 25	+	4	0	1	2	2	0.057	2	2	1
	−	17	4		1	20		12	9	
Progression of sacroiliitis n = 33	+	10	1	0.6	5	6	0.03	7	4	0.7
	−	17	4		2	19		11	10	

However an association was seen between development of AS (PPV 67%, NPV 91%, LR: 10) and progression of sacroiliitis (PPV 71%, NPV 76%, LR: 4.8) when using the Leeds definition of severe MRI sacroiliitis.

Conclusion: Neither arm of the new ASAS classification criteria predicted the progression of radiographic sacroiliitis (including the development of mNYC AS) over an 8 year period in this cohort of very early IBP. This

may be due to the inclusion of "mild" MRI sacroilitis in the ASAS definition of a "positive MRI" since severe MRI sacroiliitis was a better predictor.

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The Prevalence of Cardiovascular Risk Factors in Patients with Early Psoriatic Arthritis. Majed M. Khraishi[3], Rana Aslanov[1] and Don MacDonald[2]. [1]Memorial University of Newfoundland, [2]Newfoundland and Labrador Centre for Health Information, [3]Nexus Clinical Research, St Johns, NL, Canada

Background: Psoriatic Arthritis (PsA) is a chronic inflammatory disease affecting 5–35% of patients with psoriasis(PsO). Recently, both diseases were associated with an increased risk and a higher prevalence of cardiovascular (CVD) risk factors when compared to the general population.

Objective: To examine the prevalence of the risk factors of cardiovascular disease in patients with Early PsA (EPSA) and compare the prevalence of co-morbidities to those of established PsA patients.

Methods: The patients were recruited prospectively from a clinic specializing in treating patients with PsO and PsA. We set out to determine the prevalence of CVD risk factors including the Framingham Risk Score in the cohort of patients with early PsA of less than 2 years symptoms (EPSA cohort). Co-morbidities considered potential risk factors for cardiovascular disease (e.g. obesity, diabetes) were evaluated in the EPSA patients. Markers of inflammation and skin and joint disease severity and as risk factors for CVD were assessed by using CRP, ESR, DAS28, HAQ and PASI scores. The co-morbidities were compared to those of an established PsA cohort (more than 2 years of symptoms)

Results: A total of 72 patients with Early PsA and 108 patients with Established PsA were included in this analysis. Females prevailed over males in EPSA cohort (58.3% vs. 41.7%) and their age at the onset of PSO (49.80 vs. 45.13) and PsA (50.42 vs. 44.65). Females were at higher risk for CVD in association with the Framingham Risk Category above 10% (58.3% vs. 32.0%). The prevalence of hypertension in EPSA was higher in males (50% vs. 38.5%; p=0.0329), while the prevalence of diabetes in EPsA was higher in females (30.8% vs. 18.8%; p=0.0025). Generally, the distribution of conventional risk factors was similar in both cohorts, except for obesity. From total number of 35 (50%) obese people in EPSA, 19 (54.3%) were females and 16 (45.7%) were males. Odds of being obese were 2.34 times higher for patients in EPSA compared to Established PsA (OR = 0.427; p = 0.0076). The prevalence of severe psoriasis was higher in patients with Established PsA (p = 0.0507); however, the expected PASI values were 1.52 units lower in patients in Established Cohort (p= 0.0001). Also, the ESR values in EPSA were significantly lower than those in Established PsA (p = 0.0008).Tthe utilization of NSAIDs, DMARDs and Biologics was significantly higher in Established PsA compared to EPsA (p= 0.0001), while the differences in using other medications remained non-significant.

Conclusion: These results support the hypothesis that PsA even at early stages may be associated with increased co-morbidities and cardiovascular risks. Obesity was more prevalent in patients with early arthritis, raising the possibility that the metabolic syndrome that is reported to be associated with established psoriasis is also present at the onset of arthritis (PsA). Longitudinal follow-up of these patients and analysis of their genetic background may help better understand the pathogenesis of these diseases. The PsA-specific risk factors reflected the disease activity, duration and severity, which suggest a need for a multidisciplinary approach so that patients can be identified and treated effectively.

Disclosure: M. M. Khraishi: None; **R. Aslanov:** None; **D. MacDonald:** None.

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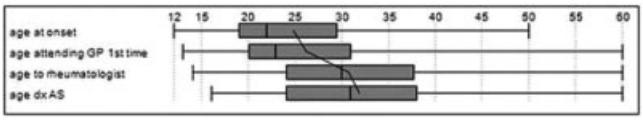
Time to Diagnosis of Ankylosing Spondylitis in an Irish Cohort and the Effect on Work Disability. Catherine Sullivan[2] and Oliver M. FitzGerald[1]. [1]Department of Rheumatology, St Vincents University Hospital, Ranelagh Dublin, Ireland, [2]Department of Rheumatology, St Vincents University Hospital, Elm Park, Dublin 4, Ireland

Introduction: Ankylosing Spondylitis (AS) is characterised by inflammatory back pain which may be associated with peripheral arthritis, enthesitis or uveitis. It has an insidious onset and results in radiographic progression with resultant pain, stiffness and loss of function. Studies have shown a delay in diagnosis of up to 7 years from onset of symtpoms.[1] Because there is no unique laboratory test to help in the diagnosis in primary care it is difficult to identify the 5% of patients with lower back pain who may have a spondyloparthropathy (SpA), including AS.[2] Research has demonstrated that patients with AS may have substantial periods of sick leave leading to a significant socioeconomic cost.[3]

Aim: We sought to identify the average time to diagnosis of AS from sypmtom onset in an Irish cohort and further to identify patterns of work disability in this group.

Methods: Patients with AS (n=100) were identified from the physiotherapy database of a Dublin tertiary referral rheumatology department. Patients were sent a postal questionnaire about disease onset, diagnosis, treatment and employment status. All replies were anonymous and 59% responded.

Results: Of the respondants 59% were male, the average age of onset of symptoms was 25 years (yrs), with diagnosis at 32 yrs and the average age when completing the survey was 44 yrs. 96.6% had some spinal involvement with 23.7% having only spinal involvement. The average time from symptom onset to diagnosis was 7.25 yrs (min 0, max 23).



74.6% of patients were on an anti-TNF agent alone, with 8.5% on an anti-TNF agent plus a synthetic disease modifying agent (DMARD), 3.4% on DMARD alone and 13.5% on neither. The time to diagnosis of AS did not impact on treatment protocol.

In total 30.5% of respondants reported not being in employment as a result of AS. 20% of those diagnosed in under 4 yrs from symptom onset were unemployed. This rose to 29.4% in those diagnosed between 5 and 9 yrs after onset and a staggering 41% of patients were unemployed in patients whose disease diagnosis was delayed by more than 10 yrs. 62.5% of participants who were off work said they did not anticipate returning to emplyment in the next 12 months.

Conclusion: In this cohort of Irish patients we see a delay in diagnosis of AS of 7 years, similar to that seen in studies in 1998 and 2003. This suggests a persistent problem with under recognition of SpA in primary care. Additionally, while not designed to look at all aspects of work disability, these data suggest a correlation between the time to diagnosis of AS and work disability. In light of these results a new diagnostic pathway for SpA has been developed and distributed to Irish General Practitioners.

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Disclosure: C. Sullivan: None; **O. M. FitzGerald:** None.

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Urolithiasis in Ankylosing Spondylitis—Are Stone Formers Also Bone Formers? Nai Lee Lui[1], Adele Carty[5], Nigil Haroon[3], Hua Shen[2], Richard Cook[2] and Robert D. Inman[4]. [1]Department of Rheumatology and Immunology, Singapore General Hospital, Singapore, [2]Department of Statistics and Actuarial Science, University of Waterloo, Canada, [3]Division of Rheumatology, Toronto Western Hospital, Toronto, ON, Canada, [4]Toronto Western Hospital, Toronto, ON, Canada, [5]Toronto Western Hospital

Objective: The frequency with which urolithiasis occurs in patients with ankylosing spondylitis (AS) has not been systematically analyzed in a large cohort. Urolithiasis represents an inherent propensity for calcium precipitation and calcification which might influence the osteoproliferation process in AS. We performed a cross-sectional analysis to determine risk factors for stone formation in AS and to address differences association with clinical features and osteoproliferation profiles.

Methods: In a longitudinal study of 504 AS patients, we conducted an analysis of all AS patients who developed urolithiasis. All patients met the modified New York criteria for AS. Demographics, clinical features, extra-articular features and co-morbidities are recorded in the database. We compared disease activity, functional indices, medical therapy and radiographic damage using the modified Stoke Ankylosing Spondylitis

Spinal Score (mSASSS) between AS patients with and without urolithiasis.

Results: Thirty eight AS patients had a history of urolithiasis, a frequency of 7.5% in this AS cohort. Seventy six AS patients with no history of urolithiasis, matched for age, gender and ethnicity, were selected as controls. There was no difference in the incidence of urolithiasis in terms of gender, ethnic groups, HLA-B27 status, smoking history or alcohol consumption. AS patients with urolithiasis were more likely to have more functional disability, as measured by Bath AS Functional Index (BASFI) (mean 5.3 versus 3.6 in control group, p=0.003). There was trends toward higher Bath AS Disease Activity Index (BASDAI) (mean 4.9 versus 4.0, p=0.09), more peripheral joint involvement (p=0.075) and higher frequency of biologic therapy (p=0.09). However, no significant difference was detected in the mSASSS scores (p=0.65) or Bath AS Metrology Index (BASMI) (p=0.98). There was a significant association of urolithiasis with diabetes (p=0.016) and with Crohn's disease (p=0.006).

Conclusion: There is no acceleration of syndesmophyte formation or spinal fusion associated with urolithiasis in AS. But AS patients with urolithiasis have unexpectedly more functional disability than AS patients overall. The higher risk with concomitant DM or Crohn's disease should alert clinicians to these co-morbidities in AS patients developing urolithiasis.

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Validation of the Patient Acceptable Work State (PAWS): Establishing Thresholds for Major Work Transition in Ankylosing Spondylitis. Walter P. Maksymowych[3], Sumati Rao[1], Annelies Boonen[2], Naijun Chen[1] and Mary Cifaldi[1]. [1]Abbott Laboratories, Abbott Park, IL, [2]University Hospital Maastricht, Maastricht, Netherlands, [3]University of Alberta, Edmonton, AB

Background: Restrictions in paid and unpaid work are a feature of AS and is measured using several instruments that score impairment on a continuous scale, although the significance of these scores in relation to major work transition such as sick leave and disability leave is unclear. Therefore, it is helpful to define work performance on a dichotomous basis as either satisfactory or not satisfactory using the patient acceptable work state (PAWS). It is further important to validate patient designation of unacceptable work state in relation to major work transition. In this study, we developed and validated 3 questions that assess PAWS.

Methods: Data were obtained from the Patient-Reported Outcomes in Employment Study (PROSE), a longitudinal, observational study of AS and work productivity. Patients with AS answered the 3 PAWS questions (yes/no) at baseline: "Considering all the different ways your disease is affecting you, if you would stay in this state for the next few months, do you consider that: 1) your ability to perform your current job is satisfactory?; 2) you will continue to work in your present job?; and 3) you may need to stop working and go on sick leave or disability leave?" Patients were considered to be PAWS responders if they answered "yes" to Questions 1 and 2 and "no" to Question 3 and nonresponders if they answered "no" to Questions 1 and 2 and "yes" to Question 3. We examined PAWS responses in relation to the BASDAI, BASFI, and the following work productivity instruments: WPAI, WLQ, QQ1 (Quality) and QQ2 (Quantity). We also compared PAWS thresholds for the WPAI, WLQ, and BASFI according to the 75th percentile of patient responders for the 3 PAWS questions.

Results: Of 204 surveys obtained, 157 were AS employed patients. Out of which, 130 indicated they would be satisfied with their current job in the next few month, given their current disease state, 145 indicated they would continue working in their present job, and 136 patients indicated they would stop working given their disease state. There were more PAWS responders than nonresponders at baseline. A significant difference was observed in BASDAI, BASFI, WPAI, WLQ, and QQ1, and QQ2 scores between PAWS1 and PAWS3 responders and nonresponders (p<0.0001). PAWS responders attained a threshold ranging from 20%–30% for WPAI presenteeism, a threshold ranging from 27.7%–30% for overall work impairment, a threshold ranging from 30%–40% for work activity impairment, a threshold of 10 for both QQ1 and QQ2, and a threshold ranging from 6.5–7 for WLQ. Similarly, PAWS responders attained a threshold ranging from 4.8–5 for BASDAI and 4.2–4.7 for BASFI.

75th percentile (with 95% confidence interval) of WPAI domain scores, BASDAI, BASFI, QQ1, QQ2, and WLQ for PAWS responders at baseline (only for employed patients)

	PAWS Question 1 Responders (N = 130)	PAWS Question 2 Responders (N = 145)	PAWS Question 3 Responders (N = 136)
WPAI presenteeism	20 (20, 30)	30 (20, 30)	30 (20, 30)
WPAI overall work impairment	29.4 (20, 30)	30 (20, 30)	30 (20, 30)
WPAI work activity impairment	30 (30, 40)	40 (30, 50)	40 (30, 40)
QQ1 (0–10)	10 (10, 10)	10 (10, 10)	10 (10, 10)
QQ2 (0–10)	10 (10, 10)	10 (10, 10)	10 (10, 10)
WLQ	6.5 (5.3,7.1)	7.0 (6.2,8.3)	6.5 (5.6,7.7)
BASDAI (0–10)	4.8 (4.0,5.4)	5.0 (4.6,5.6)	5.0 (4.4,5.6)
BASFI (0–10)	4.2 (3.5,5.4)	4.7 (3.9,5.8)	4.4 (3.5,5.4)

Conclusions: PAWS may be a valid concept defining satisfactory versus unsatisfactory work status and should be further validated for it relationship to major work transition. Further research is required to assess the change in PAWS thresholds for work productivity and health-related quality of life over time.

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Variation during Different Decades of Diagnostic and Therapeutic Delay in Patients of Ankylosing Spondylitis (AS). Giuliana Salvadorini[2], Francesca Bandinelli[2], Andrea Delle Sedie[1], Lucrezia Riente[1], Antonio Candelieri[3], Sergio Generini[2], Nicola Possemato[1], Stefano Bombardieri[1] and Marco Matucci Cerinic[2]. [1]Department Rheumatology of University of Pisa, Pisa, Italy, [2]Division of Rheumatology AOUC, University of Florence, Department of Biomedicine, DENOThe Centre, Florence, Italy, [3]Laboratory of Decision Engineering for Health Care Delivery, Department of Electronics, Informatics and Systems, University of Cosenza, Italy

Background: Ankylosing Spondylitis (AS) is a chronic, progressive, and disabling disease, but the diagnosis is often missed and markedly delayed (1). The early diagnosis is important to establish a treatment to reduce disability and modify the natural course of disease (2).

Objective: To investigate the diagnostic (DD) and therapeutic (TD) delay according to the decade of diagnosis and the correlation between DL and radiological severity score. The influence of different imaging techniques on TD has been also investigated.

Methods: 125 AS patients (45 female and 90 male, 36,5±10,2 years old at diagnosis) with disease onset between 1950 and 2008, were investigated: the time between onset and first rheumatologic visit, diagnosis (DD) and treatment (TD); the New York and ASAS criteria (3), the New York sacroiliac radiological score, the bamboo spine presence at first visit; the new imaging technique employed (magnetic resonance -MRI-, computerized tomography -CT- and scintigraphy for sacroiliac and ultrasonography -US- for periperipheral joints) at diagnosis. The difference of DD, TD and imaging technique between different onset decades ('50, '60, '70, '80, '90, '00), the correlation between DD and radiological severity, between TD and new imaging were analyzed.

Results: At first visit, 87% and 96% patients respectively met New York and mASAS criteria, with onset of symptoms 8,1±8,2 years before (28,3±10,2 years old). The delay since onset of symptoms to diagnosis and treatment was 9±8 and 12±11 years, respectively, but decreased significantly between different decades (p<0,001, Kruskal Wallis).

The severity of sacroileitis (mean 2±1, 13% IV grade at diagnosis) and bamboo spine (7,4% at diagnosis) correlated with DD (p<0,001, Pearson correlation) and decreased during decades (p<0,001, Kruskal Wallis).

The employment of new imaging technique increased significantly during decades (p<0,001) but only sacroiliac MRI significantly decreased TD (p<0,05, Mann Whitney test).

Conclusions: DD, TD, radiological severity significantly and progressively decreased during decades. In particular, the employment of sacroiliac MRI decreased time to first treatment.

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Week 12 Response Is a Better Predictor Than Baseline Disease Characteristics of Long-Term Remission in Ankylosing Spondylitis. Joachim Sieper[3], Desiree van der Heijde[4], Steve Brown[2], Frederic Lavie[1] and Aileen Pangan[2]. [1]Abbott Laboratories, Rungis, France, [2]Abbott Laboratories, Abbott Park, IL, [3]Charité Universitätsmedizin Berlin, Berlin, Germany, [4]Leiden University Medical Center, Leiden, The Netherlands

Introduction: The ASAS consensus statement for the use of anti-TNF agents for ankylosing spondylitis (AS) includes an evaluation of response after 6–12 weeks to determine if continued therapy is warranted.

Objective: To determine predictors of long-term response in AS.

Methods: In ATLAS (Adalimumab Trial Evaluating Long-Term Efficacy and Safety for AS), patients were randomized to receive adalimumab (ADA) 40 mg every other week (wk) or placebo (PBO) during a 24-wk double-blind period, followed by an open-label extension of up to 236 wks (5 yrs). Possible predictors for ASAS partial remission (PR) and low AS disease activity score (ASDAS <1.3) after 1 and 5 yrs of ADA exposure were selected *a priori*. Categorical variables included age >50 yrs, disease duration >10 yrs, abnormal baseline CRP, HLA-B27+, female gender, presence of ≥1 syndesmophyte at baseline, and responder at Wk 12 for ASAS20, ASAS40, ASAS PR, low ASDAS, MI, and BASDAI50. Continuous variables included baseline values for BASFI, BASDAI, total back pain, Patient/Physician Global Assessments of disease activity, and morning stiffness (mean of BASDAI questions 5 and 6). Logistic regression was used to assess the univariate significance of each proposed predictor for the dependent variables. A multivariate survival curve analysis was done to determine predictors of sustained (≥6 consecutive months) response.

Results: ATLAS enrolled 315 patients (208 ADA, 107 PBO). Correlation of continuous variables was tested and all are significantly different. Univariate analysis showed that Wk 12 responses were more consistent predictors of remission at 1 and 5 years than baseline disease characteristics (Table). The presence of syndesmophytes as baseline was noted to be a negative predictor for long-term remission. The multivariate survival curve analysis confirmed this observation as Wk 12 response by a specific remission criteria was a significant ($P<0.01$) predictor of achieving sustained remission using the same criteria (Hazard ratio): ASAS PR (2.59) and low ASDAS (2.92). Of those who had available data for the analysis, 57% and 46% achieved sustained low ASDAS and ASAS PR during the 5-yr study.

Table 1.

	Odds Ratio			
	ASAS PR		Low ASDAS	
Predictors	1 yr	5 yrs	1 yr	5 yrs
Age > 50 yrs	0.47†	0.39†	0.58†	0.61
Disease Duration > 10 yrs	0.74	0.77	0.78	0.77
CRP Abnormal	1.22	2.18	0.71	0.71
HLA-B27+	1.08	0.94	1.10	0.80
Female	0.94	0.51	0.73	0.72
Syndesmophyte ≥1 (BL)	0.29*	0.28	0.32*	0.15*
BASFI (BL)	0.97*	0.96*	0.97*	0.97*
BASDAI (BL)	0.89	0.85	0.88	0.79*
Total Back Pain (BL)	0.98*	0.99	0.98*	0.97*
Patient Global Assessment (BL)	0.98*	0.98†	0.98*	0.97*
Physician Global Assessment (BL)	0.99	0.98†	0.99	0.99
Morning stiffness (BL)	0.95	0.84†	0.94	0.86†
Wk 12 ASAS20	5.37*	2.95*	4.76*	2.47*
Wk 12 ASAS40	5.35*	5.97*	5.68*	3.23*
Wk 12 ASAS PR	27.86*	28.56*	10.27*	9.19*
Wk 12 ASDAS MI	4.84*	5.53*	4.32*	4.23*
Wk 12 low ASDAS	6.49*	7.22*	10.19*	10.45*
Wk 12 BASDAI50	8.40*	6.02*	5.55*	3.98*

*$P < 0.01$; †$P < 0.05$; BL - at baseline

Conclusion: Early response (Wk 12) to ADA in AS patients is a better predictor than baseline disease characteristics of who would achieve sustained remission and continue to benefit from long-term therapy of up to 5 years. Presence of syndesmophytes at baseline was a negative predictor for remission, suggesting that earlier treatment of AS patients prior to syndesmophyte formation may be beneficial.

Disclosure: J. Sieper: Abbott Laboratories, 2, 5, 8, Bristol-Myers Squibb, 2, 5, 8, Centocor, Inc., 2, 5, 8, Merck Pharmaceuticals, 5, 8, Novartis Pharmaceuticals Corporation, 5, 8, Pfizer Inc, 2, 5, 8, Roche, 2, 5, 8, sanofi-aventis, 5, 8, Schering-Pl; **D. van der Heijde:** Abbott Laboratories, 5, Amgen Inc., 5, Bristol-Myers Squibb, 5, Centocor, Inc., 5, Chugai, 5, Merck Pharmaceuticals, 5, Novartis Pharmaceuticals Corporation, 5, Pfizer Inc, 5, Roche, 5, sanofi-aventis, 5, Schering-Plough; **S. Brown:** Abbott Laboratories, 1, 3; **F. Lavie:** Abbott Laboratories, 1, 3; **A. Pangan:** Abbott Laboratories, 1, 3.

ACR Poster Session A
Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's - Clinical Aspects and Therapeutics I
Monday, November 8, 2010, 9:00 AM–6:00 PM

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A Multi-Center, Open-Label, Proof of Concept Study of Imatinib Mesylate Demonstrates No Benefit for the Treatment of Fibrosis in Patients with Early, Diffuse Systemic Sclerosis. Oliver Distler[8], Jorg H. W. Distler[9], John Varga[4], Christopher P. Denton[7], Robert A. Lafyatis[1], Fredrick M. Wigley[3], Georg Schett[2], Marco Matucci-Cerinic[10], Timothy M. Wright[5], Arthur P. Bertolino[6] and Peter Gergely, Jr[6]. [1]Boston University School of Medicine, Arlington, MA, [2]Friedrich Alexander Univ, Erlangen, Germany, [3]Johns Hopkins University, Baltimore, MD, [4]Northwestern Univ Feinberg School, Chicago, IL, [5]Novartis Institutes for Biomedical Research, Cambridge, MA, [6]Novartis Institutes for Biomedical Research, [7]Royal Free Hospital, London, United Kingdom, [8]University Hospital Zurich, Zurich, Switzerland, [9]University of Erlangen, Erlangen, Germany, [10]University of Florence, Firenze, Italy

Background and Purpose: Preclinical evidence and preliminary clinical data have suggested that imatinib mesylate may beneficially influence disease course in systemic sclerosis (SSc) mainly by suppressing TGFbeta and PDGF mediated fibrosis through the selective inhibition of the PDGFR and c-abl kinases. A multi-center, open-label, Proof of Concept (PoC) phase IIa study was conducted to evaluate the efficacy and tolerability of imatinib for the treatment of fibrosis in patients with early diffuse SSc.

Methods: Twenty-seven diffuse cutaneous SSc patients, older than 18 years, with disease duration less than 18 months and with modified Rodnan Skin Score (mRSS) of 16 – 36 were enrolled. Imatinib was initiated at an oral dose of 200 mg/day for 4 weeks then up-titrated to 400 mg/day for 2 weeks followed by 600 mg/day until Week 24, if safety and tolerability permitted. After discontinuation of imatinib, patients were followed for additional 24 weeks. Concomitant treatment with high-dose corticosteroids or immunosuppressants was not allowed. Primary outcomes were efficacy as assessed by the change in the mRSS and safety and tolerability. A 25% or greater decrease in mean mRSS with at least 50% level of proof after 24 weeks of treatment was pre-defined as a positive PoC. Further important efficacy assessments included lung functions and patient and physician global assessments. For biomarker assessments, immunohistochemistry and gene expression profiling of skin biopsy samples and assays for soluble markers were performed.

Results: Of the 27 patients enrolled, 16 completed 24 weeks of treatment with imatinib and 13 patients were followed up until week 48. Discontinuations were due to adverse events (6 patients, 22%), informed consent withdrawn (3 patients, 11 %) and other causes (5 patients, 19%). There were 5 patients with serious adverse events which included generalized edema, erosive gastritis, anemia, peripheral and facial edema, upper respiratory tract infection, viral infection, neutropenia and neutropenic infection, nausea and vomiting. No meaningful clinical improvement was observed during the treatment period for any endpoint. Positive PoC was not achieved as the mean change in mRSS at Week 24 was +9.9 %. No significant changes were observed in pulmonary function tests. Trends towards improvement in mRSS, patients and physicians global assessments were observed in the follow up period by Week 48. Biomarker analyses demonstrated a reduction of the mRNA levels of col1a1 and fibronectin.

Conclusions: The adverse events and tolerability in this study were as expected for imatinib and for the diffuse SSc population. Despite

preclinical and some preliminary clinical evidence, inhibition of PDGFR/c-abl/c-kit tyrosine kinases by imatinib had no major effect on the disease course of early diffuse systemic sclerosis in our study.

Disclosure: O. Distler: Actelion Pharmaceuticals US, 5, Bristol-Myers Squibb, 5, Ergonex, 5, Fibrogen, 5, Novartis Pharmaceuticals Corporation, 9, Pfizer Inc, 5; **J. H. W. Distler:** Novartis Pharmaceuticals Corporation, 9; **J. Varga:** Novartis Pharmaceuticals Corporation, 9; **C. P. Denton:** Novartis Pharmaceuticals Corporation, 9; **R. A. Lafyatis:** Novartis Pharmaceuticals Corporation, 9; **F. M. Wigley:** Novartis Pharmaceuticals Corporation, 9; **G. Schett:** Novartis Pharmaceuticals Corporation, 9; **M. Matucci-Cerinic:** Novartis Pharmaceuticals Corporation, 9; **T. M. Wright:** Novartis Pharmaceuticals Corporation, 3; **A. P. Bertolino:** Novartis Pharmaceuticals Corporation, 3; **P. Gergely, Jr:** Novartis Pharmaceuticals Corporation, 3.

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Baseline Differences in the "Borderline" Pulmonary Hypertension vs. "Normal" Hemodynamics: PHAROS Registry. Dinesh Khanna[4], Rajeev Saggar[4], Daniel Furst[4], Lorinda Chung[3], James Seibold[5], Tracy Frech[7], ELENA Schiopu[6], Rajan Saggar[4], Marcy Bolster[2], Virginia Steen[1] and PHAROS Investigators. [1]Georgetown University, [2]MUSC, [3]Stanford, [4]UCLA, [5]Univ of Connecticut, [6]Univ of Michigan, [7]Univ of Utah

Background: The Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) is a prospective longitudinal study of patients at risk of developing PAH and those who have definite PH. The 4th World Symposium on Pulmonary Hypertension(PH) reclassified WHO group I patients with mean pulmonary artery pressure (mPAP) on right heart catheterization(RHC) of ≤ 20 mmHg as "Normal" and 21–24 mmHg as "Borderline (boPH)" PH. Data regarding natural history and outcome of boPH PH are lacking.

Objective: To examine 1) the baseline demographics and clinical features and 2) explore long –term outcomes in SSc patients with normal resting hemodynamics vs. boPH from the PHAROS study.

Methods: Entry criteria for patients at high risk for PAH included a DLCO<55% predicted, a FVC%/DLCO% ratio >1.6 or an estimated PASP on echo > 35mmHg. Patients complete questionnaires every 6 months and are seen yearly for physician evaluation, PFTs, echocardiogram, 6 minute walk, and clinical outcomes. Right heart catheterizations (RHC) are performed based on the clinical judgment of the physician.

Results: Of 379 enrollees, 127 patients had PH at baseline. Of remaining 262 patients with SSc, 50 had mPAP <25 at baseline and 15 follow-up first RHC (N=65) and form the analysis group. Of these 65 patients, 37 (57%) had normal hemodynamics (Normal, mPAP≤20 mmHg) and 28 (43%) had boPH (boPH; mPAP21–24 mmHg). The average age of the whole group was 55.4 years, mean disease duration was 8.7 years, 83% were women, and 63% had limited cutaneous SSc. There were no differences in baseline demographics between normal and boPH groups.

Pulmonary function tests showed lower FVC% in the boPH group (69 vs. 81, $p< 0.05$); A higher proportion of patients with boPH had FVC < 70% (63% vs. 31%, $p< 0.05$). There were no significant differences in scores of patient reported outcomes (UCSD dyspnea instrument, Scleroderma-HAQ, and SF-36 scores) between 2 groups. Patients with boPH had a significantly higher RVSP, mPAP, pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistance (PVR), and transpulmonary gradient (TPG) compared to Normal, $p<0.05$ (Table). Only 1 patient in each group had PCWP≥15 at rest.

On exercise, boPH patients were more likely to have a mPAP>30 than the Normal group, 14/16 (88%) vs 11/20 (55%, p=0.04). 4 of the boPH patients had follow up caths. Of these, 1 was normal and 3 had WHO Group II PH (PVH). For Normal, 6 had repeat cath. Of these, 4 were normal, and 1 each had PAH and PVH. 2 patients died in the boPH group (PH-ILD and lung fibrosis) and 1 in the Normal group (non-SSc related).

Baseline Characteristics of Normal vs. Borderline PH

	NORMAL (N = 37)	BORDERLINE (n = 28)	p-value
Age in years, mean (SD)	56 (12)	55 (10)	0.7
Female, N%	34 (81)	27 (86)	0.5
Type of SSc, N (%)			
Limited	28 (67)	18 (62)	0.9
Disease Duration, yrs	9 (8)	8 (6)	0.5
PFT			
FVC %, mean (SD)	81 (19)	69 (16)	0.02
DLco %, mean (SD)	45 (11)	41 (18)	0.3
FVC/Dlco	1.9	2.1	0.3
Echo RVSP mmHg, mean (SD)	36 (8)	45 (13)	0.001
RHC			
mPA, mmHg, mean (SD)	17 (3)	23 (1)	<0.001
PCWP, mmHg, mean (SD)	7.7 (3.4)	10.3 (3.4)	0.02
CO, L/min, mean (SD)	5.7 (1.2)	5.4 (1.3)	0.2
PVR, dyns/cm5, mean (SD)	141 (74)	193 (66)	<0.001
TPG, mean (SD)	9 (3)	13 (4)	<0.001
6MW, meters, mean (SD)	448 (83)	396 (123)	0.08

Conclusion: Preliminary analysis of this group shows that SSc patients with borderline PH are likely to have lower FVC, higher PVR and TPG and have an abnormal response to exercise. Larger investigations on the prognostic and therapeutic implications of such borderline findings are warranted.

Disclosure: D. Khanna: Actelion Pharmaceuticals US, 2, 8, Gilead Sciences, Inc., 2, 8, NIAMS-NIH, 2, United Therapeutics, 5; **R. Saggar:** None; **D. Furst:** Abbott Laboratories, 2, 5, 8, 9, Actelion Pharmaceuticals US, 2, 5, 8, 9, Amgen Inc., 2, 5, 9, Bristol-Myers Squibb, 2, 5, 9, Centocor Ortho Biotech Inc., 9, Centocor, Inc., 5, Corrona, 3, Genentech and Biogen IDEC Inc, 2, 5, 9, Gil; **L. Chung:** Actelion Pharmaceuticals US, 8, Gilead Sciences, Inc., 2, United Therapeutics, 2; **J. Seibold:** Actelion Pharmaceuticals US, 2, 5, Gilead Sciences, Inc., 2, Pfizer Inc, 2, 5, United Therapeutics, 2, 5; **T. Frech:** None; **E. Schiopu:** Actelion Pharmaceuticals US, 8, United Therapeutics, 8; **R. Saggar:** None; **M. Bolster:** None; **V. Steen:** Actelion Pharmaceuticals US, 2, Gilead Sciences, Inc., 2, 5, United Therapeutics, 2, 5; **PHAROS Investigators:** None.

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Cigarette Smoking Is Not a Risk Factor for Systemic Sclerosis. Prateek Chaudhary[3], Xing Chen[6], Shervin Assassi[3], Olga Gorlova[7], Hilda Draeger[5], Emilio Gonzalez[8], Terry McNearney[1], Marilyn Perry[3], Jason Anderson[4] and Maureen D. Mayes[2]. [1]Indianapolis, IN, [2]University of Texas Health Science Center at Houston, Houston, TX, [3]University of Texas Health Science Center Houston, Houston, TX, [4]University of Texas Health Science Center Houston, [5]University of Texas Health Science Center San Antonio, San Antonio, TX, [6]University of Texas MD Anderson Cancer Center, Houston, TX, [7]University of Texas MD Anderson Health Science Center, Houston, TX, [8]University of Texas Medical Branch at Galveston, Galveston, TX

Background: Cigarette smoking has been well established as a risk factor for seropositive rheumatoid arthritis. Although smoking has been reported to worsen the vascular complications of systemic sclerosis (SSc), the role of cigarette exposure in susceptibility to SSc has not been previously reported. Our objective was to investigate the association of smoking with susceptibility to SSc in a large well-defined patient population.

Methods: We conducted a review of 1,417 SSc patients enrolled in the *Scleroderma Family Registry and DNA Repository* and/or the *GENISOS (Genes versus Environment in Scleroderma Outcomes Study)* cohort. Smoking history was obtained from questionnaire data, chart review and, in some cases, via telephone interview with patients if sufficient information was not provided in medical records. Information extracted or asked included questions related to smoking status, duration and quantity.

SSc patients were subsequently categorized as never smokers, past smokers or current smokers. SSc patients with available smoking data were matched 2:1 by age, gender and ethnicity with a control group from the National Health and Nutrition Examination Survey (NHANES, 1999–2006). Furthermore, past smokers and current smokers were grouped as ever smokers in the comparative analysis.

Results: The average age of 1417 enrolled patients was 53.6 years and most were female (88.1%). The majority of cases were White (78.3%) with an almost identical percentage of Latinos and Blacks (8.9% and 8.4%, respectively). Most patients had limited disease type (58.8%).

Smoking data were available in 759 (53.6%) patients. There was no significant difference in age, gender, ethnicity and SSc disease type between patients with or without available smoking data. The majority of patients had never smoked (57.4%). Patients with a smoking history classified themselves as past smokers or current smokers in 32.1% and 10.4% of cases, respectively. The average duration of smoking prior to the diagnosis of SSc in ever smokers was 18.3 years.

Overall, 42.6% (323/759) of SSc patients were ever smokers whereas 46.6% (709/1489) of matched controls in the NHANES survey had ever smoked. A Chi-Square analysis comparing cases and controls revealed that patients with SSc were less likely to be ever smokers than controls (p=0.04, OR: 0.83, 95% CI: 0.7–0.99).

Conclusion: Unlike in rheumatoid arthritis, smoking does not confer a risk for development of SSc. In fact, these data would suggest a small protective effect of smoking. Further studies are needed to investigate whether

cigarette smoking modulates auto-antibody expression or disease manifestations of SSc.

Disclosure: P. Chaudhary: None; **X. Chen:** None; **S. Assassi:** None; **O. Gorlova:** None; **H. Draeger:** None; **E. Gonzalez:** None; **T. McNearney:** None; **M. Perry:** None; **J. Anderson:** None; **M. D. Mayes:** None.

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Clinical Characteristics of Systemic Sclerosis Sine Scleroderma Associated Interstitial Lung Disease. Rohit Aggarwal[3], Mary Lucas[2], Noreen Fertig[2] and Thomas A. Medsger[1]. [1]Univ of Pittsburgh, Pittsburgh, PA, [2]University of Pittsburgh, [3]University of Pittsburgh Medical Center, Pittsburgh, PA

Aim: To describe the clinical characteristics features of systemic sclerosis sine scleroderma associated interstitial lung disease from a single tertiary care center over a 36- year period.

Methods: All 3322 patients from the tertiary care database with a clinical diagnosis of systemic sclerosis (SSc) with first visit between 1972–2008 were evaluated. Patients were classified as SSc-sine scleroderma (ssSS) if they had a clinical diagnosis of SSc with no skin thickening (Modified Rodnan skin score = 0) on physical examination and one or more of the following visceral involvement typical of SSc: distal esophageal hypomotility, pulmonary interstitial fibrosis, pulmonary arterial hypertension, SSc cardiac or renal disease. Pulmonary interstitial fibrosis was defined as the presence of pulmonary fibrosis seen on chest radiography (CXR) or high-resolution computed tomography (HRCT) scan, with or without pulmonary function criteria for restrictive lung disease: forced vital capacity in 1 second [FVC1] < 70% of predicted plus forced expiratory volume [FEV1] in 1 second/ FVC > 80% of predicted). All SSss patients with pulmonary fibrosis at first visit formed our final cohort of SSss-ILD patients, who were further studied for clinical and serological features. Serological evaluation for all SSc specific/associated autoantibodies was done on all patients with available serum.

Results: Our final cohort had 45 SSss patients with ILD at baseline. Demographics were: female (36/45, 80%), Caucasians (37/45, 82.2%), African American (7/45, 15.6 %). The mean (±SD) age (yrs) at first CTD symptom, first CTD diagnosis and first visit were 42.5 (17.2), 49.6 (16.9), and 53.5 (15.5), respectively. Mean diagnosis delay from first CTD symptom was 8.1 (9.6) yrs. Mean age at first pulmonary symptom was 51.5 (15.0) yrs. Mean duration from first non-pulmonary CTD symptom to pulmonary symptom was 8.6 (10.5) yrs, and most common first symptom was raynauds 29/45 (64.4%), followed by dyspnea (5/45, 11.1%), GI involvement (3/45, 6.7%). Most patients had multiple clinical features for SSc before the development of pulmonary disease: raynauds 36/41, 87.8 (median delay of 14.5 years from raynauds to pulmonary symptoms), arthritis 76.4%, esophageal symptoms 60.0%. 50% patients (18/36) had pulmonary symptoms before SSss diagnosis. Among various SSc-specific autoantibodies most common was ThTo 14/38 (36.8%), followed by U1 (or U2) 9/38 (23.7%), centromere 5/38. Positive ANA was seen in 93.3% (42/45) patients. Approximately 50% of patients (19/41, 46.3%) had nucleolar pattern, followed by speckled 10/41, centeromere 5/41. Most common clinical features at baseline evaluation were raynaud 39/45 (86.6%), telangiectasia 20/44, digital swelling 16/43, pyrositis 17/44, distal dysphagia 10/44. The Median, 5 and 10 year survival from the diagnosis was 16.9 years, 83.7% and 68.5% respectively.

Conclusion: Clinical features like Raynaud, arthritis and esophageal symptom generally precedes the development of pulmonary fibrosis and thus along with positive ANA can help diagnose SSss associated ILD. Nucleolar ANA pattern and anti-ThTo and anti-U1/U2 were the most common autoantibodies seen in SSss-ILD patients.

Disclosure: R. Aggarwal: None; **M. Lucas:** None; **N. Fertig:** None; **T. A. Medsger:** None.

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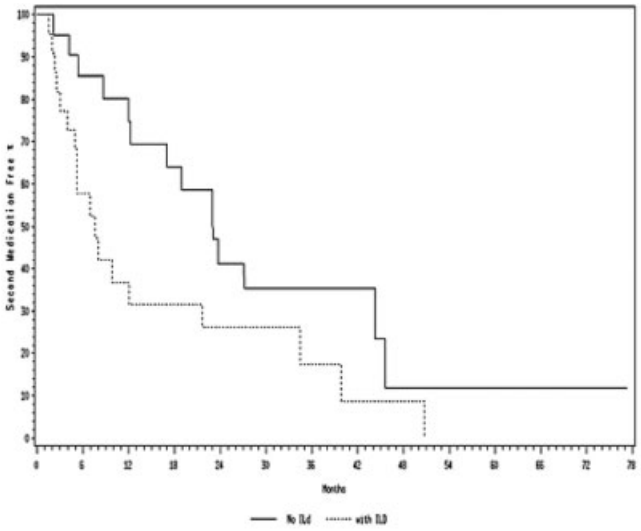
Clinical Predictive Factors on Response to Oral Monotherapy in Patients with Systemic Sclerosis-Associated Pulmonary Arterial Hypertension. Yih Chang Lin, Soumya Chatterjee, Meng Xu, Raed Dweik and Joseph Parambil. Cleveland Clinic

Rationale: Despite significant advances on vasodilator therapies for pulmonary arterial hypertension (PAH), the overall survival in systemic sclerosis-associated pulmonary arterial hypertension (SSc-PAH) remains poor and most patients eventually require more than one agent to help palliate their symptoms. This retrospective study was undertaken to better understand the relationship between clinical predictive factors and failure of oral monotherapy in SSc-PAH patients presenting in WHO functional class II/III.

Objective: To determine the time to initiation of a second therapeutic agent in SSc-PAH patients. Various parameters including demographic data, type of scleroderma and duration of disease, presence of interstitial lung disease (ILD), pulmonary function findings, hemodynamic parameters, and echocardiographic features were extracted in patients with SSc-PAH and analyzed in context with response to medical therapy with regards to time to addition of a second therapeutic agent.

Methods: We performed a retrospective review of electronic medical records between 2001–2008 involving patients with SSc-PAH. All patients had received upfront monotherapy with either an endothelin receptor antagonist or a phosphodiesterase type-5 inhibitor. Relationships of clinical predictive factors with monotherapy failure and time to utilization of a second therapeutic agent were analyzed using the Cox proportional hazard function with backward variable selection procedures.

Results: There were 66 WHO functional class II/III patients with SSc-PAH who received upfront monotherapy with either Bosentan or Sildenafil. 30 patients (45%) failed oral monotherapy after a mean duration of 13.1 ± 7.8 months. By univariate assessments African-American race ($p = 0.011$), limited type of scleroderma ($p = 0.028$), the presence of ILD ($p = 0.005$), pulmonary vascular resistance ≥6 Wood units ($p = 0.012$), and cardiac index < 2.25 L/min/m^2 ($p = 0.029$) appeared to have a significant association with the need to add a second medication. Multivariate analysis indicated that patients with ILD had a higher chance of needing a second agent with a hazard ratio of 4.12 (95% CI: 1.71– 9.94; $p = 0.001$). Patients who have SSc-PAH with ILD also had a shorter time period on monotherapy (8.9 months) compared to SSc-PAH without ILD (22.1 months) [log-rank p-value = 0.021] (**Figure 1**).



Conclusion: SSc-PAH patients who have underlying interstitial lung disease appear to be more likely to fail vasodilator monotherapy and also appear to require earlier utilization of a second therapeutic agent.

Disclosure: Y. C. Lin: None; **S. Chatterjee:** None; **M. Xu:** None; **R. Dweik:** None; **J. Parambil:** None.

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Combined Analysis of Outcomes of Sitaxentan Treatment of Pulmonary Arterial Hypertension (PAH) Associated with Systemic Sclerosis (Scleroderma). James R. Seibold[5], Marco Matucci-Cerinic[6], Michael Louie[3], Stephen Watt[3], Simon A. Teal[4], Xuexuan Liu[1], Lie-Ju Hwang[3] and David Langleben[2]. [1]Aerotek, Houston, TX, [2]Cardiology, Montreal Jewish Hospital, Montreal, Canada, [3]Pfizer Inc, New York, NY, [4]Pfizer Ltd, Tadworth, Surrey, UK, [5]Rheumatology, University of Connecticut, Farmington, Farmington, CT, [6]University of Florence, Firenze, Italy

Background: PAH is a leading cause of mortality and late disease morbidity in scleroderma. In PAH, endothelin (ET)-1 is a key vasoconstrictor, predominantly via ET_A receptors, and ET receptor antagonists are established therapies. Sitaxentan sodium is a once daily, orally bioavailable, highly selective (6500:1

ET_A vs ET_B) ET-receptor antagonist. This report is a post-hoc analysis of pooled data from the STRIDE (Sitaxentan To Relieve ImpaireD Exercise) 1, 2, and 4 trials. The aim is to describe the efficacy and safety of oral sitaxentan 100 mg once daily (QD; the currently approved dose in the European Union, Canada, and Australia) vs bosentan 125 mg twice daily (BID) and placebo in patients with PAH-scleroderma.

Methods: The STRIDE trials were double-blind, randomized, placebo-controlled trials of sitaxentan use in patients aged 12–75 years with WHO FC II–IV (predominantly II and III) idiopathic PAH or PAH associated with connective tissue disease or congenital heart disease. The trials ranged from 12 to 18 weeks in duration. The bosentan comparator arm in STRIDE- 2 was open-label.

Summary of the Results: Fifty four patients with scleroderma were included in the pooled, post-hoc analyses. Except for a higher mean (± SD) age in the sitaxentan group vs the bosentan group (62± 8 vs 55±15 y; P=0.0493), demographics and baseline disease severity were not statistically different across the 3 treatment groups. All patients were WHO FC II or III at baseline except for 1 FC IV placebo-recipient. Change in 6 minute walk distance (6MWD) and WHO FC, and time to clinical worsening were as follows:

	Placebo (N = 15)	Bosentan 125 mg bid (N = 15)	Sitaxentan 100 mg QD (N = 24)
Mean (SD) change in 6 MWD, m	−22 (79.0)	−14 (110.4)	18 (48.9)
Placebo-subtracted difference		7	39
Bosentan-subtracted difference			32
P-value vs placebo		NS	NS
P-value vs bosentan			
Change in WHO FC, n (%)			
Improved	1 (7%)	3 (20%)	6 (25%)
No Change	13 (87%)	8 (53%)	18 (75%)
Deteriorated	1 (7%)	4 (27%)	0 (0%)
P-value vs placebo		NS	NS
P-value vs bosentan			
Response*	14 (93%)	11 (73%)	24 (100%)
P-value vs placebo		NS	NS
P-value vs bosentan			0.011
Clinical Worsening, n (%)	3 (20%)	7 (47%)	0 (0%)
P-value vs placebo†		NS	0.033
P-value vs bosentan†			0.002

NS = nonsignificant.
*Improved or no change.
†P-values from log rank test for time to clinical worsening.

All therapies were well tolerated. For the safety analysis population (16 placebo, 24 sitaxentan 100 mg QD, and 16 bosentan 125 mg BID), the incidence of ALT/AST >3×ULN was 6% (placebo), 0% (sitaxentan), and 19% (bosentan). The incidence of discontinuations due to adverse events was 0% (placebo), 0% (sitaxentan) and 13% (bosentan).

Conclusions: Sitaxentan 100 mg QD appears to be an effective and well tolerated therapy for patients with PAH-scleroderma. Sitaxentan 100 mg QD significantly reduced the incidence of clinical worsening events, with fewer discontinuations due to adverse events and fewer cases of elevated ALT/AST compared with bosentan. These findings warrant further investigation in a large, prospective study.

Disclosure: J. R. Seibold: Actelion Pharmaceuticals US, 2, 5, Gilead Sciences, Inc., 2, 5, NexMed, 2, 5, Pfizer Inc, 2, 5, United Therapeutics, 2, 5; **M. Matucci-Cerinic:** Actelion Pharmaceuticals US, 2, 8, GlaxoSmithKline, 8, Pfizer Inc, 2, 8; **M. Louie:** Pfizer Inc, 3; **S. Watt:** Pfizer Inc, 3; **S. A. Teal:** Pfizer Inc, 3; **X. Liu:** Pfizer Inc, 3, 5; **L.-J. Hwang:** Pfizer Inc, 3; **D. Langleben:** Encysive Pharmaceuticals, 2, 5, Pfizer Inc, 2, 5.

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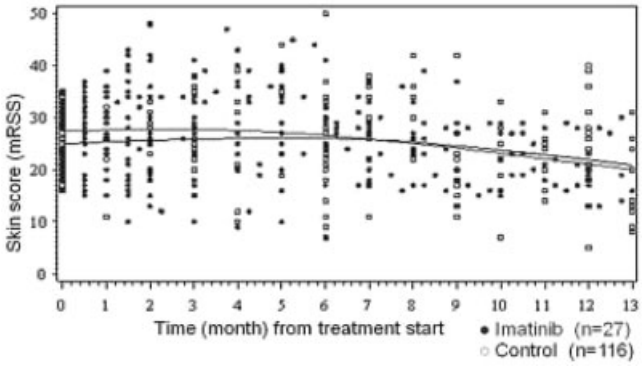
Comparative Analysis of Change in Modified Rodnan Skin Score in Patients with Diffuse Systemic Sclerosis Receiving Imatinib Mesylate Suggests Similar Disease Course to Matched Patients Receiving Standard Therapy. Christopher P. Denton[9], Svetlana I. Nihtyanova[2], John Varga[5], Oliver Distler[10], Fredrick M. Wigley[4], Robert A. Lafyatis[1], Jorg H. W. Distler[11], Georg Schett[3], Marco Matucci-Cerinic[12], Timothy M. Wright[6], Monica Costa Antunes[8], Amy Racine[8], Arthur P. Bertolino[7] and Peter Gergely, Jr[7]. [1]Boston University School of Medicine, Arlington, MA, [2]Center for Rheumatology and Connective Tissue Diseases, UCL Medical School, London, United Kingdom, [3]Friedrich Alexander Univ, Erlangen, Germany, [4]Johns Hopkins University, Baltimore, MD, [5]Northwestern Univ Feinberg School, Chicago, IL, [6]Novartis Institutes for Biomedical Research, Cambridge, MA, [7]Novartis Institutes for Biomedical Research, [8]Novartis Pharma, [9]Royal Free Hospital, London, United Kingdom, [10]University Hospital Zurich, Zurich, Switzerland, [11]University of Erlangen, Erlangen, Germany, [12]University of Florence, Firenze, Italy

Background and Purpose: Despite preclinical evidence and anecdotal case reports supporting potential benefit, clinical trials of the selective tyrosine kinase inhibitor imatinib mesylate in systemic sclerosis (SSc) have provided conflicting results with regard to efficacy as assessed by the modified Rodnan Skin score (mRSS). Our aim was to compare the course of mRSS in patients treated with imatinib in a multi-center, open-label, Proof of Concept (PoC) study in diffuse SSc [*submitted in parallel to ACR 2010*] and in patients receiving standard therapy in a well characterized large single centre cohort.

Methods: 27 cases of diffuse cutaneous SSc were treated with imatinib mesylate in an open-label prospective clinical trial. To develop a comparator cohort to help interpret clinical outcome in this trial, data from a SSc patient database (n>2000) from a large tertiary referral centre for SSc, were analyzed to select dcSSc patients whose main characteristics (disease duration and mRSS at baseline, age, sex, and concomitant diseases) matched those of the patient population in our PoC study. Patients (n=116 selected) in the control group received standard immunomodulatory treatment except for 19 (16 %) patients who received no immunosuppressive treatment. Imatinib was initiated at an oral dose of 200 mg/day for 4 weeks then up-titrated to 400 mg/day for 2 weeks followed by 600 mg/day until Week 24. A data driven descriptive analysis as well as a longitudinal mixed effects model were utilized to compare the changes in mRSS in the imatinib treated group (n=27) and in the control group (n=116).

Results: In the imatinib group in our PoC study, mean mRSS increased by 9.9 % at Week 24, however, there was a trend towards an improvement in mRSS (−21%) at Week 48, 24 weeks after the end of treatment. As compared to the control group, after an initial increase in mRSS in the imatinib group, the time course of mRSS was similar to that of the control group.



For two patients treated with imatinib who demonstrated a mRSS decrease greater than 25% at week 24, there were matching individuals from the control group with a similar profile.

Conclusions: Our data suggest that the changes in mRSS after 24 week treatment with imatinib in our PoC study are similar to those observed in cases receiving standard therapy. Such comparative analyses using large databases of well characterized cases may help better interpret results in further Proof of Concept studies of systemic sclerosis where the enrollment of a large number of patients is usually not feasible. Thus we provide a model for future early stage clinical studies in SSc.

Disclosure: C. P. Denton: Novartis Pharmaceuticals Corporation, 9; **S. I. Nihtyanova:** Novartis Pharmaceuticals Corporation, 9; **J. Varga:** Novartis Pharmaceuticals Corporation, 9; **O. Distler:** Actelion Pharmaceuticals US, 5, Bristol-Myers Squibb, 5, Ergonex, 5, Fibrogen, 5, Novartis Pharmaceuticals Corporation, 9, Pfizer Inc, 5; **F. M. Wigley:** Novartis Pharmaceuticals Corporation, 9; **R. A. Lafyatis:** Novartis Pharmaceuticals Corporation, 9; **J. H. W. Distler:** Novartis Pharmaceuticals Corporation, 9; **G. Schett:** Novartis Pharmaceuticals Corporation, 9; **M. Matucci-Cerinic:** Novartis Pharmaceuticals Corporation, 9; **T. M. Wright:** Novartis Pharmaceuticals Corporation, 3; **M. Costa Antunes:** Novartis Pharmaceuticals Corporation, 3; **A. Racine:** Novartis Pharmaceuticals Corporation, 3; **A. P. Bertolino:** Novartis Pharmaceuticals Corporation, 3; **P. Gergely, Jr:** Novartis Pharmaceuticals Corporation, 3.

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Comparison of Estimated Pulmonary Artery Systolic Pressure by Echocardiography ($PASP_{ECHO}$) and Right Heart Catheterization ($PASP_{RHC}$) in Patients with Systemic Sclerosis (Scleroderma, SSc). Elena Schiopu[3], Ann J. Impens[3], Melvyn Rubenfire[2], Fazleomar Mahmood[3] and Kristine Phillips[1]. [1]University of Michigan, Ann Arbor, MI, [2]University of Michigan, Division of Cardiology, Ann Arbor, MI, [3]University of Michigan, Scleroderma Program, Ann Arbor, MI

Background: Pulmonary hypertension (PH) has emerged as the leading cause of death among patients with SSc. Early diagnosis in the pre-symptomatic phase of SSc-PH may lead to early intervention and improved outcome. Right heart catheterization (RHC), the diagnostic gold standard, is invasive and a need for accurate, noninvasive predictors of SSc-PH remains. Echo-Doppler is widely used in clinical practice to calculate the pulmonary artery systolic pressure (PASP) from the tricuspid valve velocity and an estimate of the right atrial pressure. We correlated the echo-Doppler estimated PASP ($PASP_{ECHO}$) with that measured by RHC ($PASP_{RHC}$).

Methods: 133 patients with SSc who underwent a RHC at University of Michigan between 1997 and 2010 had a technically adequate echo-Doppler within ≤ 180 days of the procedure. Abstracted data included: demographics, type of SSc, duration of SSc WHO functional class, serum brain natriuretic peptide (BNP) and hemodynamics. Pearson's correlations were used to compare the measurements.

Results: 108 (81.2%) patients were female, 92 (69.2%) had limited SSc and the mean (SD) disease duration was 10.1 yrs (8.4). The mean (SD) time between the RHC and the echocardiogram was 37 days (40). The WHO functional class distribution was: 3 (2.3%) class I, 21 (15.8%) class II, 97 (72.9%) class III and 12 (9%) class IV. The mean (SD) BNP was 476.7pg/mL (782.5). 105 (78.9%) of the patients met criteria for PAH (mPA > 25mmHg with PCW < 15mmHg). The mean (SD) mPA for the whole group was 40.4 (16.3). The body mass index (BMI) did not differ between the PH and the non-PH groups (mean 27.6 kg/m^2 for each).

Mean $PASP_{ECHO}$ was 69.1 (28.7) and $PASP_{RHC}$ 63.7 (24.9). The correlation between $PASP_{ECHO}$ and $PASP_{RHC}$ was r=0.70, P<0.01. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for PAH for different cut-off values of $PASP_{ECHO}$ and $PASP_{RHC}$ were:

Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
$PASP_{ECHO}$ > 35	94.2	35.7	87.9	12
$PASP_{ECHO}$ > 40	91.4	50	82.7	17.2
$PASP_{ECHO}$ > 45	87.6	67.8	75.9	24
$PASP_{ECHO}$ > 50	84.7	75	72.1	27.8
$PASP_{ECHO}$ > 55	80	78.5	68.4	31.5
$PASP_{RHC}$ > 35	100	67.8	85.7	14.2
$PASP_{RHC}$ > 40	93.3	82.1	77.4	22.5

Conclusion: Among patients with SSc the estimated PASP by echo-Doppler correlated moderately well with the measured PASP by RHC. The sensitivity of $PASP_{ECHO}$ is high but the specificity is low when compared to the $PASP_{RHC}$. $PASP_{ECHO}$ can be part of a screening algorithm for predicting SSc-PH that would include other non-echocardiographic parameteres. The RHC remains the gold standard for establishing a diagnosis of SSc-PH.

Disclosure: E. Schiopu: None; **A. J. Impens:** None; **M. Rubenfire:** None; **F. Mahmood:** None; **K. Phillips:** None.

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Determination of the Accurate Incidence of Pulmonary Arterial Hypertension in Patients with Systemic Sclerosis, Mixed Connective Tissue Disease and Systemic Lupus Erythematosus by Prospective Study for 3-Years. Sumiaki Tanaka[1], Kenta Hoshi[4], Junichi Tanaka[4], Tatsuhiko Wada[4], Toshimichi Matsui[4], Tatsuo Nagai[4], Jun Okada[2] and Shunsei Hirohata[3]. [1]Drexel University College of MedicineDepartment of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Sagamihara, Kanagawa, Japan, [2]Drexel University College of MedicineDepartment of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Sagamihara, Japan, [3]Drexel University College of Medicine Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Kanagawa, Japan, [4]Drexel University College of MedicineDepartment of Rheumatology and Infectious Diseases, Kitasato University School of Medicine

Background: Connective tissue diseases (CTDs) are susceptible to pulmonary arterial hypertension (PAH), which has not been well evaluated.

Objective: To clarify the accurate incidence of PAH in patients with diffuse cutaneous SSc (dcSSc), limited cutaneous SSc (lcSSc), systemic lupus erythematosus (SLE), and mixed connective tissue disease (MCTD).

Patients and Methods: Prospective study of the 451 consecutive Japanese patients with dcSSc, lcSSc, SLE and MCTD enrolled from Nov 2006 until Mar 2010. All these patients had not been diagnosed of PAH before this study. The diagnosis of PAH was performed based on estimated systolic pulmonary arterial pressure (PAP) >40 mmHg with findings of right ventricular pressure and/or volume overload using ultrasound cardiography (UCG), followed by confirmation using right heart catheterization. Incidence of PAH (per 1000 person-years) was estimated using a generalized linear model (Poisson distribution, link function: log).

Results: 451 patients consisted of 75 dcSSc, 74 lcSSc, 230 SLE, and 82 MCTD patients. 8 patients were excluded due to the presence of PAH at the enrollment (Figure 1).

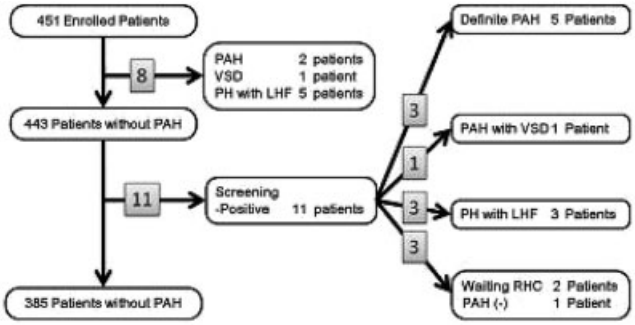

Figure 1. Follow-up Chart of Study
PAH: pulmonary arterial hypertension, VSD: ventricular septum defect, LHF: left heart failure, RHC: right heart catheterization

Thus 443 patients were enrolled and followed during 373 patient-years. Among the 443 patients, 11 patients were suspected to have PAH by UCG, and 5 of the 11 patients (2 dcSSc, 1 lcSSc, 1 SLE, 1 MCTD) were diagnosed as definite PAH. The incidence of PAH was significantly high in dcSSc and low in SLE (Table 1 and Figure 2).

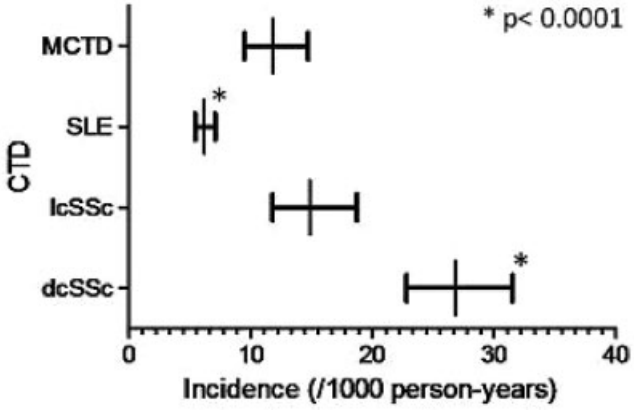

Figure 2. Incidences of PAH in various CTDs.

Table 1. Incidences of PAH in patients with various CTDs

CTDs	estimated averages	95% confidence interval
*dcSSc	26.83	22.83–31.51
lcSSc	14.87	11.81–18.74
*SLE	6.22	5.46–7.08
MCTD	11.82	9.50–14.72

Incidence:/person-years, *p < 0.0001

Conclusions: These results have disclosed the exact incidence of PAH in patients with CTDs, which was strikingly higher than that of idiopathic PAH (~2–3 per million person-years). The data also indicate that the incidence of PAH in dcSSc is much higher than that in MCTD and lcSSc.

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Difficulty Using World Health Organization Criteria To Categorize Pulmonary Hypertension in Patients with Systemic Sclerosis. Jessica K. Gordon[3], Mardi Gomberg-Maitland[5], Barbara M. Segal[2], Robyn T. Domsic[6], Ami A. Shah[4], Laura K. Hummers[4], Virginia D. Steen[1], Evelyn Horn[7] and PHAROS Investigators. [1]Georgetown University Medical Center, Washington, DC, [2]Hennepin County Medical Center, Minneapolis, MN, [3]Hospital for Special Surgery, New York, NY, [4]Johns Hopkins University, Baltimore, MD, [5]University of Chicago, [6]University of Pittsburgh, Pittsburgh, PA, [7]Weill-Cornell Medical College

Background: Pulmonary hypertension (PH) is a leading cause of death in patients (pts) with Systemic Sclerosis (SSc). The World Health Organization (WHO) classifies PH into distinct groups to provide guidance on prognosis and therapy. In SSc, pulmonary arterial hypertension (PAH, WHO group 1) is most common. However, pulmonary venous hypertension (PVH, WHO Group 2) related to heart failure with a normal ejection fraction (HFNEF, formerly known as diastolic dysfunction) and interstitial lung disease (PH-ILD, WHO group 3) occur in isolation or in combination. We examined the frequency of coincident PVH in pts with PAH and PH-ILD followed in the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) Registry.

Methods: Pts with PH were categorized by WHO criteria. A pulmonary capillary wedge pressure (PCWP) $\leq$ 15 mmHg on the initial right heart catheterization (RHC) differentiated PAH from PVH pts, with some room for clinical impression. Those with moderate or severe ILD on imaging and forced vital capacity $<$60% predicted were included in ILD-PH, regardless of PCWP. Descriptive statistics were used to show the prevalence of PVH. ANOVA, Kruskal –Wallis, and Chi Square tests were used to compare baseline features.

Results: There are 150 pts with PH in the PHAROS database: PAH – 97 (64.7%), PVH – 23 (15.3%), and PH-ILD –30 (20%) with a median duration of follow-up of 1.1 years (IQR 0.5, 2.5). There were no significant differences between groups for gender, race, or duration of disease. Pts with PAH were more likely to have limited SSc subtype (73%, 48%, and 47% for PAH, PVH, and PH-ILD groups, respectively, p=0.02) and were older (61, 55, 52 years, p $<$0.01.) There were no differences in right ventricular systolic pressure, ejection fraction, or left atrial diameter (LAD) on echo. PAH pts had higher mean PAP and pulmonary vascular resistance (PVR.) Pulmonary function test (PFT) parameters were lower in the PH-ILD group, as expected.

Of those pts classified with PAH, 14.4% had some evidence of PVH either on baseline RHC, by development of PCWP $>$15 on repeat RHC, or by exercise PCWP$>$15. Of PAH pts, 33.0% had some degree of PVH as assessed by an increased LAD of $>$ 4.0 cm on echo. (Other echo parameters of diastolic dysfunction were not available.) Of those pts classified with PH-ILD, 36.6% had evidence for PVH based on RHC, and 30% based on LAD measurement. Interestingly, there was no correlation between the LAD and the PCWP (Spearman r = 0.1437, p = 0.06.).

	WHO 1-PAH (n = 97)	WHO 2-PVH (n = 23)	WHO 3-PH-ILD (n = 30)	P-value
EVIDENCE OF PVH				
Number of pts with RHC with resting PCWP $\geq$ 16 - n (%)	8 (8.2%)	22 (95.7%)	9 (30%)	not done
Number of pts with exercise RHC with PCWP $\geq$ 16 with normal resting RHC - n (%)	6 (6.2%)	1 (4.3%)	2 (6.6%)	not done
Number of pts with LAD $>$ 4.0 cm (%)	32 (33.0%)	12 (52.2%)	9 (30%)	not done
ECHO, RHC, AND PFT DATA AT ENROLLMENT				
Ejection Fraction (echo)-%, median (IQR)	60 (55, 65)	57 (55, 60)	60 (58.5, 65)	0.27
Pulmonary Artery Systolic Pressure (echo)- mmHg, median (IQR)	56 (44, 72)	46 (37, 55)	41 (37, 57)	$<$0.001
Left Atrial Diameter - cm, median (IQR)	3.7 (3.3, 4.1)	4.0 (3.2, 4.6)	3.6 (3.4, 4.0)	0.64
Mean PAP (RHC)-mmHg, median (IQR)	35 (29, 45)	29 (26, 33.3)	29 (25.5, 31.5)	$<$0.01
Pulmonary Vascular Resistance (RHC) -dynes-sec-cm^{-5}, median (IQR)	389 (256, 643)	160 (126, 316)	285 (166, 459)	0.0001
Forced Vital Capacity-% predicted, median (IQR)	80.8 (70.8, 92.7)	78.3 (54.3, 81.7)	51.2 (44.6, 64.6)	$<$0.0001
Diffusion Capacity - % predicted, median (IQR)	39.5 (31.7, 51.5)	37.5 (33.2, 44.1)	30.6 (24.0, 36.9)	0.002

Conclusions: Despite specific classification of PH subgroups using objective information, there is evidence for some degree of PVH in a large percentage of pts categorized with PAH or PH-ILD. In SSc, strict classification using WHO criteria is difficult to accomplish. PVR and PFTs may help clarify the type of PH. The significance of these findings with respect to prognosis and treatment response will be studied in the long-term follow-up of pts in PHAROS.

Disclosure: J. K. Gordon: None; **M. Gomberg-Maitland:** ABcomm, 5, 8, Actelion Pharmaceuticals US, 2, Biomarin, 5, 8, Gilead Sciences, Inc., 2, 5, HealthmattersCME, 5, 8, Icos Corporation, 2, Lilly USA, LLC., 2, Medtronic, 5, 8, Millenium Pharmaceuticals, 5, Novartis Pharmace; **B. M. Segal:** None; **R. T. Domsic:** None; **A. A. Shah:** None; **L. K. Hummers:** None; **V. D. Steen:** Actelion Pharmaceuticals US, 2, Gilead Sciences, Inc., 2, 5, Pfizer Inc, 5, United Therapeutics, 2, 5; **E. Horn:** Actelion Pharmaceuticals US, 2, 5, 6, Gilead Sciences, Inc., 2, 5, 6, Novartis Pharmaceuticals Corporation, 5, 6, Pfizer Inc, 2, 5, 6, United Therapeutics, 2, 5, 6; **PHAROS Investigators:** Actelion Pharmaceuticals US, 2, Gilead Sciences, Inc., 2.

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Dyspnea in Scleroderma Patients from the PHAROS Registry: A Major Contributor to Disability. Lorinda Chung[2], Hubert Chen[3], Dinesh Khanna[5], Ann J. Impens[4], Virginia D. Steen[1] and PHAROS Investigators. [1]Georgetown University Medical Center, Washington, DC, [2]Stanford Univ Medical Center, Palo Alto, CA, [3]UCSF, [4]Univ of Michigan Lobby M 2500, Ann Arbor, MI, [5]University of California Los Angeles, Los Angeles, CA

Purpose: Patients with systemic sclerosis (SSc) experience substantial disability related to systemic manifestations of their disease. We sought to determine the impact of dyspnea, as measured by the University of California San Diego (UCSD) Shortness-of-Breath Questionnaire (SOBQ), on disability in SSc patients with incident pulmonary hypertension (PH) and those at high risk for developing PH.

Methods: We used data from patients enrolled in the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) study. Criteria for enrollment include age $>$18, clinical diagnosis of SSc, and either PH diagnosed by right heart catheterization (mean pulmonary artery pressure $\geq$25mmHg) within 6 months of enrollment (definite PH) OR evidence of "pre" PH defined as: either right ventricular systolic pressure (RVSP) of $\geq$40mmHg on echocardiogram OR either forced vital capacity (FVC) $>$70% and diffusing capacity of carbon monoxide (DLCO) $<$55% of predicted OR an FVC/DLCO ratio $>$1.6. For this analysis, we included subjects with complete data for self-reported measures at baseline. The SOBQ was scored on a scale of 0 (no dyspnea) to 5 (severe dyspnea). Pre- and definite PH groups were compared using Student's t-test and chi-squared tests. Univariate and multivariate linear regression were used to determine the extent to which individual factors predict disability as measured by the Health Assessment Questionnaire (HAQ). Correlations r$\leq$0.29 were considered to be weak, between 0.30 and 0.49 were moderate, and $\geq$0.50 were strong.

Results: 353 patients (223 pre-PH, 130 definite PH) with complete baseline data had a mean age of 56.9$\pm$11.6 years, and the majority of patients was female (86%), Caucasian (73%), and had limited cutaneous disease (69%). Patients with definite PH had a shorter disease duration from first non-Raynaud's symptom than those with pre-PH (8.3$\pm$7 vs. 12$\pm$17 years, p=0.02). Patients with definite PH had higher mean dyspnea scores on the SOBQ (1.7$\pm$1.1 vs. 1.2$\pm$1.0, p$<$0.0001) and a non-significant trend toward greater disability as measured by the HAQ (0.99$\pm$0.75 vs. 0.85$\pm$0.77, scale 0–3, p=0.09) than patients with pre-PH. Univariate analyses identified the SOBQ (r=0.69, p$<$0.0001), 6 minute walk distance (6MWD) (r=0.32, p$<$0.0001), DLCO (r=0.12, p=0.03), RVSP (r=0.16, p=0.004), and New York Heart Association functional class (FC) (r=0.33, p$<$0.0001) as significant predictors of the HAQ. After accounting for age, gender, race, SSc disease duration, 6MWD, FVC, DLCO, RVSP, FC, and pre- vs. definite PH group, the SOBQ explained an additional 36% of the observed variance in disability (increase in adjusted R^2 from 0.13 to 0.49, p$<$0.0001).

Conclusions: Dyspnea in SSc patients with incident PH and at high risk for developing PH is a major contributor to disability. The UCSD SOBQ may be a useful tool in assessing dyspnea in this patient population.

Disclosure: L. Chung: Actelion Pharmaceuticals US, 8, Gilead Sciences, Inc., 2, United Therapeutics, 2; **H. Chen:** United Therapeutics, 5; **D. Khanna:** Actelion Pharmaceuticals US, 2, 8, Gilead Sciences, Inc., 2, 8, NIH, 2, United Therapeutics, 8; **A. J. Impens:** None; **V. D. Steen:** Actelion Pharmaceuticals US, 2, Gilead Sciences, Inc., 2, 5, Pfizer Inc, 5, United Therapeutics, 2, 5; **PHAROS Investigators:** None.

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Epidemiology of Systemic Sclerosis in the Afro-Caribbean Population of Martinique, FWI: A Population-Based Study. Christophe Deligny, Vincent Goeb, Marie Elise Truchetet, Valentine Kahn, Veronique Dehlinger, Patrick Numéric, Christian Derancourt, Georges Jean Baptiste and Serge Arfi. CHU de Fort de France, Fort de France, Martinique

Background: Population-based studies of systemic sclerosis in African descent population are exceptional.

Objective: To retrospectively assess incidence, prevalence and characteristics of systemic sclerosis (SSc) in the Afro-Caribbean population of Martinique, FWI.

Methods: Martinique is a West Indian French part of European community, with high economical status and 400000 inhabitants. Health care is easily accessible and the same as in metropolitan France. We conducted in 2009 and 2010 a multiple-source study to retrieve all cases fulfilling ACR criteria before 1st January 2009. Three different sources were used: hospitalisation files from the Academic Hospital, specialist physicians in private and public practice (rheumatologist, dermatologist, internist and pneumologist)

Results: 89 patients (88 meeting the ACR criteria) were found (female 73, male 16, female/male ratio: 4.6) in a screening of more than 400000 medical reports. Onset of the disease was, for 38 cases between 1999 and 2008 (female 30, male 8). Prevalence on December 31, 2008 and mean annual incidence from 1999 to 2008 of SSc were respectively $19.1/10^5$ inhabitants (confidence interval 95%: 14.5 – 25) and $1.33/10^5$ inhabitants (CI 95%: 0.5–3.3) aged 20 years old and over (female $1.84/10^5$, CI 0.5–5.1). In the 89 patients, the characteristics were: mean age at diagnosis 42.1 years old (range 12–86); mean follow up: 9.4 years (range 1–33); diffuse cutaneous scleroderma: 59 (66.3 %) and limited form: 26 (29.2 %); deaths during the follow up: 16 patients. Relative proportion of antitopoisomerase I antibody (31.5 %) and anticentromere antibody (12.4%) were typical of black patients and different than for Caucasians. Another connective tissue disease was present for 29 patients (32.6%) and muscular involvement was found in 31 (34.8 %). Interstitial lung disease concerned 67.4 % of our patients. Pulmonary hypertension, found in 28 %, was implicated in 6 deaths (37.5% of all deaths). Small and large intestine involvement, present in 14 patients, was responsible for 4 deaths (25% of all deaths)). Scleroderma renal crisis was diagnosed in 2 patients. The frequency of diffuse cutaneous form, interstitial lung disease, pulmonary hypertension and hypopigmentation (50.6%) seen in our Afro-Caribbean patients, has already been described in South African and Afro-American populations.

Conclusion: This is the first population-based study devoted to SSc in an African-descent population outside of the USA. It suggests that SSc is more frequent in our population than in most Caucasians populations already studied, but less frequently encountered than in African American population. Mean clinical and biological manifestations are close to African descent populations and also seem characteristic of the disease in Black populations.

Disclosure: C. Deligny: None; **V. Goeb:** None; **M. E. Truchetet:** None; **V. Kahn:** None; **V. Dehlinger:** None; **P. Numéric:** None; **C. Derancourt:** None; **G. Jean Baptiste:** None; **S. Arfi:** None.

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European Scleroderma Study Group (ESCSG) Activity Index Is Correlated to Quality of Life Measures Both at Admission and Overtime. Gabriele Valentini[2], Michele Iudici[3], Giuseppina Abignano[3], Serena Vettori[1] and Giovanna Cuomo[3]. [1]Italy, [2]Rheumatology Unit - Second University of Naples, Napoli, Italy, [3]Rheumatology Unit- Second University of Naples, Italy

Objectives: EScSG activity index has been validated for construct validity (1). Its discriminant validity awaits to be investigated. In order to address this aspect, we investigated the relationships between the activity index and Health Assessment Questionnaire-Disability Index, and physical and mental component scores (PCS and MCS) of Short Form-36 (SF36).

Methods: 149 SSc patients consecutively admitted to a tertiary center were investigated for EScSG activity index, HAQ-DI and PCS and MCS of SF36 at enrolment and after 1 year. The change (Δ) for each measure was calculated.

Results: EScSG activity index was found to be correlated to HAQ-DI, PCS and MCS both at admission (Rho=0.41, p<0.0001; Rho=−0.41, p<0.0001; Rho= −0.29, p=0.0004, respectively) and after 1 year (Rho= 0.33, p <0.0001; Rho −0.35, p<0.0001; Rho=−0.21, p=0.0094 respectively). Moreover, the change between the value of the activity index at 1 year and that at admission (Δ activity index) was significantly correlated to ΔHAQ-DI, Δ PCS, ΔMCS (Rho=0.16, p=0.04; Rho= −0.24, p=0.003; Rho=- 0.48, p=0.0036, respectively).

Conclusion: HAQ-DI and SF36 (PCS and MCS) are considered to be validated outcome measures in SSc. Our results support the construct and the discriminant validity of EScSG activity index.

References:

1 –Valentini G. et al. European Scleroderma Study Group to define disease activity criteria for systemic sclerosis. III. Assessment of the construct validity of the preliminary activity criteria. Ann Rheum Dis 2003.

Disclosure: G. Valentini: None; **M. Iudici:** None; **G. Abignano:** None; **S. Vettori:** None; **G. Cuomo:** None.

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Evaluation of an Imatinib Response Gene Signature in Patients with Systemic Sclerosis. Lorinda Chung[3], Pedro Ruiz[5], Tammara Wood[1], Stanford Shoor[2], William Robinson[4], Michael Whitfield[1], Howard Chang[5] and David Fiorentino[5]. [1]Dartmouth Medical School, [2]Kaiser Permanente of Northern California, [3]Stanford Univ Medical Center, Palo Alto, CA, [4]Stanford Univ School of Med, Stanford, CA, [5]Stanford University School of Medicine

Purpose: We previously defined a set of imatinib-regulated genes from lesional skin of 2 patients with systemic sclerosis (SSc), termed the "imatinib response signature." We sought to further evaluate the clinical effects and gene expression changes induced by imatinib in patients with SSc.

Methods: Patients were treated with imatinib for 24 weeks at 100–400 mg daily as tolerated. The primary endpoints of the study were safety and change in modified Rodnan Skin Score (mRSS, scale 0–51) at 24 weeks compared with baseline. Lesional skin biopsies of the upper extremities were obtained at baseline, 4 and 24 weeks after therapy. Total RNA was extracted from skin biopsies using Qiagen RNeasy fibrous tissue kit. RNA was amplified using Agilent's Quick Amp Labeling Kit, no dye. Amplified skin RNA (labeled with NEN brand Cyanine 3-CTP, 100 nmol) and amplified Stratagene Human Universal Reference RNA (labeled with NEN brand Cyanine 5-CTP, 100 nmol) were competitively hybridized to Agilent Whole Human Genome 4×44K oligo microarrays.

Results: 7 patients with diffuse cutaneous SSc (dcSSc) and progressive skin disease (median disease duration 1 year, range 0.5–13) and 2 patients with limited cutaneous SSc (lcSSc) and interstitial lung disease (ILD) were enrolled in the study. Baseline mRSS in the dcSSc patients ranged from 19–49 (median 36). 7 patients (6 dcSSc, 1 lcSSc) completed 24 weeks of imatinib at a median dose of 300 mg daily. 1 patient withdrew at 4 weeks due to a keratopathy related to SSc, and 1 patient with lcSSc and severe ILD died after 8 weeks of therapy due to pneumonia and sepsis. Adverse events affecting 2/3 of patients included gastrointestinal complaints, edema, and infections. The mean mRSS improved by 32% at week 24 (p=.005).

Skin biopsies pre- and post-treatment were available from 4 additional patients, all of whom showed gene expression changes that were significantly enriched for the originally defined "imatinib response" gene set (p=.025 to 2.27×10^{-11}, hypergeometric distribution). 1 patient with lcSSc showed imatinib-induced changes in gene expression that were very similar to our original 2 patients ($p=4.6 \times 10^{-6}$). This patient had clinical improvement at week 24 with mRSS decreasing from 6 to 2, decreased ground glass opacities on high resolution chest CT, and decreased right ventricular systolic pressure from 69 to 54 mmHg on echo. The remaining 3 patients demonstrated significant repression of the genes induced by imatinib in our initial patients ($p=.029$ to 4.9×10^{-9}). These 3 patients had variable clinical responses to imatinib: 1 patient with dcSSc had mild improvement in skin but worsening ILD; the second was the lcSSc patient who died; and the third was a dcSSc patient who experienced minimal improvement in skin score. In the 3 responding patients only, imatinib upregulated genes involved in collagen metabolism and morphogenesis, while downregulating genes involved in mitosis and the cell cycle.

Conclusions: Imatinib therapy at low to moderate doses is tolerated by patients with SSc and may result in clinical improvement in a subset of patients. The cutaneous molecular response to imatinib is heterogeneous and may be partially reflected in the clinical response to the drug.

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Evaluation of the Effect of Ambrisentan on Digital Microvascular Flow in Patients with Systemic Sclerosis Using Laser Doppler Perfusion Imaging. Nilanjana Bose[2], James F. Bena[2], Charles M. Trunick[3], Debora J. Bork[2], Geetha Krishnan[2], John Petrich[2] and Soumya Chatterjee[1]. [1]Cleveland Clinic, Richmond Heights, OH, [2]Cleveland Clinic, Cleveland, OH, [3]Cleveland Clinic

Background: Raynaud's phenomenon (RP) occurs in about 95% of patients with systemic sclerosis (SSc). Vasodilators such as calcium channel blockers may not be as helpful as in primary RP, as they have little effect on the vascular fibro-proliferative changes that lead to chronic digital ischemia in SSc. Ambrisentan (Am) is a selective endothelin receptor type A (ETA)

antagonist FDA approved for the treatment of pulmonary hypertension. Am differs from bosentan in its ability to permit the vasodilatory effect of endothelin through its interaction with the endothelin-B receptor, while inhibiting its vasoconstrictive effect through its interaction with the ETA receptor. Laser Doppler perfusion imaging (LDPI) is a non-invasive technique that involves perfusion mapping of areas of skin, rather than examination of blood flow at a single point. We hypothesized that Am would increase digital microvascular flow (as measured by LDPI) in patients with SSc-induced digital ischemia.

Methods: In this randomized, double-blinded, placebo controlled trial, we enrolled 20 patients with limited SSc for < 7 years. Smokers, patients desiring pregnancy, and those with pulmonary hypertension or active digital ulcers were excluded. After initial screening, there were 2 visits: day 0 (baseline) and day 7. Raynaud's Condition Score (RCS), Scleroderma Health Assessment Questionnaire (S-HAQ) and Pain-Visual Analog Scale (P-VAS) were completed at each visit. Fifteen patients received Am 5 mg orally daily and 5 received placebo. Patients were monitored for adverse events. At each visit, 3 baseline blood flow readings of fingers of the non-dominant hand were obtained at room temperature (RT) (25°C) and after cold challenge (CC) (10°C). The primary outcome measure was mean change of blood flow in selected regions of interest (ROI) of the fingers after 1 week of therapy. Secondary outcome measures included changes in RCS, S-HAQ, and P-VAS.

Results: There were 16 females (80%); mean age was 50 years (range: 20 to 70). Patients in the Am group showed similar median changes in RCS ($p = 0.51$), S-HAQ ($p = 0.93$), and P-VAS ($p = 0.62$) scores. Overall, a median increase of 0.12 units (8%) was observed at RT, with a lower overall median change of 0.06 units (8%) after CC. Across all ROIs, the Am group tended to show larger median actual and percentage changes in perfusion [RT: 0.14 (14%); CC: 0.07 (12%)] than the placebo group [RT: −0.10 (−6%); CC: −0.28 (−18%)]. Changes were similar within ROI as well. However, none of these differences overall or within ROI reached statistical significance. No adverse events occurred. A 3-month follow up study while on drug/placebo is ongoing.

Conclusion: While on average, small improvements in perfusion were seen in the Am group, these changes were too small to reach statistical significance. Though the trend observed may imply efficacy of Am, it is also possible that vasodilation may not be its predominant mechanism of action in improving digital ischemia, and reversing the microvascular remodeling process over a longer period may be more important. We are currently evaluating this hypothesis by continuing our present study for 3 months, when data will be collected and analyzed again.

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Identification of New Autoantibody Specificities in Different Subsets of Systemic Sclerosis Patients. Guillaume Bussone[3], Hanadi Dib[4], Mathieu C. Tamby[1], Cédric Broussard[5], Loïc Guillevin[2] and Luc Mouthon[2]. [1]Université Paris Descartes, Institut Cochin, INSERM U1016, CNRS (UMR 8104), Paris, France, [2]Universite Paris Descartes, Faculte de Medecine, Pole de Medecine Interne et Centre de Reference Pour les Vascularites Necrosantes et la Sclerodermie Systemique, Hopital Cochin, Assistance Publique-Hopitaux de Paris, Paris, [3]Universite Paris Descartes, Institut Cochin, INSERM U1016, CNRS (UMR 8104), Paris, France, [4]Universite Paris Descartes, Institut Cochin, INSERM U1016, CNRS (UMR 8104), Paris, France, [5]Universite Paris Descartes, Institut Cochin, INSERM U1016, CNRS (UMR 8104), Plate-forme Proteomique Paris 5, Paris

Objectives: To identify new target auto-antigens in patients with systemic sclerosis (SSc) and antinuclear antibodies (ANA) without identified specificity, i.e. without anti-centromere, anti-topoisomerase 1 and anti-RNA-polymerase III antibodies.

Methods: We have used two-dimensional electrophoresis and immunoblotting with Hep-2 cell total and nuclear protein extracts as sources of auto-antigens. Sera from 45 SSc patients were tested in 15 pools of 3 phenotypically identical patients. Sera pool of 12 healthy blood donors was used as control.

Results: Serum IgG in 15 pools of SSc patients recognized 142±44 and 175±77 protein spots in total and nuclear protein extracts, respectively. Nineteen spots were specifically recognized by IgG from at least 4/10 pools of patients with ANA without identified specificity. Fourteen and 12 proteins were recognized by IgG from at least 75% of the 15 pools of patients in total and nuclear protein extracts, respectively. A number of these antigens were recognized with a higher intensity by IgG from patients with ANA without identified specificity than by IgG from other patients and healthy controls, including triosephosphate isomerase and superoxide dismutase [Mn], mitochondrial precursor in total protein extract, heterogeneous nuclear ribonucleoprotein L in nuclear protein extract and lamin A/C in both extracts. In addition, we identified antigens specifically recognized by IgG from subsets of phenotypically identical patients with ANA without identified specificity, including cofilin-1, peroxiredoxin-2 and calreticulin.

Conclusions: In SSc patients with ANA without identified specificity, we have identified a number of new target antigens either shared among these patients or specific for a given phenotype.

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Intravenous Immunoglobulin (IVIg) in the Treatment of Systemic Sclerosis (SSc) Associated Myopathy. Arnaud Dzeing-Ella[7], Alice Bérezné[7], Brigitte Ranque[4], François-Jérôme Authier[1], Yannick Allanore[5], Jean Cabane[3], Eric Hachulla[2], Loïc Guillevin[7] and Luc Mouthon[6]. [1]Service d'Histologie, Hôpital Henri-Mondor, Creteil, France, [2]Service de Medecine Interne, Hôpital Claude-Huriez, Lille, [3]Service de Medecine Interne, Hôpital Saint-Antoine, Paris, France, [4]Service de Medecine Interne, HEGP, Paris, France, [5]Service de Rhumatologie A, Hôpital Cochin, Paris, France, [6]Universite Paris Descartes, Faculte de Medecine, Pole de Medecine Interne et Centre de Reference Pour les Vascularites Necrosantes et la Sclerodermie Systemique, Hopital Cochin, Assistance Publique-Hopitaux de Paris, Paris, France, [7]Universite Paris Descartes, Faculte de Medecine, Pole de Medecine Interne et Centre de Reference Pour les Vascularites Necrosantes et la Sclerodermie Systemique, Hopital Cochin, Assistance Publique-Hopitaux de Paris, Paris

Background: Skeletal muscle involvement is a common feature in systemic sclerosis (SSc). Conflicting results have been reported regarding the correlation between clinicobiological presentation and pathological muscle features, nevertheless there is a general agreement that histologically proven inflammatory myopathies usually regress under high-dose corticosteroid therapy. However, use of high dose of corticosteroids could participate to the induction of scleroderma renal crisis. IVIg are used for years in the treatment of dermatomyositis and polymyositis. In association with corticosteroids and methotrexate, IVIg could help control the SSc-associated inflammatory myopathy, allowing to avoid high dose corticosteroids.

Objective: To evaluate the efficacy and the tolerance of IgIV in the treatment of SSc-associated inflammatory myopathy.

Patients and Methods: Sixteen patients (14 females, 87.5%) with SSc-associated myopathy and available muscle biopsy were restrospectively investigated from the charts of four hospital centres for the efficacy of IVIg. All of them fulfilled the American College of Rheumatology and/or Leroy and Medsger criteria for the diagnosis of SSc. Inflammatory myopathy was either biopsy proven or based on We retrospectively include 16 patients. All patients fulfilled the American College of Rheumatology and/or Leroy and Medsger criteria for the diagnosis of SSc and had a history of myopathy explored by muscle biopsy. Myopathy was defined as the presence of muscle weakness, myalgia, or creatine kinase (CK) greater than 5 N (upper normal range), together with evidence of muscle involvement on electromyography (low voltage and/or short duration potential during maximal contraction, fibrillation or sharp wave) or on muscle biopsy.

Results: The 16 patients had a mean age of 40.4 years, a diffuse SSc in 87.5% of the cases with a mean Rodnan score of 16 at the time of inclusion into the study. Patients were followed for a mean of 2 years. Ninety three percent of patients had interstitial lung disease. Fifty percent of the patients had pulmonary fibrosis and/or left ventricular failure. Anti-PM-Scl and anti-RNP autoantibodies were detected in 18.75% and 12.5% of the patients, respectively. All patients received IVIg in the setting of failure of corticosteroids and immunosuppressants. IVIg were prescribed at a dose of 2 mg/kg every 4 weeks. Fourteen (87.5%) patients had a favorable outcome, with complete response in 5 patients and partial response in others. Half of patients relapsed after a mean follow up of 6.4 months after interruption of IVIg treatment. The treatment was well tolerated and no case of renal failure was notified.

Conclusion: IVIg may be helpful in the treatment of SSc-associated myopathy in case of failure of corticosteroids and/or methotrexate. However, the therapeutic effect is only suspensive. Prospective randomized studies are needed in order to evaluate the true efficacy of IVIg in SSc-associated myopathy.

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Modeling Smoking in Systemic Sclerosis: A Comparison of Different Statistical Approaches. Marie Hudson[3], Ernest Lo[2], Russell Steele[3] and Murray Baron[1]. [1]Jewish General Hospital, Montreal, QC, Canada, [2]Lady Davis Institute, Jewish General Hospital, [3]McGill University

Background: Vascular disease is ubiquitous in SSc and cigarette smoking is well known to contribute to vascular disease. There is no standard way of modelling smoking in epidemiologic studies. The purpose of this study was to demonstrate the impact of different methods of modelling smoking when determining vascular outcomes in SSc.

Methods: We undertook a study using data from the Canadian Scleroderma Research Group Registry. Patients self-reported their smoking history, including intensity, duration and time since cessation. Vascular outcomes were severity of Raynaud's phenomenon, presence of finger ulcers and severity of finger ulcers. Five regression models using various definitions of smoking were developed: Model 1 compared ever to never smoking; Model 2 compared current and past smoking to never smoking; Model 3 modeled smoking using polynomial contrasts, treating never, past and current smoking as ordered values of a single variable; Model 4 modeled smoking status as current versus non-current; and, Model 5 represented smoking using the Comprehensive Smoking Index, which integrates smoking intensity, duration and time since cessation into a single covariate (Leffondre K et al. 2006 Stat Med 25:4132–46). All regression models were adjusted for age, sex, ethnicity, disease duration and limited or diffuse skin involvement.

Results: This study included 606 SSc patients, of which 87% were women, 90% were white, mean age was 55 (± 12) years, mean disease duration was 11 (± 9) years, and 36% had diffuse disease. Of these, 16% were current, 42% past and 42% never smokers. Current and past smokers smoked a mean of 25 (±17) and 17 (±18) pack-years, respectively. Smoking duration varied from 1 to 60 years, with past smokers having a shorter duration than current smokers (18.3 vs. 31.7 years, respectively). Past smokers stopped smoking approximately 16 (±12) years prior to their baseline registry visit, although this varied from 1 to 50 years. The results of the regression analyses for the five models of smoking are summarized in Table 1.

Table 1. Summary of the regression results of the 5 different models of smoking

Model 1: Ever vs. Never Smoking						
Outcome Variable	**b-EVER[a]**	**p-value**				
Severity of Raynaud's (0–10)	0.007	0.92				
Presence of finger ulcers	−0.03	0.88				
Severity of finger ulcers (0–10)	−0.01	0.69				
Model 2: Current vs. Never and Past vs. Never						
Outcome Variable	**b-CURRENT[b]**	**p-value**		**b-PAST[c]**	**p-value**	
Severity of Raynaud's (0–10)	0.20	0.05	.	−0.06	0.41	
Presence of finger ulcers	0.40	0.15		−0.18	0.36	
Severity of finger ulcers (0–10)	0.04	0.35		−0.03	0.33	
Model 3: Polynomial Contrasts						
Outcome Variable	**b-LINEAR[d]**	**p-value**		**b-QUAD[e]**	**p-value**	
Severity of Raynaud's (0–10)	1.14	0.18		1.85	0.03	*
Presence of finger ulcers	2.19	0.35		4.41	0.05	*
Severity of finger ulcers (0–10)	0.19	0.65		0.66	0.10	*
Model 4: Current vs. Non-current Smoking						
Outcome Variable	**b-CURRENT[f]**	**p-value**				
Severity of Raynaud's (0–10)	0.23	0.01	*			
Presence of finger ulcers	0.50	0.06	.			
Severity of finger ulcers (0–10)	0.06	0.16				
Model 5: Comprehensive Smoking Index (CSI)						
Outcome Variable	**b-CSI[g]**	**p-value**				
Severity of Raynaud's (0–10)	0.52	0.002	**			
Presence of finger ulcers	1.21	0.002	**			
Severity of finger ulcers (0–10)	0.12	0.07	*			

. p < 0.1, *p < 0.05, **p < 0.01
[a]Estimated regression coefficient for Ever vs. Never smokers;
[b]Estimated regression coefficient for Current vs. Never smokers;
[c]Estimated regression coefficient for Past vs. Never smokers;
[d]Estimated regression coefficient for the linear contrast covariate;
[e]Estimated regression coefficient for the quadratic contrast covariate;
[f]Estimated regression coefficient for Current vs. Non-current smokers;
[g]Estimated regression coefficient for the CSI

Model 1 *did not detect any significant effect of smoking on the vascular outcomes*. Models 2 and 3 showed a 'U-shaped' trend in the effect of smoking, with *past smokers appearing healthier than both never and current smokers,* with this effect reaching statistical significance in Model 3 only. Model 4 detected a negative effect of smoking on the severity of vascular outcomes, reaching statistical significance for the severity of Raynaud's and showing a strong trend for the presence of finger ulcers. The results of Model 5 were similar to those of Model 4, but with much stronger statistical significance.

Conclusions: These findings highlight the importance of proper modeling of smoking. Simple models may mask important effects of smoking on vascular outcomes in SSc. The CSI was the most sensitive model because it accounts for the wide range of smoking exposure.

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Nailfold Microangiopathy and Pheripheral Blood Perfusion Correlate with Internal Organ Involvement in Sistemic Sclerosis. Alberto Sulli[1], Carmela Ferrone[2], Carmen Pizzorni[2], Elisa Alessandri[2], Francesca Ravera[2], Giuseppe Zampogna[2], Bruno Seriolo[2] and Maurizio Cutolo[1]. [1]Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy, [2]Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy

Background: Nailfold microangiopathy and peripheral blood hypoperfusion are key features of early systemic sclerosis (SSc) and internal organ involvement/skin lesions are frequently discovered during the follow-up.

Aim: The aim of the study was to investigate possible correlations between nailfold capillary abnormalities, pheripheral blood perfusion (PBP), and internal organ involvement in patients affected by SSc.

Methods: Seventy-one consecutive SSc patients (mean age 61±13 years, disease duration 7±5 years) were evaluated. Nailfold microangiopathy was detected by nailfold videocapillaroscopy (NVC), which was performed on 2nd to 5th finger of both hands, and the average semiquantitative scores for the capillaroscopic parameters were calculated1,2. PBP was analyzed by laser Doppler flowmetry at the central area of the fingertips of the same fingers, and the average value of PBP was recorded as perfusion units (PU)3. Oesophageal involvement was detected by manometry, pulmonary function by lung volume tests, DLCO and CT; cardiac performance was investigated by Doppler echocardiography, renal function by laboratory tests and arterial Doppler echography; active or recent history of ulcers were assessed by both clinical interview and examination. Statistical analysis was performed by non-parametric tests.

Results: PBP was found significantly lower in SSc patients with active or recent history of ulcers (median 28 PU), when compared with those without ulcers (median 55 PU) ($p=0.02$). PBP was also lower in patients with esophageal, lung, renal, and pulmonary arterial involvement (median 29, 28, 29, 25 PU, respectively), than in those without (median 51, 46, 41, 57 PU, respectively), but this was not statistically significant ($p=0.11$), possibly due to the small study population. SSc patients showing higher microvascular abnormalities scores for NVC parameters like microhaemorrhages, capillary number, and capillary disorganization had significantly lower PBP ($p<0.03$). Oesophageal involvement correlated with higher NVC scores for capillary number and disorganization ($p=0.03$); lung disease with higher score for capillary disorganization ($p=0.04$); renal function impairment with higher scores for capillary number and disorganization ($p=0.04$); pulmonary arterial hypertension with higher scores for enlarged capillaries, capillary number, ramification and disorganization ($p=0.05$); digital ulcers with higher scores for capillary number, ramification and disorganization ($p=0.01$), as well as with lower score for giant capillaries ($p=0.003$).

Conclusions: Nailfold capillary abnormalities extent negatively correlates with PBP and positively with internal organ involvement. Internal organ involvement seems to be associated with reduced PBP, but this should be confirmed on a larger SSc population. Finally, the occurrence of skin digital ulcers is associated with blunted peripheral blood perfusion in SSc patients, as well as with higher scores for several NVC parameters.

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Oral N-acetylcysteine in the Treatment of Raynaud's Phenomenon Secondary to Systemic Sclerosis: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Marcelo José Uchoa Correa[2], Henrique A. Mariz[3], Luis Eduardo Coelho Andrade[3] and Cristiane Kayser[1]. [1]Universidade Federal de São Palo, Brazil, [2]Universidade Federal de São Paulo, São Paulo, Brazil, [3]Universidade Federal de São Paulo, Brazil

Purpose: Intravenous N-acetylcysteine has been suggested to be useful in the treatment of Raynaud's phenomenon (RP) in patients with systemic sclerosis (SSc). This study aimed to evaluate the safety and the efficacy of oral N-acetylcysteine on the digital skin microvascular blood flow in patients with RP secondary to SSc.

Methods: This was a randomized, double-blind, placebo-controlled clinical trial with 42 patients with RP secondary to SSc. Patients were randomly assigned to receive oral N-acetylcysteine 600 mg three times daily or placebo three times daily for 4 weeks. Primary outcome was changes in digital skin microvascular blood flow before and after cold stimulus (CS) using laser Doppler imaging (LDI) at baseline and at week 4. Frequency of Raynaud's attacks, RP severity visual analog scale (VAS), RP pain VAS, and the number of digital ulcers were also evaluated at baseline and at week 4.

Results: 21 SSc patients (mean age 45.6±9.5 years) were randomly assigned to receive oral N-acetylcysteine and 21 patients (mean age 45.0±12.7 years), to receive placebo. Oral N-acetylcysteine was generally well tolerated, and at the end of 4 weeks nobody discontinue the treatment. There were no significant changes in digital skin blood flow measured by LDI before or after CS following 4 weeks of N-acetylcysteine or placebo. Both groups showed significant improvement of the frequency of Raynaud's attacks, RP severity VAS, and RP pain VAS after 4 weeks of treatment, with no difference between groups. There was no significant change in the number of digital ulcers in both groups after placebo or N-acetylcysteine treatment.

Conclusions: Oral N-acetylcysteine did not demonstrate increase on the digital skin blood flow measured by laser Doppler imaging in this short-time study in patients with SSc. Oral N-acetylcysteine was not significantly better than placebo in improving severity of RP in patients with RP secondary to SSc.

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Outcomes of Barrett's Esophagus Related to Systemic Sclerosis: A 3-Year EULAR/EUSTAR Prospective Follow-Up Study. Julien Wipff[11], Romain Coriat[9], Michela Masciocchi[5], Paola Caramaschi[2], Chris T. Derk[7], Eric Hachulla[8], Valeria Riccieri[12], Luc Mouthon[10], Dorota Krasowska[1], L. P. Ananyeva[6], Andre Kahan[3], Marco Matucci-Cerinic[13], Stanislas Chaussade[9] and Yannick Allanore[4]. [1]Department of Dermatology, Medical University of Lublin, Lublin, [2]Department of Medicine, Verona University, Verona, [3]Hopital Cochin, Paris, France, [4]Hopitaux de Paris Cochin, Paris, France, [5]Immunological Clinic, Mangiagalli Regina Elena Fundation, Milan, [6]Institute of Rheumatology, Russian Academy of Medical Science, Moscow, [7]Jefferson Medical College, Philadelphia, PA, [8]National Scleroderma Centre, Lille Cedex, France, [9]Paris Descartes University, Gastroenterology Dpt, Cochin Hospital, [10]Paris Descartes University, Internal Medicine Dpt, Cochin Hospital, [11]Paris Descartes University, Rheumatology A Dpt, Cochin Hospital, [12]Sapienza University of Rome, Medical Clinic and Therapy Department, Rome, [13]University of Florence, Firenze, Italy

Background: Barrett's esophagus (BE) is the major risk factor for esophageal adenocarcinoma (EAC). Systemic sclerosis (SSc) is associated with an increased risk of BE related to chronic reflux.

Objectives: To determine the outcomes of BE and estimate the EAC risk in SSc patients over a 3-year prospective study.

Methods: SSc patients were recruited through EUSTAR network centers. Inclusion criterion was a recent histological finding of BE. The patients were then prospectively followed and, as recommended, a second esophageal endoscopy was performed according to the presence at baseline of BE-related dysplasia.

Results: 50 SSc patients with BE (40 without and 10 with dysplasia) were included and 46 completed the follow-up (138 patients-year). During the 3-year follow-up, 4/46 BE patients (3%/year) were diagnosed with high-grade dysplasia/EAC, of which one developed cardial EAC. EAC incidence in the BE sub-group with dysplasia increased to 4%/year compared to the absence of EAC case in the BE sub-group without dysplasia at baseline.

Conclusion: Our results, in accordance with previous published data suggesting an increased risk of esophageal or cardial adenocarcinoma in SSc, highlight the need for accurate follow-up of BE SSc patients at risk of developing adenocarcinoma.

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Preclinical Evaluation of Cardiac Involvement in Systemic Sclerosis Patients by Speckle Tracking Strain Analysis. Anne A. Schouffoer[3], Kai H. Yiu[1], Maarten K. Ninaber[2], Jan Stolk[2], Thea P. M. Vliet-Vlieland[3], Eduard R. Holman[1], Tom W. J. Huizinga[3], Jeroen J. Bax[1], Nina Ajmone Marsan[1] and Annemie J. M. Schuerwegh[4]. [1]Department of Cardiology, Leiden, The Netherlands, [2]Department of Pulmonology, Leiden, The Netherlands, [3]Department of Rheumatology, Leiden, The Netherlands, [4]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands

Background: Cardiac involvement is common in patients with systemic sclerosis (SSc) and a well-known prognostic factor. Preclinical identification is therefore of crucial importance, although conventional echocardiography assessment showed limited sensitivity for the assessment of subtle changes in cardiac function. The aim of the study was to assess the value of the novel echocardiographic speckle tracking 3 directional (longitudinal, circumferential and radial) strain analysis to detect cardiac involvement in SSc patients and to investigate the association with rhythm disturbances, lung function parameters and cardiopulmonary exercise (CPET) parameters.

Methods: A total of 104 patients were included during a SSc screening program, which included pulmonary function tests, CPET, 24-hr ECG Holter recording and echocardiography with speckle tracking analysis. Echocardiographic data were compared with those obtained from 37 age and sex matched healthy controls.

Results: The mean age of the study population was 54 ± 11 years. Fifhty-seven patients presented a diffuse (d) SSc and 47 a limited (l) SSc. Disease duration was 8.1 ± 6.2 yr; Vital Capacity was 94.4 ± 14.4 % predicted, and % predicted maximum oxygen uptake (VO2max) was 90.6 ± 20.4%. Twenty-eight patients (27.7 %) had abnormal ECG holter findings defined by ventricular tachycardia or frequent ventricular ectopics >100 per day. Echocardiographic findings in SSc patients are shown in table 1. At the multivariable analysis, decreased left ventricular (LV) systolic function as assessed by global circumferential strain (B −0.52, 95% CI −5.63, −2.23, $p<0.01$) was independently associated with of lower % predicted VO2 max. Patients with 24-hr ECG Holter abnormalities showed significantly more decreased longitudinal (−18.5 ± 1.5 vs −17.1 ± 2.1, $p<0.01$) and circumferential (−18.7 ± 2.0 vs −17.3 ± 2.5, $p=0.01$) strain then patients without

abnormalities and circumferential strain was independently associated (HR 1.55, 95% CI 1.18 – 2.03, p<0.01) with abnormal Holter findings. For both % predicted VO2max and ECG holter the conventional LV echocardiografic parameter ejection fraction showed no significant difference.

	Controls (n = 37)	SSc (n = 104)	p value	SSc (n = 47)	dSSc (n = 57)	p value
Conventional echocardiographic parameters						
LV end diastolic volume (ml)	70.6 ± 20.6	76.0 ± 25.4	0.21	73.6 ± 23.1	77.9 ± 27.3	0.38
LV end systolic volume (ml)	26.6 ± 5.7	29.1 ± 13.1	0.13	29.6 ± 14.3	28.7 ± 12.2	0.75
LV ejection fraction (%)	64.6 ± 4.4	63.5 ± 7.2	0.20	64.8 ± 6.3	62.0 ± 6.3	0.18
PASP (mmHg)	21.7 ± 6.3	28.9 ± 8.7	**<0.01**	29.5 ± 7.9	28.3 ± 9.3	0.51
Diastolic function						
E diastolic velocity (cm/s)	75.8 ± 13.8	78.0 ± 18.1	0.45	76.5 ± 19.1	79.3 ± 17.3	0.45
A diastolic velocity (cm/s)	63.0 ± 14.5	74.8 ± 21.0	**<0.01**	17.3 ± 21.7	75.2 ± 20.5	0.84
E/A ratio	1.3 ± 0.3	1.1 ± 0.4	**0.04**	1.09 ± 0.37	1.1 ± 0.41	0.61
E′velocity (cm/s)	9.0 ± 2.3	7.0 ± 2.2	**<0.01**	6.6 ± 2.2	7.3 ± 2.2	0.08
E/E′ ratio	8.7 ± 2.3	11.9 ± 3.8	**<0.01**	12.3 ± 3.8	11.6 ± 3.8	0.38
Speckle tracking						
Global longitudinal strain (%)	−21.3 ± 1.7	−18.2 ± 1.8	**<0.01**	−18.7 ± 1.5	−17.9 ± 1.9	**0.01**
Global circumferential strain (%)	−21.3 ± 2.1	−18.3 ± 2.3	**<0.01**	−19.1 ± 2.0	−17.6 ± 2.2	**<0.01**
Global radial strain (%)	40.3 ± 12.4	37.0 ± 13.9	0.18	37.5 ± 13.5	36.5 ± 14.3	0.73

LV = Left ventricular; PASP = pulmonary arterial systolic pressure; E = early; A = late; E′ = early diastolic velocity at basal mitral annulus

Conclusion: Speckle tracking strain analysis is able to detect subtle myocardial systolic dysfunction in patients with SSc. Decreased global circumferential strain was associated with lower exercise tolerability and rhythm disturbances, whereas LV ejection fraction was not. Therefore, the use of speckle tracking analysis may facilitate preclinical identification of cardiac involvement in SSc.

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Preliminary Composite Response Index for Raynaud's Phenomenon. Dinesh Khanna[2], Paul Maranian[2], Daniel Furst[2], James Seibold[3], Marco Matucci Cerinic[4], Jeff Gregory[1] and Harold Paulus[2]. [1]MediQuest, [2]UCLA, [3]Univ of Conneticut, [4]Univ of Florence

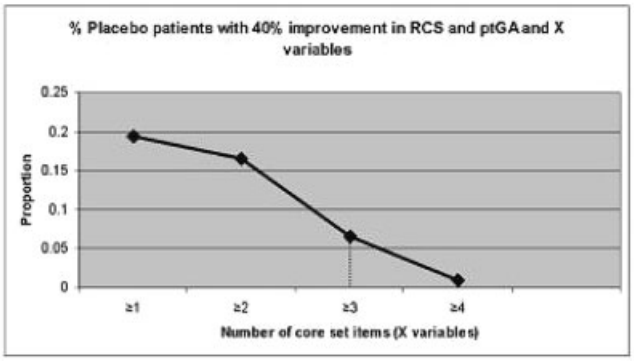
Background: In interventional studies of RP, variable responses are seen in different outcome measures and high placebo response is common. Our goal was to develop a Composite Response Index in RP that would improve the ability to measure efficacy of an investigational drug and facilitate the ability to compare responses across trials.

Methods: We analyzed 249 patients with primary or secondary RP in the placebo group who participated in 3 RCT (MediQuest Therapeutics). 8 core set measures were assessed in these studies: Raynaud's Condition Score (RCS- assesses the level of difficulty experienced due to RP), pt. assessment of RP, physician assessment of RP, pain, numbness, tingling, average number of attacks per day and duration of attacks. We conducted an online survey of scleroderma experts and asked them to rank all items on their importance for RCT and to identify core set items that must be included in RCTs.

Daily patient logs of Raynaud attacks were used to compute average number of attacks per day, average duration of attacks, daily averages of pt-reported pain, numbness, and tingling associated with each reported attack and a daily RCS. pt (ptGA) and physician assessments of RP were recorded weekly. Daily averages were used to compute weekly averages for the period between physician visits, and the weekly averages were averaged for the run-in period and for the treatment period. Percent improvement between run-in and treatment periods was calculated for 8 outcome measures. Since pain, numbness, and tingling showed a high degree of correlation (pairwise Pearson correlations of 0.76, 0.69, and 0.78), they were combined into a single measure (Attack symptoms) by selecting the %improvement of the outcome that showed the highest level of improvement, resulting in 6 core measures.

Preliminary definitions required ≥ x% improvement in y of the 6 variables where x was set at 10%, 20%, 30%, 40%, 50%, and 60% and y was set as 2, 3, 4, 5, or 6, variables. We hypothesized that placebo response should be <10% to show a difference from an effective drug.

Results: 50% and 40% of experts (N=71) ranked RCS and ptGA as top two measures for RCT and 93% and 92% stated that RCS and ptGA must be included in a composite index. Therefore, we assessed a definition requiring RCS and ptGA improvement by xx% along with y of the 4 other core set items to define a composite improvement. 92.8% of placebo-treated patients showed ≥10% improvement in at least one core set item with 38.5% showing ≥60% improvement in at least one variable. An improvement of 40% in both RCS and in ptGA, and 40% in 3 of the remaining 4 variables was associated with placebo response of 6% and provided greatest discrimination between 10–30% vs. 50–60% improvement in core set measures.



Conclusion: We have developed a preliminary composite response index for RCTs in RP. This index needs to be compared with an effective agent in a RCT to see if it can improve the ability to measure efficacy.

Disclosure: D. Khanna: MediQuest, 5; **P. Maranian:** None; **D. Furst:** None; **J. Seibold:** None; **M. Matucci Cerinic:** None; **J. Gregory:** MediQuest, 3; **H. Paulus:** None.

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Prevalence of Coronary Heart Disease in a Cohort of Australian Scleroderma Patients. Gene-Siew Ngian[2], Joanne Sahhar[7], Jill Byron[14], Susanna Proudman[9], Catherine Hill[8], Janet Roddy[11], Peter Youssef[12], Kathleen Tymms[1], Leslie Schrieber[10], Wendy Stevens[14], Jane Zochling[6], Peter Nash[15], Allan Sturgess[13], Gabor Major[5], Ian Wicks[3] and Sharon Van Doornum[4]. [1]Canberra Rheumatology, Australia, [2]Department of Medicine (RMH/WH), University of Melbourne, Melbourne, Victoria, Australia, [3]Department of Medicine (RMH/WH), University of Melbourne, Melbourne, Australia, [4]Department of Medicine (RMH/WH), University of Melbourne, [5]John Hunter Hospital, Newcastle, Australia, [6]Menzies Research Institute, University of Tasmania, Hobart, Australia, [7]Monash Medical Centre, Melbourne, Australia, [8]Queen Elizabeth Hospital, Adelaide, Australia, [9]Royal Adelaide Hospital, Adelaide, Australia, [10]Royal North Shore Hospital, Sydney, Australia, [11]Royal Perth Hospital, Perth, Australia, [12]Royal Prince Alfred Hospital, Sydney, Australia, [13]St George Hospital, Sydney, Australia, [14]St Vincent's Hospital, Melbourne, Australia, [15]Sunshine Coast Rheumatology, Australia

Background: It is not established whether accelerated atherosclerosis occurs in scleroderma (SSc). Increased rates of peripheral vascular disease have been reported[1], however the prevalence of coronary heart disease (CHD) remains unknown.

Methods: We reviewed the prevalence of CHD and traditional and non-traditional cardiovascular risk factors in a well-characterized cohort of Australian SSc patients. Data were collected prospectively at 12 centres around Australia from January 2007 to May 2010 as part of a longitudinal cohort study instituted by the Australian SSc Interest Group.

Patients were identified as having CHD if they reported percutaneous coronary intervention, coronary artery bypass grafting, angina or myocardial infarction. Data from the patient's most recent review were used to obtain a cross-sectional view of the cohort.

We compared the prevalence of CHD in our cohort with Australian population prevalence estimates from the National Health Survey 2007 – 2008[2]. Chi square and two-sample *t* tests were used to analyze differences between SSc patients with and without CHD.

Results: Of the 850 SSc patients included in the analysis, 88 had CHD. The prevalence of CHD in our cohort was therefore 10.3% (95% confidence interval 8.3%–12.4%). Patient characteristics are summarized in table 1).

Table 1. Demographics and cardiovascular risk factors in SSc patients with and without CHD

	CHD present (n = 88)	CHD absent (n = 762)	p-value
	N (%) or mean ± standard deviation		
Female	68 (77.3%)	667 (87.5%)	0.009
Subclass			
- limited	65 (73.9%)	510 (66.9%)	0.21
- diffuse	21 (23.9%)	231 (30.3%)	
- sine	0	2 (0.3%)	
- not documented	2 (2.3%)	19 (2.5%)	
Mean age	67.5 ± 9.7 years	58.3 ± 12.3 years	<0.001
Hypertension	59 (67.1%)	277 (36.4%)	<0.001
Hypercholesterolaemia	42 (47.7%)	145 (19.0%)	<0.001
Diabetes mellitus	12 (13.6%)	25 (3.3%)	<0.001
Family history of heart disease*	31 (60.8%)	162 (40.1%)	0.006
Ever smoked	51 (58.6%)	354 (47.3%)	0.047
Obesity (BMI ≥ 30 kg/m^2)	22 (25%)	145 (19.0%)	0.18
Age at diagnosis of SSc	50.8 ± 15.3 years	45.3 ± 13.9 years	0.001
Duration of SSc	16.4 ± 10.8 years	12.8 ± 10.2 years	0.004
Corticosteroid use ever	45 (51.1%)	314 (41.2%)	0.08
Pulmonary arterial hypertension	27 (30.1%)	112 (14.7%)	<0.001
Interstitial lung disease	28 (31.8%)	188 (24.7%)	0.15
SSc renal crisis	3 (3.4%)	34 (4.4%)	0.65
Antiphospholipid antibodies (anticardiolipin or anti-β_2-microglobulin)	25 (32.1%)	156 (25.2%)	0.20

* Family history data missing in 37 patients with CHD and 358 without CHD

On stepwise logistic regression hypertension, diabetes, smoking, age, duration of SSc and pulmonary arterial hypertension were still significant predictors of CHD.

The prevalence of CHD in our SSc cohort compared with the general population is shown in table 2. Stratified by age, prevalence was slightly higher in SSc patients, with the difference more marked in younger patients.

Table 2. Prevalence of CHD in SSc compared to the Australian population

Age group (years)	Prevalence of CHD in SSc cohort	Estimated population prevalence of CHD
35–44	1.4%	0.7%
45–54	4.6%	2.9%
55–64	9.8%	6.8%
65–74	15.4%	12.3%
75 and over	24.7%	19.9%

Conclusion: The prevalence of CHD in SSc has not been previously reported. Our data suggests a higher prevalence of CHD in SSc patients than in the general population, particularly in those less than 55 years of age. These data need confirmation by comparison with a closely matched cohort of controls with similar methods of CHD ascertainment. Further investigation is needed to determine which SSc-specific factors contribute to the aetiology of CHD.

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2. Australian Bureau of Statistics. National Health Survey: Summary of Results, 2007–2008. Canberra; 2009.

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Pulmonary Artery Diameter Is Associated with Pulmonary Hypertension in Patients with Systemic Sclerosis (SSc). Elena Schiopu[4], Ann J. Impens[4], Barry H. Gross[3], Fazleomar Mahmood[4], James R. Seibold[1] and Kristine Phillips[2]. [1]University of Connecticut Health Center, Farmington, CT, [2]University of Michigan, Ann Arbor, MI, [3]University of Michigan, Department of Radiology, Ann Arbor, MI, [4]University of Michigan, Scleroderma Program, Ann Arbor, MI

Background: Early diagnosis of pulmonary hypertension (PH) in scleroderma remains challenging. The purpose of this study is to compare imaging and non-invasive cardio-pulmonary testing with right heart catheterization (RHC) results in patients with SSc.

Method: 141 patients with SSc seen at University of Michigan between 1998 and 2010 were retrospectively identified with a RHC, at least one set of pulmonary function tests (PFT), echocardiogram and brain natriuretic peptide (BNP) within 6 months and a chest computed tomography (CCT) within 16 months. Abstracted data include: clinical functional assessment (WHO class), forced vital capacity (FVC), diffusion capacity (DLco) and total lung capacity (TLC) (% predicted), six minute walk distance (6MWD), right ventricular systolic pressure (RVSP) and presence of right ventricular enlargement (RVE) by Doppler echocardiogram. A blinded cardio-thoracic radiologist measured the diameter of the pulmonary arteries (DPA) on the available CCTs. Student's t test, chi-square test and ANOVA were used to determine group differences.

Results: The mean (SD) age at RHC was 57.3 yrs (11.4) with mean disease duration (from time of first non-RP symptom to RHC) of 10.2 yrs (8.5). 117 (83%) patients were female, and 92 (65.2%) had limited SSc. 75 (53.2%) patients were dead at the time of analysis. One patient (0.7%) was WHO class I, 18 (12.8%) were WHO class II, 113 (80.1%) of patients were WHO class III and 9(6.4%) were WHO class IV. In our cohort, 103 (73%) subjects had ILD as evaluated by the blinded radiologist, of which 85 (60.3%) were described as non specific interstitial pneumonitis (NSIP) and 18 (12.8%) as usual interstitial pneumonitis (UIP); 30 (21.3%) subjects had no parenchymal involvement and the rest of the CCTs were not evaluable due to technique or pleural effusions. 108 (76.6%) patients had PH by RHC criteria (mPAP of > 25 mmHg at rest or > 30 mmHg with exercise and PCWP < 15 mmHg). The mean measured DPA was 3.3 (0.4) cm and the CCT techniques most often used were high resolution (75.9%) and PE protocol (17.7%). There was no difference between the mean/SD DPA in females (3.2/.4) and males (3.3/.4). The mean/SD of the body mass index (BMI) was not significantly different between the groups with PH (27.7/6) and without PH (27.6/5.5). Mean differences between the PH and non-PH groups were:

	N (%) or Mean (SD)	
	PH N 108	Non-PH N 33
Limited Scleroderma	71 (65.7)	21 (63.6)
Gender (Females)	88 (81.4)	29F (87.8)
Time to RHC (years)	10.7 (8.9)	8.7 (6.9)
WHO class*		
I	0	1 (3.0)
II	8 (7.4)	10 (30.3)
III	91 (84.2)	22 (66.6)
IV	9 (8.3)	0
Number of deaths*	67 (62)	8 (24.2)
% FVC	68.23 (20.7)	64.7 (18.8)
% DLco	34.0 (13.3)	38.72 (14.2)
%FVC/%DLco*	2.3 (1.0)	1.8 (0.7)
%TLC	79.4 (20)	72.9 (20)
RVSP*	74.2 (25.5)	43.3 (15.5)
RVE*	83 (76.8)	9 (27.2)
BNP*	588.3 (903)	132.2 (337.5)
DPA (cm)*	3.4 (.4)	3.0 (.4)
mPAP (by RHC)*	43.8 (13.4)	22.1 (10.2)
6MWD*	263.6 (122.7)	361.8 (88.4)
ILD*		
None	28 (25.9)	2 (0.6)
NSPI & UIP	73 (67.5)	30 (90.9)

*$p < 0.05$

Conclusion: The results of the RHC were comparable to the echocardiographic and the hemodynamic parameters. Both an elevated ratio of %FVC to

%DLco and elevated BNP was seen in patients with PAH/PH. CCTs are routinely performed in assessment of lung involvement in SSc. These data suggest that measurement of DPA can be an useful adjunct in identifying patients at risk of PAH and PH in SSc. Prospective studies to assess the predictive value of the non-invasive cardio-pulmonary measures in SSc-PH are in progress.

Disclosure: E. Schiopu: None; **A. J. Impens:** None; **B. H. Gross:** None; **F. Mahmood:** None; **J. R. Seibold:** None; **K. Phillips:** None.

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Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS): Comparison of Outcomes in Subtypes of Pulmonary Hypertension. Robyn T. Domsic[6], Lorinda Chung[3], Mardi Gomnberg-Maitland[4], Jessica K. Gordon[2], Barbara M. Segal[5], Virginia D. Steen[1] and PHAROS Investigators. [1]Gerogetown University Medical Center, Washington, DC, [2]Hospital for Special Surgery, New York, NY, [3]Stanford University Medical Center, Palo Alto, CA, [4]University of Chicago Medical Center, Chicago, IL, [5]University of Minnesota, Minneapolis, MN, [6]University of Pittsburgh, Pittsburgh, PA

Background: PHAROS is a multi-center, longitudinal study designed to assess risk factors and outcomes in patients with systemic sclerosis (SSc) who have definite pulmonary hypertension (PH), or at high risk to develop PH. This study looks at the differences in clinical features and outcomes among SSc patients with different types of PH: pulmonary arterial hypertension alone (PAH), PH associated with interstitial lung disease (PH-ILD), and those with pulmonary venous hypertension (PVH).

Methods: Patients complete questionnaires every 6 months and are seen yearly for physician evaluation. Information collected includes New York Heart Association functional classification (NYHA), vital status, six minute walk distance (6MWD), hospitalizations, pulmonary function tests and medication use. Differences among groups at baseline and in follow-up were assessed by chi-square test. We defined a worsening of 6MWD as a decline of $> 15\%$. We assessed the impact of PAH subgroup on survival using multivariate Cox proportional hazards models.

Results: Of the 151 patients with PH enrolled, 97 have PAH, 30 PH-ILD and 24 PVH. Mean age at enrollment was 58 years (SD 11.7), and 84% were female. The frequency of patients with limited cutaneous disease was higher in PAH (73%), compared to PH-ILD (47%) or PVH (50%; p=.009). The median duration since onset of Raynaud was 8.9 years (interquartile range (IQR) 4.3, 16.0), and median duration of PHAROS follow-up 1.1 years (IQR 0.5, 2.5).

There was a nonstatistically significant difference in initial drug therapy among the PH subgroups (p=0.06), as depicted in Table 1. With follow-up there was no difference in the frequency of progression to combination drug therapy between groups.

Table 1. Initial PAH-specific drug therapies for PAH subgroups (p = 0.06)

	No therapy	Endothelial receptor antagonist	Phospo-diesterase inhibitor	Prostacyclin	Combination
SSc-PAH (n = 97)	24%	26%	33%	14%	3%
SSc-ILD (n = 30)	37%	7%	37%	10%	10%
PVH (n = 24)	50%	21%	25%	0%	4%

There was no significant difference in functional status at baseline among groups. However, in patients with one or more years of follow-up (n=79), 32% of PAH patients had worsening NYHA class, compared to 29% in PH-ILD and 7% in the PVH group (p=0.02). No difference in the frequency of worsening 6MWD was found (p=0.82), with more than 65% in all groups either stable or improved.

As of last follow-up there was no significant difference in risk of death associated with PAH subgroup after adjustment for age (p=0.54). Patients with PAH had a higher frequency of all-cause hospitalizations (55%) compared to PH-ILD (30%) and PVH (44%; p=0.05).

Conclusions: Analysis of the PHAROS cohort suggests that PAH patients have a higher frequency of hospitalization than those with PVH or PH- ILD, although there is no difference in age-adjusted survival. The majority of patients in all classes are functionally stable by NYHA class and 6MWD at one year of follow-up. Although half of the patients with PVH were not treated with PH-specific therapies, their outcomes are comparable or better than PAH and PH-ILD. Longer follow-up of the PHAROS cohort will further elucidate differences between groups.

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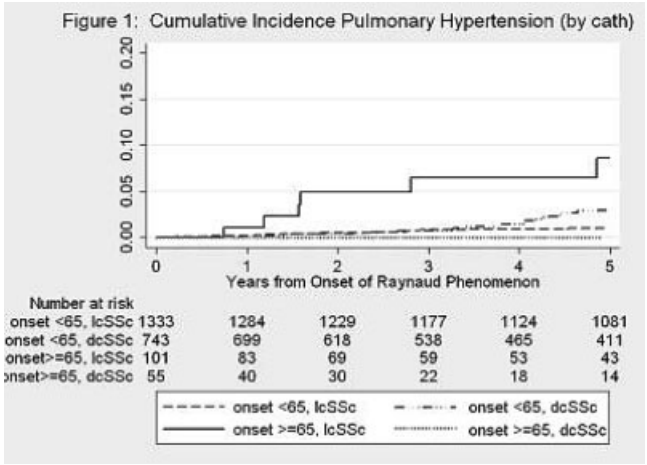
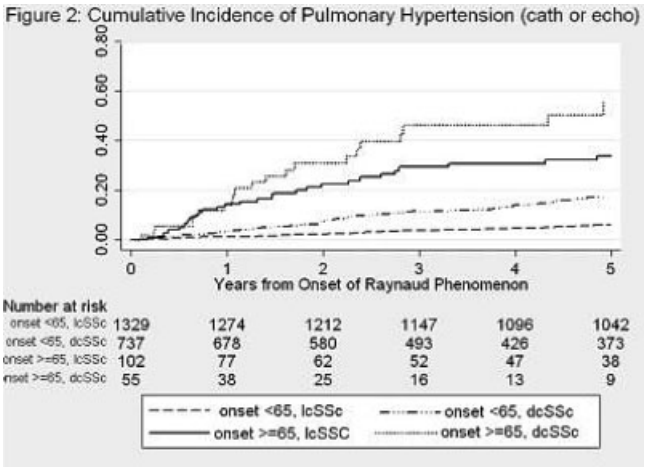
Pulmonary Hypertension by Age of Scleroderma Onset and Subtype. Rebecca L. Manno[2], Fredrick M. Wigley[1] and Laura K. Hummers[2]. [1]Johns Hopkins University, Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD

Purpose: Pulmonary hypertension (PH) is a leading cause of death among scleroderma (SSc) patients. Historically, PH has been considered a late complication of SSc with predominance among those with the limited cutaneous subtype (lcSSc) and an older age of SSc onset. However, we hypothesize that the risk of PH will be the same among lcSSc and diffuse cutaneous (dcSSc) patients when SSc onset is defined at Raynaud phenomenon (RP) onset. We sought to determine the risk of pulmonary hypertension among a large cohort of SSc patients stratified by SSc skin subtype and age of disease onset.

Methods: Data were retrospectively reviewed from a comprehensive database at a University based Scleroderma Center. Patients were categorized by SSc subtype (lcSSc vs dcSSc), age of SSc onset (late-age onset $\geq$ 65years), and the presence of PH. Analyses were completed defining SSc onset in 2 ways: 1) onset of RP; 2) onset of first non-RP SSc symptom. PH was defined 2 ways: 1) mean pulmonary artery pressure $\geq$25 and pulmonary capillary wedge pressure $<$15 by right heart catheterization; 2) RVSP$\geq$40 mmHg by echocardiogram. Kaplan-Meier (KM) failure curves were generated to determine the cumulative incidence of PH. Cox proportional hazard models were generated to determine the risk of PH controlling for age of SSc onset, subtype, gender, race, and FVC. Sensitivity analyses were conducted excluding patients with FVC$<$60.

Results: 2282 patients were included in our analyses. With SSc onset defined by RP onset, 162 had late-age SSc onset (64% lcSSc, 32% +anti-centromere); 2118 had younger-age SSc onset (64% lcSSc, 28% +anti-centromere). Figure 1 depicts KM for PH by cath and figure 2 by cath or echo.





The risk of developing PH (by cath) was significantly greater (HR 4.49; 95% CI 2.22, 9.05) for those with SSc onset ≥65 years compared to younger-age onset. The risk of PH did not differ by SSc subtype (HR 1.19; 95% CI 0.82, 1.73). Sensitivity analyses excluding patients with FVC<60 yielded comparable results (late-age SSc HR 4.83; 95% CI 1.86, 13.41; dcSSc HR 1.46; 95% CI 0.88, 2.42). With SSc onset defined by first non-RP symptom, similar results were obtained results (late-age SSc HR 4.42; 95% CI 2.56, 7.63; dcSSc HR 0.96; 95% CI 0.66, 1.38).

Conclusions: Age of SSc onset impacts the risk of PH but SSc subtype does not. These data suggest benefit for routine screening for PH among all cutaneous SSc subtypes, especially those with late-age onset of disease.

Disclosure: R. L. Manno: None; **F. M. Wigley:** None; **L. K. Hummers:** None.

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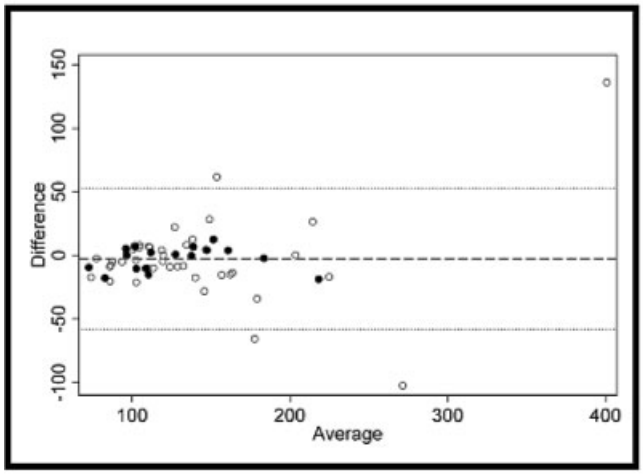
Reproducibility of Semi-Automated Quantitative Nailfold Capillaroscopy Measurements in Patients with Systemic Sclerosis. Andrea K. Murray[4], Tonia L. Moore[4], Andy Vail[1], Joanne Manning[2] and Ariane L. Herrick[3]. [1]Rheumatology Directorate, HealthMethodology Research Group, Manchester Academic Health ScienceCentre, The University of Manchester, Salford Royal Hospital, Salford, UK, [2]Salford Royal NHSFoundation Trust, Salford, [3]The University of Manchester, Manchester Academic Health Science Centre, Manchester, Salford Royal Hospital, Salford, Greater Manchester, United Kingdom, [4]The University of Manchester, Manchester Academic Health Science Centre, Manchester, Salford Royal Hospital, UK

Background: High magnification nailfold videocapillaroscopy allows measurement of capillary density and dimensions and therefore has the potential of being a non-invasive biomarker for systemic sclerosis (SSc)-related microvascular disease. However, quantifying abnormality brings enormous challenges: (a) in SSc, capillaries across any one nailbed are highly heterogeneous (many have very abnormal architecture) (b) measurement is subjective (c) current measurement methods are very time-consuming meaning that in practice only a small number of capillaries in any one nailfold are selected for study and these may be unrepresentative of the whole nailfold. Newly developed software allows rapid semi-automated quantification of capillary density and dimensions over the whole nailbed with results comparable to manual measurements. While this is likely to be a major advance, the system requires user input to identify and 'mark-up' the apex of each capillary in the image. This study aimed to assess the intra-and inter-observer variability and test-retest reliability.

Methods: Two nailfold images were taken from 60 patients with SSc over two visits. Two blinded observers familiar with capillaroscopy cropped image 1 independently to a standard size of 3 mm and then marked-up capillaries in order to assess inter-observer variability. One of the blinded observers then performed a repeat crop/mark-up on image 1 to assess intra-observer variability and crop/mark-up on image 2 to assess test-retest reliability.

Results: Reproducibility of independently cropped images was poor. Further investigation revealed that this was due to positioning of the cropped area. When images were categorised according to the amount of cropped area overlap, those with a high degree of overlap had statistically significantly improved reproducibility (example of Bland Altman plot shown in Figure below, solid circles representing high degree of overlap).



Conclusions: This study demonstrates the heterogeneity of nailfold architecture in patients with SSc and the importance of ensuring that quantitative measurements of nailfold capillaries are carried out on the same microvessels in longitudinal studies. The novel ability to make measurements across the whole bed and to compare current and previous visits is a significant advantage, as this ensures the same capillaries are measured at each visit. This fast, reliable method of quantifying microvascular disease could be a reliable outcome measure in future longitudinal studies including those of treatment response.

Disclosure: A. K. Murray: None; **T. L. Moore:** None; **A. Vail:** None; **J. Manning:** None; **A. L. Herrick:** None.

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Risk Associated with African American Race in Relation to Prevalence of Cardinal Organ System Manifestations in Scleroderma. Elizabeth N. Le[3], Rebecca L. Manno[3], Laura K. Hummers[3], Fredrick M. Wigley[2] and Allan C. Gelber[1]. [1]Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD, [3]Johns Hopkins University, Baltimore, MD

Purpose: Scleroderma is a severe multisystem rheumatic disorder with a broad spectrum of organ involvement. There are several known risk factors for particular organ system manifestations, including the cutaneous subset of disease (limited vs. diffuse) and age at disease onset. Whereas race has been related to risk for interstitial lung disease and diffuse cutaneous disease, there are few systematic examinations of race in relation to risk for each cardinal organ manifestation of scleroderma.

Method: A prospective clinical database was begun at a single university scleroderma referral center in 1990. Each patient satisfied at least one of the following three diagnostic criteria: (1) the ACR criteria for scleroderma; (2) 3 of 5 features of the CREST syndrome; or (3) a combination of definite Raynaud's phenomenon, abnormal nailfold capillaries and a scleroderma-specific autoantibody. Demographic data including age, sex, and race, together with cutaneous subtype (based on Leroy classification criteria), and smoking status were uniformly ascertained. Disease duration, from disease onset, at age of the first non-Raynaud's symptom, to evaluation at the Scleroderma Center was determined. Clinical data, including organ system involvement, were recorded using a uniform protocol at cohort entry, and updated every six months when available. The outcomes of interest were the Medsger severity scores [(MSS); J Rheumatol 1999;26:2159], determined for each cardinal organ system involved in scleroderma. The association of African American in comparison to Caucasian race with the MSS parameters were examined using logistic regression analysis, with adjustment for potential confounding by age at disease onset, sex, disease subtype, disease duration and smoking status (for pulmonary outcome).

Results: Between January, 1990 and June, 2009, a total of 2481 patients with scleroderma were enrolled. Overall, mean age at disease onset was 45.5 years. 63% of patients manifested the limited cutaneous subset; half were ever-smokers. In terms of the various MSS outcomes, the overall proportion with digital ischemia (score≥2) was 55%; for lung MSS ≥1 was 77%; heart MSS ≥1 25%; kidney MSS ≥1 18%; gastrointestinal MSS ≥2 40%; and

muscle MSS ≥1 was 24%. Importantly, in multivariate analysis, compared to the Caucasian members of the cohort, the African American members had a 50% increase in peripheral vascular disease, a >6-fold increase in lung involvement, 60% increase in heart, 70% increase in risk of kidney involvement, a 70% increase in gastrointestinal, and 90% increase in risk of muscle weakness.

MSS	Univariate OR	95% CI	Multivariate OR	95% CI
Peripheral Vascular	1.7	1.3–2.1	1.5	1.2–2.0
Lung	5.6	3.6–8.9	6.1	3.8–9.9
Heart	1.2	0.9–1.6	1.6	1.2–2.2
Kidney	1.4	1.1–1.9	1.7	1.2–2.2
Gastrointestinal tract	1.4	1.1–1.9	1.7	1.2–2.2
Muscle	2.0	1.5–2.6	1.9	1.4–2.4

Conclusion: These data imply that among patients presenting in rheumatology consultation for the evaluation and management of scleroderma, that African Americans are at notably increased risk to develop the full range of cardinal organ system features of disease.

Disclosure: E. N. Le: None; **R. L. Manno:** None; **L. K. Hummers:** None; **F. M. Wigley:** None; **A. C. Gelber:** None.

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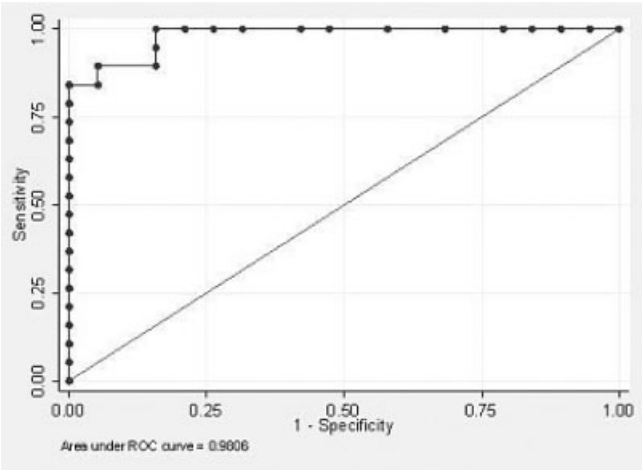
Role of N-Terminal Pro-BNP in Detecting Clinically-Significant Cardiac Involvement in Systemic Sclerosis Patients. Cecilia Chighizola[3], Benjamin Schreiber[2], Pier Luigi Meroni[3], Gerry Coghlan[1], Christopher P. Denton[4] and Voon Ong[1]. [1]Center for Rheumatology and Connective Tissue Diseases, UCL Medical School, Royal Free Hospital, London, United Kingdom, [2]Center for Rheumatology and Connective Tissue Diseases, UCL Medical School, Royal Free Hospital, London, 0', [3]Rheumatology Division, Department of Internal Medicine, Istituto G. Pini, University of Milan, Milan, Italy, [4]Royal Free Hospital, London, United Kingdom

Background: Cardiac involvement is common in Systemic Sclerosis (SSc) and is often clinically occult. However, it is recognised as a poor prognostic factor contributing significantly to mortality among these patients. Early detection of cardiac disease with non-invasive tools is therefore critical.

Aim: To assess the role of N-TproBNP in SSc related cardiac involvement in a retrospective cohort of patients.

Methods: 19 SSc patients (13 dcSSc and 6 lcSSc) patients with cardiac involvement were enrolled in this study. Cardiac involvement was defined as haemodynamically significant arrhythmias, pericardial effusion or congestive heart failure, requiring specific treatment. All patients had normal pulmonary artery systolic pressure and none had serum creatinine above 140 mmol/l. This group of patients was compared with 19 age- and sex-matched SSc patients without evidence of cardiac involvement or pulmonary arterial hypertension. Serum N-TproBNP levels were measured with the Roche Modular Analytics E-170 (Eleccys module) immunoassay. Normal N-TproBNP levels were less than 20 pmol/l. Unpaired t-test was used to compare N-TproBNP values between subgroups based upon presence of cardiac involvement. ROC curves were drawn to identify N-TproBNP levels which gave optimal sensitivity and specificity for diagnosis of SSc-related cardiac involvement. N-TproBNP levels were compared at presentation of cardiac involvement and at six month follow up using a paired t-test. Univariate mortality analysis was performed with Kaplan-Meier method, the level of significance of the differences among survival curves was assessed by Log-rank test

Results: Compared to those without cardiac involvement, N-TproBNP was significantly increased in SSc patients with heart involvement (mean±SD 14.9±14.5 pmol/l versus 1043±2053 pmol/l respectively, p=0.037; 95%CI 67,1989). Figure 1 shows a ROC curve of N-TproBNP that predicts the presence of heart involvement in SSc. A sensitivity of 100% was achieved at a cut-off N-TproBNP level of 28 pg/mL, with a specificity of 84% (95% CI 0.95–1). Moreover, a significant progressive reduction in N-TproBNP after the acute phase of cardiac involvement (mean±SD 301±330 pmol/l) was observed during 6 months follow-up (mean±SD 87±113 pmol/l; p=0.048, 95%CI 2.8,425). In addition, within the group with cardiac involvement, N-TproBNP levels were categorized as high if above the median value of 219 pmol/l; however, higher levels of N-TproBNP did not predict survival (p=0.959, at Log rank analysis).



Conclusions: These data suggest that N-TproBNP peptide may be a surrogate marker for cardiac involvement in SSc. It may selectively identify those patients with severe impairment of cardiac function. Further studies are required to evaluate the utility of N-TproBNP levels for cardiac assessment in SSc patients.

Disclosure: C. Chighizola: None; **B. Schreiber:** None; **P. L. Meroni:** None; **G. Coghlan:** None; **C. P. Denton:** None; **V. Ong:** None.

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Scleroderma Autoantibodies and Disease Subtype Predict Pulmonary Hypertension Classification in the PHAROS Registry. Monique E. Hinchcliff[5], Aryeh Fischer[4], Nadera Sweiss[6], Maureen Mayes[7], Marcy Bolster[3], Virginia Steen[1] and PHAROS Investigators[2]. [1]Georgetown University, [2]Gerogetwon University, [3]Medical University of South Carolina, [4]National Jewish Health, [5]Northwestern University, [6]University of Chicago, [7]University of Texas-Houston Medical School

Background and Purpose: Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (SSc), PHAROS, is a multi-center, prospective, observational study of SSc patients who are at high risk for pulmonary arterial hypertension (PAH) or who have definite pulmonary hypertension (PH) by right-heart catheterization (RHC). We sought to describe the relationship and predictive value of SSc-specific autoantibodies for pre-PAH and World Health Organization (WHO) PH classification: group 1 (PAH), 2 (pulmonary venous hypertension, PVH) and 3 (PH attributed to interstitial lung disease PH-ILD).

Methods: SSc patients with echo RVSP > 40mmHg, FVC/DLCO>1.6, FVC < 55% (Pre-PAH) or definite PH by RHC are enrolled in PHAROS. Objective (PFT, echo, and the presence of autoantibodies (ab) including anticentromere (ACA), anti-topoisomerase (Scl-70), an isolated nucleolar pattern on ANA testing (NUC), anti U1-RNP (U1RNP), RNA polymerase III (Pol III) and others) and clinical data (disease subtype, limited SSc (lcSSc) and diffuse SSc (dcSSc) according to the LeRoy criteria) are collected. Patients with mean pulmonary pressure (mPAP) ≥25 mmHg on RHC were classified according to WHO PH criteria. Statistical analyses were conducted using SPSS (Chicago, IL) and Bonferroni correction was used for multiple pair-wise comparisons.

Results: The majority of patients have lcSSc (65% l, 31% d, 4% other). Ab data were available on 322 of the 383 PHAROS patients. Patients with an isolated NUC ab were over represented in this registry compared to the usual scleroderma population and were more frequently entered as definite PH (groups 1–3) as opposed to Pre-PAH (p≤0.001). ACA and NUC patients more frequently had PAH compared to the Scl-70 patients who more frequently had PH-ILD. Patients with lcSSc and a positive NUC ab were more likely to have PAH (p=0.033). Patients with dcSSc and a positive Scl-70 had PH-ILD more commonly (p=0.025).

Conclusion: PHAROS is a multi-institutional registry that continues to provide insights into SSc-PH. Among this national SSc cohort of patients at high risk or with definite PH, we have shown that both SSc clinical phenotype and autoantibody profile predict WHO PH classification. Although less common in SSc in general, an isolated NUC ab is common in PH patients. Diffuse patients with a positive Scl-70 ab are less likely to have PAH and

more likely to have PH-ILD. In contrast, patients with lcSSc and a positive NUC ab are more likely to have PAH.

Clinical Implications: Scleroderma autoantibodies and disease subtype may be helpful in identifying patients who are more likely to have PAH or PH-ILD.

Antibody N (%)	All = 322	Pre-PAH	WHO 1 (PAH)	WHO 2 (PVH)	WHO 3 (PH)
ACA	86 (23)	51 (22)	27 (28)	6 (27)	2 (7)
Scl-70	52 (14)	35 (15)*	6 (6)*	2 (9)*	9 (30)*
Nuc	66 (20)	28 (12)*	29 (30)*	6 (27)*	3 (10)*
U1 RNP	21 (7)	13 (6)	8 (8)	0	0
Pol III	6 (2)	2 (1)	3 (3)	1 (5)	0
Other ANA	70 (22)	42 (18)	13 (14)	4 (18)	8 (27)

*denotes $p \leq 0.05$, χ^2 test performed between pre-PAH and definite WHO groups (1–3).

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Scleroderma Lung Disease: Effect of Co-Existent Pulmonary Hypertension on Progression of Interstitial Lung Disease. Anupama Shahane, Joseph Parambil, Meng Xu and Soumya Chatterjee. Cleveland Clinic

Background: Pulmonary involvement is the leading cause of mortality in systemic sclerosis. The two most commonly seen patterns of lung disease, interstitial lung disease (ILD) and pulmonary hypertension (PH) often co-exist, with worse outcomes than either ILD or PH alone. We retrospectively studied patients with scleroderma lung disease to evaluate the effect of co-existent PH on progression of ILD.

Methods: Patients were identified from the Cleveland Clinic scleroderma database and the pulmonary hypertension database. Patients satisfied the ACR criteria for systemic sclerosis; pulmonary function tests and thoracic high resolution CT scans were used to identify ILD. PH was diagnosed on the basis of right heart catheterization. We described two cohorts of scleroderma patients: scleroderma with ILD alone (SSc-ILD) and scleroderma with both ILD and PH (SSc-ILD/PH). We further divided patients with ILD into limited and extensive disease based on extent of lung involvement on HRCT (Goh *et al*, Respir Crit Care Med, 2008). Disease progression was measured in terms of longitudinal values of forced vital capacity (FVC) and carbon monoxide diffusion capacity (DLco). We collected annual data for 6 years. Chi square or Fisher's exact test was used for comparison of categorical variables, and Wilcoxon rank sum test was used for continuous variables. Mixed model was used for longitudinal measures of FVC and DLco.

Results: We identified 86 patients with SSc-ILD (55 limited, 31 extensive) and 47 patients with SSc-ILD/PH (27 limited, 20 extensive). In our cohort, all subtypes of lung disease were more prevalent in females and Caucasians. Average duration of lung disease since time of diagnosis of scleroderma was 4 years (3.7–4.3 years). Significant difference was not noted in progression of patients with SSc-ILD in comparison with patients with SSc-ILD/PH ($p = 0.42$). Patients with limited ILD showed a trend towards faster disease progression in the presence of PH, but this was not noted in patients with extensive ILD ($p = 0.054$). Patients with extensive ILD had lower FVC and DLco at baseline and showed faster rate of progression ($p < 0.001$). Patients with SSc-ILD/PH had significantly faster decline in DLco compared to patients with SSc-ILD, in patients with both limited as well as extensive lung disease ($p < 0.001$). Moreover, extensive ILD was associated with faster rate of disease progression than limited ILD, irrespective of presence of PH ($p < 0.001$).

Conclusions: Our study showed that limited (but not extensive) ILD is likely to progress faster in the presence of PH. Also, patients with SSc-ILD/PH have faster rate of decline in DLco compared to patients with SSc-ILD. Lung disease is not only worse in extensive ILD patients but also progresses faster when compared to those with limited ILD, regardless of co-existent PH.

Disclosure: A. Shahane: None; **J. Parambil:** None; **M. Xu:** None; **S. Chatterjee:** None.

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Sildenafil Increases Vasodilation in Systemic Sclerosis: An Interim Analysis from a Single Centre Pilot Study. Silvia Bellando-Randone, Irene Miniati, Serena Guiducci, Maria Letizia Conforti, Jelena Blagojevic, Ginevra Fiori, Francesca Bartoli, Francesca Nacci and Marco Matucci-Cerinic. Department of Biomedicine Section of Rheumatology University of Florence, Italy

Background: Vasculopathy is an early and prominent feature in systemic sclerosis (SSc) and it is reflected by Raynaud's Phenomenon (RP) and digital ulcers. Reduced nitric oxide levels have been proposed to play a role in the pathogenesis of vascular disease in scleroderma. Sildenafil represents an attractive candidate for the treatment of SSc-associated vasculopathy as a selective inhibitor of cGMP-specific phosphodiesterase type 5 and potent agent to increase the endogenous NO levels.

Objective: In this pilot study, the effect of sildenafil on RP was analysed. Primary outcome was the improvement of RP and changes in other clinical symptoms. This an interim analysis after 3 months of treatment.

Methods: Fourtyfive SSc patients were randomized in 3 groups: 15 treated with maximally tolerated sildenafil dose (20 mg three times daily), 15 with combination therapy (sildenafil and prostanoids i.v.) and 15 with prostanoids i.v. Symptoms were assessed by diary cards including a 10-point Raynaud's Condition Score, SF-36 and sHAQ: videocapillaroscopy was performed in all patients at baseline and every 3 months. Results were analysed with ANOVA using Bonferroni correction.

Results: After 3 months there was a statistically significant difference between the 3 groups for RCS ($p=0.03$). No significant differences were found for SF36 (all domains) and SHAQ. NVC pattern was unmodified in all patients.

Four patients (three treated with sildenafil, one with combination therapy) reported side effects leading to discontinuation of the study drug. Two patients on prostanoids and 1 patient on SILDENAFIL were switched to a combination therapy due to inefficacy.

Conclusion: s: This study indicates that sildenafil improves RP and associated symptoms and is a well-tolerated treatment in SSc patients. Long term results are necessary to confirm these results and investigate the effect on other outcome measures

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Subclinical Atherosclerosis Is Increased in Systemic Sclerosis—A Case-Control Study. Karen M. Au[1], Maureen A. McMahon[1], Daniel E. Furst[3], Bevra H. Hahn[4], Nagesh Ragavendra[1], Amber Bechtel[1], Lori Sahakian[1] and Dinesh Khanna[2]. [1]UCLA School of Medicine, Los Angeles, CA, [2]University of California Los Angeles, Los Angeles, CA, [3]University of California Los Angeles Medical School, Los Angeles, CA, [4]University of California Los Angeles School of Medicine, Los Angeles, CA

Objective: Systemic sclerosis (SSc) is associated with vasculopathy and endothelial cell injury, which could potentially increase the risk of atherosclerosis. Carotid artery ultrasound can detect subclinical atherosclerosis by measuring carotid intima-media thickness (IMT) and presence of carotid plaque. Studies have suggested that IMT is elevated in SSc, but there is little evidence that plaque is more prevalent in SSc compared to healthy patients.

Normal high-density lipoprotein (HDL) is anti-inflammatory and prevents low-density lipoprotein (LDL) oxidation. While HDL is protective, an altered form known as pro-inflammatory high-density lipoprotein (piHDL) may increase atherosclerotic risk and may actually potentiate LDL oxidation. Serum piHDL is a novel marker of atherosclerotic risk in lupus and rheumatoid arthritis. The objective of the study was to determine 1) the prevalence of subclinical atherosclerosis (carotid plaque and IMT measurement) in SSc and 2) serum piHDL levels as a potential novel marker of atherosclerotic risk in SSc.

Methods: A cross-sectional study of 32 patients with SSc and 32 age-, sex-, and race-matched healthy controls in a single center was conducted. All subjects received bilateral carotid ultrasounds measuring plaque and IMT and were read by a single reader (NR) who was blinded to the diagnosis. Cholesterol studies and a cell free assay to measure presence of piHDL were performed.

Results: The average age of the patients was 48 (mean age SSc 48, controls 47) and included 15 limited SSc and 17 diffuse SSc subjects. Total cholesterol ($P=0.20$) and LDL ($P=0.13$) were similar between SSc and controls. SSc patients had lower HDL (SSc 54.2 vs. controls 63.4, $P=0.01$) and higher triglycerides compared to controls (142.3 vs. 110.1, $P=0.02$). Carotid plaque was significantly more prevalent in SSc patients compared to controls (14 SSc patients vs. 7 controls; $P = 0.043$). Presence of carotid plaque was equally distributed among limited and diffuse SSc patients (9 limited, 8 diffuse). Average IMT was higher in patients with SSc than controls (0.582 ± 0.11 vs. 0.557 ± 0.14; $P = 0.059$). SSc patients had similar rates of piHDL compared to controls (SSc 21.4%, controls 25%). piHDL was not

associated with plaque ($P=0.65$) nor with average IMT ($P=0.10$) in our SSc cohort.

Conclusion: Prevalence of subclinical atherosclerosis is greater in patients with SSc compared with healthy controls. This preliminary data suggests that pro-inflammatory HDL is not a marker of atherosclerosis in SSc.

Disclosure: K. M. Au: None; **M. A. McMahon:** None; **D. E. Furst:** None; **B. H. Hahn:** None; **N. Ragavendra:** None; **A. Bechtel:** None; **L. Sahakian:** None; **D. Khanna:** NIH, 2.

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Symptom Burden, Quality of Life and Attitudes toward Palliative Care in Patients with Pulmonary Hypertension with and without Systemic Sclerosis. Nicole M. Orzechowski[1], Keith M. Swetz[2], Tait D. Shanafelt[3], Jeff A. Sloan[3], Paul J. Novotny[3], Robert P. Frantz[3] and Michael D. McGoon[3]. [1]Dartmouth Hitchcock Med Center, Lebanon, NH, [2]Mayo Clinic, Rochester, MN, [3]Mayo Clinic

Background: Systemic Sclerosis (SSc) is a potentially devastating connective tissue disorder affecting multiple organ systems. Pulmonary hypertension (PH) can be a serious and life threatening complication of SSc. Little is known about health related quality of life (QOL) and the use of palliative care (PC) in patients with this complication. We sought to examine symptom burden, QOL and attitudes regarding PC in a large international sample of PH patients with and without SSc.

Methods: Patient members of four Pulmonary Hypertension Association listservs were sent an internet-based survey by email. Symptom burden and QOL were assessed using a standardized QOL assessment tool including the Linear Analog Self-Assessment (LASA) and the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR). Surveys were administered anonymously by a third party and the investigators were blinded to the identity of the respondents. PH patients with and without SSc were compared to assess any potential differences.

Results: Out of a total of 276 unique patient responses, 45 had PH associated with SSc. Primary PH accounted for 117, other lung disease 18, left heart failure 12, another condition 51, and uncertain 33. Patients with SSc were older both at the time of this survey and at the time of PH diagnosis ($p=0.0014$ and $p=<0.001$). Responders in both groups were predominantly female and Caucasian. Approximately 40% of patients in each group had LASA scores ≤ 5 which is considered profoundly low and clinically significant. Substantial numbers in both groups reported LASA scores≤ 5 for the physical well being, emotional well being, social activity, pain frequency, pain severity and fatigue components. Mean CAMPHOR score for total symptoms was near the 50th percentile for each group. Despite high symptom scores, no SSc patients and only four patients in the non-SSc group had a palliative care (PC) physician involved in their care. Reasons for this included confusion between PC and hospice, the misperception that medications would have to be stopped and patients' perceptions that they were not sick enough for PC. A minority of patients in each group completed a living will or discussed advanced care planning with their physician.

	Systemic Sclerosis N = 45	Others N = 231	p-value
Mean Age (years ± SD)	56.1 ± 13	47.5 ± 16	0.0014
Mean Age at PH Diagnosis (years ± SD)	52.2 ± 13	42.5 ± 17	<0.001
Female	41 (91.1)	194 (85.5)	0.31
Caucasian	42 (93.3)	192 (83.1)	0.08
LASA overall QOL ≤5	17 (37.8)	93 (40.3)	0.75
LASA Physical Well Being ≤5	29 (64.4)	125 (54.6)	0.22
LASA Emotional Well Being ≤5	16 (35.6)	94 (40.9)	0.50
LASA Social Activity ≤5	20 (45.5)	114 (49.8)	0.59
LASA Pain Frequency ≤5	30 (66.7)	138 (61.1)	0.47
LASA Pain Severity ≤ 5	31 (72.1)	159 (69.4)	0.72
LASA Fatigue ≤5	19 (42.2)	101 (43.7)	0.85
CAMPHOR total symptoms 0–25: High worse (SD)	11.5 (6.4)	12.7 (7.1)	0.26
Palliative Medicine MD involved in PH care	0	4 (1.7)	0.3739
Completed Living Will	18 (40)	75 (32.5)	0.3281
MD discussed advanced care	3 (20)	31 (31.3)	0.3721

All values are numbers (%) unless otherwise specified

Conclusions: A substantial proportion of PH patients with SSc have profound reduction in QOL, but they are no worse than patients with PH from other causes. Despite high symptom burden from PH, the use of PC was low, possibly due to patient or caregiver misperceptions. The integration of PC into the management of SSc patients with PH may provide an opportunity to improve QOL and requires further examination.

Disclosure: N. M. Orzechowski: None; **K. M. Swetz:** None; **T. D. Shanafelt:** None; **J. A. Sloan:** None; **P. J. Novotny:** None; **R. P. Frantz:** None; **M. D. McGoon:** None.

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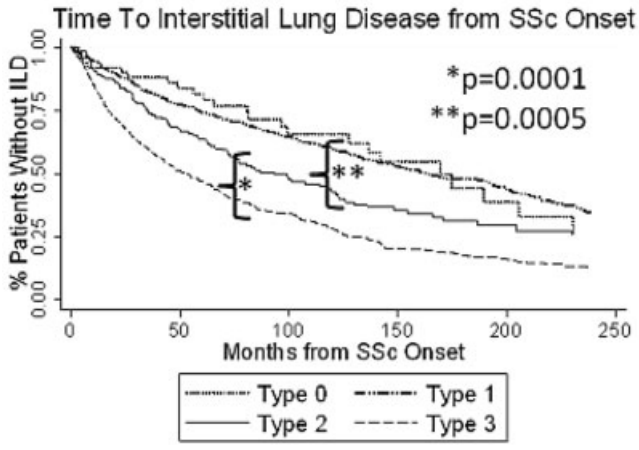
The Degree of Skin Involvement Predicts Distinct Interstitial Lung Disease Outcomes in Systemic Sclerosis. Tricia R. Cottrell, Fredrick Wigley, Robert Wise and Francesco Boin. Johns Hopkins University, Baltimore, MD

Purpose: Systemic sclerosis (SSc) is conventionally classified into limited and diffuse based on the extent of skin fibrosis. While this classification has some clinical utility and facilitates compatibility among patient groups for research purposes, the cutaneous involvement in SSc is heterogeneous and more specific skin subsets may be associated with unique clinical outcomes. In this study, we analyzed longitudinal data from a large cohort of well-characterized SSc patients to determine whether specific SSc skin subtypes can be associated with the development and severity of interstitial lung disease (ILD).

Methods: A retrospective analysis was conducted on a longitudinal cohort of 2054 SSc patients seen at the Johns Hopkins University Scleroderma Center between 1976 and 2010. Based on the maximum extent of skin fibrosis, 4 SSc subsets of patients were identified: Type 0 if no cutaneous sclerosis (sine scleroderma) was present; Type 1 if sclerosis was distal to the metacarpophalangeal joints with or without involvement of the face; Type 2 if skin changes were distal to the elbows or knees; Type 3 if sclerosis extended proximally to the elbows or knees. The primary outcomes were the presence of interstitial lung disease (ILD) defined as a forced vital capacity (FVC) < 80% of predicted with no evidence of obstructive lung disease, and time from disease onset (1st non-Raynaud's symptom) to development of ILD. Chi squared test and analysis of variance were used to compare cumulative frequency and severity of ILD, while Kaplan-Meier method, log-rank test and Cox proportional hazard ratio were used to compare ILD-free survival curves from SSc onset and to estimate the probability of developing ILD in the different disease subsets.

Results: The proportion of patients diagnosed with ILD significantly increased from type 0 to type 3 SSc subtypes ($p<0.0001$), while the average minimum FVC decreased ($p<0.0001$). Analysis of ILD free survival curves showed that over time, a greater extent of skin fibrosis was associated with a higher risk of developing ILD.



In particular, patients with type 2 SSc exhibited a distinct risk of ILD development (vs. Type 1 $p = 0.0005$; vs. Type 3 $p=0.0001$). This difference was supported also by the Cox proportional hazard ratio analysis demonstrating a significantly increased hazard of developing ILD for type 2 patients relative to type 1 (HR 1.5 [1.2–1.9], $p<0.001$), which was even higher for type 3 patients relative to type 1 (HR 2 [1.8–2.4], $p<0.001$).

Conclusions: The degree of skin involvement is predictive of different outcomes in SSc-ILD. In particular, SSc patients with an intermediate level of skin fibrosis (type 2), who normally are classified into the limited SSc group, exhibit a distinct risk profile for lung involvement and therefore their identification and characterization may be relevant in term of prognosis and proper clinical management.

Disclosure: T. R. Cottrell: None; **F. Wigley:** None; **R. Wise:** None; **F. Boin:** None.

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The Effect of Gastric Acid Suppression with Esomeprazole on Treprostinil Diethanolamine Pharmacokinetics in Healthy Volunteers. Kristan Rollins[2], Susan Walker[2], Jennifer Kates[2], Kevin Laliberte[2] and Allison Lim[1]. [1]United Therapetutics, Research Triangle Park, NC, [2]United Therapeutics

Background: Treprostinil diethanolamine (TRE) is a prostacyclin analog currently being evaluated as a sustained release osmotic tablet for the treatment of digital ulcers in patients with systemic sclerosis (SSc). Esophageal manifestations of SSc are common requiring many patients to utilize acid suppressing therapies such as proton pump inhibitors (PPI). The use of acid suppressing therapies may alter the pharmacokinetics of concomitantly administered oral therapies via alterations in drug dissolution, absorption and metabolism. This study assessed the effect of steady-state esomeprazole induced gastric acid suppression on the pharmacokinetics of TRE.

Methods: This was a 9-day, single-center, open-label, single sequence study in which healthy volunteers were given a single dose of TRE SR 1 mg prior to and following repeated once daily oral dosing of esomeprazole 40 mg capsules over 7 days (Days 3–9). A single 1 mg oral dose of TRE was administered immediately following a 500 calorie meal on Days 1 and 8. Eighteen blood samples were obtained over 36 hours following each TRE dose. Plasma concentrations of treprostinil were quantified by liquid chromatography/mass spectrometry. Safety was assessed via adverse event reporting, clinical laboratories, physical exams, and ECGs.

Results: Fifteen male and fifteen female healthy volunteers with a mean age of 34 years (range 20–55 years) were enrolled. Concomitant administration of TRE and esomeprazole (test) following repeated esomeprazole dosing resulted in equivalent treprostinil exposure (Cmax and AUC) as compared to TRE dosing alone (reference) as described in Table 1. The most commonly reported adverse events included headache (8 subjects), flushing (2 subjects) and dizziness (2 subjects). There were no clinically significant treatment emergent changes in clinical laboratories, ECGs or vital signs.

Table 1. Preliminary Treprostinil Pharmacokinetic Parameters

Parameter	Least Squares Geometric Means		Ratio of Geometric Mean (Test/ Reference)	90% Confidence Interval
	Reference	Test		
C_{max} (ng/mL)	0.84	0.84	1.00	(0.85, 1.17)
AUC_{inf} (ng*hr/mL)	4.01	3.80	0.95	(0.87, 1.04)
AUC_{last} (ng*hr/mL)	3.93	3.79	0.96	(0.89, 1.05)

Conclusions: Esomeprazole-induced gastric acid suppression had no impact on single dose TRE pharmacokinetics in healthy volunteers.

Disclosure: K. Rollins: United Therapeutics, 3; **S. Walker:** United Therapeutics, 3; **J. Kates:** United Therapeutics, 3; **K. Laliberte:** United Therapeutics, 3; **A. Lim:** United Therapeutics, 3.

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The Pulmonary Arterial Hypertension Quality Enhancement Research Initiative (PAH-QuERI): Comparing Baseline Characteristics, Management and Survival in Patients with Idiopathic PAH (IPAH) to Patients with Systemic Sclerosis Related PAH (SSc-PAH). Philip J. Clements[2], Amparo Casanova[1], Tan Mary[1], Channick Richard[4], Valerie McLaughlin[6], Ron Oudiz[2], Lew Rubin[5], Tapson Victor[3] and Langer Anatoly[1]. [1]Canadian Heart Research Center, [2]David Geffen School of Medicine at UCLA, [3]Duke University Medical Center, Durham, NC, [4]Massachusetts General Hospital, [5]University of California at San Diego, [6]University of Michigan Health System

Purpose: To compare the baseline characteristics, management, and survival in patients with IPAH to patients with SSc-PAH in the prospectively-enrolled PAH-QuERI registry.

Methods: Between October 2005 and June 2007, physicians at 62 US specialist practices enrolled patients into the registry, entering diagnostic work-up, management and outcome data into an electronic data management system. Automatic queries were generated at each of the prescheduled follow-up visits if the tests recommended by American College of Chest Physicians' guidelines (2007) were not performed at least once.

Results: 287patients with IPAH and 253 with SSc-PAH were entered and followed for one year. At baseline, most of the clinical and laboratory characteristics of the two groups were similar, with only those listed in the table being judged clinically important and statistically different enough to warrant discussion. A few other variables (BMI, heart rate, hemoglobin) were statistically different but the differences were not deemed clinically important.

Both groups were composed largely of middle-aged (57 y/o) Caucasian women (see table). The patients with SSc-PAH were older at the time of PAH diagnosis (56 vs 53 y/o), were more likely to be ANA positive, had lower %DLCO, and more frequently had %FVC/%DLCO ratios $>$ 1.4 and/or DLCO $<$ 55%. The SSc-PAH patients were also more likely to have elevated BNP, shorter 6-minute walk distances (6-MWD), and lower mean pulmonary artery pressures (mPAP) and pulmonary vascular resistance (PVR) than patients with IPAH.

Table. Clinically interesting and statistically significant differences in variables at baseline between IPAH and SSc-PAH and in survival at 12 months

Baseline Variables	IPAH	SSc-PAH	p-value
Age of PAH diagnosis (years old)	53	56	0.001
Sex (% females)	77%	90%	<0.001
Abnormal ANA (%)	25%	85%	<0.001
%DLCO	62	44	<0.001
%FVC/%DLCO ratio >1.4 (median values)	34	67	<0.001
DLCO <55% (%)	35%	70%	<0.001
Abnormal BNP (>140 pg/ml) (%)	51%	64%	0.03
6-minute walk distance (6-MWD in meters)	356	305	0.001
Mean pulmonary artery pressure (mPAP in mm Hg)	48	40	<0.001
Pulmonary vascular resistance (PVR in Woods units)	8.95	7.01	0.02
Survival			
Mortality rate at one year (% death)	7%	17%	<0.001

During the one year follow-up period, both groups were managed with prostacyclin derivatives, endothelin-receptor antagonists (ERA) and/or phosphodiesterase-type-5 inhibitors (PDE-5i), singly or in combinations. There were minimal differences in how these drugs were administered over the year of follow-up, with these exceptions: SSc-PAH patients were more likely than IPAH patients to be treated with PDE-5i agents alone or with the combination of ERA and PDE-5i agents.

At 12 months, the mortality rate of the SSc-PAH patients (17%) was significantly greater than that of the IPAH patients (7%, $p < 0.001$).

Conclusion: In conclusion: 1) In this prospective registry of IPAH and SSc-PAH patients, the SSc-PAH patients at baseline were more likely to be older and female and to have lower %DLCO and more often had %FVC/%DLCO ratios $>$ 1.4 and DLCO $<$55%. Although they had better hemodynamics (lower mPAP and lower PVR), they were frequently "sicker" (elevated BNP and shorter 6-MWD). 2) patients with SSc-PAH were more likely to be managed with PDE5i alone or in combination with an ERA than IPAH patients. 3) Survival at one year was significantly lower in the SSc-PAH group than the IPAH group.

Disclosure: P. J. Clements: Gilead Sciences, Inc., 5; **A. Casanova:** Actelion Pharmaceuticals US, 2; **T. Mary:** Actelion Pharmaceuticals US, 2; **C. Richard:** Actelion Pharmaceuticals US, 2, 5, Gilead Sciences, Inc., 2, 5, Pfizer Inc, 2, United Therapeutics, 2, 5; **V. McLaughlin:** Actelion Pharmaceuticals US, 2, 5, Bayer, 5, Gilead Sciences, Inc., 2, 5, Novartis Pharmaceuticals Corporation, 2, United Therapeutics, 2, 5; **R. Oudiz:** Actelion Pharmaceuticals US, 2, 5, Bayer, 2, 5, Gilead Sciences, Inc., 2, 5, Lung Research, 2, 5, United Therapeutics, 2, 5; **L. Rubin:** Actelion Pharmaceuticals US, 2, Gilead Sciences, Inc., 2, Pfizer Inc, 2, United Therapeutics, 2; **T. Victor:** Arena, 2, Bayer, 2, Gilead Sciences, Inc., 2, Lung Rx, 2, United Therapeutics, 2; **L. Anatoly:** Actelion Pharmaceuticals US, 2.

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Validation of 6 Minute Walking Distance in Patients with Pulmonary Arterial Hypertension Associated with Systemic Sclerosis. Dörte Huscher[11], Nicholas Roubinis[17], Jerome Avouac[18], Frank Behrens[10], Christopher P. Denton[1], Daniel E. Furst[8], Ivan Foeldvari[14], Marc Humbert[19], Otylia Kowal-Bielecka[4], Marco Matucci-Cerinic[3], Peter Nash[6], Christian F. Opitz[2], David Pittrow[13], Lewis J. Rubin[7], James R. Seibold[9], Marius M. Hoeper[12], Mark F. Morris[15], Simon A. Teal[16] and Oliver Distler[5]. [1]Centre for Rheumatology, Royal Free Campus, University College Medical School, London, United Kingdom, [2]Department of Internal Medicine, DRK-Kliniken Berlin Köpenick, Berlin, Germany, [3]Department of Medicine, Division of Rheumatology, Denothe Center, University of Florence, Italy, [4]Department of Rheumatology and Internal Medicine, Medical University of Bialystok, Poland, [5]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [6]Dept. of Medicine, University of Queensland, Queensland, Australia, [7]Division of Pulmonary and Critical Care Medicine, University of California, San Diego School of Medicine, La Jolla, [8]Division of Rheumatology, Department of Medicine, David Geffen School at UCLA, Los Angeles, CA, [9]Division of Rheumatology, University of Connecticut, Farmington, CT, [10]Division of Rheumatology/ZAFES, J.W. Goethe University, Frankfurt, Germany, [11]German Rheumatism Research Centre, Berlin, Germany, [12]Hannover Medical School, Department of Pneumology, Hannover, Germany, [13]Institute for Clinical Pharmacology, Medical Faculty, Technical University, Dresden, Germany, [14]Pediatric Rheumatology Clinic, General Hospital Eilbek, Germany, [15]Pfizer Ltd, Sandwich, UK, [16]Pfizer Ltd, Tadworth, UK, [17]Quanticate Ltd, Hitchin, UK, [18]Rheumatology A Department, RDU, Paris, France, [19]Service de Pneumologie et Reanimation Respiratoire, Centre des Maladies Vasculaires Pulmonaires, Hopital Antoine-Beclere, Université Paris-Sud, Clamart, France

Objective: To validate 6 minute walking distance (6MWD) as an outcome measure in patients with pulmonary arterial hypertension associated with systemic sclerosis (PAH-SSc) using the OMERACT filter of truth, discrimination and feasibility.

Methods: 6MWD was validated in PAH-SSc patients using data from randomized controlled clinical trials (SUPER-1 and STRIDE-1) and from an observational registry (CompERA-XL) reflecting clinical practice. All patients had PAH confirmed by right heart catheterization (RHC). Databases were assessed for the different aspects of the OMERACT filter. 6MWD was compared to pulmonary vascular resistance (PVR) obtained by RHC as the gold standard.

Results: A total of 57 PAH-SSc patients from trial data were available. Analysis of registry data was restricted to PAH-SSc patients where documented PVR and 6MWD were measured within a 30-day span (n=61) to allow for correlation analysis. In trials, both measurements were taken within 4 days. Regarding criterion validity, a linear correlation between 6MWD and PVR of −0.28 was found in the trials, −0.36 in the observational data. In trial data, 6MWD partially correlated with PVR in patients with moderate ($500 \leq PVR < 800$; $r = -0.28$) and severe ($PVR \geq 800$; $r = -0.33$) but not in mild ($PVR < 500$; $r = -0.03$) SSc-PAH. Change in 6MWD after 12 weeks of treatment correlated with change in PVR in the trials ($r = -0.25$). Regarding construct validity, 6MWD partially correlated with relevant dimensions of the SF-36 (e.g. physical functioning $r > 0.33$) in the trials, and discriminated for NYHA class and Borg index for both trial and observational data. Available data did not allow a reliable assessment of sensitivity to change over time (in placebo or untreated patients) or an assessment of reliability.

In comparison, 398 trial patients and 314 registry patients with IPAH were analyzed. Linear correlation of 6MWD and PVR was small ($r = -0.22$, $r = -0.06$). Correlation was better in mild and moderate than severe IPAH. Correlation of changes 12 weeks after treatment start was low ($r = -0.12$). 6MWD correlated with physical functioning of the SF36 ($r > 0.45$), and showed discriminating value for Borg index in both cohorts, for NYHA class only in trial data.

Conclusion: 6MWD and PVR have both demonstrated clinical utility in evaluating patients with PAH, but their relationship is unclear. Assessed by linear correlation between 6MWD and PVR, we found weak criterion validity in these cohorts of PAH-SSc patients. Due to differing correlation patterns between different stages of severity we could show only partial content validity. Construct validity was confirmed by the discriminating value for NYHA class and Borg index. Trial data were confirmed by registry data on most points. Notably, there were no major differences between patients with SSc-PAH and IPAH for the assessed OMERACT criteria. Limitations of this analysis include the small sample size, and retrospective, post hoc analysis of pooled data from different trials. However, taken together these data illustrate limitations of 6MWD as a single outcome measure in SSc-PAH clinical trials or clinical practice.

*both authors contributed equally

Disclosure: D. Huscher: see study sponsor, 2; **N. Roubinis:** Pfizer Ltd, UK, 3; **J. Avouac:** see study sponsor, 2; **F. Behrens:** see study sponsor, 2; **C. P. Denton:** see study sponsor, 2; **D. E. Furst:** see study sponsor, 2; **I. Foeldvari:** see study sponsor, 2; **M. Humbert:** see study sponsor, 2; **O. Kowal-Bielecka:** see study sponsor, 2; **M. Matucci-Cerinic:** see study sponsor, 2; **P. Nash:** see study sponsor, 2; **C. F. Opitz:** see study sponsor, 2; **D. Pittrow:** see study sponsor, 2; **L. J. Rubin:** see study sponsor, 2; **J. R. Seibold:** see study sponsor, 2; **M. M. Hoeper:** see study sponsor, 2; **M. F. Morris:** Pfizer Ltd, UK, 3; **S. A. Teal:** Pfizer Ltd, UK, 3; **O. Distler:** see study sponsor, 2.

ACR Poster Session A

Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Pathogenesis and Animal Models I

Monday, November 8, 2010, 9:00 AM–6:00 PM

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Adenosine A2A Receptor Occupancy Promotes Dermal Fibrosis by Modulating FLI1 and CTGF Expression. Hailing Liu[3], Edwin Chan[2], Patricia Fernández[2] and Bruce N. Cronstein[1]. [1]New York Univ Med Ctr, New York, NY, [2]NYU School of Medicine, [3]NYU School of Medicine, New York, NY

Background: Increased production of extracellular matrix in the skin is the hallmark of Scleroderma. We have previously reported that adenosine, a purine nucleoside produced in ischemic tissue, acting at A2A receptors, enhances dermal collagen production both in vitro and in a murine model of dermal fibrosis, although the mechanism by which adenosine receptor stimulation promotes collagen production is not clear. Fli1 is a known transcriptional repressor of fibrillar collagen genes and connective tissue growth factor (CTGF/CCN2) in dermal fibroblasts. To further clarify the mechanism by which A2A receptor stimulation induces dermal collagen accumulation, we explored the effects of A2A receptor occupancy on Fli1 and downstream mediators of fibroblast matrix production.

Methods: Primary human dermal fibroblasts were stimulated with the selective adenosine A2AR agonist CGS21680 (1μM) for varying time periods and message levels (real time-RTPCR) for fli1 and CTGF were quantitated. In addition we measured cell associated and supernatant levels of collagen I and nuclear levels of fli1 by Western Blot.

Results: Adenosine A2A receptor stimulation for 4 hours reduced Fli1 mRNA expression by 47±18% (4 hrs, $p<0.05$ vs. control, n=4) and reduced nuclear protein levels of Fli1 by 32±13% (24hrs, $p<0.05$, n=4). Because diminished nuclear fli1 should increase CTGF levels we next examined the effect of A2A receptor stimulation on CTGF mRNA and protein secretion. CTGF mRNA level was increased following A2A receptor stimulation for 8 hours by 3.7 fold.Consistent with the change in CTGF mRNA, CGS21680 stimulated a 4.7 fold increase in CTGF protein secretion at (24 hours) as well ($p<0.03$, n=4). As expected A2A receptor stimulation increased collagen I secretion (1.8-fold vs. control, $p<0.05$, n=3) and the increase in collagen production was completely abrogated by an antibody to CTGF (1.1+0.04 fold of control, $p<0.05$ vs.CGS, n=3) but not by control antiserum (1.6 +0.03fold of control, n=3).

Conclusion: A2AR occupancy promotes dermal matrix production by suppressing expression of the transcriptional repressor fli1 leading to an increase in CTGF expression which acts in an autocrine fashion to stimulate collagen production. These findings further suggest that modulation of A2AR function may be a novel therapeutic target for limiting fibrosis in such conditions as scleroderma.

Disclosure: H. Liu: None; **E. Chan:** None; **P. Fernández:** None; **B. N. Cronstein:** Canfite Pharma, 1, Celizone, Sepracor, Endocyte, Protalex, Allos, Kyowa Hakka, Avidimer Therapeutics, 2, 5, King Pharmaceuticals, 2, NIH, 2, vilcek Foundation, 2, 5.

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Adipocyte-Targeted Wnt Activation Results in Spontaneous Dermal Fibrosis and Subcutaneous Lipoatrophy. Jun Wei[3], Denisa S. Melichian[2], Kazuhiro Kumora[2], Ormond Macdougald[4] and John Varga[1]. [1]Northwestern Univ Feinberg School, Chicago, IL, [2]Northwestern University Feinberg School of Medicine, [3]Northwestern University Feinberg School of Medicine, Chicago, IL, [4]University of Michigan

Background: Fibrosis and subcutaneous lipoatrophy are hallmarks of scleroderma, and are thought to reflect mesenchymal cell differentiation into

activated fibroblasts. The Wnts are a family of extracellular ligands and are involved in development and cell fate determinations. Canonical Wnt signaling drives preadipocyte differentiation into osteoblasts in part through negative modulation of PPAR-γ expression and function. Recent studies implicate abnormalities in the canonical Wnt pathway in scleroderma and pulmonary fibrosis. Because Wnt signaling has profound effects on regulating mesenchymal cell lineage, we examined the effect of adipocyte-specific ectopic Wnt10b expression on skin homeostasis and differentiation in transgenic mice.

Methods: Female transgenic mice harboring Wnt10b under the control of the FABP4 promoter were studied. Adiponectin levels were determined by ELISA. Dermal thickness was measured. Collagen accumulation in the skin was determined histochemical stains, and by colorimetric assays. Mast cells were identified by Astra Blue staining. Fibroblasts were explanted from the skin and evaluated in vitro at early passage. Gene expression was assessed by real-time qPCR and Western blot analysis.

Results: At six months of age, female FABP4-Wnt10b transgenic mice showed a marked loss of subcutaneous and visceral adipose tissue. Serum levels of adiponectin were >80% lower than in wildtype littermates. In the skin from Wnt10b transgenic mice, a dramatic increase in Wnt10b mRNA expression was noted, and mRNA level for axin 2 was significantly elevated. The dermis showed a >60% increase in thickness, with a striking reorganization of the collagenous matrix, and a >80% increase in soluble collagen content. Degranulating mast cells were seen in the reticular dermis and among muscle bundles in Wnt10b transgenic mice but not in wildtype littermates. mRNA levels for Type I collagen and α-smooth muscle actin were elevated. Explanted dermal fibroblasts showed elevated Wnt10b expression. Expression of the adipogenic markers PPAR-γ and FABP4 were reduced, whereas mRNA levels for Type I collagen α-SMA were elevated, compared to wildtype fibroblasts examined in parallel.

Conclusion: Ectopic Wnt10b expression targeted to adipocytes results in progressive loss of cutaneous and visceral adipose tissue accompanied by the spontaneous development of dermal fibrosis with increased expression of fibrotic markers. Dermal fibroblasts explanted from Wnt10b transgenic mice show sustained activation of Wnt10b-driven canonical signaling and upregulation of collagen gene expression in vitro, suggesting that ectopic Wnt10b drives a shifts in mesenchymal cell fate toward myofibroblasts by induction of fibrotic genes while simultaneously suppressing adipogenic gene expression. This shift appears to be driven, at least in part, by suppression of the adipogenic master regulator transcription factor PPAR-γ. The results implicate that Wnt signaling plays an important role in the pathogenesis of scleroderma. Modulating Wnt activity may therefore represent a novel therapeutic approach for the treatment of scleroderma.

Disclosure: J. Wei: None; **D. S. Melichian:** None; **K. Kumora:** None; **O. Macdougald:** None; **J. Varga:** None.

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Cadherin 11 Promotes Pulmonary Fibrosis through Production of TGF β and the Regulation of Epithelial to Mesenchymal Transition. Daniel J. Schneider[1], Minghua Wu[4], Thuy T. Le[2], Seo-Hee Cho[3], Michael B. Brenner[5], Michael R. Blackburn[2] and Sandeep K. Agarwal[4]. [1]Department of Biochemistry and Molecular Biology, University of Texas Health Science Center, Houston, TX, [2]Department of Biochemistry and Molecular Biology, University of Texas Health Science Center, [3]Department of Pediatrics, Pediatric Research Center, University of Texas Health Science Center, [4]Division of Rheumatology and Clinical Immunogenetics, The University of Texas-Houston Medical School, Houston, TX, [5]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital and Harvard Medical School

Background: A devastating component of autoimmune disorders including systemic sclerosis is pulmonary fibrosis (PF). PF is characterized by excess deposition of extracellular matrix by myofibroblasts. Epithelial to mesenchymal transition (EMT) is a potential source of myofibroblasts. Cadherin 11 (CDH11) may contribute to processes that parallel those seen in PF and EMT, thus we hypothesized that CDH11 is a key mediator of PF.

Methods: CDH11 expression was determined in lung tissue from idiopathic pulmonary fibrosis (IPF) patients with severe (n=10) and mild (n=10) airway restriction and in the mouse model of bleomycin (BLM)-induced PF. Utilizing CDH11 knockout (Cdh11 −/−) mice and CDH11-neutralizing antibodies, we characterized the contribution of CDH11 in the BLM model. An alveolar epithelial cell line, A549, was used to investigate the role of CDH11 in EMT.

Results: CDH11 expression was increased in patients with severe (1.6±0.1 Δ-ct) versus (vs) mild IPF (1.0±0.1 Δ-ct, p=0.004). CDH11 expression was localized to hyperplastic alveolar epithelial cells and alveolar macrophages in IPF patients and mice given BLM. Compared to wild type (WT), Cdh11 −/− mice given BLM showed reductions in histopathological evidence of lung fibrosis (Ashcroft score: WT 3.9±0.3 vs Cdh11 −/− 2.6±0.5, p=0.04) and reductions in soluble collagen (WT 342±41 μg/ml vs Cdh11 −/− 208±35 μg/ml, p=0.02). Furthermore, TGF-β levels were reduced in bronchoalveolar lavage (BAL) fluid (74±8 pg/ml) and BAL cell pellets (38±8 pg/ml) from Cdh11 −/− vs WT mice given BLM (214±11 BAL pg/ml, p<0.001) (106±16 cell pellet pg/ml, p=0.009). Similar reductions in lung fibrosis and TGF-β were obtained in WT mice given neutralizing CDH11 antibodies beginning 10 days after BLM. In vitro studies of A549 cells demonstrated Cdh11 upregulation by TGF-β and Cdh11 siRNA resulted in a reduction in EMT endpoints including TGF-β-induced collagen production and Snail2/Slug transcription.

Conclusion: We conclude that CDH11 contributes to pulmonary fibrosis through promotion of TGF-β production and the regulation of EMT. This suggests CDH11 may be a novel therapeutic target for PF.

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Cadherin-11 in Systemic Sclerosis and Its Role in Dermal Fibrosis. Minghua Wu[3], Michael B. Brenner[1], Maureen D. Mayes[4], Frank C. Arnett[5], Filemon K. Tan[6] and Sandeep K. Agarwal[2]. [1]Brigham & Womens Hospital, Boston, MA, [2]Division of Rheumatology and Clinical Immunogenetics, University of Texas Health Science Center at Houston, Houston, TX, [3]Division of Rheumatology and Clinical Immunogenetics, University of Texas Health Science Center at Houston (UTHSC-H), Houston, TX, [4]University of Texas-Houston, Houston, TX, [5]UT Medical School, Houston, TX, [6]UT-Houston Med School, Houston, TX

Background: Cadherin-11 (Cad-11) is a mesenchymal cadherin initially identified in osteoblasts but subsequently found to be expressed on other cells including synovial fibroblasts where it confers a mesenchymal phenotype and promotes cellular invasion. Cad-11 has been reported to be increased during wound healing. Recently, Cad-11 was observed to be upregulated in scleroderma (SSc) skin in two independent microarray studies. These results led to the hypothesis that Cad-11 is a critical mediator of dermal fibrosis.

Methods: SSc and normal skin biopsies were used for qRTPCR to quantitate Cad-11 levels and for immunohistological (IHC) analyses to determine the expression pattern of Cad-11. Dermal fibroblasts were stimulated with TGFb and qRTPCR was used to determine if TGFb increased Cad-11 expression. To determine if Cad-11 is a mediator of dermal fibrosis, Cad-11 deficient (def) and wild type (WT) mice were compared using the bleomycin (bleo) induced skin fibrosis model. Anti-Cad-11 monoclonal antibodies (mAb) also were used to confirm these findings in the bleo-induced skin fibrosis model.

Results: Cad-11 transcript levels were increased in SSc skin biopsies (n=6) relative to healthy control skin biopsies (n=9). IHC analyses of skin biopsies demonstrated Cad-11 reactivity in the dermis of SSc biopsies, but not control biopsies, predominantly on fibroblast-like cells. TGFb upregulated Cad11 expression on cultured dermal fibroblasts from healthy controls and SSc patients. Using the bleo-induced dermal fibrosis model, Cad-11 def. mice had markedly attenuated dermal fibrosis as quantitated by skin thickness (Cad11 def:194±14 μm, WT: 255±17 μm, p=0.003), collagen levels (Cad11 def: 230±24 μg/mg, WT: 319±20 μg/mg, p=0.01) and myofibroblast accumulation in the lesional skin. Administration of two neutralizing anti-Cad-11mAb to WT mice resulted in a significant amelioration of collagen deposition and dermal thickness in bleo-induced dermal fibrosis. Lastly, Col1a1 and CTGF mRNA levels but not IL-6 levels were significantly decreased in lesional skin of Cad-11 def. compared to WT mice.

Conclusions: These results demonstrate that Cad-11 is a critical mediator of dermal fibrosis, and suggest that Cad-11 is a potential therapeutic target in SSc.

Disclosure: M. Wu: None; **M. B. Brenner:** Allergy Therapeutics Limited, 1, 5, Calcimedica Inc, 1, 5, SR One, Inc, 1, 5, Synovex Corp, 1, 5; **M. D. Mayes:** None; **F. C. Arnett:** None; **F. K. Tan:** None; **S. K. Agarwal:** None.

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Dabigatran Etexilate, an Oral Direct Thrombin Inhibitor, Represses Fibrotic Changes in a Murine Model of Pulmonary Fibrosis. Galina Bogatkevich[3], Anna Ludwicka-Bradley[3], Paul J. Nietert[4], Joanne van Ryn[1] and Richard M. Silver[2]. [1]Boehringer Ingelheim, [2]Medical University of South Carolina, Charleston, SC, [3]Medical University of South Carolina, Charleston, SC, [4]Medical University of South Carolina

Rationale: Activation of the coagulation cascade and generation of thrombin has been extensively documented in pulmonary fibrosis, both in acute and chronic lung injury, including scleroderma and in animal models of lung injury. The oral direct thrombin inhibitor (DTI), dabigatran etexilate, modulates the coagulation cascade and inhibits thrombin-induced profibrotic signaling in lung fibroblasts, including scleroderma lung fibroblasts. This study tested whether thrombin inhibition by dabigatran etexilate attenuates bleomycin-induced pulmonary fibrosis in a murine model of lung injury.

Methods: Lung injury was induced in 6–8 week old female C57BL/6 mice by intratracheal instillation of bleomycin. Dabigatran etexilate was given as supplemented chow (10 mg/g chow) or as matching placebo beginning on day 8 following bleomycin. Two and three weeks after bleomycin instillation mice were euthanized, and lungs, bronchoalveolar lavage fluid (BALF) and plasma were collected. Lung collagen was measured by hydroxyproline assays; dabigatran concentration by LC-MS/MS; thrombin activity by fluorometric assays; TGF-β1 concentrations by ELISA; connective tissue growth factor (CTGF) and smooth muscle α-actin (α-SMA) were assessed by immunoblotting. The association between hydroxyproline levels in lung tissue and dabigatran concentration in plasma was tested using Spearman rank correlation test.

Results: In BALF we observed significant reduction of active thrombin and TGF-β1 from 46.05$\pm$19.4ng/ml and 54.9$\pm$6.1pg/ml in bleomycin + placebo-treated mice to 11.95$\pm$4.4ng/ml ($p< 0.001$) and 31.144$\pm$8.7pg/ml ($p<0.01$) respectively in bleomycin + dabigatran etexilate-treated mice. Dabigatran treatment was also associated with two-fold decrease in the absolute number of cells in BALF of bleomycin-treated mice. A quantitative evaluation of histopathology by Ashcroft scale demonstrated a significant decrease in fibrosis of dabigatran-treated mice (5.76$\pm$1.64 vs. 2.98$\pm$0.88, $p<0.05$). A strong negative correlation between hydroxyproline levels in lung tissue and dabigatran concentration in plasma was observed in mice with bleomycin-induced lung fibrosis ($R=-0.96$, $p=0.0005$). There was no correlation between hydroxyproline and dabigatran in control sham-injured mice. Additionally, dabigatran reduced CTGF 9-fold and α-SMA 2.5-fold in mice with bleomycin-induced lung fibrosis, whereas it did not interfere with basal levels of the proteins.

Conclusions: Inhibition of thrombin using the oral DTI dabigatran etexilate has marked anti-fibrotic effects in a bleomycin-induced mouse model of pulmonary fibrosis. Dabigatran etexilate treatment reduces collagens, TGF-β1, CTGF, and α-SMA induced by tissue injury, while not interfering with basal levels of these proteins in normal lung tissue. Our data suggest that dabigatran etexilate may be beneficial in the treatment of fibrosing lung diseases, e.g. scleroderma lung disease and idiopathic pulmonary fibrosis.

Disclosure: G. Bogatkevich: Boehringer Ingelheim, 2; **A. Ludwicka-Bradley:** None; **P. J. Nietert:** None; **J. van Ryn:** Boehringer Ingelheim, 3; **R. M. Silver:** Boehringer Ingelheim, 2.

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Endothelial Dysfunction and Abnormal Collagen V Deposition in Pulmonary Vasculature of Experimental Systemic Sclerosis Model. Roberta G. Marangoni[2], Edwin R. Parra[1], Ana Paula P. Velosa[3], Walcy R. Teodoro[3], Vera L. Capelozzi[1] and Natalino H. Yoshinari[3]. [1]Pathology Department, Faculdade de Medicina da Universidade de São Paulo, [2]Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil, [3]Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo

Purpose: We have recently described a collagen type V (COL V) rabbit experimental model that resembles the human systemic sclerosis (SSc). None of the profibrotic models for SSc to date have reproduced the vascular involvement observed in human disease. We therefore have evaluated in our model the intrapulmonary arteries for neovascularization (CD31 expression), endothelial apoptosis (caspase-3 induced), endothelial activity (endothelin-1 and VEGF expression) and COL V deposition.

Methods: Female rabbits from New Zealand lineage (n=6) were immunized with human COL V plus Freund's adjuvant. Animals immunized only with Freund's adjuvant (n=6) were used as controls. Two hundred and ten days after the first immunization, the animals were sacrificed and the lungs submitted to hematoxylin&eosin staining, electron microscopy, immunofluorescence, immunohistochemistry and morphometry.

Results: The histopathological analysis revealed a clear preponderance of intrapulmonary arteries with irregularity and wall thickness only in COL V immunized rabbits. Type V collagen was also increased and structurally altered. Ultrastructural analysis of same lungs showed increased rate of apoptosis, organelles with degenerative changes and cytoplasmic tumefaction of the endothelial cells which appeared detached from the basement membrane. Additionally, COL V group displayed increased expression of the immunomarkers for neovascularization, endothelial apoptosis and endothelial activation compared to controls ($p<0.01$).

Conclusions: Our experimental model reproduced the endothelial dysfunction and abnormal COL V deposition in pulmonary vasculature observed in SSc patients, confirming its suitability to study the vascular involvement of this disease.

Disclosure: R. G. Marangoni: None; **E. R. Parra:** FAPESP, 2; **A. P. P. Velosa:** None; **W. R. Teodoro:** Federico Foundation Grants, 2; **V. L. Capelozzi:** FAPESP, 2; **N. H. Yoshinari:** None.

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Genetic Deletion or Pharmacologic Antagonism of LPA1 Ameliorates Dermal Fibrosis in a Mouse Model of Systemic Sclerosis. Flavia V. Castelino[3], Jon Seiders[1], Gretchen Bain[1], Chris King[1], James Swaney[1], Dan Lorrain[1], Jerold Chun[5], Andrew D. Luster[2] and Andrew M. Tager[4]. [1]Amira Pharmaceuticals, [2]Massachusetts General Hospital, Charlestown, MA, [3]Massachusetts General Hospital, Boston, MA, [4]Massuchusetts General Hospital, [5]Scripps Research Institute

Rationale: Systemic sclerosis (SSc) is a potentially fatal autoimmune disease of unknown etiology, characterized by progressive multi-organ fibrosis that is refractory to current therapies. We previously implicated the lipid mediator lysophosphatidic acid (LPA) in the pathogenesis of pulmonary fibrosis. Here, we studied the roles of LPA and two of its G protein-coupled receptors, LPA1 and LPA2, in dermal fibrosis using the bleomycin mouse model of SSc in mice deficient for these receptors. Additionally, we investigated the therapeutic potential of targeting LPA1, by using the novel LPA1-selective antagonist AM095 in this model.

Methods: Wild type (WT) and LPA1- and LPA2-deficient (LPA1 KO, LPA2 KO) mice received subcutaneous injections of bleomycin (10 μg/ml) or phosphate buffered saline (PBS) once per day. After 28 injections, full thickness 6 mm punch biopsies were obtained. Dermal thickness was measured between the epidermal-dermal and dermal-fat junctions using H&E stained skin sections. Collagen was visualized by Masson's trichrome stain, and quantified by hydroxyproline measurement. Myofibroblasts and cells responding to TGF-β, were identified in skin sections by immunohistochemical staining with anti-α-smooth muscle actin (α-SMA) and anti-phosphoSmad2 antibodies (p-Smad2), respectively. The LPA1 antagonist, AM095 or vehicle control was administered to bleomycin- or PBS-challenged C57Bl/6 mice by oral gavage twice daily on weekdays and once daily on weekends. AM095 or vehicle treatment was either administered concurrently with bleomycin or PBS, or initiated at 7 or 14 days after bleomycin, for total treatment durations of 28, 21 or 14 days, respectively. At the conclusion of these treatment schedules, dermal thickness and collagen content were assessed as above.

Results: LPA1 KO mice were markedly protected from dermal fibrosis. Comparing LPA1 KO and WT mice, genetic deletion of LPA1 attenuated bleomycin-induced increase in dermal thickness by 91% and hydroxyproline content by 90%. Dermal α-SMA+ and pSmad2+ cells were also markedly attenuated in bleomycin-challenged LPA1 KO mice. The number of α-SMA+ myofibroblasts increased by 70% in WT mice, but only by 5% in LPA1 KO mice. Similarly, bleomycin challenge increased pSmad2+ cells by 81% in WT mice, with no increase in LPA1 KO mice. In contrast, LPA2 KO mice were not protected from bleomycin-induced increases in dermal thickness and collagen content when compared to WT mice. Pharmacologic antagonism of LPA1 with AM095 also significantly attenuated bleomycin-induced dermal fibrosis. Although the greatest reductions in dermal fibrosis were seen with 28-day administration of AM095, both delayed treatment regimens significantly reduced dermal fibrosis as well.

Conclusions: These results suggest that LPA signaling through LPA1 but not LPA2 is required for bleomycin-induced dermal fibrosis, and is required for both myofibroblast accumulation and TGF-β-Smad signaling. Both

genetic deletion and preventive or therapeutic pharmacological inhibition of LPA1 attenuated bleomycin-induced dermal fibrosis. Targeting LPA1 therefore has the potential to be an effective new therapeutic strategy for SSc.

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Inactivation of the Transcription Factor STAT4 Prevents Inflammation-Driven Fibrosis in Systemic Sclerosis Animal Models. Jerome Avouac[3], Barbara G. Fürnrohr[2], Michal Tomcik[4], Katrin Palumbo[2], Pawel Zerr[2], Angelika Horn[2], Clara Dees[2], Alfiya Akhmetshina[2], Christian Beyer[2], Oliver Distler[1], Georg Schett[5], Yannick Allanore[6] and Jorg H. W. Distler[7]. [1]Center of Experimental Rheumatology and Zurich Center of Integrative Human Physiology, University Hospital Zurich, Zurich, Switzerland, [2]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [3]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, Paris Descartes University, Rheumatology A Department, Cochin Hospital, and INSERM U781, Necker Hospital, Paris, Fr, [4]Department of Internal Medicine III, University of Erlangen-Nuremberg, Erlangen, Germany and Institute of Rheumatology and Connective Tissue Research Laboratory, Department of Rheumatology of the First Faculty of Medicine, Charles University i, [5]Friedrich Alexander Univ, Erlangen, Germany, [6]Paris Descartes University, Rheumatology A Department, Cochin Hospital, and INSERM U781, Necker Hospital, Paris, France, [7]University of Erlangen, Erlangen, Germany

Objective: STAT4 is a transcriptional factor regulating various cytokines and in particular interferon type 1 and IL12-IL23 pathways. STAT4 has been recently identified as a genetic susceptibility factor to systemic sclerosis (SSc) and also to other autoimmune diseases. Our aim was to investigate the contribution of STAT4 in the development of a fibrotic phenotype in two different mouse model of experimental dermal fibrosis.

Methods: The role of STAT 4 was first evaluated in the mouse model of bleomycin-induced dermal fibrosis, a model for early, inflammatory stages of SSc. Mice deficient for STAT4 (stat4−/−) and wildtype littermates (stat4+/+) were injected with bleomycin or NaCl. Infiltrating leukocytes and T cells in lesional skin of STAT4−/− and STAT4+/+ mice were quantified respectively on hematoxylin and eosin stained sections and by immunohistochemistry for CD3. Th1 and Th2 cytokine levels were also measured in the serum or lesional skin samples of stat4−/− and stat4+/+ mice. The invalidation of STAT4 was also investigated in the tight-skin (tsk-1) mouse model, which serve as a model of later, less inflammatory stages of SSc.

Results: stat4−/− mice were protected from bleomycin-induced dermal fibrosis with reduced dermal thickening (65±3% reduction, p=0.03), hydroxyproline content (68±5% decrease, p=0.02) and myofibroblast counts (71±6% reduction, p=0.05). The numbers of leukocytes, especially infiltrating T cells, were also decreased in lesional skin of stat4−/− mice (respectively 62±4%, p=0.02 and 63±5%, p=0.02). Moreover, stat4−/− mice displayed in lesional skin decreased levels of cytokines involved in inflammatory and fibrotic processes such as IL-6 (50±4% decrease), TNFα (71±5%), INFγ (58±3%) and IL-2 (63±4%). Similar results were observed in the serum.

Consistent with a primary role of STAT4 on inflammation, STAT4 deficiency did not improve the fibrotic phenotype in tsk-1 mice. No differences in hypodermal thickness, hydroxyproline content and myofibroblasts counts were observed between stat4−/−/tsk-1 mice and their stat4+/+/tsk-1 littermates.

Conclusion: This is the first translational study demonstrating the role of the transcription factor STAT4, an established genetic susceptibility factor of SSc and different autoimmune diseases, in animal models of SSc. We herein demonstrate that STAT4 exerts potent profibrotic effects in inflammation-driven models of fibrosis. STAT4 indirectly regulates the activation of fibroblasts by promoting the infiltration of T cells into lesional skin and the production of inflammatory cytokines. These findings confirm the results of the genetic studies on the role of STAT4 in the development of SSc.

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Induction of Peripheral Tissue Ischemia and Anti-Endothelial Antibodies after B Cell Adoptive Transfer from RNP-Immunized Mice. YunJuan Zang[3], Irina Fernandez[3], Maite Chavez[3], Laisel Martinez[1] and Eric L. Greidinger[2]. [1]Miami VA Medical Center, [2]Miami VA Medical Center and University of Miami Miller School of Medicine, Miami, FL, [3]University of Miami Miller School of Medicine

Background: We have previously developed a murine model of induced anti-RNP autoimmunity with clinical manifestations including interstitial lung disease and nephritis, in which disease manifestations were transferable to naive syngeneic mice by T cell or dendritic cell adoptive transfer. To pursue the hypothesis that autoimmune Raynaud's Phenomenon (RP) may be mediated by B cells, B cell adoptive transfer studies were performed.

Methods: C57BL/6 female mice transgenic for expression of HLA-DR4 were immunized with 70k and U1-RNA following our published protocol, and confirmed to have anti-RNP humoral responses by ELISA. Unimmunized syngeneic mice housed together with the immunized mice were used as control B cell donors. Two months after immunization, mice were sacrificed, spleens were collected and processed into RBC-depleted single-cell suspensions, and CD20+ cells were positively selected by AutoMACS. Four million cells per recipient were transferred via the tail vein into syngeneic 10 week old female mice. Recipients were followed clinically for up to two weeks after cell transfer. Loss of ear and tail tissue (thermoregulatory tissues in mice) was noted by personnel blinded to the treatment status of the mice, and documented photographically. Serum was collected from sacrificed mice, and organs were analyzed histologically. The immunoreactivity of collected sera was tested by immunofluorescence and immunoblot against HUVEC and Jurkat cells, and compared to reference human sera from patients with RP and controls.

Results: B cell adoptive transfer induced episodes of cyanosis and resulted in loss of ear and/or tail tissue in 14/17 recipients of B cells from RNP+ donors, but in 0/5 recipients of B cells from unimmunized donors (Fisher's Exact p = 0.002). No evidence of vasculitis or thrombosis was observed histologically. Like human RP sera but unlike human control sera or RNP+ B cell donor sera, the sera from mice with tissue loss had anti-endothelial reactivity, and induced morphological changes and cell death in HUVEC cultures. B cell recipients from RNP+ donors had lower titer anti-RNP responses than their respective B cell donors. Serum transfer from mice with tissue loss but not from RNP+ B cell donors also induced ear and/or tail tissue loss.

Conclusions: B cell adoptive transfer from RNP+ donors induces a novel murine model of Raynaud's Phenomenon. This model provides a novel link between the autoimmune and vasospastic manifestations of systemic autoimmune diseases, and specifically implicates B cells in RP pathogenesis.

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Mice Lacking the Receptor-Like Protein Tyrosine Phosphatase CD148 Are Protected from Bleomycin-Induced Pulmonary Fibrosis. Tamiko R. Katsumoto[1], Kevin K. Kim[2], Alexis N. Brumwell[2], John X. Nguyen[2], Jing W. Zhu[2], Mark R. Looney[2], Harold A. Chapman[2] and Arthur Weiss[2]. [1]UCSF, South San Francisco, CA, [2]UCSF

Purpose: The molecular mechanisms underlying pulmonary fibrosis, one of the most morbid complications of scleroderma, remain incompletely characterized. Protein tyrosine phosphatases and kinases regulate the equilibrium of tyrosine phosphorylation signaling pathways important in cell growth and differentiation. Tyrosine kinases have been implicated in fibrosis, and studies testing the anti-fibrotic activity of tyrosine kinase inhibitors such as imatinib in scleroderma patients are underway. The receptor-like protein tyrosine phosphatase (RPTP) CD148 is widely expressed on various hematopoietic and non-hematopoietic lineages, including lung epithelial cells, endothelial cells, and fibroblasts. Given the importance of tyrosine phosphorylation pathways in fibrosis, we explored the role of CD148 in the bleomycin mouse model of pulmonary fibrosis.

Methods: Mice with a targeted deletion of the CD148 transmembrane domain (CD148KO) have been generated by our lab and are used in all studies described. Acute lung injury was measured using extravasation of radioactive iodine-labeled albumin and wet-to-dry ratios. Fibrosis was evaluated by both Masson Trichrome staining of lung sections as well as by the Sircol Collagen Assay (Biocolor).

Results: Following intratracheal instillation of bleomycin at a dose of 3 units/kg, WT mice showed significantly impaired survival, with 4 of 6 WT mice (67%) dying between 10–16 days, whereas none of the 8 CD148KO mice (0%) died (p=0.007). Masson Trichrome staining of lungs demonstrated markedly increased fibrosis in WT mice, whereas fibrosis was significantly attenuated in the CD148KO mice. At day #13 following a lower dose of bleomycin (2.5 U/kg), WT bleomycin-treated mice had a 4.2-fold increase in lung collagen content whereas CD148KO mice showed only a 1.7-fold increase in collagen (p=0.0009). Lung collagen levels in WT bleomycin mice (66.1+/−6.1 ug/ml) were significantly higher than in WT saline mice (15.8+/−0.8 ug/ml) (p=0.0008), whereas lung collagen levels in CD148KO bleomycin mice (46.1+/−8.2 ug/ml) vs. CD148KO saline mice (26.6+/−7.2 ug/ml) were not significantly different (p=0.157). The acute lung injury response at day #5 post bleomycin (2.5 U/kg) was equivalent between genotypes. Endothelial permeability was 1.7% +/−0.33% in WT saline mice vs. 1.5% +/−0.39% in CD148KO saline mice. Following bleomycin, the increase in endothelial permeability in WT mice to 3.9% +/−0.67% and in CD148KO mice to 3.9% +/−0.39% was equivalent between genotypes (n=4 mice per genotype).

Conclusion: Mice lacking CD148 phosphatase activity show improved survival. Attenuation of bleomycin-induced fibrosis does not appear to be the consequence of a diminished early acute lung injury response to bleomycin. Future studies will interrogate the specific cell types mediating this response, as well as elucidating the pathways regulated by CD148 underlying this phenotype. These data suggest that inhibition of the RPTP CD148 may present an attractive anti-fibrotic therapeutic strategy.

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Noggin$^{+/LacZ}$ Heterozygous Mice Have Reduced Pulmonary Fibrosis in the Bleomycin Induced Model. Ellen de Langhe[2], Vanessa De Vooght[2], Frank P. Luyten[1] and Rik Lories[1]. [1]KU Leuven, Leuven, Belgium, [2]KU Leuven

Introduction: Noggin (Nog) is an extracellular antagonist of the Bone Morphogenetic Protein (BMP) signaling pathway. The BMP pathway plays an important role in embryonic development, postnatal growth, tissue homeostasis and disease. The molecular mechanisms underlying pulmonary fibrosis in diseases such as systemic sclerosis and idiopathic pulmonary fibrosis (IPF) are poorly understood. The role of the BMP antagonist gremlin in IPF has been published.

Objectives: We hypothesize that the BMP signaling pathway plays a role in fibrogenesis. Here we study the role of Nog and the BMP pathway in bleomycin induced pulmonary fibrosis using Nog$^{+/LacZ}$ heterozygous mice.

Material and Methods: Pulmonary fibrosis was induced in 8-week old male wild-type (WT) or Nog$^{+/LacZ}$ mice, both on the C57/Bl6 background by intratracheal instillation of 0.05U bleomycin (BLM) or phosphate buffered saline (PBS) as a control (WT: BLM n=23, PBS n=17; Nog$^{+/LacZ}$: BLM n=14, PBS n=7). 4 weeks after baseline induction invasive pulmonary function tests were performed using the Flexivent® SCIREC system. The mice were subsequently sacrificed and pulmonary tissue was collected for histopathology, immunohistochemistry and gene expression analysis. Pulmonary architecture was evaluated and scored on haematoxylin-eosin (H&E) sections using the validated Ashcroft score for pulmonary fibrosis. Total collagen content was quantified using the hydroxyproline quantification assay. Immunohistochemistry for phosphorylated Smad 1/5/8 was performed to demonstrate active BMP signaling during the process of fibrosis.

Results: Pulmonary fibrosis was successfully induced in the BLM treated groups, evident on H&E stainings and quantified by high Ashcroft scores. The increased nuclear staining for phosphorylated Smad 1/5/8 in the fibrotic areas indicated active BMP signaling. When pulmonary fibrosis was induced in the Nog$^{+/LacZ}$ mice, it was associated with an attenuated fibrotic response with a significant decrease in the Ashcroft score as compared to the WT controls, as well as a significantly decreased collagen content. This was further confirmed at the functional level by significantly higher lung compliance.

Conclusion: The BMP signaling pathway appears activated in bleomycin induced pulmonary fibrosis. When bleomycin is administered to Nog$^{+/LacZ}$ mice, partial loss of gene function is associated with an attenuated fibrotic response both at the histomorphological and at the functional level. Further experiments are needed to clarify whether this effect results from increased BMP signaling or from possible interactions with the TGFβ signaling pathway.

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Nr4a1 Ameliorates the Pro-Fibrotic Effects of TGFβ in Systemic Sclerosis (SSc) and Might Be an Interesting Target for Anti-Fibrotic Therapies. Katrin Palumbo[1], Alfiya Akhmetshina[1], Pawel Zerr[1], Michal Tomcik[1], Angelika Horn[1], Clara Dees[1], Oliver Distler[3], Georg Schett[2] and Jorg H. W. Distler[4]. [1]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]Friedrich Alexander Univ, Erlangen, Germany, [3]University Hospital Zurich, Zurich, Switzerland, [4]University of Erlangen, Erlangen, Germany

Background: Nuclear receptor 4 a 1 (Nr4a1) is a unique transcription factor which belongs to the superfamily of orphan nuclear receptors. Unlike most nuclear receptors, members of Nr4a receptors do not seem to require ligand binding for activation. Nr4a1 is known to be a regulator of macrophage gene expression in inflammation, cell death and cell growth. The aim of the present study was to investigate the role of Nr4a1 in TGFβ signaling and in the pathogenesis of SSc.

Methods: The expression of Nr4a1 in cells and tissue was analyzed by real-time PCR, Western Blot and immunofluorescence. Collagen synthesis was quantified by real-time PCR, SirCol- and hydroxyproline assay. The role of Nr4a1 in fibrosis and potential therapeutic implication were evaluated in three different mouse models: bleomycin-induced dermal fibrosis, tight-skin-1 (tsk-1) mice and mice infected with adenovirus overexpressing constitutively active TGFβ receptor I.

Results: The expression of Nr4a1 was significantly elevated in the skin of SSc patients compared to healthy controls. Moreover, mRNA levels of Nr4a1 were increased in cultured SSc fibroblasts. Stimulation with TGFβ strongly increased the mRNA and protein levels of Nr4a1 in cultured fibroblasts, indicating that TGFβ might drive the overexpression in SSc. siRNA-mediated knock-down of Nr4a1 in human fibroblasts potently induced the expression of collagen mRNA and protein. An increased release of collagen was also observed in murine fibroblasts isolated from Nr4a1 deficient mice. On the other hand, stimulation of Nr4a1 signaling, either by overexpression of Nr4a1 or by incubation with the Nr4a1 agonist Cytosporone B, strongly reduced the collagen synthesis in cultured fibroblasts. These data suggest that Nr4a1 is in the centre of a negative feedback loop, which restricts the pro-fibrotic effects of TGFβ in SSc. Consistently, mice lacking Nr4a1 were more sensitive to bleomycin induced fibrosis with 2 fold more pronounced dermal thickening, myofibroblast counts and hydroxyproline content upon challenge with bleomycin compared to wildtype mice. Moreover, AAV-TGFRI virus infected Nr4a1 deficient mice and tsk-1 mice lacking Nr4a1 showed also significantly increased fibrosis compared to control mice expressing Nr4a1. Next, we investigated, whether therapeutic activation of Nr4a1 by Cytosporone B prevents experimental fibrosis. Treatment with Cytosporone B completely prevented fibrosis in all mouse models and reduced dermal thickness, myofibroblast counts and hydroxyproline content to levels similar to control mice.

Conclusion: We demonstrate that Nr4a1 is upregulated in SSc in a TGFβ dependent manner. Nr4a1 negatively regulates the extracellular matrix (ECM) production by limiting the pro-fibrotic effects of TGFβ in vitro as well as in vivo. Thus, we first describe a negative feedback loop, in which the concomitant upregulation of Nr4a1 limits the pro-fibrotic effects of TGFβ in SSc. In addition, activation of Nr4a1 signaling by Cytosporone B might be a novel therapeutic approach for fibrotic diseases.

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Osteopontin in Systemic Sclerosis and Its Role in Dermal Fibrosis. Minghua Wu[2], Daniel J. Schneider[1], Maureen D. Mayes[3], Shervin Assassi[2], Frank C. Arnett[4], Filemon K. Tan[5], Michael R. Blackburn[1] and Sandeep K. Agarwal[2]. [1]Department of Biochemistry and Molecular Biology, UTHSC-H, Houston, TX, [2]Division of Rheumatology and Clinical Immunogenetics, University of Texas Health Science Center at Houston, Houston, TX, [3]University of Texas-Houston, Houston, TX, [4]UT Medical School, Houston, TX, [5]UT-Houston Med School, Houston, TX

Background: Osteopontin (OPN) is a multifunctional cytokine produced during inflammation and tissue repair. OPN has been implicated in certain autoimmune diseases such as rheumatoid arthritis and as well as with fibrosis in disorders such as idiopathic pulmonary fibrosis and in mouse models of pulmonary fibrosis. Given the importance of autoimmunity and fibrosis in systemic sclerosis (SSc), we hypothesized that OPN is elevated in SSc patients and plays a critical role in the development of dermal fibrosis.

Methods: Plasma from a cohort of SSc patients (n= 319) and non-autoimmune disease controls (n= 144) were used to determine OPN levels by ELISA. Skin biopsies from SSc patients and healthy controls were used for immunohistological (IHC) analyses. To determine if OPN is a mediator of dermal fibrosis, OPN deficient (def) and wild type (WT) mice were compared in the bleomycin (bleo)-induced dermal fibrosis model.

Results: Circulating levels of OPN were elevated in SSc patients (47.9±3.6 ng/ml) compared to healthy controls (28.3±3.8ng/ml, p=0.0009). OPN levels were elevated in both patients with limited and diffuse disease as well as anticentromere, anti-topoisomerase I and anti-RNA polymerase III positive SSc patients relative to controls. Compared to controls, SSc skin biopsies expressed OPN that localized to both fibroblast-like cells and macrophages on IHC analyses. Similarly, skin biopsies from mice treated with subcutaneous bleo had increased levels of OPN compared to PBS injected mice. Interestingly, using the bleo-induced dermal fibrosis model, OPN def. mice had markedly attenuated dermal fibrosis as quantitated by skin thickness (OPN def: 253±14 μm, WT 318±12 μm, p=0.001), collagen levels (OPN def: 263±35 μg/mg, WT 420±46 μg/mg, p=0.01) and myofibroblast accumulation in the lesional skin. Furthermore, OPN def. mice had decreased dermal inflammation, including decreased number of Mac-3 positive macrophages. Lastly, Col1a1, IL-6, PAI-1 and CTGF mRNA levels were significantly decreased in lesional skin of OPN def. compared to WT mice.

Conclusions: These data demonstrate that OPN is a mediator of dermal fibrosis, and suggest that OPN may be a potential biomarker and/or therapeutic target in SSc.

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Relevance of Epithelial Phenotypic Switching in the Pathogenesis of Systemic Sclerosis. Xu Shiwen[1], S. Sonnylal[3], A. Tam[2], R. Stratton[2], A. Leask[2], C. P. Denton[2], J. Norman[2] and D. Abraham[2]. [1]Rheumatology, London, United Kingdom, [2]Rheumatology, United Kingdom, [3]UT M. D. Anderson Cancer, Houston, TX

Systemic sclerosis (SSc) is a complex disorder of uncertain etiology characterised by progressive vascular and interstitial fibrosis. Recently, we found that epidermal compartment in SSc skin exhibits abnormalities, taking on an activated phenotype reminiscent of that during the wound healing response. Fibroblast-Epithelial cell interactions are believed important during normal tissue repair and aberrant cellular cues may underlie important aspects of scarring and fibrosis. Transgenic mice in which the fibroblast expressed a constitutively active TGFb type I receptor (ALK5) or which expressing CTGF, develop progressive tissue fibrosis most prominent in the skin and lung. Our *in vivo* data also suggests that activation of TGFb signalling or CTGF over-expression by fibroblasts not only causes stromal activation, but also pathological changes in the phenotype of adjacent epithelium. Here, we focus on the phenotypic profile of the SSc epithelium, the role of fibroblast-derived CTGF in epithelial switching into a mesenchymal-like phenotypic and the contribution this process may play to fibrogenesis.

Methods: Whole skin biopsies were obtained from SSc and controls. The epidermis was prepared from some of the skin biopsies, and processed for phospho-kinase profiling (Kinexus: Vancouver, Canada). Human and rodent type II epithelial cells lines (A549 and T2) were grown in grown in DMEM + 10%FBS. Epithelial cells were stimulated with TGFb after serum starvation in the presence and absence of siRNA for specific for CTGF. Markers of epithelial cells and fibroblasts including CTGF, snail, E-cadherin, aSMA, collagen type I and fibronectin were examined using western blot analysis.

Results: Phosphorylation arrays were performed on the epidermal tissue from SSc patients and healthy controls to identify signaling pathways activated in SSc epidermis. A number of EMT-related proteins were found to have elevated phosphorylation states in SSc tissues versus controls, including c-Met, Wee1 protein-tyrosine kinase, STAT3, Integrin-linked protein-serine kinase 1($p<0.05$). Further *in vitro studies,* A549 and T2 epithelial cells exposed to TGF-β develop a mesenchymal-like morphology and molecular markers associated with EMT (snail and CTGF). CTGF-specific siRNA dose-dependently suppressed TGFβ-induced snail and CTGF protein expression towards basal levels in A549 cells. Transgenic mouse fibroblasts over-expressing CTGF showed significantly higher expression levels for matrix genes and proteins including collagen type I, fibronectin and increased expression of aSMA.

Conclusion: In this study we show that phosphorylation array analysis revealed induction of EMT-like protein kinase signaling in SSc epidermis. Important growth factor, TGF-β promotes and triggers epithelial cells to undergo a phenotypic switch which is attenuated upon CTGF knock-down by RNA interference. Our data suggests that in SSc, the enhanced expression of TGFb signaling and CTGF expression is likely to indirectly contribute to disease pathogenesis by triggering epidermal cells phenotypic switching towards a mesenchyml cell-like programme.

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S100A4 as a Novel Mediator of TGF-β Driven Dermal Fibrosis in Systemic Sclerosis. Michal Tomcik[4], Pawel Zerr[2], Katrin Palumbo[2], Barbara G. Fürnrohr[2], Jerome Avouac[3], Angelika Horn[2], Clara Dees[2], Alfiya Akhmetshina[2], Christian Beyer[2], Radim Becvar[7], Oliver Distler[1], Mariam Grigorian[6], Ladislav Senolt[7], Georg Schett[5] and Jorg H. W. Distler[8]. [1]Center of Experimental Rheumatology and Zurich Center of Integrative Human Physiology, University Hospital Zurich, Switzerland, [2]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [3]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany and Paris Descartes University, Rheumatology A Department Cochin Hospital, Paris, France, [4]Department of Internal Medicine III, University of Erlangen-Nuremberg, Erlangen, Germany and Institute of Rheumatology and Connective Tissue Research Laboratory, Department of Rheumatology of the First Faculty of Medicine, Charles University i, [5]Friedrich Alexander Univ, Erlangen, Germany, [6]Institute of Cancer Biology, Danish Cancer Society, Copenhagen, Denmark, [7]Institute of Rheumatology and Connective Tissue Research Laboratory, Department of Rheumatology of the First Faculty of Medicine, Charles University in Prague, Czech Republic, [8]University of Erlangen, Erlangen, Germany

Background: S100A4 (metastasis associated protein) is a calcium binding protein exerting regulatory functions in diverse biological processes. It promotes cancer progression and metastasis by regulating the remodelling of the extracellular matrix.

Objectives: The aim of this study was to investigate the contribution of S100A4 to the pathologic activation of fibroblasts in SSc and its role in the development of a fibrotic phenotype in a mouse model of experimental dermal fibrosis.

Methods: Activation of S100A4 in human skin and experimental dermal fibrosis was determined by real-time PCR, immunohistochemistry and western blot. Collagen synthesis of SSc and healthy dermal fibroblasts was quantified by real-time PCR and SirCol collagen assay. Bleomycin-induced dermal fibrosis, a model for early, inflammatory stages of SSc, was used to assess the role of S100A4 in vivo using mice deficient for S100A4 ($^{-/-}$) and wildtype littermates ($^{+/+}$).

Results: Increased expression of S100A4 was detected in the upper layer of the dermis of SSc patients and was clearly colocalized with alpha-smooth muscle actin-positive fibroblasts. The overexpression of S100A4 persisted in cultured SSc fibroblasts and might contribute to their activated phenotype. A similar increase in S100A4 expression was observed in the skin samples from mice challenged with bleomycin and tsk-1 mice, both on mRNA (3.5- and 15.5-fold increase, respectively) and protein level. TGF-β stimulation of both healthy and SSc fibroblasts led to an increased expression of S100A4 protein. Of particular interest, knockdown of S100A4 by siRNA fully abrogated the stimulatory effects of TGF-β on the collagen synthesis of SSc fibroblasts. In agreement with the role of S100A4 as a novel mediator of the pro-fibrotic effects of TGF-β, mice lacking S100A4 were protected from experimental fibrosis. In the model of bleomycin-induced dermal fibrosis, inhibition of S100A4 decreased dermal thickening by 53±2% ($p<0.01$), significantly reduced the hydroxyproline content by 30±4% ($p<0.01$) and the number of myofibroblasts by 254±16% ($p<0.01$). Reduced induction of dermal fibrosis in S100A4 $^{-/-}$ mice might result from inhibition of TGF-β signaling as evidenced by reduced nuclear accumulation of phosphorylated Smad 3 in the skin sections of S100A4 $^{-/-}$ mice treated with bleomycin compared to their wildtype ($^{+/+}$) littermates.

Conclusion: This is the first study reporting on the role of S100A4 in SSc. We demonstrate an upregulation of S100A4 in SSc in a TGF-β dependent manner, and that inhibition of S100A4 reduces collagen synthesis in activated SSc fibroblasts. Knockdown of S100A4 protected from fibrosis in the murine model of bleomycin-induced dermal fibrosis due to inhibition of TGF-β signaling. Thus, the S100A4 pathway could be an interesting novel target for the treatment of SSc.

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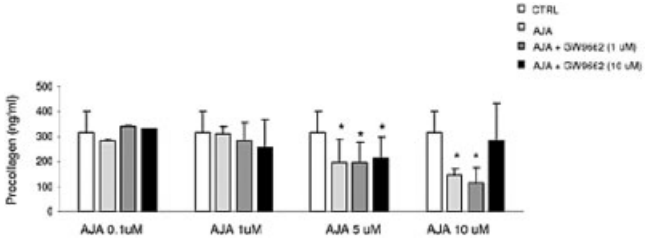
The Synthetic Cannabinoid Ajulemic Acid Targets Scleroderma Fibrosis. Estrella Garcia Gonzalez[3], Enrico Selvi[2], Balistreri Epifania[3], Alfiya Akhmetshina[1], Sauro Lorenzini[3], Kathrin Palumbo[1], Mauro Galeazzi[3] and Jorg W. H. Distler[1]. [1]Departement of Internal Medicine III and Institute for Clinical Immunology -Friedrich-Alexander University-Erlangen-Germany, [2]Rheumatology Unit - Departement of Clinical Medicine and Immunological Sciences-University of Siena, Siena, Italy, [3]Rheumatology Unit - Departement of Clinical Medicine and Immunological Sciences-University of Siena-Italy

Background: Substantial evidence supports the involvement of the endocannabinoid system in pathologic fibrosis and the capability of cannabinoids to modify fibrogenesis in scleroderma. Ajulemic acid (AjA) is a non-psychoactive, synthetic analog of tetrahydocannabinol (THC), the main psychoactive ingredient of Cannabis-sativa. AjA binds the peroxisome proliferator-activated receptor-γ(PPAR-γ), and PPAR-γ receptor activation modulates fibrogenesis. Therefore, we performed experiments to determine whether AjA can modify fibrogenesis in scleroderma.

Material and Methods: skin fibroblasts from scleroderma patients were cultured and treated with increasing concentrations of AjA (0.1, 1, 5 and 10 μM) in the presence or absence of the PPAR-γ irreversible antagonist GW9662 (1 and 10 μM) in order to evaluate procollagen production. Cell viability was evaluated using MTT assay and trypan-blue exclusion test. To evaluate AjA effect in vivo, three groups of DBA/2J mice (n=7 in each group) were studied. Group I and II received bleomycin subcutaneously (100 μl/ every other day) for 21 days. In addition to bleomycin, group II was treated orally with AjA (1 mg/kg) for 21 days. Group III only received subcutaneously 100 μl/day of NaCl 0.9%. At day 21 animals were sacrificed. Skin fibrosis was histologically evaluated by quantification of skin thickness and hydroxyproline content. As a marker of fibroblast activation,α-smooth muscle actin (α-SMA) was examined.

Results: AjA as well as the selective PPAR-γ antagonist GW9662 did not show any significant toxicity at the concentrations used. Addition of AjA to scleroderma fibroblasts significantly reduced supernatant procollagen concentrations in a dose-dependent manner. This effect was completely reversed by the PPAR-γ antagonist GW9662 (10 μM).



AjA treatment (1mg/kg/day for 21days) reduced markedly the dermal fibrosis induced by bleomycin in the animal model. Dermal thickness and hydroxyproline content appeared similar to the untreated control group. AjA treatment also reduced substantially the number of α-SMA positive cells in lesional skin.

Conclusions: we have demonstrated that AjA reduces fibrogenesis, at least in part, through a PPAR-γ mediated mechanism. These results and the demonstrated safety of AjA, suggest AjA as an interesting molecule targeting fibrosis in patients with scleroderma.

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The Transcription Factor AP-1 Mediates the Pro-Fibrotic Effects of TGFβ and Contributes to the Development of Experimental Dermal Fibrosis. Jerome Avouac[3], Katrin Palumbo[2], Michal Tomcik[4], Pawel Zerr[2], Clara Dees[2], Angelika Horn[2], Alfiya Akhmetshina[2], Christian Beyer[2], Shunichi Shiozawa[5], Oliver Distler[1], Georg Schett[6], Yannick Allanore[7] and Jorg H. W. Distler[8]. [1]Center of Experimental Rheumatology and Zurich Center of Integrative Human Physiology, University Hospital Zurich, Zurich, Switzerland, [2]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [3]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, Paris Descartes University, Rheumatology A Department, Cochin Hospital and INSERM U781, Necker Hospital, Paris, Fra, [4]Department of Internal Medicine III, University of Erlangen-Nuremberg, Erlangen, Germany and Institute of Rheumatology and Connective Tissue Research Laboratory, Department of Rheumatology of the First Faculty of Medicine, Charles University i, [5]Division of Rheumatology, Department of Medicine, Kobe University Graduate School of Medicine, Kobe University Hospital, Kobe, Japan, [6]Friedrich Alexander Univ, Erlangen, Germany, [7]Paris Descartes University, Rheumatology A Department, Cochin Hospital and INSERM U781, Necker Hospital, Paris, France, [8]University of Erlangen, Erlangen, Germany

Background: Tissue fibrosis caused by pathological activation of fibroblasts is a major hallmark of systemic sclerosis (SSc). The activation of the transcription factor AP-1, composed of members of Jun and Fos families, regulates cell proliferation, apoptosis, inflammation, wound healing and tumorigenesis. AP-1 is also one of the transcriptional targets of TGFβ signaling, one of the key growth factors in SSc.

Objectives: The aims of the present study were to investigate whether AP-1 contributes to the pathologic activation of fibroblasts in SSc and to evaluate the anti-fibrotic potential of AP-1 inhibition for treatment of SSc.

Methods: Activation of AP-1 in human skin was determined by real-time PCR for c-Jun and c-Fos and immunohistochemistry for N-terminal residues of human c-Jun. SSc and healthy dermal fibroblasts were stimulated with TGFβ and incubated with T5224, a small-molecule inhibitor of c-Fos/AP-1 (1). Collagen synthesis was quantified by real-time PCR and hydroxyproline assay. Differentiation of resting fibroblasts into myofibroblasts was assessed by staining for α-smooth muscle actin and stress fibers. To evaluate the anti-fibrotic potential of specific AP-1 inhibition by T5224 in vivo, we used the mouse model of bleomycin induced dermal fibrosis or attenuated adenoviruses overexpressing a constitutively active TGFβ receptor I.

Results: Increased levels of AP-1 were detected in the skin of SSc patients. The overactivation of AP-1 persisted in cultured SSc fibroblasts. Inhibition of AP-1 reduced the basal mRNA levels of col1a1 and col1a2 in SSc fibroblasts by up to 46$\pm$3% ($p<0.05$) but did not reduce the collagen synthesis in resting healthy dermal fibroblasts. Similar results were obtained on the protein level. Stimulation of healthy fibroblasts with TGFβ lead to AP-1 activation and inhibition of AP-1 abrogated the stimulatory effects of TGFβ on collagen synthesis. Inhibition of AP-1 also prevented the differentiation of resting fibroblasts into myofibroblasts. Consistently, inhibition of AP-1 exerted potent anti-fibrotic effects in different models of experimental fibrosis. In the mouse model of bleomycin-induced fibrosis, inhibition of AP-1 decreased dermal thickening by 53$\pm$3% ($p<0.05$). In addition, the collagen content and the number of myofibroblasts were significantly reduced (respectively 46$\pm$2% and 66$\pm$4%, $p<0.05$). In the TGFβRI model, selective inhibition of AP-1 also exerted potent anti-fibrotic effects and reduced dermal thickening, collagen content and myofibroblast counts by 70$\pm$5%, 52$\pm$3% and 51$\pm$2%, respectively ($p<0.05$). T5224 was well tolerated: no weight loss, alterations of the skin texture or affected activity were recorded during the whole treatment period.

Conclusion: We demonstrate that AP-1 is activated in a TGFβ dependent manner in SSc and that inhibition of AP-1 specifically reduces collagen synthesis in activated SSc fibroblasts. The specific AP-1 inhibitor T5224 efficiently prevented the development of dermal fibrosis in different mouse models of SSc and was well tolerated. Thus, AP-1 might be a promising new molecular target for the treatment of SSc.

(1) Aikawa Y, Morimoto K, Yamamoto T et al, Nat Biotechnol 2008;26:817–23

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The Triterpenoid CDDO Abrogates Canonical TGF-beta Signaling and Fibrotic Responses in Normal and Scleroderma Fibroblasts by Stabilizing the Anti-Oxidant Nuclear Factor-Like 2 (Nrf2). Kazuhiro Komura[2], Jun Wei[2], Gabriel Lord[2] and John Varga[1]. [1]Northwestern Univ Feinberg School, Chicago, IL, [2]Northwestern University Feinberg School of Medicine

Background: Scleroderma is characterized by excessive collagen accumulation and fibrosis in multiple organs. TGF-β stimulates collagen synthesis and is implicated in the pathogenesis of fibrosis. 2-Cyano-3,12-Dioxooleana-1,9-Dien-28-Oic acid (CDDO) is a synthetic triterpenoid that is known to activate peroxisome proliferator activated receptor (PPAR)-γ. We previously demonstrated that PPAR-γ ligands abrogated the stimulation of collagen synthesis induced by TGF-β in fibroblasts, by disrupting canonical TGF-β signaling in a PPAR-γ dependent manner. The objective of the current study is to address the anti-fibrotic effect of CDDO in fibroblasts.

Methods: The mesenchymal progenitor 3T3-L1 cell line was incubated with CDDO to induce adipogenesis. Expression of adipogenic markers was examined by real-time qPCR and immunofluorescence. Modulation of PPAR-g promoter activity was examined in foreskin fibroblasts incubated with CDDO. Induction of profibrotic gene expression by TGF-β was evaluated by real-time qPCR and Western analysis. PPAR-γ dependence was evaluated using GW9662 a PPAR-γ antagonist. Nrf2 expression and activity were examined by Western blot, immunofluorescence and antioxidant response element (ARE) reporter assays. Effects of Nrf2 on canonical TGF-β signaling were examined by transient transfection in foreskin fibroblasts. Skin fibroblasts from 6 patients with diffuse cutaneous SSc were incubated with CDDO and profibrotic gene levels were measured by real-time PCR and Western analysis.

Results: CDDO induced a marked adipogenic response in 3T3-L1 cells. Moreover, CDDO significantly enhances PPAR-γ transcriptional activity. CDDO abrogated TGF-βinduced stimulation of collagen and α-smooth muscle actin (α-SMA) expression in a dose-dependent manner, and abrogated the stimulation of Smad2/3-mediated transcriptional activity induced by TGF-β. These inhibitory effects were PPAR-γ–independent. CDDO also caused a marked accumulation and nuclear localization of Nrf2. Moreover CDDO stimulated Nrf2-dependent transcriptional activity. Ectopic Nrf2 was sufficient by itself to abrogate TGF-β stimulation of Smad-dependent transcription. In scleroderma fibroblasts, CDDO caused significant suppression of collagen gene expression at mRNA and protein levels, and attenuated the myofibroblast phenotype of these cells.

Conclusion: The triterpenoid and novel PPAR-γ ligand CDDO abrogates canonical TGF-β signaling and suppresses fibrotic responses in a PPAR-γ-independent manner. Nrf2, a master regulator of the antioxidant response, is activated by CDDO in normal fibroblasts, and appears to mediate the CDDO inhibitory process. Nrf2 thus is a novel target for anti-fibrotic therapy, and pharmacological modulation of the Nrf2 expression or activity might have a therapeutic potential in scleroderma.

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Urantide Prevents and Alleviates Monocrotaline Induced Pulmonary Arterial Hypertension in Wistar Rats. Yifang Mei[1], Hong Jin[3], Hao Wang[2], Wei Tian[2], Yanping Zhao[2] and Zhiyi Zhang[2]. [1]The First Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, China, [2]The First Affiliated Hospital of Harbin Medical University, Harbin, China, [3]The First Affiliated Hospital of Shantou University Medical College, Shantou, China

Background: Pulmonary arterial hypertension (PAH) is a serious complication of connective tissue disease (CTD). Urotensin II (UII) has been confirmed to be the most powerful vasoconstrictor greater than endothelin-1, which may play an important role on PAH development.

Objective: To observe the effects of urantide, an UII receptor antagonist, on monocrotaline (MCT)-induced PAH in rats.

Methods: 60 male Wistar rats were divided into six groups. For early treatment experiment, rats were divided into normal control group, MCT_{4w} model group(MCT+saline×3wks from the 8th day of MCT-injection) and urantide early treatment group (MCT+urantide 10μg/kg/d×3wks from the 8th day of MCT-injection). For late treatment experiment, rats were dived as controls, MCT_{6w} model group(MCT+saline×2wks 4 weeks after MCT injected once), and urantide late treatment group (MCT + urantide 10μg/kg/d×2wks 4 weeks after MCT injected once). The relaxation effects of urantide on the intralobar pulmonary artery rings of control and MCT 4wks model rats were investigated. Then, the mean pulmonary arterial pressures (mPAP) of rats in each group were measured by flow-directed pulmonary artery catheter. Pulmonary artery remodeling was detected by hematoxylin and eosin (HE) staining. The rats plasma endothelial nitric oxide synthase (eNOS) and nitric oxide(NO) levels in all six groups were assayed by ELISA kits.

Results: Urantide dose-dependently relaxed the pulmonary artery rings of PAH model and normal rats. Moreover, L-NAME blocked the dilation response of urantide. Urantide reduced the mPAP in both early and late treatment groups and inhibited the pulmonary vascular remodeling remarkably. eNOS and NO levels in plasma elevated in both early and late treatment rats with urantide infusion.

Conclusions: Urantide effectively alleviated MCT induced PAH, at least partly, through mediating NO releasing, which provided a novel therapy for PAH.

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Visfatin/NAMPT in Interstitial Pneumonia of Patients with Systemic Sclerosis and Scleroderma Mice Model Induced by Bleomycin. Hirahito Endo[2], Tatsuhiro Yamamoto[1], Kaichi Kaneko[3], Yoshie Kusunoki[3], Natsuko Kusunoki[3] and Shinichi Kawai[3]. [1]Division of Rheumatology, Department of Internal Medicine, Toho University School of Medicine, Ohmori-nishi, Ohta-ku, Japan, [2]Division of Rheumatology, Department of Internal Medicine, Toho University School of Medicine, Ohmori-nishi, Oh-taku, Japan, [3]Division of Rheumatology, Department of Internal Medicine, Toho University School of Medicine

Scleroderma intestinal lung disease(SLD) is a leading cause of morbidity and motality in patients with systemic sclerosis. Excessive fibrosis and inflammatory cell infiltration is a main features. Nicotinamide Phosphoribosyl Transferase/Visfatin (NAMPT/Visfatin) is an adipokine and a proinflammatory cytokine. To evaluate the significance of NAMPT/Visfatin in the diagnosis and monitoring of SLD we analyzed the concentration of NAMPT/Visfatin in bronchoalveolar lavage fluid (BALF) and plasma levels in SLD. Moreover we analyzed the role of NAMPT/Visfatin on experimental interstitial pneumonitis induced by bleomycin.

Methods: NAMPT/Visfatin concentration of BAL fluids and plasma of patients with SSc and other CTD. 12 patients with SSc and 20 patients with other CTD-IP (PM/DM,RA). Concentration of NAMPT/Visfatin were measured by enzyme- linked immunoabsorbent assay. Expression of NAMPT/Visfatin in lung tissue detected by immunohistochemistry. Expression of NAMPT/Visfatin mRNA also detected by RT-PCR. We also analyzed the NAMPT/Visfatin expression on lung injury induced by bleomycin was investigated in mice.

Results: Plasma concentration of NAMPT/Visfatin in SSc were significantly higher than healty subject (SLD 5.38 $\pm$1.09, Control 2.38$\pm$2.60 ng/ml,$P<0.05$). NAMPT/Visfatin concentration in BALF of SLD were not significantly higher than that of other CTD (SLD11.8$\pm$6.3, CTD-LD18.9$\pm$4.4 ng/ml). NAMPT/Visfatin concentration in BALF were not correlated with total lung capacity, the diffusion capacity for carbon monoxide, whereas there were correlated of BAL lymphocyte counts and serum KL-6 levels. NAMPT/Visfatin detected in macrophage and pulmonary epithelial cells of biopsy tissues of interstitial pneumonitis of patients with SSc. NAMPT/Visfatin also detected in mice bleomycin induced interstitial pneumonitis at 3 weeks(serum IP 5.28$\pm$0.25,Control 1.8 $\pm$0.68ng/ml, $P<0.05$). NAMPT/visfatin detected in pulmonary epithelial cells, macrophage, and endothelial cells in murine IP lung tissues by immunohistochemical analysis. NAMPT/Visfatin also detected in BALF in mice IP (IP 0.40$\pm$0.06 ng/ml, Control 0.18$\pm$0.12ng/ml). NAMPT/Visfatin augmented the proliferation of cultured lung fibrobrast derived from interstial peumonitis lung tissue. NAMPT/Visfatin also induced Col I, IL-6, and MCP-1 mRNA in cultured lung fibroblasts.

Conclusions: These data suggest that Visfatin/NAMPT is a new therapeutic target of SLD.

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Platelet C4d Is Associated with All-Cause Mortality in Patients with Systemic Lupus Erythematosus. Christine A. McBurney[5], Amy H. Kao[2], Abdus Sattar[3], Apinya Lertratanakul[6], Nicole L. Wilson[4], Rutman Sarah[6], Barbara Paul[6], Jeannine S. Navratil[6], Joseph M. Ahearn[1] and Susan Manzi[7]. [1]Wexford, PA, [2]Allegheny Singer Research Institute, Pittsburgh, PA, [3]Case Western University, [4]Magee Womens Hospital of UPMC, Pittsburgh, PA, [5]University of Pittsburgh Medical Center, Pittsburgh, PA, [6]University of Pittsburgh School of the Health Sciences, [7]West Penn Allegheny Health System, Pittsburgh, PA

Background: Platelets bearing complement C4d (P-C4d) are reported to be specific for a diagnosis of systemic lupus erythematosus (SLE) and are associated with ischemic stroke. We investigated the association of P-C4d with all-cause mortality and prevalent cardiovascular disease (CVD) events in our longitudinal cohort of patients with SLE.

Methods: We recruited 356 consecutive outpatients or inpatients with SLE since July 2001. Outcomes were all-cause mortality and cardiovascular events including myocardial infarction, coronary artery bypass graft, percutaneous coronary transluminal angioplasty, stroke, pulmonary embolism, deep vein thrombosis or other thrombosis. P-C4d status was determined by flow cytometry.

Results: Mean age was 44.4 years (range: 18 – 81 years), 92% were female, and 81% were Caucasian. Seventy SLE patients (20%) had positive P-C4d at baseline. PC4d-positive patients were more likely to have a history of renal disease, seizure disorder, hemolytic anemia, thrombocytopenia, anti-double stranded DNA (dsDNA) and/or antiphospholipid antibodies. Overall CVD event frequency was 21.6%. SLE patients with positive P-C4d had significantly more CVD events compared to those with negative P-C4d (35.7% vs. 18.2%, p=0.001). Positive P-C4d at baseline was associated with stroke, but not with other cardiovascular events (odds ratio 4.96, 95% confidence interval 1.75–14.06, p=0.003) after adjusting for age, race, smoking history, SLE disease duration, renal disease, dsDNA and antiphospholipid antibodies. The overall mortality was 3.9%. Causes of death were infection (n=4), cardiac arrest (n=2), congestive heart failure (n=1), cancer (n=2), hemorrhage (n=1), and unknown (n=4). Six of these 14 deceased patients had a history of cancer (ovarian carcinoma, lymphoma, lung cancer, anal squamous cell carcinoma). Positive P-C4d at baseline was associated with all-cause mortality (hazard ratio 7.92, 95% CI 2.13–29.48, p=0.002) after adjusting for age, race, sex, SLE disease duration, renal disease, cardiovascular event, cancer, dsDNA and antiphospholipid antibodies.

Conclusions: Platelet C4d is associated with all-cause mortality and stroke. Platelet C4d may be a prognostic biomarker as well as a pathogenic clue that links systemic inflammation, complement activation, and thrombosis and may represent a subset of patients with poor clinical outcomes.

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β2-Glycoprotein Exists in a Distinct Molecular Post-Translational Oxidative State in the Antiphospholipid Syndrome: Novel Prognostic Assays and Insights into Antigenicity. Yiannis Ioannou[10], Jing-Yun Zhang[8], Miao Qi[11], Gao Lu[12], Jian Cheng Qi[11], De-min Yu[7], Herman Lau[6], Allan D. Sturgess[5], Panayiotis Vlachoyiannopoulos[4], Haralampos M. Moutsopoulos[3], Anisur Rahman[9], Pericleous Charis[9], Tatsuya Atsumi[1], Takao Koike[2], Bill Giannakopoulos[11] and Krilis A. Steven[11]. [1]Hokkaido University, Sapporo, Japan, [2]Hokkaido University, Japan, [3]Natl Univ of Athens Med Schl, Athens, Greece, [4]Natl Univ of Athens Med Schl, [5]St. George Hospital, Sydney, NSW, Australia, [6]St. George Hospital, [7]Tianjin Medical University, [8]Tianjin Medical University, University of New South Wales, [9]University College London, [10]University College London, University of New South Wales, [11]University of New South Wales, [12]University of New South Wales, Tianjin Medical University

Background: We have recently reported the novel finding that the major autoantigen in the antiphospholipid syndrome (APS), β2-glycoprotein I (β2GPI), exists in serum in a biochemically reduced state with free thiols (1). This study aims to characterise the oxidative molecular state of β2GPI with respect to free thiol content in APS and evaluate relevance to antigenicity.

Methods: Through a multi-centre collaborative effort (Sydney, Athens, London, Sapporo), a total of 502 patient samples were collected from APS patients and three control groups: 182 APS (93 had an additional autoimmune disease (AID), 189 AID controls (± persistent antiphospholipid antibodies (aPL) but no APS), 38 clinical event controls (vascular thrombosis, no AID) and 93 healthy controls. Each sample was assayed for total levels of β2GPI and relative amounts of β2GPI present with free thiols. This was performed as described previously (1) and based upon a sandwich ELISA system using a biotinylated free thiol binding reagent to capture proteins with free thiols on a streptavidin plate and detect β2GPI using a monoclonal anti-β2GPI antibody. Oxidised versus reduced β2GPI binding avidity to polyclonal patient anti-β2GPI antibodies was then assessed.

Results: Total levels of β2GPI were significantly increased in the APS group (216.7 ± 79.5 μg/ml, median ± SD, n=181) as compared to all of the three control groups studied (p≤0.0001). No differences were observed between the other three groups. The relative proportion of β2GPI in the biochemically reduced form expressed as a percentage of that observed with the in-house standard was significantly less in APS patients (median ± SD, 57.15% ± 23.5, n=177) as compared to healthy control (p≤0.001), AID disease control (p≤0.001) and clinical event control (aPL negative, p≤0.001) groups. Hence, β2GPI in APS patients is in an oxidised state relative to each of the other three control groups. Sub-analyses of the APS group with anti-β2GPI positivity reveals that APS patients with LA positivity harbour the lowest proportion of β2GPI with free thiols (anti-β2GPI + LA, 47.52% ± 22.96 (median ± SD, n=49) versus anti-β2GPI without LA 74.93% ± 17.86 (median ± SD, n=28), p≤0.001). IgG from 10 patients with APS was purified. β2GPI within plasma derived from healthy volunteers oxidised by pre-incubation with H2O2 was a significantly better inhibitor of anti-β2GPI activity than untreated serum (p≤0.001, n=10).

Conclusion: In APS patients, a greater proportion of β2GPI circulates in an oxidised versus reduced state relative to disease and healthy control groups. The finding that oxidised β2GPI harbours a greater avidity for patient derived anti-β2GPI antibodies coupled with the observation that APS patients have a greater antigenic load supports the theory that high amounts of oxidised β2GPI may lower the threshold for breaking tolerance, driving antigenicity and hence anti-β2GPI production in autoimmune susceptible patients.

(1) Ioannou Y et al, Naturally occurring free thiols within β2-glycoprotein I in vivo: nitrosylation, redox modification by endothelial cells and regulation of oxidative stress induced cell injury. Blood June 2010 [Epub ahead of print]

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Normal Monocyte and Fibrocyte Behavior in Scleroderma Is Restored by Caveolin-1 Scaffolding Domain (CSD) Peptide: Implications for Treating Scleroderma Lung Disease. Elena Tourkina, James Oates, Ann Hofbauer, Michael Bonner, Richard P. Visconti, Jing Zhang, Richard M. Silver and Stanley Hoffman. Medical University of SC

Purpose: Scleroderma (systemic sclerosis, SSc) is a complex autoimmune disease characterized by inflammation and fibrosis of the skin, lungs and other organs. Despite the accepted importance of the contribution of monocyte-derived fibrocytes in the development of lung fibrosis, their role in scleroderma is not clear. The aim of this study was to investigate the role of caveolin-1 on monocyte and fibrocyte migration into injured lung tissue in scleroderma and in the animal model of bleomycin-induced lung fibrosis.

Methods: Normal lung tissue was obtained from the Brain and Tissue Bank of Developmental Disorders; Scleroderma lung tissue was obtained from autopsy of patients at the Medical University of South Carolina (MUSC). The study was approved by MUSC's IRB for Human Subject Research. Monocytes (PBM) were isolated from blood of scleroderma and healthy donors using negative selection. Scleroderma patients fulfilled the preliminary ACR criteria for the classification of systemic sclerosis. Monocyte migration was assayed in Multiwell Chemotaxis Chambers, with or without priming with TGFβ and with or without treatment with caveolin-1 scaffolding domain (CSD) peptide and control peptides. Fibrocytes in human peripheral blood and mouse lungs were detected by flow cytometry. Protocols for bleomycin-induced lung injury and CSD peptide treatment were approved by MUSC's Institutional Animal Care & Use Committee. Ten-week old,

male CD1 mice received daily i.p. injections of CSD or control peptide throughout the entire experiment from the day prior to bleomycin treatment until the day of sacrifice. Mice were treated intra-orally with bleomycin or PBS vehicle. Seven days after bleomycin treatment, lungs were removed and analyzed.

Results: Fibrocytes were observed in lung tissue of scleroderma patients (n=7), but not healthy control subjects (n=4). Upregulation of fibrocytes (CD45+/Col+, CD45+/CXCR4+, and CD45+/CXCR4+/Col+) was observed in the peripheral blood of scleroderma patients (n=7) compared to healthy control subjects (n=9): 2.5 ± 0.3 % vs 1.0 ± 0.07 %; 3.0 ± 0.5 % vs 1.0 ± 0.08 %; and 0.74 ± 0.09 vs 0.4 ± 0.08 %, respectively. Scleroderma PBM also differed from control PBM in signaling and in function. On average, SSc PBM contained less than half as much caveolin-1 and three-fold more CXCR4 compared to normal PBM. The percentage of scleroderma PBM that migrated in response to the CXCR-4 ligand, CXCL12, was more than four-fold enhanced compared to normal PBM. When scleroderma PBM were treated with the CSD peptide to overcome their diminished expression of caveolin-1, CXCR4 expression and migration in response to CXCL12 were inhibited by at least 80%. Similar results were obtained in vivo in a mouse model. CSD peptide inhibited bleomycin-induced recruitment of CD45/CXCR4/Col-positive cells into injured mouse lung tissue by > 50 %.

Conclusion: Our results support the notion that using the CSD peptide to compensate for low caveolin-1 levels may be a useful treatment strategy for scleroderma and other inflammatory/fibrotic lung diseases.

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Clinical, Radiographic and Biomolecular Features of B Cell Synovitis in Rheumatoid Arthritis. Serena Bugatti[2], Antonio Manzo[2], Barbara Vitolo[2], Chiara Fusetti[2], Roberto Caporali[2], Costantino Pitzalis[1] and Carlomaurizio Montecucco[2]. [1]Centre for Experimental Medicine and Rheumatology, John Vane Science Centre, William Harvey Research Institute, St. Bartholomew's and Royal London School of Medicine, London, [2]Chair and Division of Rheumatology, Laboratory of Rheumatology, University of Pavia, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Objective: Despite the central participation of B lymphocytes in the autoimmune process of rheumatoid arthritis (RA), the biologic and clinical impact of the B cell compartment at the site of inflammation itself, i.e. the synovial membrane, has not been consistently established. The aim of the present study was to investigate whether synovial B cell follicles are associated to specific clinical and molecular features of inflammation, immunological activity and bone remodeling in RA.

Methods: Multiple synovial biopsies were collected from 67 consecutive RA patients and evaluated histologically and by immunohistochemistry (IHC). From 25 of the 67 patients, paired paraffin and RNA samples were available and used for histological/IHC analysis and quantitative real-time polymerase chain reaction. The degree of B cell infiltration was determined semi-quantitatively (0–3) based on the size and density of CD20+ B cell aggregates and correlated to: 1) histopathologic features; 2) clinical parameters of disease activity and radiographic damage; 3) molecular markers of inflammation, T and B cell immunologic activity, bone damage and bone repair.

Results: The CD20+ B cell score was significantly related to mRNA expression levels of CXCL13 (rho 0.8, $p = 0.0001$) and lymphotoxin-β (rho 0.7, $p = 0.0006$), confirming the validity of the histological assessment. The degree of synovial B cell infiltration was associated to histological features of inflammation, such as the total inflammatory score (rho 0.6, $p < 0.0001$) and sublining infiltration of CD68+ macrophages (rho 0.4, $p = 0.001$). However, no correlation with systemic markers of inflammation was found. Instead, large-size B cell aggregates (CD20+ B cell scores 2 and 3) were independently associated to radiographic erosive disease in a multivariate logistic regression model including disease duration and serum auto-antibodies (OR 7.99, 95% CI 1.83–34.83; $p = 0.006$). Higher degrees of B cell infiltration were closely associated to increased mRNA expression of markers of activation of T cells, such as interferon-γ ($p = 0.001$) and interleukin-17 ($p = 0.005$), and B cells, such as activation-induced cytidine deaminase (AID) ($p = 0.02$). Relevantly, samples characterized by large-size B cell aggregates also exhibited an increased RANKL/osteoprotegerin (OPG) ratio ($p = 0.008$) due to reduced OPG levels ($p = 0.02$) rather than to increased RANKL ($p = 0.2$). Confirming the association with unbalanced bone remodeling, the expression levels of bone morphogenetic protein-2 and -7 tended to be lower in the presence of higher scores of B cell infiltration ($p = 0.07$ and $p = 0.05$ respectively).

Conclusions: The presence of large-size B cell aggregates in RA synovium is independently associated to a more aggressive pattern/status of the disease characterized by a higher frequency of radiographic erosions and a molecular milieu of increased immunological activity and unbalanced bone remodeling. Our data provide novel cues for further pathogenic and prospective clinical studies assessing the relationship between the synovial pattern of lymphoid infiltration and inflammation/joint damage in RA.

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Association of FRZB Variants with Hip Shape and Radiographic Hip Osteoarthritis: Preliminary Results. Julie Baker-LePain[4], Kali Luker[2], John A. Lynch[4], Neeta Parimi[1], Michael C. Nevitt[3], Mary Corr[6] and Nancy E. Lane[5]. [1]California Pacific Medical Center, [2]Stanford, [3]UCSF, San Francisco, CA, [4]UCSF, [5]Univ of California at Davis, Hillsborough, CA, [6]Univ of California-San Diego, La Jolla, CA

Background: Single nucleotide polymorphisms (SNPs) in the FRZB gene, which encodes the Wnt antagonist secreted frizzled-related protein 3 (sFRP3), are significant predictors of radiographic hip osteoarthritis (RHOA) (Lane, et al., A&R 2006). In addition to FRZB, another important predictor of incident RHOA is hip shape (Lynch, et al., O&C 2009). Since the Wnt pathway is a key regulator of joint development, we examined whether FRZB variants are associated with hip shape and to what extent the relationship between joint shape and RHOA is affected FRZB.

Methods: We performed a nested case-control study within the Study of Osteoporotic Fractures (SOF). Subjects were Caucasian women aged >= 65 years with supine pelvic radiographs at baseline visit and at follow-up (mean 8.3 years). RHOA was scored radiographically using a modified summary grade (scale 0–4). Cases (n = 451) were defined as subjects with no baseline radiographic hip OA (RHOA) in either hip at baseline and incident RHOA (summary grade ≥ 2) at follow-up. Controls (n = 601) had no RHOA at either time point. We determined hip shape at 2 sites: the proximal femur by active shape modeling (ASM) (Lynch et al., O&C 2009) and the acetabulum by the center-edge angle and acetabular depth. Genotyping for the rs288326 SNP of FRZB was performed using allele-specific polymerase chain reaction (PCR). Linear regression was used to determine the association of hip shape parameters with the presence of the rs288326 FRZB SNP.

Results: In preliminary analsis, we found that among controls, proximal femur shape (Mode 2 from ASM analysis) was associated with the rs288326 FRZB SNP (coefficient −0.18, 95% CI −0.35 to 0.03, $p = 0.05$) after adjustment for age and femoral neck BMD. The presence of the rs288326 allele modified the association between proximal femur shape Mode 2 and RHOA (p-value for trend = 0.01, see Figure). Similarly, in preliminary results (n = 202 cases and n = 512 controls), the rs288326 allele modified the association between acetabular depth/center edge angle and RHOA (p-value for trend < 0.001).

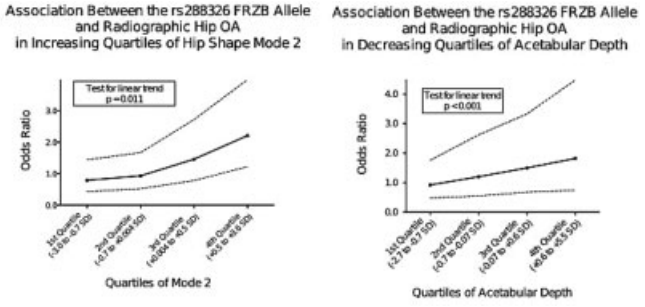

Figure. Quartiles of increasing proximal femur ASM Mode 2 or decreasing acetabular depth were created using control populations, and the association between the rs288326 FRZB allele and incident RHOA was examined in each quartile using logistic regression. Odds ratio with 95% CI is shown, together with p-value for test of linear trend. The referent group was subjects without the rs288326 FRZB allele.

Conclusions: Hip shape is known to be an important predictor of incident OA. In this preliminary analysis, we find that variants in the FRZB gene, a component of the Wnt pathway, may be involved in moderating the relationship between hip shape and OA. We hypothesize that Wnt pathway components play a key role in determination of joint shape, which in turn may predispose to development of osteoarthritis in a conducive architectural setting.

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The Assessment of Health-Related Family Functioning in Systemic Lupus Erythematosus: Preliminary Validation of the SLE-FAMILY. Afton L. Hassett[6], Tracy Li[1], Diane C. Radvanski[3], Steven Buyske[2], Samuel A. Schiff[4] and Patricia P. Katz[5]. [1]Bristol-Myers Squibb, Princeton, NJ, [2]Rutgers University, [3]UMDNJ-Robert Wood Johnson Medical School, Union City, NJ, [4]UMDNJ-Robert Wood Johnson Medical School, [5]Univ of CA San Francisco, San Francisco, CA, [6]University of Michigan Medical School, Ann Arbor, MI

Background: Patients with systemic lupus erythematosus (SLE) often experience disabling symptoms that affect family relationships. To assess the impact of SLE on health-related family functioning we developed the SLE-FAMILY which evaluates six key domains: Fatigue (fatigue-related family activity impairment), Activities (general family activity impairment), Mental Health (emotional impact on family), Isolation (feelings of isolation from family), Love (loss of intimacy) and You (fulfilling family roles). The 6-item SLE-FAMILY has scores ranging from 1–7 with higher scores indicating worse family functioning. The major objectives of this study were to pilot test and achieve preliminary validation for the SLE-FAMILY.

Methods: 52 patients with SLE completed questionnaires including the 6-item SLE-FAMILY, SF-36, Sheehan Disability Scale (SDS), Fatigue Severity Scale (FSS), Multidimensional Scale of Perceived Social Support (MSPSS), Satisfaction with Life Scale (SWLS), Positive and Negative Affect Scale (PANAS) and the Systemic Lupus Activity Questionnaire (SLAQ). Data were analyzed for internal consistency reliability with Cronbach's alpha. Next, item statistics were calculated to assess the correlations between individual items and SLE-FAMILY total score. To evaluate convergent and discriminant validity, correlations between the SLE-FAMILY and the other measures were calculated.

Results: Mean age for the 52 participants was 36.8 (SD11.9) years with a mean duration of illness of 8.4 years (SD6.7). Most were female (88.5%). The SLE-FAMILY had good test-retest reliability (0.83) and internal consistency (0.67). However, reliability analysis of individual items revealed a weakness in the performance of Item 5. Raw data were reviewed and it was determined that 9 patients likely overlooked the reverse-scoring of Item 5, thus explaining its poor reliability. When the 9 patients were excluded from the analysis, alpha increased to 0.71, while test-retest reliability remained acceptable (0.78). Spearman's rho correlations supported the validity of the SLE-FAMILY as its total score was significantly related to SDS Family ($r=0.67$, $p<.001$) and SDS Social ($r=0.60$, $p<.001$); SLAQ ($r=0.68$, $p<.001$); PANAS negative subscale ($r=0.55$, $p<.001$) and FSS ($r=0.62$, $p<.001$). Similarly, the SLE-FAMILY total score was inversely related to relevant SF-36 subscales scores including: Social Functioning ($r=-0.55$, $p<.001$), Role Emotional ($r=-0.42$, $p=.005$), Role Physical ($r=-0.59$, $p<.001$) and Mental Health ($r=-0.48$, $p=.001$).

Conclusion: The SLE-FAMILY is a promising new instrument for the more robust measurement of family functioning. Additional pilot testing using revised scoring options for Item 5 and additional validation studies are underway.

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Heart-Rate Recovery Immediately after Graded Exercise in Woman with Systemic Lupus Erythematosus. Danilo M. L. Prado[1], Fabio Baptista[1], Renata Miossi[1], Fernanda R. Lima[1], Ana Lucia S. Pinto[1], Eduardo F. Borba[3] and Eloisa Bonfa[2]. [1]USP, Sao Paulo, SP, Brazil, [2]USP, Sao Paulo, Brazil, [3]USP

Patients with systemic lupus erythematosus (SLE) are known to have lower heart rate variability suggesting impaired autonomic modulation. Heart-rate recovery after maximal graded exercise test has been identified as a strong independent predictor of cardiovascular and all-cause mortality in adults. Previous studies suggested that low heart-rate recovery is in part due to attenuated parasympathetic reactivation and sympathetic overactivity following the termination of exercise. Besides this knowledge, there is little information about this issue in SLE.

Purpose: To evaluate the heart-rate recovery after graded exercise in SLE.

Methods: Eighteen consecutive SLE women (SLE group) with low SLEDAI scores (1.0 ± 2.3) without cardiopulmonary involvement were selected and compared to 17 healthy women (control). All subjects performed a progressive treadmill cardiopulmonary test until exhaustion to determine the maximal aerobic capacity. Heart rate recovery at both one minute (ΔHRR1) and two minutes (ΔHRR2) were defined as the difference between heart rate at peak of exercise and at 1 and 2 minutes post exercise, respectively.

Results: Age (29.6 ± 1.3 vs. 26.2 ± 1.5 years, $p=0.10$) and Body-mass index (23.7 ± 0.8 vs. 21.8 ± 0.5 kg/m2, $p=0.09$) were alike between SLE and control group. SLE had significant lower peak workload (4.6 ± 0.1 vs. 5.6 ± 0.0 mph, $P=0.001$) and relative lower aerobic fitness [VO2peak] (28.3 ± 1.0 vs. 37.1 ± 1.2 mL.kg-1.min-1, $P=0.001$) compared to control.

	Heart Rate Recovery Post Graded Exercise		
	SLE	Control	P value
(ΔHRR1)	25.9 ± 1.5	32.7 ± 2.0	0.01
(ΔHRR2)	41.7 ± 1.6	52.1 ± 2.1	0.001

Values are means ± SE. ΔHRR1 - heart rate recovery at one minute; ΔHRR2 - heart rate recovery at two minutes. (Unpaired students T Test). $P < 0.05$ considered statiscally significant.

Conclusion: These findings demonstrated that woman with SLE had reduced heart rate recovery at first and second minutes after graded exercise compared to controls. Taken together, these data suggest abnormal restoration of autonomic nervous tone including a decrease in vagal tone and an increase in sympathetic activity after graded exercise in these patients.

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Body Composition, Lower Extremity Strength, and Fatigue in SLE. Patricia Katz, Laura Julian, Jinoos Yazdany, Holly Wing, Sandi Kaplan, Laura Trupin and Ed Yelin. UCSF

Background: Fatigue is widely acknowledged as a major concern for individuals with rheumatoid arthritis, but less attention has been focused on fatigue in systemic lupus erythematosus (SLE). Additionally, there has been little research addressing the relationship of body composition and fatigue. These analyses examine the role of body composition and muscular weakness in fatigue among women with SLE.

Methods: All measures were collected during an in-person research visit. Fatigue was measured with the severity subscale of the Multidimensional Assessment of Fatigue (MAF), in which scores range from 1 (mild) to 10 (severe). Body composition was assessed by dual-energy x-ray absorptiometry (DEXA), which yielded measures of total, as well as regional (appendicular and trunk) body fat and lean mass, each of which was adjusted for height to create fat and lean mass indices (FMI; LMI). Lower extremity strength was assessed using a Biodex® Unit. Peak torque at knee extension and flexion at 150 degrees/second were used in these analyses. SLE disease activity was estimated with a modified version of the SLEDAI. Regression analyses, controlling for age, duration of SLE, and disease activity, modeled the effects of body composition and lower extremity strength on fatigue. (Knee extension and flexion were examined in separate models.) This analysis focuses on the 115 women for whom complete data were available. (30 women were missing either DEXA or strength testing data).

Results: Mean age was 48 (±12) years; duration of SLE was 16 (±9) years. Mean fatigue rating was 5.9 (±2.3); 30% rated fatigue severity at 7 or

greater. Mean total percent body fat was 41%. Mean peak torques at knee extension and flexion were 38 (±12) and 29 (±8) foot-pounds, respectively. Controlling for age, disease duration, and disease activity, neither total FMI nor LMI were significantly associated with fatigue severity. However, when appendicular and trunk FMI were examined separately, greater trunk FMI was significantly associated with greater fatigue (β=0.25, p=0.01). Muscle weakness was also significantly and independently associated with greater fatigue (extension: β=−0.04, p=0.03; flexion: β=−0.06, p=0.005).

Conclusions: A substantial portion of this group of women with SLE experienced severe fatigue. Both abdominal obesity and muscle weakness play an important role in fatigue among women with SLE.

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Physical Exercise Improves Endothelial Function in Patients with Systemic Lupus Erythematosus. Edgard T. Reis Neto, Aline E. Silva, Carlos M. C. Monteiro, Luciano M. Camargo, Neusa P. Silva, Marcelo M. Pinheiro and Emilia I. Sato. Universidade Federal de São Paulo, Brazil

Background: Cardiovascular disease (CVD) is an important cause of morbidity and mortality in systemic lupus erythematosus (SLE). Endothelial dysfunction is implicated in the pathogenesis of premature atherosclerosis in SLE and there are studies showing improvement of endothelial function (EF) after physical exercise program in individuals with heart failure, diabetes and coronary arterial disease.

Objectives: to assess the effect of supervised physical exercise (SPE) on the EF, quality of life, fatigue, exercise tolerance and body composition in SLE patients.

Methods: prospective and controlled study in which women with SLE (18–45 years old) were allocated according to availability to participate in the exercise program in the exercise group (EG) or control group (CG). Intervention: SPE were performed 3 times a week for 16 consecutive weeks and consisted of 10 minutes of initial warm-up/stretching, 40 minutes of walking performed at a heart rate corresponding to the ventilatory anaerobic threshold (obtained with ergospirometric test), and 10 minutes of cooling-down. Patients were evaluated at baseline (T0) and after 16 weeks (T16) by high-resolution ultrasound of brachial artery in resting conditions, after reactive hyperaemia (flow-mediated dilation-FMD) and after oral glyceryl trinitrate (GTMD) for evaluating endothelial function; quality of life (SF-36 index); perceived exertion (Borg scale), fatigue (Krupp scale) and body composition (DEXA).

Results: Four hundred and eight patients were invited to participate in the study, 186 manifested interest but 109 were excluded due to exclusion criteria and only 21 were included in the study. Nineteen patients completed the evaluations (average age: 33.4±8.7 years and mean disease duration: 102.6±80.7 months). Twelve patients were allocated on EG and 7 on CG. Both groups were homogeneous and comparable at baseline regarding demographics variables. The average dose of prednisone was 8.5±12.9mg/day; 78.5% were using anti-malarials and 36.8% immune-suppressants. 15.8% had hypertension, 15.8% dyslipidemia and 21.8% had family history of coronary disease. In the EG we observed a significant increase in FMD (8.3±7.2% *vs* 16.4±8.9%, p=0.011) without changes in GTMD (21.3±6.1% *vs* 24,4±8.5%, p=0.334). In GC there was no increase in FMD (3.7±4.5% *vs* 5.6±4.6%, p=0.526) neither GTMD (26.1±6.2% *vs* 25.6±9.1%, p=0.884). In the EG we also found a significant improvement in exercise tolerance (11.8±2.1min *vs* 13.3±2.1min, p=0.02), maximum velocity (7.5±1km/h *vs* 8.3±1.1km/h, p=0.049), threshold velocity (5.5±0.6km/h *vs* 5.9±0.6km/h, p=0.011), functional capacity (66.2±23.8 *vs* 82.1±11.6, p=0.035) and vitality (72.9± 31.4 *vs* 78.8±19.7, p=0.007), with a tendency to improvement in fatigue (3.75±1,76 *vs* 2.49±1.13, p=0.06). None of these parameters changed significantly in the CG. There was no significant change in body composition in both groups.

Conclusion: despite the small number of patients, this is the first study demonstrating that SPE can improve endothelial function in SLE patients. Physical exercise can be a useful strategy to prevent CVD morbidity and mortality in these patients.

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TNF and IL-6 Differentially Regulate the Production of DKK-1, a Master Regulator of Bone Remodelling, by Fibroblast-Like Synoviocytes. Nataliya Yeremenko[2], Karin Polzer[3], Gemma Righter[2], Radjesh Bisoendial[2], Jochen Zwerina[3], Georg Schett[3], Paul P. Tak[1] and Dominique Baeten[1]. [1]Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, [2]Division of Clinical Immunology and Rheumatology, Academic Medical Centre/University of Amsterdam, Amsterdam, The Netherlands, [3]Internal Medicine 3, Erlangen, Germany

Background: Different inflammatory joint diseases have distinct patterns of bone damage with pronounced erosions in rheumatoid arthritis (RA), a combination of bone destruction and formation in psoriatic arthritis (PsA), and dominant new bone formation in spondyloarthritis (SpA). Although the underlying molecular mechanisms remain poorly understood, blocking of Dickkopf-1 (DKK-1), an inhibitor of the Wnt pathway, reverses the bone-destructive pattern to a bone-forming pattern in experimental arthritis. In order to delineate the role of DKK-1 in the structural phenotype of SpA versus RA, we analyzed here the regulation of DKK-1 expression in the inflamed peripheral joint of different types of inflammatory arthritis *ex-vivo* and in fibroblast-like synoviocyte (FLS) cultures *in vitro*.

Methods: Synovial fluid (SF) was obtained from actively inflamed knee joints of RA (n=45), non-psoriatic SpA (n=38), PsA (n=33), and gout (n=17) patients. The concentrations of IL-6, DKK-1, TNF, and IL-1 beta were determined by ELISA. Synovial FLS lines were established from tissue samples obtained from patients with inflammatory synovitis including RA (n=5), SpA (n=6), PsA (n=6). Expression of DKK-1 was determined by ELISA in FLS cultures following stimulation with TNF, IL-1 beta, IL-6, LPS and oncostatin M (OSM). DKK-1 serum levels were assessed before and after IL-6R blockade in RA patients.

Results: SF DKK-1 levels were similar between the 4 disease groups with, however, a striking inter-individual variability within each cohort. As we previously demonstrated that DKK-1 production is strongly upregulated by TNF, we explored this inter-individual variability by correlating DKK-1 levels with pro-inflammatory cytokines levels in the inflamed joint. TNF and IL-1 beta levels were significantly higher in RA than SpA SF and did not correlate with SF DKK-1 levels, suggesting that other factors contribute to the regulation of DKK-1 in vivo. In contrast, there was a striking inverse correlation between DKK-1 and IL-6 in both RA and SpA. Exploring the functional impact of IL-6 on DKK-1 in vitro, DKK-1 production by RA, SpA, and PsA FLS was strongly induced by TNF (but not IL-1 beta) but clearly suppressed by IL-6 and OSM. This suppression was confirmed in dose-response experiments, although lower doses of IL-6 (10 ng/ml) have a stimulatory rather than inhibitory effect. Higher doses of IL-6 (50 ng/ml) were also able to reverse the TNF-induced upregulation of DKK-1 production by FLS. Preliminary data suggest that this regulation of DKK-1 production by IL-6 is also relevant in vivo as treatment with the anti-IL-6 R antibody, tocilizumab, induced a transient upregulation of DKK-1 serum levels in RA patients.

Conclusions: DKK-1 is abundantly expressed in the inflamed joint of both destructive and remodelling forms of arthritis. However, DKK-1 production by FLS is differentially regulated by TNF and IL-6 in vitro and in vivo. The relative balance between these factors in the arthritic joints may determine the pattern of inflammation-induced tissue remodelling.

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Adipogenic and Osteogenic Switch in Differentiation of Human Mesenchymal Stem Cells (hMSCs) Is Triggered by Hypoxia in a HIF-1 Dependent Manner. Markus Wagegg[3], Timo Gaber[1], Ferenz Lohanatha[1], Manuela Jakstadt[1], Grit Kasper[2], Georg Duda[2], Paula Kolar[3], Gerd R. Burmester[4] and Frank Buttgereit[5]. [1]Berlin-Brandenburg Center for Regenerative Therapies (BCRT), [2]Charité University Hospital, Center for Musculoskeletal Surgery, Berlin, Germany, [3]Charité University Hospital, Department of Rheumatology and Clinical Immunology, Berlin, Germany, [4]Charité University Hospital, Department of Rheumatology and Clinical Immunology, Berlin, Germany, [5]Charite University Med-Berlin, Berlin, Germany

Background: Bone regeneration is often impaired in elderly people as well as in people suffering from autoimmune diseases such as rheumatoid arthritis (RA). Bone fractures initiate series of cellular and molecular events that commence with hematoma formation, induction of inflammatory cascades which regulate hMSCs recruitment and finally differentiation. Due to the disruption of supplying blood vessels, hypoxia and the induction of the transcription factor hypoxia-inducible factor (HIF)-1 are considered to have considerable influence on these events.

Objectives: Here, we analyzed the impact of hypoxia and HIF-1 on the adipogenic and osteogenic differentiation potential of hMSCs.

Methods: Human MSCs isolated from bone marrow were characterized for their ability to differentiate into adipogenic, osteogenic and chondrogenic lineage cells and for their expression of surface markers. Adipogenesis and osteogenesis were induced by respective conditioned media. The cells were cultured for 14 and 28 days under normoxia (20% O2 air fraction) and hypoxia (<2% O2 air fraction), respectively. Adipogenic differentiation was assessed by oil-red staining, osteogenic differentiation by von Kossa staining. Additionally, the expressions of the adipogenic gene peroxisome proliferator-activated receptor γ (PPARγ), and the osteogenic genes osteopontin (SPP1) and runt-related transcription factor 2 (RUNX2) were measured by real-time PCR. For defining the role of HIF-1, a knockdown of HIF-1α (the oxygen-sensitive α-subunit of HIF-1) by lentiviral transduction was performed, and the ability of the transduced MSCs to differentiate into adipogenic and osteogenic lineage cells was analyzed.

Results: Hypoxia led to the induction of HIF-1α, suppressed adipogenesis, and further enhanced osteogenesis in hMSCs. In case of adipogenesis, we observed a 13fold induction of PPARγ after 28 days under normoxia when compared to hypoxia. In the event of osteogenesis, SPP1 and RUNX2 were both found to be up-regulated under hypoxia when compared to normoxia (SPP1: 2fold; RUNX2 10.5fold; after 14 days). Furthermore, shRNA mediated knockdown of HIF-1α enhanced adipogenesis under both normoxia and hypoxia. In addition knockdown of HIF-1α suppressed hypoxia-induced osteogenesis.

Conclusion: We show that hypoxia considerably influences bone healing by promoting osteogenesis while suppressing adipogenesis of hMSCs in a HIF-1 dependent manner. Therefore, stem cell therapy in combination with chemically induced hypoxia might be a novel approach to improve fracture healing in elderly people with an impaired bone healing and in patients suffering from autoimmune diseases such as RA.

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Mitochondrial 8-Oxoguanine DNA Glycosylase (Ogg1) Regulates the Cellular Function and Survival of Osteoarthritic Chondrocytes in Response to Catabolic Stresses in Osteoarthritis. Kazuo Yudoh[2] and Rie Karasawa[1]. [1]Kawasaki, Japan, [2]St. Marianna University School Medicine, Kawasaki City, Japan

Background: During the development of osteoarthritis (OA), mechanical and chemical stresses on articular cartilage change the stable cellular activities of chondrocytes and produce excess amounts of reactive oxygen species (ROS) as well as proinflammatory cytokines and chemokines. Studies have provided ample confirmation of the generation of ROS and the depletion of cellular antioxidants in degenerated articular cartilage. 8-Oxoguanine DNA glycosylase (Ogg1) repairs 8-oxo-7,8-dihydroxyguanine (8-oxoG), one of the most abundant DNA adducts caused by oxygen free radicals. In the mitochondria, Ogg1 is thought to protect against activation of the intrinsic apoptotic pathway in response to oxidative stress by augmenting DNA repair in a variety of cells. However, it still remains unclear whether mitochondrial Ogg1 regulates the chondrocyte function and cellular survival in osteoarthritic cartilage tissue.

Objective: The aim of the study was examined the potential involvement of mitochondrial Ogg1 in the pathogenesis of OA.

Methods: Ogg1 expression was investigated in human OA cartilage and rat OA cartilage by immunohistologic analysis. We studied whether IL-1beta and H_2O_2 induce Ogg1 expression in OA chondrocytes and analyzed the relationship between cellular apoptosis phenotypes and Ogg1 expression in human chondrocytes.

Results: We observed the decreased levels of Ogg1 in osteoarthritic chondrocytes in comparison with normal chondrocytes in animal models of osteoarthritis (OA) and patients with OA, suggesting the involvement of down-regulation of Ogg1 in the degeneration of articular cartilage in OA. We found that mitochondrial Ogg1 silencing using siRNA reduced chondrocyte activity and augments apoptosis in human osteoarthritic chondrocytes. In the previous studies, we have focused on nanocarbon particle, fullerene (C60), which acts a strong free radical scavenger, as an anti-oxidative agent, to prevent the degeneration of articular cartilage in OA. We have demonstrated that water-soluble fullerene has a potential as a protective agent against the catabolic stress-induced degeneration of articular cartilage both *in vitro* and *in vivo* OA models. In the present study, we found that C60 fullerene increased the expressions of Ogg1 in osteoarthritic chondrocytes.

Conclusion: Our recent study revealed the potential involvement of accumulation of 8-Oxoguanine, an oxidized form of guanine, and impairment of mitochondrial DNA repair enzymes in the pathogenesis of OA. These findings suggest that mt-hOgg1 prevents catabolic stress-mediated chondrocyte dysfunction and apoptosis that might be important in the maintenance of articular cartilage. C60 fullerene may have a therapeutic potential, as a nanomedicine, to protect against the degeneration of articular cartilage in OA.

Disclosure: K. Yudoh: None; **R. Karasawa:** None.

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Advanced Glycation End Products (AGEs)-Induced Expression of IL-6 and IL-8 in Human Osteoarthritis Chondrocytes Correlates with the Induction of Endoplasmic Reticulum Stress. Zafar Rasheed, Nahid Akhtar and Tariq M. Haqqi. Department of Medicine, Metrohealth/CWRU, Cleveland, OH

Background: During aging, non-enzymatic glycation of protein and other molecules results in the accumulation of advanced glycation end products (AGEs) in articular cartilage. Here, we investigated (a) whether AGEs induce endoplasmic reticulum stress (ERS) in chondrocytes; (b) whether the induction of proinflammatory cytokine IL-6 and chemokine IL-8 is related to ERS; and (c) determined the signal transduction pathways required for the AGEs-mediated induction of ERS and the expression of IL-6 and IL-8 in chondrocytes.

Methods: Human chondrocytes were derived from OA cartilage by enzymatic digestion (OA chondrocytes) and were stimulated with AGE-modified BSA (AGE-BSA). Expression of IL-6 and IL-8 was determined by qRT-PCR and the production of IL-6 or IL-8 in the culture medium was quantified by ELISA. Western immunoblotting was used to analyze the expression of GRP78 and phosphorylation of eukaryotic initiation factor-2α (eIF2α),both markers of ER stress, IκBα degradation, and the activation of mitogen-activated protein kinases (MAPKs). Activation of nuclear factor (NF)-κB was determined using a highly sensitive and specific ELISA. Studies to elucidate the involved pathways were executed using transfection of OA chondrocytes with siRNAs specific for RAGE and eIF2-α and specific inhibitors of MAPKs and NF-κB.

Results: AGE-BSA induced the expression of the GRP78 with concomitant increase in the expression of IL-6 and IL-8. Transfection of OA chondrocytes with RAGE specific siRNAs inhibited the AGE-BSA-induced expression of GRP78, IL-6 and IL-8. In OA chondrocytes with SiRNA-mediated knockdown of RAGE, significant activation of MAPKs was not observed upon challenge with AGE-BSA. Inhibition of p38-MAPK (SB202190) blocked the AGE-BSA-induced expression of GRP78 in OA chondrocytes. Treatment of OA chondrocytes with SB202190 (p38 inhibitor) or PD98059 (ERK inhibitor) inhibited the AGE-BSA induced IL-6 or IL-8 mRNA and protein expression. Similar results were obtained when OA chondrocytes were treated with 2-aminopurine (an inhibitor of eIF2α). In contrast JNK inhibitor SP600125 had no effect on AGE-BSA-induced IL-6 expression but inhibited the expression of IL-8. NF-κB inhibitor Bay 11–7082 (IKKα/β inhibitors), Parthenolide (IKKβ inhibitor), NEMO-BDBP (IKKγ inhibitor) or MG-132 (proteasome inhibitor) potently suppressed the AGE-BSA induced IL-6 and IL-8 mRNA and protein expression in OA chondrocytes but had no effect on the expression of GRP78.

Conclusion: This is the first study to demonstrate that AGEs via RAGE mediated activation of p38-MAPK induce ER stress and stimulate the expression of IL-6 and IL-8 in OA chondrocytes. Our results also demonstrate that AGEs differentially induced the expression of IL-6 and IL-8 with expression of IL-6 was independent of the JNK activation but the expression of IL-8 required the JNK activation. Activation of NF-κB was an absolute requirement for ER stress-induced expression of both IL-6 and IL-8 but not of GRP78 via RAGE. Thus, our results provide important insights into the mechanisms of AGE-BSA-induced ER stress in human OA chondrocytes. Our data also suggests that AGEs-induced ER stress may contribute to the pathogenesis OA.

Disclosure: Z. Rasheed: None; **N. Akhtar:** None; **T. M. Haqqi:** None.

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MicroRNA-199a-*Mediated Regulation of Cyclooxygenase-2 Expression in Human OA Chondrocytes. Nahid Akhtar[1], Zafar Rasheed[2] and Tariq M. Haqqi[1]. [1]Metrohealth Medical Center/CWRU, Cleveland, OH, [2]Metrohealth Medical Center/CWRU

Background: Recent evidence implicate the deregulated expression of microRNAs (miRNAs) in the pathogenesis of osteoarthritis (OA). Interleukin-1β (IL-1β)-induced expression of cyclooxygenase-2 (COX-2) correlates with the production of prostaglandin E_2 and cartilage degradation in OA. Here we determined the posttranscriptional regulation of COX-2 expression by miRNAs in IL-1β-stimulated human OA and normal chondrocytes.

Methods: Human chondrocytes were derived by enzymatic digestion of OA cartilage (OA chondrocytes) and cartilage from trauma patients with no history of OA (normal chondrocytes). Chondrocytes were stimulated with IL-1β (5ng/ml) *in vitro*. Total RNA was prepared using TRIZOL reagent and miRNAs were purified using the mirVANA system. Single stranded cDNA was synthesized using stem loop-specific primers and the expression of miRNAs of interest was quantified using TaqMan miRNA Expression Assay and their target mRNA was identified using bioinformatics. Transfection of OA chondrocytes with a 3'UTR reporter construct and pre-miRNAs was employed to verify the miRNA:mRNA interaction. OA chondrocytes transfected with pre-miRNAs and anti-miRNAs were analyzed for the expression of COX-2 mRNA and protein by qRT-PCR using specific primers and Western immunoblotting, respectively.

Results: IL-1β- stimulation of OA chondrocytes resulted in the down-regulation of two miRNAs- miR-101_3 and miR-199a*-that potentially target COX-2 mRNA. Kinetic analysis showed that in OA chondrocytes, expression of miR-101_3 was down-regulated at 6 h (2.1-fold $\pm$ 1.0; n=7) but no significant change was observed at 24 h (n=11) post stimulation. Normal chondrocytes showed down-regulation of miR-101_3 (1.7-fold $\pm$ 0.53; n=3) at 24 h but no change at 6 h post-stimulation with IL-1β. Expression level of miR-199a* in OA chondrocytes stimulated with IL-1β at 24 h (3.3-fold $\pm$ 1.5; n=11, $p<0.05$) and at 6 h (0.94-fold $\pm$ 0.86; n=7) inversely correlated with the COX-2 protein expression level. Similar results were obtained with normal chondrocytes stimulated with IL-1β. Significantly lower expression of miR-199a* was observed in freshly isolated OA cartilage compared to normal cartilage (n=5; $p<0.001$). Over-expression of miR-199a* in OA chondrocytes inhibited the IL-1β-induced expression of COX-2 protein significantly compared to control OA chondrocytes ($p<0.05$). Transfection of OA chondrocytes with miR-199a* inhibitor enhanced the IL-1β-induced expression of COX-2 protein. Co-transfection of OA chondrocytes with a luciferase reporter construct containing the 3'UTR of human COX-2 mRNA and pre-miR-199a* suppressed the luciferase activity significantly ($p<0.05$). No inhibition of luciferase activity was observed in OA chondrocytes transfected with negative control miRNA. Inhibition of NF-κB and p-38MAPK activation with specific inhibitors altered the expression of miR199a* in human OA chondrocytes suggesting the regulation of miR-199a* by activation of these pathways.

Conclusions: Our data implicate miR-199a* in the posttranscriptional regulation of COX-2 expression in OA chodrocytes and identify miR-199a* as a novel therapeutic target for the treatment/prevention of OA.

Disclosure: N. Akhtar: None; **Z. Rasheed:** None; **T. M. Haqqi:** None.

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The Unfolded Protein Response (UPR) Is Impaired in Aging and Osteoarthritic Cartilage Chondrocytes. Matthew Husa[1], Ru Liu-Bryan[2], Shawn Grogan[3], Haitao Yang[2], Bing Yang[2], Martin Lotz[3] and Robert Terkeltaub[2]. [1]San Diego VA/UCSD, La Jolla, CA, [2]San Diego VA/UCSD, [3]Scripps Research Institute

Background: OA is clearly associated with cartilage aging, but these factors do not inevitably cause OA. To identify chondrocyte abnormalities that provide a foundation upon which OA is accelerated we studied the unfolded protein response (UPR), a fundamental means by which cells normally resolve stress. The UPR restores equilibrium to the stressed ER via a reprogrammed proteome rich in chaperones and protein folding catalysts. The UPR also regulates oxidative stress responses, inflammation, and cell fate (apoptosis vs. autophagy). The UPR is impaired in aging brain and liver, due to chronic oxidant damage to UPR protein mediators. Three UPR signaling/proteolytic cascades (IRE1-XBP1; ATF6; PERK- ATF4) are triggered by dissociation of distinct ER membrane proteins from the chaperone GRP78. Generation of the UPR-specific transcription factor XBP1s (spliced XBP1) is UPR-specific and pro-inflammatory. Each UPR cascade promotes terminal expression of CHOP, a sentinel of UPR activation. Triggering of cartilage pathology by loading the ER with misfolded transgenic mutant proteins (type X collagen, matrilin-3) has illustrated deleterious effects of UPR "gain of function" in cartilage. Conversely, "loss of function" of the UPR impairs bone and cartilage development. Furthermore, UPR impairment is linked with multiple aging/degenerative diseases, mediated by oxidative damage to UPR mediators and accumulation of misfolded proteins.

Hypothesis: Impaired activity of the UPR in articular cartilage chondrocytes is involved in the development and progression of OA.

Methods: Sections of human cartilage, and aging normal mouse cartilages (4–24 months) were analyzed by immunohistochemistry. Chondrocytes were isolated from graded human knee articular cartilages and compared for UPR mediators.

Results: Mouse knee cartilages demonstrated markedly decreased GRP78 and CHOP staining linked to aging. Immunohistochemistry of human knee cartilages demonstrated that in mild OA, the proportions of GRP78 and CHOP positive cells were reduced in the superficial zone (SZ), middle zone (MZ), and deep zone (DZ) compared with that in normal cartilage. In severe OA cartilages, GRP78 and CHOP expression became markedly increased, but only focally so in chondrocyte clusters in the MZ and DZ. Human knee chondrocytes demonstrated increased XBP1s mRNA and protein with more advanced OA. Last, consistent with a dysfunctional UPR in OA, the RNA microarray data showed flat GRP78 and CHOP expression in OA vs. normal cartilage, under conditions where there were spotty increases in chaperones and protein disulfide isomerase (PDI) expression, and marked increase in positive control chondrocyte hypertrophy markers (type X collagen, osteopontin).

Conclusions: We observed decreased expression by chondrocytes of the UPR mediators GRP78 and CHOP in aging mouse knee cartilages and in human cartilages with mild OA, suggesting that UPR impairment provides a foundation for OA development and/or progression in aging. Conversely, there was markedly increased GRP78 and CHOP expression in chondrocyte clusters in late stage OA, which suggests activation of the UPR is a component of cartilage regeneration and repair.

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ACR Concurrent Abstract Sessions
Cytokines, Mediators, Gene Regulation
Monday, November 8, 2010, 2:30 PM–4:00 PM

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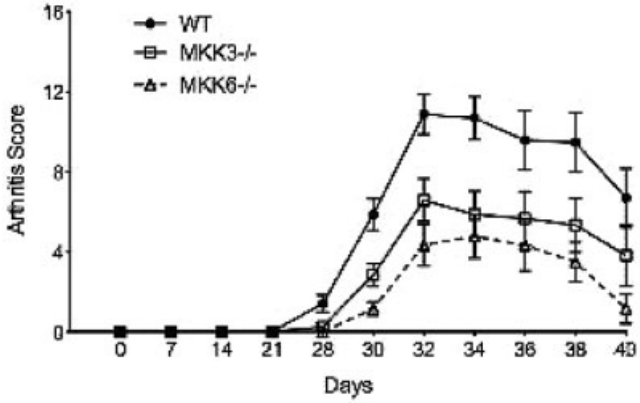
Decreased Collagen Induced Arthritis (CIA) Severity in MAPK Kinase 6 Deficient Mice: Pivotal Role of Th1 and Th17 Cytokines. Deepa Hammaker[1], Katharyn Topolewski[2], Meghan Edgar[2], David L. Boyle[1] and Gary S. Firestein[1]. [1]UCSD School of Medicine, La Jolla, CA, [2]UCSD School of Medicine

Purpose: MKK3 and MKK6 are upstream kinases that activate p38 MAP kinase and regulate distinct subsets of cytokines. Previous studies suggest that both kinases suppress innate immune responses and arthritis severity in passive K/BxN arthritis. However, their function in an adaptive model of inflammatory arthritis has is not known. This study evaluated whether these kinases play a role in collagen induced arthritis (CIA).

Method: Wild type (WT), MKK6−/−, and MKK3−/− mice were immunized on days 0 and 21 with type II bovine collagen in complete Freund's adjuvant. Joint histology was evaluated on synovitis, bone erosion, extra-articular inflammation and proteoglycan damage (max score=16). Serum anti-collagen antibodies were measured by ELISA. Cytokines in joints extracts and serum was determined by multiplex analysis. Splenocytes isolated 14 days after immunization were cultured with concanavalin A (Con A), type II collagen (CII), or medium and supernatants were assayed for cytokines.

Results: Arthritis severity was significantly lower in MKK6−/− mice than WT mice, while MKK3−/− mice had intermediate disease severity ($p=0.03$ for each compared to WT).



Scores of WT, MKK6−/− and MKK3−/− mice on day 35 were 12±1.5, 7±1.8, and 8±2.4, respectively. Histological evaluation showed significantly decreased bone erosion in MKK6−/− mice compared with WT mice (1.2±0.5 vs. 2.7±0.5, p=0.03). Decreased synovitis (50% inhibition), and proteoglycan loss (40% inhibition) were observed in MKK6−/− mice compared with WT mice. Surprisingly, inflammation and bone destruction were similar in WT and MKK3−/− mice. Anti-collagen antibodies levels in MKK6−/− mice were decreased by 45±12% compared with WT (p=0.004), but titers in MKK3−/− mice were the same as WT. Synovial IL-6, MMP3 and MMP13 gene expression was reduced by 66–79% in MKK6−/− mice compared with WT (p<0.02 for each). Expression of these genes was modestly reduced in MKK3−/− joints but did not reach statistical significance. T cell differentiation was evaluated by examining in vitro splenocyte cytokine profiles. IL-17 production in response to Con A and CII in MKK6−/− mice was reduced by 80±7% and 82±16% compared with WT and were normal in MKK3−/− cells (p≤0.03 for MKK6−/−). IFNγ production by Con A-stimulated splenocytes was inhibited by 85±5% in MKK6−/− compared with WT mice (p=0.025). IL-4 levels were not altered by MKK3 or MKK6 deficiency.

Conclusion: MKK6 deficiency suppressed CIA and joint destruction while MKK3 had an intermediate effect. Lower disease severity in MKK6−/− mice was due to decreased adaptive immune responses, especially the production of antibodies and Th1/Th17 cytokines. These data suggest that targeting MKK6 has a potential benefit in complex diseases involving adaptive immune responses like rheumatoid arthritis.

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IL-7-Related TSLP: A Novel Potent Proinflammatory Mediator in Rheumatoid Arthritis That Activates Myeloid Dendritic Cells To Stimulate Th1 and Th17 Activity. F. M. Moret, C. E. Hack, K. M. G. van der Wurff-Jacobs, F. P. J. G. Lafeber and J. A. G. van Roon. Rheumatology & Clinical Immunology, University Medical Center Utrecht, The Netherlands

Background: The IL-7-related cytokine, thymic stromal lymphopoietin (TSLP), is well known for its potent activation of myeloid dendritic cells (mDCs) resulting in Th2-mediated immune responses. TSLP signals cells via the IL-7 receptor-alpha chain (IL-7Rα), shared with IL-7, together with a distinctive receptor subunit, the TSLP receptor (TSLPR). Recently, we have demonstrated that prevention of TSLPR signalling strongly reduces Th17-driven experimental arthritis and immunopathology. Furthermore, we have shown that administration of TSLP expands T and B cells and enhances severity of inflammation and joint destruction in collagen induced arthritis.

Objective: To determine the levels of TSLP and TSLPR in joints of rheumatoid arthritis (RA) patients and the capacity of TSLP to induce mDC-dependent T-cell activation.

Methods: TSLP was measured (by ELISA) in synovial fluid (SF) of patients with RA (n=44) and osteoarthritis (OA, n=20). CD1c+ mDC numbers and TSLPR expression on these cells were assessed by FACS analysis in paired samples of SF and peripheral blood (PB) from RA patients (n=7). mDCs, isolated from PB of patients with RA (n=8) as well as SF-derived mDCs were stimulated with TSLP for 24 hours and cytokine production was measured. Washed TSLP-activated mDCs were added to autologous CD4 T cells from PB in the absence of additional stimuli, cultured for 6 days and subsequently proliferation was measured. Additionally, T-cell cytokine production was measured upon restimulation with ionomycin/PMA.

Results: TSLP levels in SF of RA patients were increased compared to OA patients (mean 460 vs. 75 pg/ml, resp., p<0.01). mDCs numbers from SF were increased compared to PB (3.8% vs. 0.7%, resp., p<0.02). CD1c+ mDCs from SF and PB expressed substantial levels of TSLPR (SF: 76% positive cells, MFI 19 ± 3; PB: 70% positive cells, MFI 15 ± 2).

TSLP significantly stimulated production of chemokines TARC and MIP1α by mDCs from PB and SF (TARC; PB: from 4 to 89 and SF: from 323 to 629 pg/ml, MIP1α; PB from 1545 to 6293 and SF from 10185 to 14313 pg/ml). Upon incubation with TSLP, TSLPR-expressing mDCs from PB potently stimulated proliferation of autologous CD4 T cells (ratio T cell:DC 5:1, mean 15019 ± 1856 cpm) as compared to unstimulated mDCs (mean 960 ± 256 cpm). TSLP-mDCs from SF had a strongly increased stimulatory capacity (from 2195 ± 686 to 16615 ± 3162 at a ratio T cell:mDC 50:1). Upon restimulation, TSLP-mDC-activated CD4 T cells from PB produced increased levels of TNFα (3724 ± 972 vs. 11559 ± 1465 pg/ml), IFNγ (218 ± 142 vs. 738 ± 181 pg/ml), and IL-17 (27.9 ± 8.2 vs. 155 ± 66 pg/ml) in addition to IL-4 (1.4 ± 1.4 vs. 25.0 ± 11.3 pg/ml). Induction of TNFα was significantly higher in RA patients compared to healthy controls (p<0.05).

Conclusion: Our data indicate that increased intra-articular TSLP concentrations in RA potently activate TSLPR-expressing mDCs from RA patients to cause chemotaxis and activation of arthritogenic T cells. This suggests that TSLP and its receptor are novel therapeutic targets for RA.

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Interleukin-12, Not the ITGAM Polymorphism (rs1143679), Correlates with Atherosclerosis Independent of Disease Activity in SLE. Manish Jain, Erin McDonnell, Jill P. Buyon and Robert M. Clancy. Department of Rheumatology, New York University School of Medicine

Background: Inflammation likely contributes to the increased prevalence of macrovascular disease in SLE. Dendritic cells (DCs) at sites of atherosclerosis may represent a double-edged sword, promoting plaque formation and restraining inflammation by inducing tolerance. Plasma IL-12 may represent a marker of DC activation, and its utility as a biomarker of macrovascular disease is underscored by the fact that in murine models, blockade of IL-12 function attenuates atherosclerosis. The integrin CR3 has been shown to decrease the release of IL-12 by DC. ITGAM polymorphism rs1143679 (exon-3 ITGAM gene, A allele frequency) encoding R77H in the alpha chain of CR3 (CD11b), is significantly associated with SLE. Accordingly, the hypothesis being raised is that macrovascular disease is linked to a skewing of DC phenotype towards activation as reflected by elevated levels of IL-12. A subgoal was to evaluate whether plaque was enriched in patients with the non-synonymous variant rs1143679.

Methods: IL-12 levels (ELISA) were measured in a previously reported cross sectional study of 116 SLE patients and 47 healthy controls in whom carotid ultrasonography was performed to evaluate Intimal Media Thickness (IMT) and the presence of carotid plaque. Complete history and physical were done to complete the SLEDAI in addition to chart review. Typing of ITGAM was performed by the allelic discrimination technique using assays and reagents optimized for the assessment of rs1143679.

Results: The mean level of IL-12 was significantly higher in SLE patients (109 ±87.9 pg/mL) than controls (67±26 pg/mL) (p=.0006). Among SLE patients, no correlation was observed between IL-12 levels and SLEDAI. SLE patients with plaque had significantly higher mean soluble IL-12 levels (130±104) than patients without plaque (93 ± 69 pg/mL) (p=.023). The top quartile of SLE patients based on IL-12 levels (29 patients) had a significantly higher prevalence of carotid plaque compared to the other SLE patients (18/29 patients or 62% versus 32/87 patients or 37%, p=.029). The mean common carotid artery IMT was higher in these top quartile SLE patients (.649 mm) versus those in the bottom three quartiles (.565 mm) (p=.037). The presence of anti-ds DNA antibodies was significantly enriched in the top quartile SLE patients (18/29, 62%) versus the remainder of SLE patients (33/87,38%) (p=.031). No differences were found for levels of cardiac CRP or complement. Representation of the rs1143679 ITGAM polymorphism was 19% within the cohort, consistent with published values in SLE (versus 10% hapmap). There were no differences in allelic frequency for patients based on plaque status or for patients with varied levels of IL-12.

Conclusion: This study highlights IL-12 as a surrogate marker for vascular damage with potential clinical applicability in monitoring patients,

particularly since it may be independent of disease activity. While CR3 has been shown to attenuate IL-12, in this cohort an association with the ITGAM variant was not observed. Although the source of IL-12 is yet to be identified in this cohort of patients, a potential link between DC and atherosclerosis in SLE should be considered.

Disclosure: M. Jain: None; **E. McDonnell:** None; **J. P. Buyon:** NIAMS-NIH, 2, NIH, 2; **R. M. Clancy:** None.

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Pro-Inflammatory Properties of IL-35 and Its Association with Disease Activity in Patients with Rheumatoid Arthritis. Maria Filkova[2], Hana Hulejova[3], Marketa Polanska[3], Lucie Andres Cerezo[3], Jiri Vencovsky[2], Karel Pavelka[4], Steffen Gay[1] and Ladislav Senolt[3]. [1]Center of Experimental Rheumatology, University Hospital and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland, [2]Institute of Rheumatology and Connective Tissue Research Laboratory, Department of Rheumatology of the 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [3]Institute of Rheumatology and Connective Tissue Research Laboratory, Department of Rheumatology of the 1st Faculty of Medicine, Charles University in Prague, Czech Republic, Czech Republic, [4]Institute of Rheumatology, Department of Rheumatology of the 1st Faculty of Medicine, Charles University in Prague, Czech Republic, Czech Republic

Background: IL-35 is a heterodimeric member of the IL-12 family consisting of p35 (IL-12a) and EBI3 (IL-27b) subunits. Expressed in murine T-reg cells, IL-35 was shown to control colitis and inhibit collagen induced arthritis in mice. In contrast to mice, human T-reg cells do not express IL-35 and both subunits are expressed in activated T-eff cells. An up-regulation of EBI3/p35 following TNF-α and IFN-γ was observed in human aortic smooth muscle cells.

Objective: To analyze the levels of IL-35 in sera and synovial fluids of patients with rheumatoid arthritis (RA), osteoarthritis (OA) and healthy controls and to study its effect(s) on peripheral blood mononuclear cells (PBMC) and RA synovial fibroblasts (RASF) in vitro.

Methods: The levels of IL-35 in sera (RA: n=40, healthy controls: n=34), synovial fluids (RA: n=32, OA: n=30) and cell culture media were determined by commercially available ELISA. PBMC and RASF were stimulated with human recombinant IL-35 protein (25, 50, 100 ng/ml) or TNF-α (10, 50, 100 ng/ml) in vitro. Taq-Man RT-PCR was performed to analyse gene expression after 6 and 24 hours and ELISA assays were used to confirm the protein secretion after 24 hours of stimulation.

Results: The levels of IL-35 in synovial fluids were significantly higher in patients with RA in comparison to patients with OA (mean$\pm$SEM: 23 583$\pm$7 474, calculated after dilution; vs. 397.5$\pm$68.7 pg/ml, $p<0.0001$). In addition, local levels of IL-35 significantly correlated with the levels of serum CRP in both RA as well as OA patients ($r=0.504$, $p=0.004$ and $r=0.453$, $p=0.02$; respectively) and with the disease activity of patients with RA assessed by DAS28 ($r=0.440$, $p=0.014$). On the other side, serum levels of IL-35 were below the detection limit in the majority of RA patients as well as healthy controls. Gene expression of both subunits of IL-35, EBI3 and p35, as well as IL-35 in cell culture supernatants, was dose- and time-dependently induced by TNF-α in PBMC. Related results show that PBMC isolated from patients with RA secreted more IL-35 than those from healthy controls. IL-35 dose-dependently up-regulated the gene expression of IL-1β (up to 6.3 fold), IL-6 (up to 9.6 fold) and MCP1 (up to 22.4 fold) but not of TNF-α in PBMC. This pattern was also confirmed by ELISA. However, there was no effect of IL-35 on RASF with respect to the tested cytokines.

Conclusion: These data show for the first time, in contrast to the immunosuppressive function observed in mice, that locally up-regulated levels of IL-35 reflect the disease activity of RA. Furthermore, the results of this study support the concept that IL-35 has also pro-inflammatory properties.

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MAPK Kinase 3 (MKK3) Regulates Osteoclast Differentiation and Activation. David L. Boyle[3], Meghan Edgar[4], Mario M. Zaiss[1], Georg Schett[2] and Gary S. Firestein[3]. [1]Department of Internal Medicine 3, University of Erlangen-Nuremberg, [2]Friedrich Alexander Univ, Erlangen, Germany, [3]UCSD School of Medicine, La Jolla, CA, [4]UCSD School of Medicine

Purpose: p38 MAPK inhibitors have modest efficacy in diseases like rheumatoid arthritis (RA), in part because exposure is limited by side effects. Two upstream kinases regulate p38 function, namely MKK3 and MKK6. These two MKKs have non-redundant functions and control expression of complementary subsets of pro-inflammatory cytokines. Deficiency of either MKK decreases inflammation in the passive K/BxN model of arthritis. To explore distinct functions of MKK3 and MKK6, we examined their relative contributions to joint damage and bone resorption by evaluating the differentiation and function of MKK deficient osteoclasts. The data could support developing MKK inhibitors for bone protection in RA and in osteoporosis.

Methods: BM monocytes from wild type (WT), MKK3$-/-$, and MKK6$-/-$ mice were differentiated with M-CSF (30ng/ml) and non-adherent cells subsequently cultured with M-CSF (30ng/ml) and RANKL (50ng/ml) for 5 days in the Osteologic Bone Cell Culture System. Osteoclast number and matrix resorption were determined by TRAP staining followed by light microscopy and automated image analysis. SB203580 was used at 3μg/ml. Gene expression and p38 phosphorylation were determined by qPCR and Western Blot analysis, respectively.

Results: The number of osteclasts generated from BM monocytes was similar in WT and MKK6$-/-$ mice. Surprisingly, MKK3$-/-$ osteoclast differentiation was lower than WT or MKK6$-/-$ (n=9, 33% inhibition, $P<0.004$). The p38 inhibitor SB203580 inhibited osteoclast differentiation by 74% ($P=0.001$). In vitro matrix resorption by osteoclasts was decreased by 46% by MKK3$-/-$ osteoclasts ($P=0.002$), while MKK6 deficiency had no effect compared with WT cells. p38 activation, as measured by determining relative P-p38/p38 ratios, for WT, MKK6$-/-$, and MKK3$-/-$ osteoclasts was 0.71$\pm$0.09, 0.54$\pm$0.05, and 0.09$\pm$0.02, respectively (n=3, $P=0.001$ for MKK3$-/-$). MMP13 expression was similar in all genotypes, but expression of the key bone resorbing proteinase cathepsin K was significantly lower in MKK3$-/-$ osteoclasts (67% inhibition; $P=0.0001$) but not in MKK6$-/-$ cells.

Conclusions: MKK3, but not MKK6, is required for osteoclast differentiation and activation, p38 phosphorylation, and cathepsin K gene expression. Selective MKK3 inhibitors could be targeted for RA in order to suppress bone erosions and inflammation while sparing p38 functions that might contribute to toxicity. In addition, an MKK3 inhibitor could have utility as an oral therapy for osteoporosis.

Disclosure: D. L. Boyle: None; **M. Edgar:** None; **M. M. Zaiss:** None; **G. Schett:** None; **G. S. Firestein:** None.

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Epidemiology and Health Services Research: Rheumatoid Arthritis
Monday, November 8, 2010, 2:30 PM–4:00 PM

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Tumor Necrosis Factor Inhibition Reduces the Incidence of Alzheimer's Disease in Rheumatoid Arthritis Patients. Richard C. Chou[2], Michael A. Kane[3], Shiva Gautam[1] and Sanjay Ghirmire[4]. [1]Beth Israel Deaconess Medical Center, [2]Dartmouth-Hitchcock Medical Center, Milton, MA, [3]Massachusetts General Hospital and Massachusetts Institute of Technology, Georgetown, MA, [4]Verisk Health

Objective: To investigate the relationship between different rheumatoid arthritis treatments and Alzheimer's dementia.

Background: A complication of chronic inflammation in rheumatoid arthritis (RA) is the deposition of amyloid proteins, resulting in secondary amyloidosis. Alzheimer's dementia (AD) is associated with the local deposition of beta-amyloid peptide in the brain, although the pathogenetic mechanisms of AD are unclear. The relationship between RA and AD has not been established.

Design/Methods: We reviewed medical and pharmacy claims data from January 2000 to November 2007 for a commercially insured cohort of 8.5 million adults throughout the US. We derived a subcohort of 42,193

patients with a pre-existing diagnosis of RA. In this subcohort, we conducted a nested case-control study of the incidence of AD. We excluded individuals with psoriatic arthritis, inflammatory bowel disease, previous stroke or previous AD. For each individual with newly diagnosed AD (cases) we matched up to 10 controls who did not have a prior diagnosis of AD and were free of AD during the exposure assessment period. Matching criteria included age, gender, duration of exposure assessment period and methotrexate treatment. We examined exposure to sulfasalazine, prednisone, three anti-tumor necrosis factor (TNF) agents (infliximab, etanercept, adalimumab) and rituximab.

Results: In this nested case-control study, a total of 165 patients with AD (cases) were matched to 1,383 controls without AD. Treatment with anti-TNF agents in RA was associated with lower risk for incident AD [adjusted odds ratio (OR) 0.440; 95% confidence interval (CI) 0.223–0.868; p=0. 0178). The risk of AD was not affected by exposure to sulfasalazine, prednisone or rituximab. The results were similar [adjusted OR 0.448; 95% CI 0.225–0.892; p = 0.0222) after adjustment for covariates, including hypertension, hyperlipidemia, diabetes mellitus, peripheral vascular disease, and coronary artery disease.

Conclusion: In this population of adults with RA, we observed that the risk of AD was reduced by TNF inhibitor therapy, but not by other disease modifying agents used for treatment of RA. Tumor necrosis factor may be an important component in the pathogenesis of AD.

Disclosure: R. C. Chou: None; **M. A. Kane:** verisk health, 5; **S. Gautam:** None; **S. Ghirmire:** verisk health, 3.

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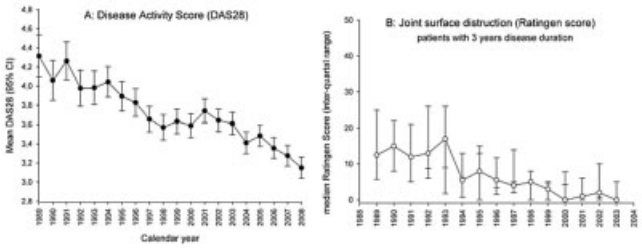
Major Improvements in Outcomes of Rheumatoid Arthritis Since the Biologic Era and beyond: An Historical Overview from 1989 until 2008 in a Large Inception Cohort of RA Patients. Wietske Kievit[1], Jaap Fransen[2], Maarten De Waal Malefijt[2], Alfons Den Broeder[3] and Piet van Riel[2]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, [2]Radboud University Nijmegen Medical Centre, [3]Sint Maartenskliniek

Background: Already since the early 80's there has been a movement towards intensified treatment for RA with an increasing use of methotrexate in higher doses up to 30 mg per week in individual patients and DMARD combination therapy.

Objectives: We hypothesized that the trend of better RA outcomes precedes the era of biologic response modifiers.

Methods: Data available from the period between 1989 and 2008 in the Dutch Nijmegen inception cohort was used, including DAS28, HAQ-DI, X-rays and orthopedic surgery. Patients with RA were regularly assessed at scheduled visits. For each individual patient, the average DAS28 and HAQ-DI scores for each calendar year were calculated. X-rays of hand and feet were taken annually and joint surface destruction was scored according to the Ratingen score (range 0–190) (data available until 2003). Population mean DAS28 and HAQ-DI over time were corrected for age, gender, rheumatoid factor and disease duration by means of repeated measures analysis (mixed models). Conditional means of DAS28 and HAQ-DI were plotted by calendar year. Median Ratingen scores were compared between calendar years non-parametrically. Orthopedic surgery was analyzed as incidence rates with 95% confidence limits based on a Poisson distribution. To describe treatment, the percentage of patients being treated with MTX or SASP, a biological response modifier, and the mean MTX dose per year were calculated.

Results: Per 2008, 992 RA patients were included, resulting in 8618 patient years. From 1989 onwards, the percentage of patients being treated with SASP decreased to 18% and the percentage of patients being treated with MTX increased to 62% in 2008. The percentage of patients being treated with a biologic was increased to 22% (166/765) in 2008. The MTX dose increased significantly from a mean dose (sd) of 6.7 (1.3) mg/week with a maximum of 7.5 mg/week in 1989 to a mean dose (sd) of 16.1 (5.5) mg/week with a maximum of 30 mg/week in 2008. The Figure A shows the mean DAS28 per calendar year conditional on disease duration, age, gender and rheumatoid factor. According to the repeated measures analysis the mean DAS28 and HAQ-DI were statistically significant higher ($p<0.008$) in all years compared to 2008, where mean DAS28 was 3.2 and the mean HAQ-Di was 0.47. Median Ratingen score for patients with 3 years disease duration decreased from 12.5 in 1989 to zero in 2003 (Figure B). Analysis of the incidence of orthopedic surgeries showed a trend towards lower rates of orthopedic surgery with non-overlapping 95% confidence intervals in the years 2006, 2007 and 2008 compared to almost all previous years.



Conclusion: The better controlled RA that we show is not only attributable to the introduction of anti-TNF, but also to the DMARDs (and especially MTX) which were largely available before the biologic era. We think that utilization of the available therapies can still be enhanced by tight control strategies.

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Propensity-Adjusted Medication Effects on Survival in Rheumatoid Arthritis: 22-Year Follow-Up of 5629 Patients. Mary Chester Wasko[3], Abhijit Dasgupta[1], Helen Hubert[2], Bharathi Lingala[2], James Fries[2] and Michael Ward[1]. [1]NIAMS/NIH, Bethesda, MD, [2]Stanford University, Palo Alto, CA, [3]University of Pittsburgh, Pittsburgh PA

Background: Medications used to treat rheumatoid arthritis (RA) may affect mortality, though prescription patterns are influenced by patient demographics, comorbidities, and physician preference, all factors that change over time. The propensity for prescribing RA medications may influence the likelihood of drug use and thus also should be considered when evaluating if particular anti-rheumatic medications influence mortality in patients with RA.

Methods: Using a longitudinal multicenter observational database of 5629 RA patients followed biannually with the Health Assessment Questionnaire (HAQ) from 1981–2003, we calculated propensity scores at each HAQ for the use of methotrexate (MTX), prednisone (PRED), and anti-tumor necrosis factor (TNF) agents. Scores were time-dependent and based on RA duration at study entry, age, ethnicity, education level, gender, marital status, work status, body-mass index (BMI), pain and RA severity indices, comorbidities, other drug use, and phase of study. Time-varying Cox proportional hazards regression models were then constructed to determine the relationship between drug use and survival, adjusting for propensity score, age, BMI, HAQ-disability index, ethnicity, education level, gender, RA duration at entry, presence of any comorbidities, and concurrent use of MTX, prednisone, anti-TNF agents, hydroxychloroquine, other disease-modifying drugs, nonsteroidal anti-inflammatory drugs, and cyclooxygenase-2 inhibitors.

Results: Median age was 58y, 75% were women, 90% Caucasian, with median education 12 years. For MTX, PRED and anti-TNF users, median RA duration at entry was 5.7, 7.2, and 10.9y; 50%, 50%, and 39% had ≥1 comorbidity at baseline respectively. Overall, 1027 (18%) died during observation. MTX propensity increased over time, but PRED propensity was fairly constant. Time-varying Cox proportional hazards modeling adjusting for drug-specific propensity and covariates showed a strong protective effect for MTX on mortality (Hazard Ratio [HR]=0.27, 0.11–0.70 95% CI, $p<0.001$) but no statistically significant impact of PRED (HR=1.48, 0.69–3.17 95% CI, p=0.31) or anti-TNF (HR=0.59, 0.00–5e8 95% CI, p=0.96) on the outcome. However, the models for PRED without propensity score showed a significantly increased risk of mortality (HR=1.62, 95% CI 1.41–1.87, $p<0.001$).

Conclusions: Adjusting for propensity and other covariates, MTX use is strongly associated with reduced mortality in this RA cohort. These results underscore the important role of MTX in the management of patients with RA. Use of PRED is not associated with increased mortality in propensity-adjusted analysis, uniquely suggesting that factors associated with prescribing patterns play a role in the reported mortality rates for patients on PRED. Our findings do not indicate an increase in mortality with use of anti-TNF agents over 5 years of observation following introduction of these agents for commercial use.

Disclosure: M. C. Wasko: Amgen Inc., 2, Centocor, Inc., 5, 9, UCB, Inc., 5; **A. Dasgupta:** None; **H. Hubert:** None; **B. Lingala:** None; **J. Fries:** None; **M. Ward:** None.

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Renal Dysfunction in Rheumatoid Arthritis Is Associated with Incident Cardiovascular Disease, Independently of Traditional Risk Factors: The CARRE Study. Alper M. van Sijl[3], Ingrid M. Visman[1], Inge A. M. van den Oever[1], Mike J. L. Peters[5], Alexandre E. Voskuyl[5], Ben A. C. Dijkmans[4] and Michael T. Nurmohamed[2]. [1]Jan van Breemen Institute, [2]Jan van Breemen Institute and VU Medical Centre, Amsterdam, The Netherlands, [3]Jan van Breemen Institute and VU Medical Centre, [4]VU Medical Centre, Amsterdam, The Netherlands, [5]VU Medical Centre

Background: Individuals with rheumatoid arthritis (RA), a chronic inflammatory disease, have an increased risk of developing cardiovascular disease (CVD), that persists after correction for traditional risk factors, e.g. smoking, hypertension, dyslipidemia, previous CV event or diabetes. Renal dysfunction is predictive of CVD in the general population but also in patients with diabetes or hypertension, independently of traditional CV risk factors. In these cases, low-grade inflammation is thought to have an essential role. To date, there have been no studies investigating the association of renal dysfunction with incidence of CVD in RA.

Methods: The CARRE study is a prospective cohort study of Dutch patients with RA aged between 50 and 75 years old, in which traditional CV risk factors, RA related factors and CV morbidity and mortality are investigated. CV events are defined as documented myocardial infarction, cerebrovascular accident, transient ischaemic attack, peripheral arterial reconstruction or coronary stent- or by-pass procedure. Renal function was assessed by the estimated Glomerular Filtration Rate (GFR) using the abbreviated Modification of Diet in Renal Disease (MDRD) formula. A GFR of less than 60 ml/min/1.73 m^2 is considered unfavourable. Multivariate Cox proportional hazard analyses were performed to determine the association between renal dysfunction and incident CV disease.

Results: 353 patients were followed for 3 years and 23 patients developed a CV event within this study period. Higher GFR (>60) was significantly associated with a lower risk for CVD, hazard ratio (95%-confidence interval): 0.185 (0.079–0.438). This association remained significant even after correction for: 1. Age, sex and previous CVD 2. Nodular disease and antihypertensive agents 3. Use of methotrexate, corticosteroids and non-steroidal anti-inflammatory drugs and 4. Traditional CV risk factors.

Conclusion: Renal dysfunction is associated with incident CV disease in RA, even after correction for traditional risk factors. These results indicate that a decreased renal function helps to identify RA patients at increased risk for future CV disease. Future studies should further investigate the relationship between chronic inflammation and renal dysfunction.

Table 1. Cox proportional hazard model for GFR and cardiovascular incidence

	Hazard Ratio	95%-Confidence Interval
Crude model	0.185*	0.079–0.438
Model 1	0.240	0.063–0.907
Model 2	0.174	0.039–0.776
Model 3	0.223	0.060–0.828
Model 4	0.125*	0.027–0.572

*p < 0.01. Results as hazard ratios (95%-confidence interval).
GFR-MDRD as categorical variable ≥60 and <60
Model 1: Adjustment for age, gender, previous CVD
Model 2: Adjustment for age, gender, previous CVD, nodular disease, use of antihypertensives
Model 3: Adjustment for age, gender, previous CVD, use of methotrexate, use of prednisone, use of non-steroidal anti-inflammatory drugs
Model 4: Adjustment for age, gender, previous CVD, systolic blood pressure, total cholesterol, triglycerides, prevalence of diabetes, current smoking and body mass index

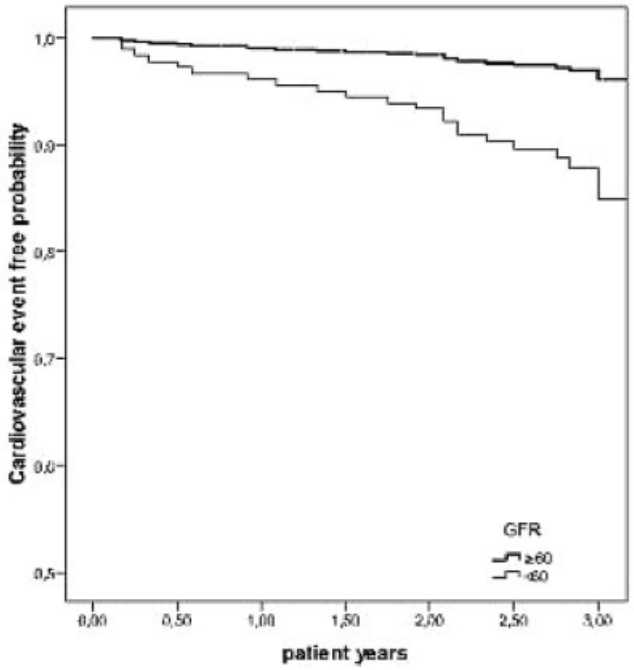

Figure 1. Cox-regression analysis of CV event free probability for individuals with GFR <60 compared to individuals with GFR >=60 corrected for age, gender and previous CVD.

Disclosure: A. M. van Sijl: None; **I. M. Visman:** None; **I. A. M. van den Oever:** None; **M. J. L. Peters:** None; **A. E. Voskuyl:** None; **B. A. C. Dijkmans:** None; **M. T. Nurmohamed:** Abbott Immunology Pharmaceuticals, 2, Bristol-Myers Squibb, 2, 8, Roche, 2, Schering-Plough, 2, Wyeth Pharmaceuticals, 2.

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Do Structural Damage and Inflammation Impact Physical Functioning Differently Based on Duration of Rheumatoid Arthritis? Martin J. Bergman[2], Sanjoy Roy[1], Naijun Chen[1] and Mary A. Cifaldi[1]. [1]Abbott Laboratories, Abbott Park, IL, [2]Arthritis and Rheumatology, Ridley Park, PA

Background: Impairment of physical function, caused by a combination of inflammation and structural damage, leads to eventual disability among patients with rheumatoid arthritis (RA). It has been suggested that the relative impact of inflammation and structural damage on physical function differ over time during the progression of the disease.[1] This study tests the hypothesis by assessing the relative associations of these two important factors with physical functioning among patients with RA.

Methods: Data from two trials of adalimumab—PREMIER (patients with early RA) and DE019 (patients with longstanding RA) —were pooled to assess the relationship of physical functioning (measured by the HAQ and the Physical Component Score [PCS] and Physical Functioning [PF] domain of the SF-36 questionnaire) with structural damage (measured by modified total Sharp scores [mTSS]) and inflammation (measured by C-Reactive Protein [CRP] levels). Baseline patient-level data were used from both trials regardless of treatment arm. Spearman's correlations were assessed between HAQ, PCS and PF with TSS and with CRP. Correlations were calculated separately for patients with duration of disease up to 3 years (early RA) and for those with more than 3 years (longstanding RA) across the two trials. Strengths of correlation between HAQ-TSS and HAQ-CRP were tested using Fisher's Z transformation technique.

Results: Combining patients from the two studies, there were 908 patients with disease duration ≤3 years and 507 with disease duration >3 years. The mean (SD) HAQ, TSS, and CRP values were 1.5 (0.6), 20.05 (20.3), and 3.73 (3.9) respectively in early RA, and 1.47 (0.6), 77.89 (55.9), and 1.69 (1.9) in longstanding RA. In early RA, all measures of physical functioning were correlated with CRP: Spearman's correlation coefficients with HAQ, PCS, and PF of 0.395, –0.288, and –0.357, respectively ($p<0.05$ for all). However, none of the physical function measures were correlated with TSS. In established RA, on the other hand, TSS was correlated with HAQ, PCS, and PF with coefficients of 0.238, –0.119, and –0.137, respectively. Correlations of the physical function measures with CRP were also significant in longstanding RA, but the strengths of such associations were weaker compared with those in early RA. Fisher's Z-transformed estimates of

correlation between HAQ and TSS increased significantly with longer duration of disease (0.034 vs. 0.242; p=0.0003), while it decreased significantly between HAQ and CRP (0.417 vs. 0.261; p=0.005).

Conclusion: This study shows that deterioration of physical functioning as a result of RA may be driven by inflammation earlier in the disease, but is driven more by structural damage as the disease progresses. This suggests that earlier treatment with appropriate therapy (that inhibits both inflammation and radiographic progression) prior to structural damage could dramatically improve long-term physical functioning and disability outcomes among patients with RA.

References:

[1]Kirwan J. *J Rheumatol.* 1999; 26:720–5.

Disclosure: M. J. Bergman: Abbott Laboratories, 2, 5, 8, Bristol-Myers Squibb, 2, 5, 8, Roche, 5, UCB, Inc., 2, 5; **S. Roy:** Abbott Laboratories, 1, 3; **N. Chen:** Abbott Laboratories, 1, 3; **M. A. Cifaldi:** Abbott Laboratories, 1, 3.

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Common Vaccinations among Adults and the Risk of Developing Rheumatoid Arthritis; Results from the Swedish EIRA Study. Camilla Bengtsson[2], Meliha Kapetanovic[1], Henrik Källberg[2], Berit Sverdrup[2], Birgitta Nordmark[3], Lars Klareskog[3] and Lars Alfredsson[2]. [1]Institute for Clinical Sciences, Department of Rheumatology, Lund University, Lund, Sweden, [2]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, [3]Rheumatology Unit, Department of Medicine, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden

Background: Vaccinations are among the events frequently considered as inciting agents for rheumatoid arthritis (RA), but no sufficiently powered epidemiological studies have been published addressing whether vaccinations commonly used in industrialised societies constitute risk factors for RA[1].

Objectives: To investigate whether common vaccinations given to adults were associated with an increased risk of RA, and whether vaccinations have different impact on two subsets of RA, characterized by presence/absence of antibodies to citrullinated peptides (ACPA). In addition we examined potential interactions between vaccinations and smoking and between vaccinations and HLA-DRB1 SE alleles regarding risk of ACPA-positive RA.[2]

Methods: Data from the Swedish population-based EIRA (Epidemiological Investigation of Rheumatoid Arthritis) case-control study encompassing 1998 incident cases aged 18–70 years and 2252 randomly selected controls, matched on age, sex and residency, was analysed. All cases were diagnosed by rheumatologists according to the ACR criteria of 1987. Those vaccinated within five years prior to disease onset were compared with those not vaccinated within five years before disease onset, by calculating odds ratios (OR) with 95% confidence interval (CI). Biological interaction, defined by departure from additivity of effects was evaluated between vaccination and smoking and between vaccination and HLA-DRB1 SE alleles.

Results: In total, 31% of the cases and 31% of the controls had been vaccinated. Vaccinations did neither increase the risk of RA overall (OR=1.0 (95% CI 0.9–1.1) nor the risk of ACPA-positive or ACPA-negative disease. Furthermore, there was no association between any specific vaccine (influenza, tetanus, diphtheria, tick-borne encephalitis, hepatitis (A, B, C together), polio, pneumococcus) and the risk of RA. Finally, no interaction was found between any vaccination and smoking or between any vaccination and SE alleles regarding risk of ACPA-positive disease.

Conclusions: Our results indicate that immunological provocation with common vaccines given to adults in their present form is not a major risk factor for RA, at least not vaccines administered within five years before onset of disease. In addition, the results indicate that active immunisation does not increase the risk of RA in individuals with established risk factors, i.e smokers or those carrying HLA-DRB1 SE alleles. These findings should be implemented among clinicians and health care providers in order to encourage common vaccinations according to recommended vaccinations schedule for adults.

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Individually Tailored Exercise and Telephone-Delivered Cognitive Behaviour Therapy in the Management of Chronic Widespread Pain (CWP): Results from a Primary Care Based Randomised Controlled Trial. Gary J. Macfarlane[1], Chrysa Gkazinou[2], Marcus Beasley[2], Elizabeth A. Jones[2], Gordon J. Prescott[2], Phil Hannaford[2], Phil Keeley[3], Karina Lovell[3], Paul McNamee[2], Deborah P. M. Symmons[3], Steve Woby[3], John McBeth[3] and the MUSICIAN Study Team. [1]University of Aberdeen, Aberdeen, Scotland, United Kingdom, [2]University of Aberdeen, [3]University of Manchester

Background: Epidemiological and clinical studies have improved our understanding of the aetiology and consequences of chronic widespread pain. The challenge now is to use such information to improve outcome for patients. Despite recent innovations in pharmacological management, non-pharmacological therapies will remain the principal approach to improving quality of life in such patients. We aimed to determine whether exercise and/or cognitive behaviour therapy (CBT) would improve outcome in patients with CWP attending primary care.

Methods: We conducted a 2×2 factorial randomised controlled trial of an individually tailored exercise programme in community leisure facilities and CBT delivered by telephone (T-CBT). Interventions were of six months duration and were compared to usual care. Patients were recruited by means of a brief postal screening survey of all persons registered with 8 primary-care practices in the city of Aberdeen and suburbs of Manchester, United Kingdom. Patients were eligible if they satisfied the definition of CWP in the 1990 ACR criteria for fibromyalgia, reported disabling symptoms, had consulted their family doctor with symptoms in the past year and had no contraindications to exercise or a pain condition requiring other specific treatment. Severity of pain was measured by the Chronic Pain Grade (CPG) from I (low intensity) to IV (severely limiting). The outcome measure was a 7-point patient global assessment scale of change in symptoms since the time of recruitment from "very much worse" through "no change" to "very much better". A positive outcome was defined as "much better" or "very much better". Data were analysed as % reporting a positive outcome and logistic regression was used to describe the individual and combined effects of intervention(s) on outcome with results expressed as odds ratios (ORs) and 95% Confidence Intervals (CI).

Results: 14386 persons were screened of whom 878 were identified as potentially eligible for the trial. 442 individuals attended for assessment, were recruited to the trial and randomised to one of the four study arms. Participants had a median age of 58 years (IQR: 48–65), 69% were female and the distribution of CPG was: I 21%, II 38%, III 21%, IV 21%. At the end of the six month intervention period 361 provided outcome data (82%). The percentages reporting a positive outcome were: usual care 8%, T-CBT only 30%, exercise only 35% and both interventions 37% ($p < 0.0005$). T-CBT (OR 4.9 95% CI (2.0, 12) or exercise only (6.1; 2.5,15) resulted in improved outcomes but there was no significant additional benefit in receiving both interventions (OR combined multiplicative effect 0.22; 0.08, 0.67).

Conclusions: This study has demonstrated substantial and statistically significant improvement in the global assessment of their condition by patients with CWP who consult with their family practitioner and are provided with a 6-month exercise or T-CBT programme. This is the first trial of telephone delivered CBT in CWP. These results provide encouragement for patients with CWP that short-term improvement is possible in a substantial proportion with either of these interventions.

Disclosure: G. J. Macfarlane: None; **C. Gkazinou:** None; **M. Beasley:** None; **E. A. Jones:** None; **G. J. Prescott:** None; **P. Hannaford:** None; **P. Keeley:** None; **K. Lovell:** None; **P. McNamee:** None; **D. P. M. Symmons:** None; **S. Woby:** None; **J. McBeth:** None; **the MUSICIAN Study Team:** None.

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Non-Invasive Cortical Electrostimulation in the Treatment of Fibromyalgia. Jeffrey B. Hargrove[2], Robert M. Bennett[5], David G. Simons[1], Susan J. Smith[3], Sunil Nagpal[3] and Donald E. Deering[4]. [1]Emory University, [2]Kettering University, Flint, MI, [3]Michigan State University, [4]NeuroHealth Associates, [5]Oregon Health & Science Univ, Portland, OR

Purpose: The purpose of this study was to test the feasibility, efficacy and safety of an innovative form of non-invasive cortical electrostimulation (NICE) in the treatment of fibromyalgia (FM), where areas of the brain that may be involved in dysfunctional sensory processing were targeted.

Methods: A randomized placebo controlled, double-blind trial design was used to evaluate the efficacy of NICE in 77 FM patients (ACR 1990 criteria). Non-invasive leads were applied to the scalp with the aim of stimulating the centro-parietal area, including the somatosensory cortex. Monopolar electrical stimulation was used that employed high frequency carrier components to overcome skin and scalp impedance, and low frequency components designed to stimulate and modulate lower frequency cortical activity in the targeted areas. NICE consisted of 22 treatment sessions administered twice a week for approximately 11 minutes. As the signal is sub-threshold for cutaneous stimulation, the placebo arm (PL) was created by simply not delivering the signal. Patients were evaluated at baseline and no less than 7 days after completion of therapy. At both time-points all subjects completed the FIQ and a sleep VAS. A blinded investigator evaluated the number of positive tender points (TePs), and the summated tender point pain threshold (TPPT) was assessed using dolorimetry. The FIQ was re-administered at an average of 17 months post-termination of the study.

Results: Baseline demographic and clinical features were comparable in both treatment groups. Compared to PL, the NICE group had a significant improvement in the total FIQ score, pain VAS and sleep VAS scores. NICE group patients improved in the number of positive TePs (~ 43%), whereas the PL group did not change. The pain threshold (TPPT) for the NICE group improved 61% whereas the control group got slightly worse (−4%). Between-group analysis of TePs and TPPT scores showed significant improvement in the NICE arm compared to PL. Long-term follow-up showed a sustained improvement in the FIQ scores over baseline (average total FIQ scores: baseline 59, post-treatment 42; long-term 37; $p < 0.001$). NICE did not result in any significant adverse events.

Baseline to Post-Treatment Outcomes [Mean Raw Change (% change)]	NICE Group	PL Group
Number of positive TePs (range 0–18)	−7.4 (−43%), $p < 0.001$	−0.2 (0%), $p = 0.68$
Post-therapy group difference in number of positive TePs	−6.8 (41%, $p < 0.001$)	
Change in TPPT (range 9–72)	+19.7 (61%) $p < 0.001$	−3.1 (−4%) $p = 0.04$
Post-therapy group difference in TPPT	+20.8 (37%, $p < 0.001$)	
Post-therapy change in FIQ pain VAS (range 0–10)	−2.0 (30%) $p < 0.001$	−0.6 (9%) $p = 0.20$
Post-therapy group difference in FIQ pain VAS	−1.4 (23%, $p = 0.02$)	
Post-therapy change in total FIQ score (range 0–100)	−15.5 (25%) $p < 0.001$	−5.5 (9%) $p = 0.052$
Post-therapy group difference in total FIQ score	−6.5 (12%, $p = 0.03$)	
Percent of patients achieving 30% reduction in TePs	66%	5%
Percent of patients achieving 30% improvement in TPPT	71%	8%
Percent of patients achieving 30% improvement in Total FIQ	39%	20%
Percent of patients achieving 30% improvement in FIQ pain VAS	53%	29%

Conclusions: Using a cortical electrostimulation technique specifically designed to enhance signal penetration to centro-parietal brain regions, this study yielded clinically significant improvements in pain, tenderness and other typical features of FM. The treatment was well tolerated without significant adverse effects. This modality may augment current approaches to the treatment of FM.

Disclosure: J. B. Hargrove: Cerephex Corporation, 4; **R. M. Bennett:** None; **D. G. Simons:** None; **S. J. Smith:** None; **S. Nagpal:** None; **D. E. Deering:** None.

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Effect of Adding Milnacipran to Pregabalin for Managing Fibromyalgia: A Randomized, Open-Label, Controlled Study. Mildred V. Farmer[3], Joel M. Trugman[2], Yong Wang[2] and R. Michael Gendreau[1]. [1]Cypress Bioscience, Inc., San Diego, CA, [2]Forest Research Institute, [3]Meridien Research, St. Petersburg, FL

Purpose: Fibromyalgia (FM) is characterized by a multitude of symptoms that include chronic widespread pain, fatigue, stiffness, impaired physical functioning, sleep disturbances, cognitive dysfunction, and depressed mood. Medications used to manage FM often do not treat the full spectrum of symptoms that a patient with FM may experience. Patients may benefit from augmenting their current treatment regimen with medications that have complementary mechanisms of action. This randomized, open-label, controlled study evaluated the efficacy and tolerability of milnacipran 50 mg BID when added to pregabalin 150 mg BID or 225 mg BID in FM patients who had an incomplete response to pregabalin during a 4- to 12-week open-label run-in phase.

Methods: This was a randomized, controlled, open-label study. After the pregabalin run-in period, incomplete responders to pregabalin (patients with weekly recall VAS pain score ≥40 and ≤90 [0 to 100 scale], Patient Global Impression of Severity score ≥4 [ranging from "moderately ill" to "extremely ill"], and Patient Global Impression of Change [PGIC] score ≥3 [ranging from "minimally improved" to "very much worse"]) were randomized to pregabalin alone (n=180) or milnacipran added to pregabalin (n=184) for 11 weeks. The primary efficacy assessment was the percentage of PGIC responders at endpoint, defined as patients reporting a PGIC rating of "much improved" or "very much improved". The secondary efficacy assessment was the change from baseline in VAS 1-week pain recall score. Additional efficacy measures included SF-36 Physical and Mental Component Summary Scores (PCS and MCS, respectively), Multidimensional Fatigue Inventory (MFI), and Multiple Ability Self-report Questionnaire (MASQ). Treatment-emergent adverse events (TEAEs) occurring in the randomized treatment period were defined as AEs that were newly reported or increased in severity during the randomization period.

Results: The overall completion rate was higher in patients receiving milnacipran added to pregabalin (76.6%) than those receiving pregabalin alone (68.3%). At endpoint, milnacipran added to pregabalin treatment resulted in a significantly higher percentage of PGIC responders than pregabalin alone (46.4% vs 20.8%; $P<.001$). The addition of milnacipran to pregabalin also resulted in a significantly greater reduction in least squares mean weekly recall VAS pain score compared with pregabalin alone (−20.8 vs −6.4; $P<.001$). Patients receiving milnacipran added to pregabalin had significantly improved physical and mental function, fatigue, and cognition (SF-36 PCS and MCS, MFI, and MASQ, $P<.001$, all outcomes) than patients receiving pregabalin alone. During the randomized treatment period, the most common TEAE in patients receiving milnacipran added to pregabalin was nausea; peripheral edema and weight increased were most common in patients receiving pregabalin alone.

Conclusion: This open-label study is the first randomized controlled study to demonstrate that adding milnacipran to pregabalin therapy is both tolerable and effective in improving global status and reducing pain in patients with FM experiencing an incomplete response to pregabalin alone.

Disclosure: M. V. Farmer: Forest Laboratories, 5; **J. M. Trugman:** Forest Laboratories, 3; **Y. Wang:** Forest Laboratories, 3; **R. M. Gendreau:** Cypress Biosciences, Inc., 3.

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Hypothalamic-Pituitary-Adrenal Axis Response to Mental Stress Predicts Chronic Widespread Pain Onset—Results from the SPICE Study. Gareth T. Jones, Gordon D. Waiter, Marcus Beasley, Chrysa Gkazinou and Gary J. Macfarlane. University of Aberdeen, Aberdeen, United Kingdom

Background: The role of the Hypothalamic-Pituitary-Adrenal (HPA) axis stress response, as assessed by salivary cortisol, has been investigated in modifying risk of chronic widespread pain (CWP). It has been shown that, amongst those at high risk of CWP (high levels of adverse psychosocial factors), those with diminished diurnal variation and those who fail to suppress HPA axis function after a dexamethasone suppression test, are at particularly high risk of developing CWP.

The aims of the current study are (1) to determine the importance of HPA axis dysfunction in a general population sample; and (2) to examine the response of the HPA axis to mental, as opposed to pharmacological, stress.

Methods: Baseline: potential participants aged 25–70yrs, randomly selected from 4 primary care practices in Aberdeen, UK, were sent a postal questionnaire. They were asked: "Thinking back over the past month, have you had any pain that has lasted for one day or longer?" Those answering positively were asked to identify the location(s) of this pain on a body manikin. CWP was then determined as per the ACR-1990 classification for fibromyalgia.

Participants were then sent a saliva sampling kit, for 2 samples: approxi-

matly 1hr after waking (AM) and 1hr before going to bed (PM). In addition, a sub-group of respondents were invited into the laboratory and undertook a computerised version of the Stroop "Word-and-Colour" Test – a test known to induce mental stress among study participants. Salivary cortisol was assessed at baseline, and immediately post-Stroop.

Follow-up: new onset CWP was identified, by questionnaire, at 12 months.

Analysis: Poisson regression was used to examine the relationship between HPA axis function (salivary cortisol concentration, divided into tertiles for analysis) and new onset CWP. Thus, associations are expressed as risk ratios (RR) with 95% confidence intervals.

Results: Of 758 participants free of CWP, 461 (61%) participated at follow-up: 41 (9%) reported CWP. While, there was some evidence to suggest that higher AM cortisol was associated with a lower risk of CWP ($RR_{3rd\ vs\ 1st\ tertile}$: 0.6; 95%CI: 0.2–1.7), there was no association between between PM cortisol levels and the risk of CWP ($RR_{3rd\ vs\ 1st\ tertile}$: 1.2; 0.5–2.9); nor with AM-PM cortisol variation ($RR_{3rd\ vs\ 1st\ tertile\ of\ difference}$: 0.8: 0.3–2.1).

56 participants completed the Stroop Test, of whom 50 (89%) participated at follow-up. Those with the lowest stress response were more likely to report CWP than other individuals ($RR_{1st\ vs\ 3rd\ tertile\ of\ difference}$: 4.9; 0.6–39.5) and ($RR_{2nd\ vs\ 3rd\ tertile\ of\ difference}$: 3.6; 0.4–29.6).

Discussion: This is the first study to examine HPA axis function and CWP onset in the general population. The study is small, and the findings should therefore be interpreted with care. However, the results replicate findings from previous studies in high-risk samples and provide new evidence that persons with the lowest stress response to mental stress are at highest risk of CWP onset. Future work should examine this relationship in the context of —and possibly as a modifier of—environmental (psychosocial) stressors and, in particular, should determine the mechanisms underpinning this relationship.

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Altered Resting Connectivity between Individuals with Fibromyalgia and Healthy Controls. Tobias Schmidt-Wilcke[2], Rupal Bhavsar[2], Daniel J. Clauw[1] and David A. Williams[1]. [1]University of Michigan, Ann Arbor, MI, [2]University of Michigan

Background: Fibromyalgia (FM) is a chronic pain condition characterized by widespread pain in addition to fatigue, disturbed mood, non-restorative sleep, and dyscognition. fMRI studies investigating brain activity in response to pressure and heat pain in FM have identified augmented activation of pain processing regions when exposed to these experimental pain stimuli. The use of functional connectivity (fc) to analyze "resting state" imaging data holds promise for revealing differences between FM and HC with regards to how brain regions differentially communicate with one another under conditions of spontaneous (i.e., chronic) pain versus these other studies which use experimentally-induced pain. Specifically, we were interested in whether individuals with FM differed from healthy controls (HCs) in resting state connectivity in the insular cortex (IC), a region that plays a critical role in pain perception and modulation and other regions associated with affect, cognition, and sensory experiences.

Methods: Using SPM8 and the SPM-based connectivity toolbox *Conn,* functional connectivity from resting state fMRI scans of 17 individuals with FM and 8 HCs used seed regions in the anterior, middle and posterior IC. After pre-procecessing (e.g., realignment, normalisation and smoothing) connectivity maps were generated indicating the temporal correlation of a given voxel with a seed region in the IC (i.e., in total, 6 connectivity maps). After Fisher z-transformation one and two sample t-tests were performed to determine IC connectivity both within and between groups.

Results: Highly correlated, low-frequency oscillations (< 0.1 Hz) between specific IC and cingulate cortex (CC) subdivisons were identified in both groups. Group differences were found in the connectivity of the left posterior IC and the left thalamus (i.e., hyperconnectivity in FM patients), the right IC and posterior mid-cingulate cortex/posterior cingulate cortex (i.e., hyperconnectivity in FM patients) and the right anterior IC and right middle frontal gyrus (hypoconnectivity in FM patients).

Conclusions: These data suggest that at rest, individuals with FM have stronger concurrent activations between brain regions known to participate in pain perception and modulation than do HCs. These data also add further support to the notion that central mechanisms play a critical role in the pain experience of individuals with FM.

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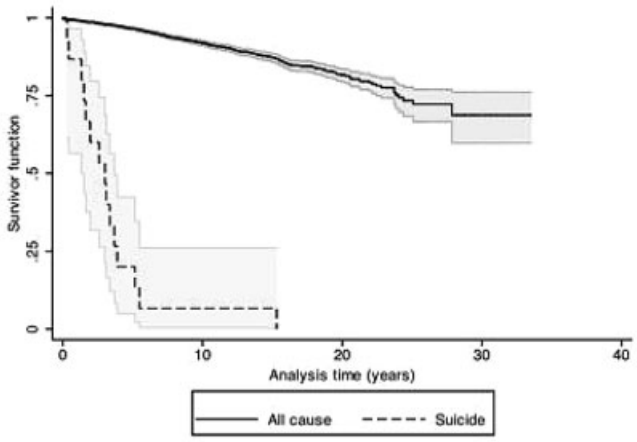
Mortality in Fibromyalgia: An 8,186 Patient Study over 35 Years. Frederick Wolfe[1], Afton L. Hassett[3], Brian T. Walitt[4] and Kaleb D. Michaud[2]. [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]Univ of Nebraska Med Ctr, Omaha, NE, [3]University of Michigan Medical School, Ann Arbor, MI, [4]Washington Hospital Center, Washington, DC

Purpose: The issue of mortality in fibromyalgia (FM) is important because, if increased, it supports the seriousness of FM. One population based epidemiological study found that chronic widespread pain, effectively a criterion of the 1990 and 2010 ACR FM criteria, was associated with the risk of increased mortality, although that finding was not confirmed in another large population-based study. Reasons that mortality might be increased in fibromyalgia include substantial use of analgesics and anti-depressants, high levels of somatic symptoms, and high rates of depression. It seems possible that depression, socio-demographic characteristics or iatrogenesis could lead to increased mortality. The risk could also be increased if fibromyalgia is a representation of more extensive widespread pain or more severe symptoms. In this study we determined if mortality is increased among patients diagnosed with fibromyalgia.

Methods: We studied 8,186 fibromyalgia patients seen between 1974 and 2009 in 3 settings: all fibromyalgia patients in a clinical practice, patients participating in a longitudinal outcome study and patients invited to participate in the outcome study who refused participation. Internal controls included 12, 329 patients with osteoarthritis. Deaths were determined by multiple source communication, and all patients were also screened in the US National Death Index (NDI). We calculated standardized mortality ratios (SMR) based on age and sex stratified US population data, after adjustment for NDI non-response.

Results: There were 539 deaths, and the overall SMR was 0.90 (95% CI 0.61, 1.26). Among 1,665 clinic patients the SMR was 0.92 (95% CI 0.81, 1.05). Sensitivity analyses varying the rate of NDI non-identification did not alter the non-association. Adjusted for age and sex, the hazard ratio for fibromyalgia compared with osteoarthritis was 1.05 (95% CI 0.94, 1.17). The standardized mortality odds ratio compared with the US general population was increased for suicide, OR 3.31 (2.15, 5.11), for accidental deaths, 1.45 (1.02, 2.06), pneumonia 1.69 (1.12, 2.57) and septicemia 2.49 (1.61, 3.68), but not for malignancy 0.95 (0.76, 1.18).



Deaths were predicted by BMI, smoking, HAQ, fatigue, pain, mood and SF-36 in separate analyses adjusted for age and sex.

Conclusions: Mortality does not appear to be increased in patients diagnosed with fibromyalgia, but the risk of death from suicide and accidents was increased. The data are consistent with an in submission Danish study that reported no increase in overall mortality or cancer, but an increase in suicides.

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Detection of Specific Markers Using Proteomics: Our Research on the Marker in Patients with Kawasaki Disease (KD). Rie Karasawa[3], Mikiya Fujieda[1], Kazuhide Ohta[2] and Kazuo Yudoh[3]. [1]Department of Pediatrics, Kochi Medical School, Kochi University, Japan, [2]Department of Pediatrics, National Hospital Organization Kanazawa Medical Center, [3]Institute of Medical Science, St. Marianna University School of Medicine, Kawasaki, Japan

Purpose: Anti-endothelial cell antibodies (AECA) are thought to be involved in pathophysiology of vasculitis. However, target molecules of AECA have been poorly identified, which hampers understanding of roles of AECA in detail. We tried to detect and identify target proteins of AECA comprehensively by proteomics. Further, we investigated clinical importance of the identified autoantigens in patients with KD.

Methods: We separated proteins extracted from HUVEC and HeLa cells respectively by 2-dimensional electrophoresis and then transferred them onto membranes. By WB using serum samples from patients with vasculitis, we detected autoantigens that were positive only in the HUVEC samples but not in the HeLa cell samples. We next identified the detected proteins by peptide mass finger-printing and characterized antigenecity by preparing recombinant autoantigens and antibodies to them.

Results: One of the identified 63 proteins was found peroxiredoxin2 (Prx2), an anti-oxidative enzyme. IgG antibodies to Prx2 were detected in 60% of the patients with KD, but not in healthy controls. IgM antibodies to Prx2 were detected in 10% of the KD patients, but also in 7% of healthy controls. IgA antibodies to Prx2 were not detected in both groups. Interestingly, IgG antibodies to Prx2 were detected in all the tested KD patients with coronary artery lesions. In contrast, IgM and IgA antibodies to Prx2 weren't detected in them. IIF staining revealed existence of Prx2 on the cell surface of HUVEC and WB using cell lysate proved expression of Prx2 not only in HUVEC but also in other endothelial cells (ECs), including human coronary artery endothelial cells(HCAEC). Anti-Prx2 antibodies also increased various inflammatory cytokine secretions significantly, in particular, IL-6 in HUVEC and G-CSF in HCAEC. IL-6 secretion of ECs stimulated with serum samples of patients with high anti-Prx2 titers was detected. WB using cell lysate and conditioned medium from ECs stimulated by H_2O_2 showed elevated expression levels of Prx2. Further, the addition of anti-Prx2 antibodies to the ECs resulted in increased concentration of H_2O_2 in the cell lysate. We measured Prx2-specific IgG titers on the pre- and posttreatment (within a week after therapy) in KD patients treated by IVIG. As a result, the titers on the posttreatment was higher than them on pretreatment in almost all tested KD patients.

Conclusions: IgG antibodies to Prx2 would be a useful marker for KD. Anti-Prx2 antibodies may have a pathogenic role in KD via inflammatory cytokine production and inhibition of anti-oxidative activity of Prx2 by binding Prx2 on ECs.

Disclosure: R. Karasawa: None; **M. Fujieda:** None; **K. Ohta:** None; **K. Yudoh:** None.

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Specific Subgroup of New-Onset Systemic Juvenile Idiopathic Arthritis without Overt Macrophage Activation Syndrome Shares Similar Gene Expression Signature with a Distinct Subset of Familial Hemophagocytic Lymphohistiocytosis. Keith A. Sikora, Ndate Fall, Michael G. Barnes, Janos Sumegi, Alexandra H. Filipovich and Alexei A. Grom. Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Background: Systemic juvenile idiopathic arthritis (sJIA) is a rheumatologic condition characterized by quotidian fevers, evanescent rash, lymphadenopathy, serositis, and arthritis. One of its feared complications is the macrophage activation syndrome (MAS), characterized by marked hyperferritinemia, pancytopenia, fever, hepatosplenomegaly, and presence of hemophagocytosis within the bone marrow, which closely resembles the primary hystiocytic disorder familial hemophagocytic lymphohistiocytosis (fHLH). The aim of this study was to compare the gene expression signatures of patients with new-onset sJIA, but without overt MAS, to HLH gene expression signatures.

Methods: Peripheral blood mononuclear cells (PBMCs) from 14 untreated new-onset sJIA without overt MAS, 11 fHLH patients, and 27 healthy controls were isolated from whole blood. Purified RNA was labeled using the Nugen Ovation RNA amplification and labeling system, and gene expression profiles were generated using the Affymetrix HG-U133 Plus 2.0 GeneChip. The list of differentially expressed genes was generated using Student's *t*-test, with Bonferroni-corrected P values less than 0.05 considered significant. Four of the 11 fHLH patients had known mutations in either their perforin or MUNC13-4 genes.

Results: A list of genes differentially expressed in systemic JIA was used in the hierarchical clustering analysis of samples obtained from healthy controls and patients with sJIA and fHLH. This analysis revealed distinct gene expression patterns among the sJIA and HLH patients, separating them into subgroups. One specific subgroup of sJIA patients (n=9) clustered together with a particular subgroup of HLH patients (n=4). This sJIA subgroup was characterized by an increase in peripheral CD34+ cells, increased peripheral myeloid precursors, and a general upregulation of cell cycle genes. Highly increased serum ferritin was another characteristic feature of this group. The patients in this corresponding HLH subgroup were more likely to have a rapidly progressive course of HLH and an identifiable mutation in either their perforin or MUNC13-4 gene.

Conclusions: There exists a distinct subgroup of new-onset sJIA, but without overt MAS, that displays a gene expression pattern that is shared with a specific subgroup of rapidly progressive, relapsing, and mostly mutation positive HLH patients. This subgroup of sJIA is characterized by an increase in peripheral CD34+ cells, increased peripheral myeloid precursors, and a general upregulation of cell cycle genes, perhaps reflecting increased turnover of hematopoietic cells.

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A Genome-Wide Association Study for Juvenile Idiopathic Arthritis Identifies Chromosome Region 3q13 near the T Cell Receptor Co-Stimulatory Molecule CD80. Susan D. Thompson[1], Miranda Marion[10], Marc Sudman[2], Paula S. Ramos[10], Wendy Thomson[8], Anne Hinks[8], J. Peter Haas[7], Sampath Prahalad[4], John F. Bohnsack[9], Carol Wise[6], Marilynn G. Punaro[5], Carlos D. Rose[3], Mary Ryan[2], Monica Tsoras[2], Michael Wagner[2], Mehdi Keddache[2], Timothy Howard[10], Carl Langefeld[10] and David N. Glass[1]. [1]Childrens Hospital Med Ctr, Cincinnati, OH, [2]Cincinnati Children's Hospital Medical Center, [3]duPont Hospital for Children, Wilmington, DE, [4]Emory Children's Center, Atlanta, GA, [5]Texas Scottish Rite Hospital for Children, Dallas, TX, [6]Texas Scottish Rite Hospital for Children, [7]University of Greifswald, [8]University of Manchester, [9]University of Utah, Salt Lake City, UT, [10]Wake Forest University

Objective: Juvenile idiopathic arthritis (JIA) is a complex genetic trait. Like other autoimmune diseases, JIA has strong HLA associations, and is often found in families with a history of other autoimmune diseases. Furthermore, many of the loci associated with JIA are shared across several autoimmune diseases. Here we report a large genome-wide association study of oligoarticular and polyarticular rheumatoid factor negative forms of JIA.

Methods: The Discovery Cohort consisted of 814 JIA cases, 658 local controls and 2400 out-of-study controls from the Non-Gain Schizophrenia Study who self-identified as Non-Hispanic, European ancestry. The Replication Cohort consisted of 1621 cases and 1630 controls representing five independent JIA case and control sample collections originating from the United Kingdom (CAPS and BSPAR study group), Germany, Utah, Delaware or Texas. Additional out-of-study controls were available for the UK cohort (Wellcome Trust Case Control Consortium, n=5984) and used in the replication analysis. For the Discovery Cohort, genotyping was done using the Affymetrix SNP Array 6.0 and tests for association were adjusted for potential confounding affects of population structure via covariates in logistic regression models. Analyses were repeated adjusting for key HLA associations. Ten SNPs representing five loci, which to our knowledge have not yet been reported in JIA, were selected based on statistical evidence and biologic information and genotyped by Taqman or Sequenom chemistries in the Replication Cohort. Association testing and meta-analyses were performed.

Results: Testing for genome-wide association in the Discovery Cohort identified multiple loci outside the MHC region associated with JIA. Previously identified loci associated with JIA and overlapping with other autoimmune disease associations include PTPN22 (rs6679677, $p=1.98\times10^{-12}$,

rs2476601, $p=1.90\times10^{-13}$ and rs2488457, $p=6.74\times10^{-8}$), and PTPN2 (rs1893217, $p=1.60\times10^{-9}$ and rs7234029, $p=1.86\times10^{-10}$). Novel loci with consistent findings in both the Discovery and Replication cohorts are shown in the table and include c3orf1, IL15, and REEP3.

		Discovery Cohort				Replication Cohort				Meta Analysis
		MAF			OR	MAF		p-value	OR	
SNP	Chr Gene	JIA	Ctrls	p-value	[95%CI]	JIA	Ctrls		[95%CI]	p-value
rs6766899	3q13.33 CD6AP	0.26	0.22	3.62E-04	1.26 [1.11-1.43]	0.24	0.22	0.0464	1.18 [1.04-1.36]	3.15E-04
rs4688011	3q13.33 C3orf1	0.24	0.19	1.88E-06	1.37 [1.21-1.57]	0.21	0.19	0.0037	1.1 [1.01-1.21]	5.20E-07
rs13139575	4q31.21 IL15	0.44	0.48	2.44E-04	0.73 [0.62-0.86]	0.45	0.46	0.0249	0.92 [0.84-0.99]	1.07E-04
rs12411988	10q21.3 REEP3	0.18	0.13	1.17E-07	1.57 [1.33-1.84]	0.14	0.13	0.0953	1.07 [0.96-1.21]	1.92E-05

Conclusions: We provide strong evidence in both the Discovery Cohort and Replication Cohort for a novel autoimmune disease and JIA association with 3q13, a region containing the TCR co-stimulatory molecule CD80. Fine mapping and integration with gene expression data is underway to further define this locus.

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Gene Expression Profiling in Peripheral Blood Mononuclear Cells Predicts Disease Flares in Children with Polyarticular Juvenile Idiopathic Arthritis Who Have Achieved Clinical Remission on Medication. Nicholas Knowlton[2], Mark Barton Frank[2], Nicholas E. Armstrong[1], Kaiyu Jiang[1], Yanmin Chen[1], Jeanette Osban[2] and James N. Jarvis[1]. [1]Dept of Pediatrics, U of OK College of Medicine, [2]Oklahoma Medical Research Foundation

Background: Children with polyarticular juvenile idiopathic arthritis (JIA) patients pursue variable clinical courses, even after disease control has been achieved. Developing biomarkers to identify which children can come off therapy and which children need continued or more aggressive therapy has been elusive.

Objective: To better understand the underlying biology of disease flares in polyarticular, RF-negative juvenile idiopathic arthritis (JIA), and to determine the feasibility of developing gene array-based prognostic biomarkers to guide therapy in this disease.

Methods: We performed gene expression profiling and *in silico* pathway analysis on peripheral blood mononuclear cells (PBMC) of 17 children with RF-negative polyarticular JIA at the time they achieved inactive disease (ID) status. Of these children, 8 subsequently experienced a disease flare within 11 months of achieving ID status, while the remaining 9 experienced sustained disease control over observation periods ranging from 18 months to 6 years. Computational analyses were undertaken in an attempt to distinguish the 2 groups.

Results: Gene expression profiling identified 103 genes that distinguished the Flare and No-flare groups. Gene expression profiling comparing children in ID/CRM who were fated to flare with those who were not ("baseline specimens") showed distinct differences between the two groups. The group fated to flare was already distinguishable from the group that remained stable at the time of baseline sampling. One hundred forty-four genes were differentially expressed between the two groups, all of which were over-expressed in children fated to flare. *In silico* modeling demonstrated that the differentially expressed genes could be incorporated into 4 large, linked networks. These networks incorporated genes associated with MAP kinase signaling, type 1 interferon production, and genes regulating the cell cycle. Furthermore, the gene expression profile remained largely stable in each group over the 5–15 month period over which the patients were followed. That is, comparison of the "flare" group at the time they achieved ID/CRM with the same patients at the time of their flare revealed only a single gene whose expression differed from the baseline sample. Similarly, children who remained stable also demonstrated a stable gene expression profile. In addition, network analysis suggests a role hepatocyte nuclear factor 4a (HNF4a), a transcription factor not previously identified in leukocytes, in maintaining treatment response in JIA.

Conclusions: Although the number of patients studied here is small, this work demonstrates the feasibility of developing prognostic biomarkers in JIA. These findings also cast light on the nature of the inflammatory networks that sustain the disease process in polyarticular JIA even when the illness clinically appears to be inactive.

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Levels of beta2-Glycoprotein-I May Reflect a Protective Effect on the Development of Heart Block in Fetuses Exposed to Maternal Anti-Ro Antibodies. Joanne H. Reed, Tom P. Gordon, Robert M. Clancy and Jill P. Buyon. New York University School of Medicine

Purpose: Identification of congenital heart block (CHB) in a fetus predicts with near certainty that the mother, who may have a rheumatic disease or be asymptomatic, will have autoantibodies to a 60kD Ro protein (Ro60). Injury is thought to be initiated by surface binding of maternal anti-Ro60 autoantibodies to apoptotic cardiocytes during physiological remodelling of the fetal heart. The low penetrance of disease suggests that a factor in the microenvironment of the fetal hearts which remain unaffected may inhibit binding of maternal anti-Ro60 autoantibodies. The plasma protein beta2-glycoprotein I (β2GPI) is a potential candidate since it binds to Ro60 on the surface of apoptotic cells and inhibits opsonization by anti-Ro60 autoantibodies. The current study evaluated the opsonization of fetal apoptotic cardiocytes by IgG from mothers of infants with CHB in the presence or absence of β2GPI and determined whether fetal levels of β2GPI correlate with CHB.

Methods and Results: To test the role of β2GPI as a protective factor in CHB, in vitro studies were conducted on human fetal apoptotic cardiocytes (induced by staurosporine or loss of anchorage). Flow cytometry analysis revealed dose-dependent binding of β2GPI to apoptotic cardiocytes. IgG from a mother of a child with CHB (CHB IgG), but not IgG from a healthy control, bound the apoptotic cardiocytes (mean fluorescence intensity, MFI 3,998 vs 462). In the presence of β2GPI, the binding of CHB IgG to apoptotic cardiocytes was significantly inhibited in a dose-dependent manner (range 20–64%). Enzyme linked immunosorbent assay (ELISA) was used to measure levels of β2GPI in the umbilical cord blood from unaffected (n=25) and CHB (n=28) anti-Ro exposed infants. β2GPI levels were lower in CHB children (mean units 234 ± 17) compared to those unaffected (365 ± 29 SEM), ($p = 0.0004$). Ventricular rates were positively correlated with levels of β2GPI ($r = .512$, $p=0.042$). Among the cord blood samples, four twin pairs discordant for CHB, were assessed for β2GPI levels. In each pair, the twin with CHB had lower levels of β2GPI (169 ± 12) compared to the healthy twin (283 ± 20 however, this trend did not reach significance. β2GPI levels tended to be higher in those fetuses delivered by C-section but were not associated with maternal use of dexamethasone. Children with a higher weight at birth had significantly higher levels of β2GPI ($r=.51$, $p=0.01$) consistent with the observation that the neonates with CHB had significantly lower birth weights than those who were unaffected. Fetal β2GPI levels were not associated with gestational age at birth. β2GPI levels were not significantly associated with the requirement for a pacemaker.

Conclusion: Lower levels of fetal β2GPI are associated with CHB in anti-Ro60-positive mothers. β2GPI may protect the developing fetal heart from injury by binding to Ro60 on apoptotic cardiocytes and preventing opsonization by maternal anti-Ro60 autoantibodies. Factors such as infection, inflammation, or a genetic predisposition could reduce β2GPI levels in the fetus, thereby promoting conditions where the fetal heart is vulnerable to autoantibody-mediated tissue injury.

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Pathogenic Consequences of Mutations of *NLRP12* Gene. A New Cold-Induced Autoinflammatory Disease. Silvia Borghini[2], Sara Tassi[1], Sabrina Chiesa[3], Francesco Caroli[2], Sonia Carta[1], Roberta Caorsi[3], Marco Di Duca[2], Denise Lasiglié[3], Alberto Martini[3], Isabella Ceccherini[2], Anna Rubartelli[1] and Marco Gattorno[3]. [1]Institute for Cancer Research, Genoa, Italy, [2]Lab of Molecular Genetics, G. Gaslini Institute, Genoa, Italy, [3]Rheumatology Unit, G. Gaslini Institute, Genoa, Italy

Purpose: mutations of the *NLRP12* gene have recently been described in patients affected with a new Autoinflammatory disease. NLRP12 belongs to the NLRPs family and its role in the activation of the inflammasome and regulation of NF-kB activation is currently being under investigation. We report about the clinical features and pathogenic findings of 4 patients carrying a novel p.D294E missense mutation of the *NLRP12* gene affecting the Walker B sequence of the protein crucial for ATP binding.

Patients and Methods: Four individuals, carrying the p.D29E NLRP12 mutation were analyzed. NF-kB activity was evaluated in *NLRP12*-mutated monocytes after 24 hour of TNF stimulation using TransAM NFkB p65 Kit. IL-1β secretion, production of ROS and activation of antioxidant systems in resting conditions and after PAMPs stimulation were also assessed. *In vitro* analysis of the NLRP12 mutation effect on NF-kB activity was performed after co-transfection of a *luciferase*-NF-kB promoter reporter construct with the mutant and wild type NLRP12 expression plasmids in HEK293 cells.

Results: the p.D294E mutation segregates in association with a particular sensitivity to cold exposure (especially arthralgia and myalgia), but not always with an inflammatory phenotype (urticarial rash or fever). The p.D294E mutated protein did maintain the same inhibitory activity shown by wt NLRP12. Unexpectedly, this was also observed when the already reported p.Arg284X nonsense mutation (Jéru et al., 2008) was analyzed in the same system. Consistently, NLRP12-mutated monocytes showed neither increased levels of p65 NF-kB activity nor higher amounts of IL-1b secreted. However, the kinetics of PAMP-induced IL-1b secretion was significantly accelerated, and a high production of ROS and an upregulation of antioxidant systems were demonstrated, in patients carrying NLRP12 mutations compared to healthy controls.

Conclusions: Even with a variable range of associated manifestations, the extreme sensitivity to cold exposure represents the main clinical hallmark of individual carrying the p.D294E mutation of the *NALP12* gene. The regulation of NF-kB activity does not seem to be affected in NLRP12-mutated patients. Redox alterations and accelerated secretion of IL1b may be responsible for the mild autoinflammatory phenotype observed

Disclosure: S. Borghini: None; **S. Tassi:** None; **S. Chiesa:** None; **F. Caroli:** None; **S. Carta:** None; **R. Caorsi:** None; **M. Di Duca:** None; **D. Lasiglié:** None; **A. Martini:** None; **I. Ceccherini:** None; **A. Rubartelli:** None; **M. Gattorno:** None.

ACR Concurrent Abstract Sessions
Rheumatoid Arthritis - Clinical Aspects: Preclinical RA and Early RA
Monday, November 8, 2010, 2:30 PM–4:00 PM

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Application of the New ACR/EULAR Classification Criteria for Rheumatoid Arthritis to At-Risk Populations May Identify RA Prior to Clinical Presentation. Jason R. Kolfenbach[5], Lezlie Derber[5], Kevin D. Deane[9], Jan Hughes-Austin[4], Michael H. Weisman[3], Jane Buckner[2], Ted R. Mikuls[11], James R. O'Dell[8], Peter K. Gregersen[6], Richard M. Keating[1], Jill Norris[10] and V. Michael Holers[7]. [1]Oak Park, IL, [2]Benaroya Research Institute at Virginia Mason, [3]Cedars-Sinai Medical Center, Los Angeles, CA, [4]Department of Epidemiology, Colorado School of Public Health, University of Colorado Denver, [5]Division of Rheumatology, University of Colorado at Denver, Aurora, CO, [6]N Shore Univ Hosp Rsch Ctr, Manhasset, NY, [7]Univ of Colorado School of Med, Aurora, CO, [8]University of Nebraska Medical Center, Omaha, NE, [9]University of Colorado at Denver, Aurora, CO, [10]University of Colorado Denver, Aurora, CO, [11]University of Nebraska Medical Center, Omaha, NE

Objective: The proposed ACR/EULAR classification criteria were developed in part to identify early RA. Applying the new criteria to at-risk populations prior to evaluation in the health care setting may identify a unique cohort in which to study the evolution of very early symptomatic RA. We have established prospective cohorts of subjects at potentially higher risk for RA based on genetic risk factors as part of the SERA study (Studies of the Etiology of RA). The purpose of the current analysis was to identify and characterize a cohort within these populations with 'definite RA' according to the newly proposed criteria.

Methods: We have established a cohort of first-degree relatives (FDRs) of probands with RA. FDRs without RA by the 1987 ACR criteria undergo a joint exam and have laboratory data obtained. Identical data is collected on a second at-risk DR4-enriched population containing parents of children with high risk HLA alleles and/or Type I diabetes. The proposed RA criteria were applied to subjects in these cohorts with swelling suggestive of synovitis in $\geq$ 1 joint on clinical exam after exclusion of findings attributed to alternative diagnoses (e.g. trauma, osteoarthritis). Data regarding joint distribution, duration of symptoms, antibody status and presence of elevated inflammatory markers were used to apply the new criteria. Descriptive statistics were calculated for the identified cases.

Results: 1790 subjects were available for analysis. 153 subjects (8.5%) had synovitis in $\geq$ 1 joint on clinical exam. 21 subjects (1.17%) had 'definite RA' according to the proposed algorithm. 17/21 (81%) subjects were female with a mean age of 48.9 years old. 6/21 subjects (28.6%) were positive for rheumatoid factor (RF), one (4.8%) was positive for anti-cyclic citrullinated peptide antibody, and 11 (52.4%) had elevated levels of CRP. Median swollen and tender joint counts were 3 and 11, respectively. The average total score in the 21 subjects was 6.76. The mean scores for joint involvement, serology, acute phase reactant and duration were 4.33, 0.9, 0.52 and 1.0, respectively (Table 1).

Table 1. Relative contribution of Clinical & Serologic factors to the designation of 'Definite RA' by the newly proposed ACR/EULAR Classification Criteria for RA*

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
ACR Joint score	5	3	5	5	3	2	5	5	5	5	5	5	2	5	5	5	5	5	5	3	3
ACR Serology score	0	3	0	0	2	3	0	0	0	0	0	0	3	0	0	0	0	3	0	2	3
Acute Phase Reactant Score	1	1	0	0	0	1	1	1	1	1	0	0	0	0	0	0	1	1	0	1	1
Duration score	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Total score	**7**	**8**	**6**	**6**	**6**	**7**	**7**	**7**	**7**	**7**	**6**	**6**	**6**	**6**	**6**	**6**	**7**	**10**	**6**	**7**	**8**

Score $\geq$ 6 indicates 'definite RA' according to the proposed algorithm
*Scores derived from a single visit in which the subject achieved a score $\geq$ 6. Some subjects have additional visits 3 subjects with >1 visit with a score $\geq$ 6; first is depicted.

Conclusion: Individuals with 'definite RA' according to the new criteria can be identified in these unique at-risk populations. A score $\geq$ 6 was driven primarily by joint involvement with the majority stemming from tender rather than swollen joints, a finding which may indicate an earlier phase of RA development than individuals presenting for clinical care. The identification of these subjects in a research rather than clinical setting may allow us to study an earlier phase of RA than possible in usual clinical practice. These subjects will be followed prospectively with multiple modalities including serial joint evaluations and biomarker assessments to evaluate the relationship between the new RA criteria and the longer-term evolution of RA.

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The Revised 2010 ACR/EULAR Diagnostic Criteria for Rheumatoid Arthritis Identify Many More Patients Who Are Eligible for Treatment and for Clinical Trials. Vivian P. Bykerk[5], Gilles Boire[2], Boulos Haraoui[4], Carol A. Hitchon[8], Ed C. Keystone[9], J. Carter Thorne[6], Diane S. Ferland[3], Janet E. Pope[7] and CATCH Investogators[1]. [1]Canada, Canada, [2]CHUS - Sherbrooke University, Sherbrooke, QC, Canada, [3]Hopital Maisonneuve Rosement, Montreal, LaSalle, QC, Canada, [4]Institut de Rhumatologie, Montreal, QC, Canada, [5]Mt Sinai Hospital, University of Toronto, Toronto, ON, Canada, [6]Southlake Regional Health Care, Newmarket, ON, Canada, [7]St Joseph Health Care London, London, ON, Canada, [8]University of Manitoba, Winnipeg, MB, Canada, [9]University of Toronto, Toronto, ON, Canada

Background: The 2010 revised ACR/EULAR criteria for the classification of RA were developed to enable earlier diagnosis. These criteria identify patients with RA likely to have persistent and/or erosive inflammatory arthritis. The revised criteria have not been validated in North American

patients or shown to identify patients who would be eligible for clinical trials that recruit for patients with a DAS28 of ≥ 3.2.

Objectives: To determine what proportion of patients with recent onset early inflammatory arthritis (IA) of < 1 year duration the revised ACR/EULAR criteria newly identify as having rheumatoid arthritis. To determine if these newly identified patients would be eligible for clinical trials in early RA.

Methods: Baseline (BL) data collected from patients (n=1146) enrolled into the Canadian Early Arthritis Cohort (CATCH) study, a multi-centre observational prospective "real world" cohort of patients with early IA recruited since July 2007 were analysed for this study. Inclusion Criteria were: age >16, symptom duration 6–52 weeks of persistent synovitis, ≥2 effused joints or 1 swollen MCP/PIP + ≥1 of: + RF, +anti-CCP, AM stiffness >45 minutes, response to NSAIDs, or a painful MTP squeeze test. The new 2010 ACR/EULAR criteria were applied to determine what proportion of patients with EIA fulfill the new criteria at BL. Most patients were treatment naive or had only received a few weeks of DMARDs. Patients newly identified as having RA by the new criteria were evaluated for disease activity and the proportion of patients with a DAS28 ≥3.2 were considered as potentially being eligible treatment of for an early RA clinical trial. Patients previously used for criteria development were excluded from this analysis.

Results: BL characteristics were: mean age 52±16 years, 73% female, median symptom duration 5.5 months, mean DAS28 ESR 4.9±1.6; 27% were initially treated with oral glucocorticoids and 50% treated with MTX. 26% (226/874) already had erosions at BL. 57% of patients were eligible for this analysis. Of the remaining 648 patients, 68% (N=441) of patients met 1987 ACR criteria for RA at BL. 31% (N=201) of patients had undifferentiated IA (UIA). Of these 74% (N=478) had a score of ≥ 6 on the new criteria. Of the 68% of patients who met old criteria, 82%(N=362) met new criteria. Of the UIA patients remaining, 57%(N=115) could now be diagnosed with RA using the new criteria. These patients had a mean (DAS28=4.0). 79% of the formerly UIA patients now meeting the new criteria had a DAS28 of ≥3.2.

Conclusions: Based on data from a Canadian cohort, revised ACR/EULAR 2010 criteria can identify a substantial number of new patients previously being designated as UIA as having RA. The majority of these patients would be eligible for clinical trials in ERA. Most of patient who fulfill the 1987 ACR criteria also fulfill the revised 2010 criteria.

Disclosure: V. P. Bykerk: Amgen Inc., 2, Wyeth Pharmaceuticals, 2; **G. Boire:** None; **B. Haraoui:** None; **C. A. Hitchon:** None; **E. C. Keystone:** Amgen Inc., 2, Wyeth Pharmaceuticals, 2; **J. C. Thorne:** None; **D. S. Ferland:** None; **J. E. Pope:** None; **CATCH Investogators:** Amgen Inc., 2, Pfizer Inc, 2, Wyeth Pharmaceuticals, 2.

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A Novel Diagnostic Marker for RA, Anti-MCV. Rong W. Zablocki[1], Annette Van der Helm-van Mil[3], Tom Huizinga[3] and Srinivas Rao[2]. [1]Cypress Bioscience Inc, San Diego, CA, [2]Cypress Bioscience Inc, [3]Leiden University Medical Center, The Netherlands

Purpose: Early identification of undifferentiated arthritis (UA) patients at greatest risk for developing rheumatoid arthritis (RA) may facilitate better treatment. Rheumatoid factor (RF IgM) and antibodies against cyclic citrullinated peptide (anti-CCP) are widely used in diagnosing RA. It has been suggested that the enzyme-linked immunosorbent assay (ELISA) to detect mutated, citrullinated vimentin (anti-MCV) may have a different diagnostic spectrum versus anti-CCP. The purpose of the current study was to evaluate the diagnostic performance of combinations of these biomarkers in UA-RA patients.

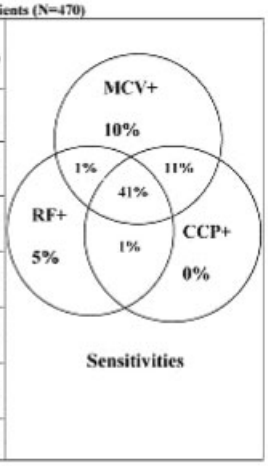
Methods: Clinical and laboratory data were analyzed from a 470 patient subset of the previously described 570 patient Leiden Early Arthritic Clinic cohort (A. Van der Helm-van Mil, et al., 2007). These patients presented with UA, and a fraction (n=153) progressed to RA within 1 year, based on the fulfillment of the American College of Rheumatology (ACR) criteria. Anti-MCV, Anti-CCP2 and RF IgM tests were performed. A positive result for a combination was defined as resulting when all constituents were positive; a negative result of any constituent was defined as the combination negative. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), as well as their 95% confidence intervals (CI), were calculated for each individual biomarker as well as their combinations.

Results: Table 1 presented the diagnostic performance of the biomarkers and their combinations. Overall, anti-MCV demonstrated the highest sensitivity (63%) and NPV (82%), though at the cost of reduced PPV (60%). Combining Anti-CCP2 and Anti-MCV barely reduced sensitivity comparing to Anti-CCP2 alone (52% vs. 53%), and exhibited a favorable balance in sensitivity/specificity and in PPV/NPV. Further, the sensitivity diagram (at right) revealed that anti-CCP2 did not provide additional information (sensitivity=0%) in the context of both RF IgM and anti-MCV being positive. However, anti-MCV and RF IgM still respectively retained 10% and 5% sensitivity despite positivity of the other 2 assays.

Conclusions: Anti-MCV showed the highest sensitivity and NPV. Nearly all Anti-CCP2 positive RA patients were also Anti-MCV positive, though not vice versa, reinforcing the notion that the diagnostic spectrum of the 2 assays is not identical. In the context of positive results for both anti-MCV and RF IgM, anti-CCP2 became redundant in term of sensitivity. In summary, incorporating anti-MCV as an adjunctive diagnostic tool to prognosticate future RA in patients who present with UA enhances sensitivity.

Table 1. Performance of the biomarkers in UA-RA patients (N=470)

Biomarkers	Sensitivity % (95%CI)	Specificity % (95%CI)	PPV % (95%CI)	NPV % (95%CI)
Anti-CCP2	53 (45-61)	88 (84-91)	69 (60-76)	80 (75-83)
RF IgM	48 (41-56)	84 (79-88)	59 (50-67)	77 (72-81)
Anti-MCV	63 (55-70)	80 (75-84)	60 (52-67)	82 (77-85)
Anti-CCP2 & Anti-MCV	52 (44-59)	91 (87-94)	73 (64-81)	80 (75-83)
Anti-CCP2 & RF IgM	42 (34-50)	93 (90-95)	74 (64-83)	77 (72-81)
Anti-MCV & RF IgM	42 (35-50)	92 (88-94)	71 (61-80)	77 (72-81)
Triple-Combination	41 (33-48)	93 (90-96)	75 (64-83)	76 (72-80)



Disclosure: R. W. Zablocki: Cypress Biosciences, Inc., 1, 3; **A. Van der Helm – van Mil:** Leiden University Medical Center, Leiden, The Netherlands, 3, 9; **T. Huizinga:** EU & Dutch Arthritis Foundation, 2, 3, 5, 6, 8, Leiden University Medical Center, Leiden, The Netherlands, 2, 3, 5, 6, 8, Meteor Board, 2, 3, 5, 6, 8, Schering Plough, UCB, Bristol Myers Squibb, Biotest AG, Wyeth/Pfizer, Novartis; **S. Rao:** Cypress Biosciences, Inc., 1, 3, Huya Biosciences Inc, 5.

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Smoking Is a Predictor of Very Early Presentation with Rheumatoid Arthritis. David W. Sharpley[1], Sarang Chitale[2], Cristina Estrach[2], Robert N. Thompson[2], Robert J. Moots[2] and Nicola J. Goodson[2]. [1]Academic Rheumatology Department, Aintree University Hospitals, University of Liverpool, Liverpool, Merseyside, United Kingdom, [2]Academic Rheumatology Department, Aintree University Hospitals, University of Liverpool

Background: Starting disease modifying anti-rheumatic drug (DMARD) treatment very soon after rheumatoid arthritis (RA) symptoms develop may significantly alter the disease course in early RA (eRA) (1). Early arthritis clinics (EAC) have been set up to allow for rapid assessment and initiation of DMARD therapy for eRA. Symptom duration varies in eRA patients with some presenting with very early RA (veRA), defined as a symptom duration ≤12 weeks. These veRA presenters may differ from eRA patients with longer symptom duration at presentation.

Aim: The aim of this study is to identify predictors and disease characteristics associated with veRA presentation to an EAC.

Methods: New attendees at an EAC between May 2006 & March 2010 with eRA or probable eRA by ACR-EULAR 2010 criteria were identified. Symptom duration (weeks), smoking status, disease activity score (DAS-28), baseline radiograph & ultrasound findings, ESR, rheumatoid factor (RF) & anti-citrullinated protein antibody (ACPA) status, and other variables were recorded at presentation. Univariate, age & gender adjusted, & multivariate logistic regression were performed to identify predictors of very early presentation. Stratified analysis by ACPA status was also performed.

Results: 225 patients with eRA or probable eRA had a median age of 59 yrs [IQR 48, 70]. 140 (62%) female, 157 (70%) ACPA positive & 164 (73%) RF positive patients were identified. 189 (84%) had eRA by ACR-EULAR 2010 criteria & 89 (40%) presented within 12 weeks. Age & gender adjusted analyses revealed that, compared to later eRA presenters, veRA patients had higher ESR titres, tender & swollen joint counts & DAS-28 scores, but were less likely to be ACPA positive at presentation. Multivariate modelling identified smoking, ACPA negative status and ESR as independent predictors

of veRA presentation (Table 1). ACPA stratified analyses revealed that the association between smoking & veRA presentation was considerably stronger in ACPA negative patients (OR 15.55, 95% CI 1.61, 149.70) compared to that seen in ACPA positive patients (OR 2.23, 95% CI 1.11, 4.46).

Table 1. Multivariate model predicting veRA presentation

Presentation with veRA	Odds Ratio	95% Confidence Interval	
Age	1.00	0.98	1.02
Gender	1.12	0.62	2.02
Current smoker	2.76	1.45	5.25
ACPA positive	0.32	0.17	0.62
ESR	1.02	1.01	1.03

Conclusions: Smoking is associated with very early presentation and this association appears to be influenced by ACPA status in eRA. Interestingly, veRA patients were less likely to be ACPA positive at baseline. This may represent very early capture of patients prior to the development of ACPA.

Those with veRA had more active disease but less joint damage on ultrasound investigation. These veRA patients may benefit from early DMARD therapy to prevent joint damage and treatment within the window of opportunity may alter their disease course. It is interesting to note that in established RA, smoking is associated with more severe radiological, disability and mortality outcomes. Early remission induction in veRA presenters who smoke could improve these long-term outcomes.

1) van Dongen et al (Arthritis Rheum 2007; 56(5):1424)

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Long-Term Remission in Daily Clinical Practice: Excellent 2 Year Results with Treatment To Target in Very Early Rheumatoid Arthritis, Results of the DREAM Remission Induction Cohort. Marloes Vermeer[5], Ina H. Kuper[5], Monique Hoekstra[1], Hein J. Bernelot Moens[6], Marcel D. Posthumus[4], Herman L. M. Brus[3], Piet L. C. M. van Riel[2] and Mart A. F. J. van de Laar[5]. [1]Isala Klinieken, Zwolle, The Netherlands, [2]Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, [3]TweeSteden Ziekenhuis, Tilburg, The Netherlands, [4]University Medical Center Groningen, Groningen, The Netherlands, [5]University of Twente and Medisch Spectrum Twente, Enschede, The Netherlands, [6]Ziekenhuisgroep Twente, Almelo/Hengelo, The Netherlands

Background: Remission is the primary target of treatment of rheumatoid arthritis (RA). Clinical trials have proven that systematic monitoring of disease activity and adjusting medication on the basis of the disease activity outcome is effective in reaching this goal. Therefore, in current guidelines and recommendations on RA it has been advocated to treat RA to target. However, aiming for remission is not yet implemented and data on inducing and achieving remission in daily clinical practice are limited. The objective of this study was to evaluate disease activity in very early RA patients in daily clinical practice after 2 years of applying a tight control treatment strategy.

Methods: Since January 2006, 534 newly diagnosed patients with early RA (clinical diagnosis of RA, symptom duration ≤ 1 year) were enrolled in the Dutch Rheumatoid Arthritis Monitoring (DREAM) remission induction cohort study. Treatment adjustments (4–8 weekly) were based on the DAS28, aiming at DAS28 < 2.6. The medication protocol consisted of initial MTX, addition of SSZ, exchange of SSZ by anti-TNF in case of insufficient response. Primary outcome was the disease activity according to the DAS28, EULAR response criteria and ACR criteria for clinical remission after 1 and 2 years. Additional outcomes included time to first remission and sustainability of remission.

Results: Baseline characteristics were as follows: mean (SD) age 57.7 (13.9) years, 62.8% female, 56.6% RF positive, 62.4% anti-CCP positive, median (IQR) symptom duration 15 (8–26) weeks, mean (SD) baseline DAS28 5.0 (1.1) and 82.8% of patients fulfilled the ACR classification criteria for RA. Of all patients, 1 year follow-up data was available in 392 patients and 2 year data in 210 patients. At 1 year (n=392), 55.1% of patients achieved DAS28 remission, 64.8% had a good EULAR response and 45.1% satisfied the ACR remission criteria (Table 1). At 2 years (n=210), 64.3% of patients achieved DAS28 remission, 75.7% had a good EULAR response and 54.4% satisfied the ACR remission criteria (Table 1). Median (IQR) time to first DAS28 remission was 22 (12–37) weeks. In more than 60% (127/210) of patients sustained DAS28 remission (≥ 6 months) was observed during the first 2 years of follow-up. The majority of patients achieved remission on conventional DMARDs (mono or combination therapy). Results were independent of the definition of RA (i.e. clinical diagnosis/ACR 1987 criteria) or presence of traditional prognostic factors for RA (i.e. RF/anti-CCP).

Table 1. Clinical outcomes alter 1 and 2 years.

	1 year (n = 392)	2 year (n = 210)
DAS28		
Remission (DAS28 < 2.6)	216 (56.1)	135 (64.3)
Low (2.6 ≤ DAS28 ≤ 3.2)	62 (15.8)	37 (17.6)
Moderate (3.2 < DAS28 ≤ 5.1)	103 (26.3)	32 (15.2)
High (DAS28 > 5.1)	11 (2.8)	6 (2.9)
EULAR response		
Good	254 (64.8)	159 (75.7)
Moderate	102 (26.0)	35 (16.7)
None	36 (9.2)	16 (7.8)
ACR remission	143/317 (45.1)*	93/171 (54.4)*

Values are presented as number (%). *ACR remission could not be evaluated in all patients, due to missing values for morning stiffness.

Conclusion: This study shows that long-term remission is a realistic goal in very early RA patients in daily clinical practice. Implementation of a tight control treatment strategy results in rapid and high remission rates, regardless of the definition used. The management of very early RA patients in clinical care can go beyond the control of signs and symptoms, and should aim at remission.

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The Association of Joint Damage and Treatment Response with ACPA Status in Recent Onset RA. M. van den Broek[3], N. B. Klarenbeek[4], M. L. Westedt[1], H. D. Boom[5], P. J. S. M Kerstens[2], T. W. J. Huizinga[4], B. A. C. Dijkmans[6] and C. F. Allaart[4]. [1]Bronovo Hospital, The Hague, The Netherlands, [2]JBI, Amsterdam, The Netherlands, [3]LUMC, Leiden, The Netherlands, [4]LUMC, Leiden, The Netherlands, [5]Spaarne Hospital, Hoofddorp, The Netherlands, [6]VU Medical Centre, Amsterdam, The Netherlands

Objective: To compare clinical and radiological response to disease activity score (DAS) steered treatment in patients with recent onset RA who were positive or negative for anti-citrullinated protein antibodies (ACPA).

Methods: In the BeSt study, 508 recent onset RA patients were randomized to 4 treatment strategies, aimed at a DAS ≤2.4: sequential monotherapy, step-up combination therapy, initial combination therapy including prednisone and initial combination therapy including infliximab. Chances of damage progression >5 (Sharp/vd Heijde score (SHS)) in 1 year, and >25 in 5 years, and rate of (drugfree) remission were compared for ACPA positive and ACPA negative patients, using logistic regression analysis. Functional ability over time, measured with the Health Assessment Questionnaire (HAQ), was compared using linear mixed models. The analyses were adjusted for gender, smoking habits and baseline age, DAS, and SHS

Results: At baseline, ACPA positive patients (N=297) had more radiographic damage than ACPA negative patients (N=183): median SHS 4.0 (IQR 1.0–10.5) vs 1.5 (IQR 0–6.1), and a lower DAS (4.3 for the ACPA positive group, vs 4.6, $p<0.001$) and HAQ (1.3 vs 1.5, $p=0.02$). More ACPA positive patients were male ($p=0.01$) and more were smokers ($p=0.01$). DAS reduction was achieved similarly in ACPA positive and ACPA negative patients in all treatment groups (figure). After 1 year of follow-up, the Odds ratio (OR) of SHS progression >5 was 3.27 (95% C.I. 1.68–6.35) for ACPA positive patients. After 5 years the OR of progression >25 was 5.95 (95% C.I. 2.02–17.52). Over time, there were no significant differences in HAQ between ACPA positive and negative patients. Odds ratio of ever achieving remission was 1.09 (95% C.I. 0.63–1.88) for ACPA positive patients, and of achieving remission during at least 1 year 0.75 (95% C.I. 0.49–1.16)). However, ACPA positive patients did have a lower chance of ever achieving drugfree remission (OR 0.46 (95% C.I. 0.28–0.72)) and a higher chance of restarting medication (OR 8.47 (95% C.I. 3.09–23.25)).

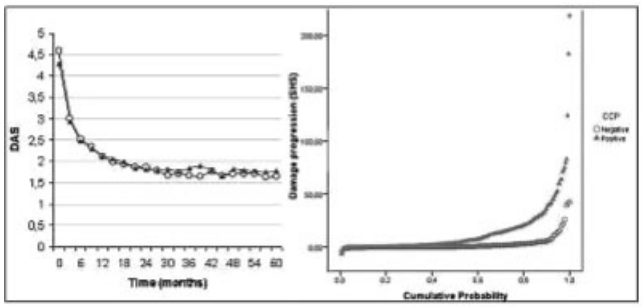

Figure. DAS over time and probability plot depicting radiographic progression (change in SHS) for ACPA positive and ACPA negative patients in 5 years.

Conclusion: Not the chance of remission, but the chance of (persistent) drugfree remission was lower in ACPA positive patients compared to ACPA negative patients. Treatment response was similar in both groups, irrespective of initial treatment and baseline characteristics. However, more ACPA positive patients had significant radiographic damage progression. This may suggest that, in ACPA positive patients, treatment decisions should be based on disease activity, but also on damage progression.

Disclosure: M. van den Broek: Centocor, Inc., 2, Dutch college of health insurances, 2, Schering-Plough, 2; **N. B. Klarenbeek:** None; **M. L. Westedt:** None; **H. D. Boom:** None; **P. J. S. M. Kerstens:** None; **T. W. J. Huizinga:** None; **B. A. C. Dijkmans:** None; **C. F. Allaart:** None.

ACR Concurrent Abstract Sessions
Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment - Imaging

Monday, November 8, 2010, 2:30 PM–4:00 PM

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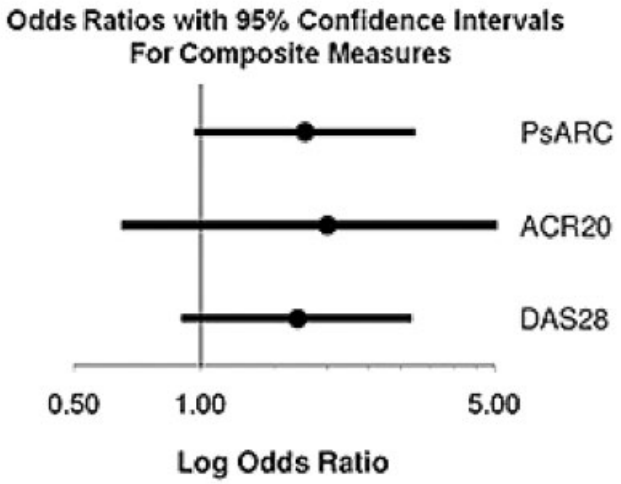
Methotrexate Is Not Disease Modifying in Psoriatic Arthritis: The MIPA Trial. Gabrielle H. Kingsley[3], Anna Kowalczyk[4], Helen Taylor[4], Fowzia Ibrahim[4], Jonathan C. Packham[2], Neil J. McHugh[7], Diarmuid M. Mulherin[1], George D. Kitas[8], Kuntal Chakravarty[6], Brian D. M. Tom[5], Peter J. Maddison[9] and David L. Scott[4]. [1]Cannock Chase Hospital, Cannock, United Kingdom, [2]Haywood Hospital, Stoke on Trent, UK, [3]Kings College London, London, United Kingdom, [4]Kings College London, UK, [5]MRC Biostatistics Unit, University of Cambridge, UK, [6]Queens Hospital, Romford, UK, [7]Royal National Hospital for Rheumatic Diseases, Bath, UK, [8]Russells Hall Hospital, Dudley, UK, [9]Sport, Health and Exercise Science, University of Bangor, UK

Background: Methotrexate (MTX) is widely used as a disease modifying drug (DMARD) in psoriatic arthritis (PsA) without definitive supporting clinical trial evidence. We tested its effectiveness in the first large multicentre randomised controlled trial (RCT) of MTX in active PsA (MIPA).

Methods: A 6-month double-blind RCT compared oral MTX (15mg/week) with placebo in patients with active PsA. The primary outcome measure was the PsA Response Criteria (PsARC); other composite measures included ACR20 and DAS28. We analysed changes in individual measures including "disease modifying" (joint counts, HAQ, ESR and CRP) and "symptom modifying" (global assessments and pain) measures, skin and nail scores.

Results: 462 patients were screened and 221 recruited. 71/109 (65%) of those who received MTX and 77/112 (69%) of those who received placebo completed 6 months therapy. 19 patients (11 MTX, 8 placebo) withdrew for toxicity and 22 (8 MTX, 14 placebo) for inefficacy. No significant treatment effects were seen on PsARC, ACR20 and DAS28 at 3 or 6 months using intention to treat logistic regression analysis (including multiple imputations for missing data and adjustment for age and sex).



There were also no significant treatment effects on tender and swollen joint counts, ESR, CRP, HAQ, pain and nail scores using ordinal linear regression analyses (adjusted for age, sex, baseline scores and disease duration). Patient and physician global scores and skin scores did improve with MTX compared to placebo but at 6 months only ($p=0.03$, $p=0.02$ and $p=0.02$). Separate analysis of polyarticular and oligoarticular PsA subsets also showed no treatment effect for PsARC, ACR20 and DAS28 at 3 or 6 months.

Conclusions: Contrary to general opinion, MTX does not act as a DMARD in PsA but has only borderline "symptom modifying" properties. Its value in active PsA is questionable when there are other agents, such as leflunomide and TNF-inhibitors, which are true DMARDs. This has important implications for current national and international guidance for the treatment of PsA.

Disclosure: G. H. Kingsley: None; **A. Kowalczyk:** None; **H. Taylor:** None; **F. Ibrahim:** None; **J. C. Packham:** None; **N. J. McHugh:** None; **D. M. Mulherin:** None; **G. D. Kitas:** None; **K. Chakravarty:** None; **B. D. M. Tom:** None; **P. J. Maddison:** None; **D. L. Scott:** None.

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Rates and Predictors of Radiographic Sacroiliitis Progression over Two Years in Patients with Axial Spondyloarthritis. Denis Poddubnyy[1], Martin Rudwaleit[1], Hildrun Haibel[1], Anja Weiss[3], Elisabeth Märker-Hermann[4], Henning Zeidler[5], Jürgen Braun[6] and Joachim Sieper[2]. [1]Charité - Campus Benjamin Franklin, Berlin, Germany, [2]Charite Campus Benjamin Frankl, Berlin, Germany, [3]Deutsches Rheumaforschungszentrum, Berlin, Germany, [4]Dr. Horst Schmidt Kliniken, Wiesbaden, Germany, [5]Medizinische Hochschule, Hannover, Germany, [6]Rheumazentrum Ruhrgebiet, Herne, Germany

Background: The current concept of axial spondyloarthritis (SpA) considers non-radiographic axial SpA and ankylosing spondylitis (AS) as two stages of one diseases suggesting progression of radiographic sacroiliitis over time. However, rates of radiographic sacroiliitis progression and predictors of such progression remain unclear until now. The objective of the study was to assess the rates of radiographic sacroiliitis progression and to explore possible progression predictors in a cohort of patients with axial SpA over a period of two years.

Methods: 210 patients with axial SpA (AS and non-radiographic axial SpA) from the German Spondyloarthritis Inception Cohort (GESPIC) have been selected for this analysis based on availability of radiographs at baseline and after 2 years of follow-up. Radiographs of pelvis at baseline were centrally digitized and the sacroiliac joints were scored independently according to the grading system of the modified New York criteria by 2 trained readers. The readers scored both time points simultaneously but were blinded for the time point and for all clinical data.

Results: In total, 115 patients (54.8%) fulfilled the modified New York criteria for AS in their radiographic part in opinion of both readers at baseline, while 95 patients (45.2%) were classified as non-radiographic axial SpA (nrSpA). After 2 years 11 patients (11.6%) from the group of nrSpA fulfilled the modified New York criteria for AS in the opinion of both readers.

Progression of sacroiliitis over two years by at least one grade at one side in opinion of both readers was found in 26 patients (12.4%). Rate of progression was higher among patients with nrSpA (16 patients or 16.8%) as compared to AS (10 patients or 8.7%), although the difference was statistically non-significant (p=0.074). At the same time, there was an improvement of sacroiliitis by at least one grade in the opinion of both readers in 11 patients (5.2%): 6 with nrSpA (6.3%) and 5 with AS (4.3%). Therefore the true radiographic sacroiliitis progression rate over two years could be estimated as 10.5% for patients with nrSpA and 4.4% for patients with AS.

The only one strong positive predictor of radiographic sacroiliitis progression was an elevated level of C-reactive protein at baseline (OR 2.61, p=0.026) - table. Interestingly, presence of definite sacroiliitis at baseline was rather negative predictor of radiographic progression (OR 0.42, p=0.038), which is also illustrated by a higher rate of progression in the group of patients with nrSpA.

Table. Odds ratios (ORs) for progression of radiographic sacroiliitis by at least one grade over 2 years in patients with axial SpA (univariate analysis).

Parameters at baseline	OR (95% CI)	p
Sex, male vs. female	0.47 (0.20–1.1)	0.080
HLA-B27, positive vs. negative	0.85 (0.32–2.3)	0.736
CRP, >6 mg/l vs. ≤6 mg/l	2.61 (1.12–6.06)	0.026
ESR, >20 mm/h vs. ≤20 mm/h	1.28 (0.54–3.06)	0.575
BASDAI, >4 vs. ≤4 points NRS	1.00 (0.44–2.28)	0.997
Disease duration, >5 years vs. ≤5 years	1.29 (0.55–3.02)	0.554
Definitive sacroiliitis* at baseline	0.42 (0.18–0.95)	0.038

* At least grade 2 unilaterally in the opinion of both readers
OR - odds ratio, CI - confidence interval, CRP - C-reactive protein, ESR - erythrocyte sedimentation rate. NRS - numeric rating scale

Conclusion: Progression of radiographic sacroiliitis by one grade after 2 years occurred in 10.5% of the patients with nrSpA and 4.4% of the patients with AS. Elevated level of CRP was found to be a strong positive predictor of sacroiliitis progression.

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High Prevalence of Axial Spondyloarthritis in Patients with Familial Mediteranean Fever, and a Greater Allelic Frequency of M694V in Familial Mediteranean Fever Patients with Radiograpic Sacroiliitis. Servet Akar[2], Ozgul Soysal[2], Feride Yuksel[1], Dilek Solmaz[2], Gercek Can[2], Merih Birlik[2], Mehmet Tunca[1], Fatos Onen[2] and Nurullah Akkoc[2]. [1]Internal Medicine, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, [2]Rheumatology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey

Background: Familial Mediterranean fever (FMF) is an autoinflammatory disease characterized by recurrent attacks of fever and serositis. Limited data suggest that the prevalence of sacroiliitis, which is a hallmark of ankylosing spondylitis (AS), is increased in patients with FMF. Moreover in most recent studies we and other groups have found a significantly higher frequency of M694V in AS patients. Therefore in the present study we assessed the prevalence of axial spondyloarthritis (SpA), including AS, in FMF patients. We also studied the presence of MEFV variants in FMF patients with and without radiographic sacroiliitis.

Patients and Methods: The first 258 patients with FMF [130 female (%50,4), mean age 38,9 ± 12] who were invited to the outpatient clinic for another study were interviewed by using a structured questionnaire to capture patients with SpA. Presence of inflammatory back pain (IBP) was judged based on both Calin and Berlin criteria and the diagnosis of AS was based on the modified New York (mNY) criteria. Standard pelvic X-rays of the sacroiliac joints (SIJ) were performed in all patients. Patients with IBP were also assessed by magnetic resonance imaging (MRI) of SIJ and HLA B27 testing. MEFV variants of the patients were extracted from the patients' medical charts.

Results: Two hundred FMF patients (108 female; 54%) patients (77,5%) reported to have current and/or past back pain. IBP according to Calin and Berlin criteria were present in 53 patients (26,5%) and 42 patients (21%), respectively. One patient had inflammatory bowel disease and one had psoriasis, and 56 (21,8%) had a positive family history for SpA. A total of 15 patients (5,8%) had radiographic sacroiliitis (bilateral grade 2 or unilateral grade 3–4) and 14 of them fulfilled the mNY criteria for AS. Additionally bone marrow edema was detected by MRI of SIJ in 13 patients with IBP (5.0%). HLA-B27 positivity was found in only one of the 12 patients with sacroiliitis on MRI and in none of the 14 patients with radiographic sacroiliitis. Allele frequency of M694V in FMF patients with radiographic sacroiliitis was significantly higher in comparison to those without sacroiliitis (67,9% vs 43,7%; p=0,017) with an OR of 2,7 (95% CI= 1,2 to 6,2).

Age, years, mean ± SD	41,1 ± 11,5
Female, n (%)	9 (60)
Age at onset of FMF; years, mean ± SD	12,4 ± 5,2
Age at onset of back pain; years, mean ± SD	31,6 ± 11,6
BASDAI, mean ± SD	3,5 ± 2,3
BASFI, mean ± SD	2,0 ± 1,8
Presence of syndesmophyte, n (%)	3/14 (21)
HLA-B27 positivity, n (%)	0 (0)
M694V positivity, n (%)	12 (85)*

* Based on 14 unrelated cases.

Conclusion: Our results suggest that axial SpA in patients with FMF and SpA is more common than in the general population. Moreover, M694V may be playing a bigger role than HLA-B27 in susceptibility to AS in FMF patients.

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Evidence That New Focal Fat Lesions Follow Resolution of Spinal Inflammation in AS but Existing Lesions Are More Likely To Resolve with TNF Blocking Agents. Praveena Chiowchanwisawakit[1], Robert G. W. Lambert[2] and Walter P. Maksymowych[2]. [1]Mahidol University, Bangkok, Thailand, [2]University of Alberta, Edmonton, AB, Canada

Purpose: MRI of the spine in SpA frequently shows focal fat lesions in the spine on T1W scans, especially at vertebral corners (VC) and adjacent to the vertebral endplate. Its histopathological basis and pathophysiological implications remain unclear. Adipose tissue has been shown capable of expressing proinflammatory cytokines. It is assumed that VC Fat reflects post-inflammatory change but there have been no prospective studies that have actually tested this hypothesis. We aimed to test the hypothesis that an active vertebral corner inflammatory lesion (CIL) on baseline MRI is more likely to evolve into a *de novo* VC Fat lesion on TIW scans than a VC which demonstrates no inflammation on baseline MRI.

Method: MRI scans were performed at baseline and 2 years in 61 AS patients of whom 28 received TNF blocking agents in open label follow up of clinical trials while 33 received either TNF blocking agents (n = 16) or standard therapy (n = 17) in an observational cohort. We recorded VC fat lesions, defined as increased signal in bone marrow on T1W MRI, and CIL, defined as increased signal on STIR MRI, at anterior and posterior VC on any central sagittal slice. Via televideoconference, reference images were developed in which VC fat lesions and CIL were assigned by consensus amongst an international MRI working group. VC Fat lesions and CIL were independently recorded dichotomously (present/absent) from lower C2 to the upper sacrum of the spine. Anonymized MRI scans were assessed independently by 2 readers who were blinded to treatment and time point. The primary analysis was based on concordant data (VC fat, CIL) and compared the development of new VC Fat lesions according to the presence of a CIL on baseline MRI and its persistence/resolution on follow up MRI. We also tested the effect of treatment on baseline VC fat lesions. Proportions were compared by Fisher's exact test.

Results: New VC Fat lesions developed significantly more frequently in those VC with (32/83 (38.6%)) as compared to those without (69/2647 (2.6%)) inflammation on baseline MRI in the anti-TNF group (p<0.0001). This was less evident in the standard therapy group (1/14 (7.1%) vs 8/1161 (0.7%), p = NS). New VC Fat lesions developed significantly more frequently from CIL that resolved compared to VC with persistent or no CIL in the anti-TNF therapy group (p<0.0001). These differences were again less evident in the standard therapy group. VC Fat lesions present on baseline MRI resolved significantly more frequently after TNF blocker (47/247 (16%)) compared to standard treatment (5/94 (5.1%)) (p = 0.005).

Table. Number (percentage) of new VC Fat lesions.

	Treatment	Resolved CIL	Persistent CIL	NO CIL
VC Fat+	Anti-TNF	16 (20.8)	1 (5.0)	34 (1.3)
VC Fat−	Anti-TNF	61 (79.2)	19 (95.0)	2578 (98.7)
VC Fat+	Standard	1 (11.1)	0	8 (0.7)
VC Fat−	Standard	8 (88.9)	5 (100)	1153 (99.3)

Conclusion: New VC Fat lesions occur more frequently at sites of prior inflammation, especially after inflammation has resolved following institution of anti-TNF. Existing VC Fat lesions are also more likely to resolve with anti-TNF.

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New Bone Formation in the Spine of Patients with Diffuse Idiopathic Skeletal Hyperostosis (DISH) and Ankylosing Spondylitis (AS)—A Detailed Comparative Analysis of the Rates of Radiographic Progression over 6 Years. Xenofon Baraliakos[3], Joachim Listing[1], Jana Buschmann[3], Anna von der Recke[3] and Juergen Braun[2]. [1]German Rheumatism Research Center, [2]Rheumazentrum Ruhrgebiet, Herne, Germany, [3]Rheumazentrum Ruhrgebiet Herne

Background: Ankylosing spondylitis (AS) and diffuse idiopathic skeletal hyperostosis (DISH) have a similar pattern of new bone formation.

Objective: To compare the natural course of radiographic progression of AS-specific (syndesmophytes) and degenerative (spondylophytes) changes in AS and DISH.

Methods: All AS and DISH patients who had lateral radiographs of the cervical and the lumbar spine at at least 2 timepoints within 6 years were included in this retrospective study. Radiographic progression was compared on the basis of deve-lop--ment of syndesmophytes and spondylophytes and by using the mSASSS. Images were scored by 3 blinded readers. The differentiation between syndesmo-phytes and spondylophytes was made as recently proposed. Baseline characteristics and follow-up rates of radiographic progression were compared by summary statistics. Covariance and logistic regression analysis were also performed for radiographic status at baseline (BL) and development of bone formation over time.

Results: A total of 146 AS (mean age 54.2±12.3y, symptom duration 23.6±11.2y, no biologics) and 141 DISH patients (n=141, mean age 60.3±7.7y, symptom duration 21.6±12.4y) were included. At BL, the mean number of syndesmophytes/patient was 5.7±5.5 in AS and 2.7±2.8 in DISH (p=0.001), while a trend for more spondylophytes was seen in DISH (1.4±1.8) vs. AS (1.0±1.4). In the covariance analysis of all patients adjusted for baseline status of radiographic damage, more new syndesmophytes/patient were seen in AS (2.0±2.7, 95%CI: 1.7–2.4) vs. DISH (0.5±0.9, 95% CI: 0.3–1.1), (p<0.001), while a trend for more spondylophytes/patient was seen in DISH (0.54±1.0, 95% CI: 0.37–0.70) vs. AS (0.46±1.10, 95%CI: 0.30–0.62).

Syndesmophytes at BL were predictive of new syndesmophytes at follow-up in AS but not in DISH, whereas spondylophytes at BL were predictive for new spondylophytes in DISH but not in AS: 2.4±2.7 vs. 1.1±2.7 new syndesmophytes/patient (p<0.001) were seen in AS patients with vs. without baseline syndesmophytes and 0.9±1.4 vs. 0.3±0.8 new spondylophytes/patient (p<0.001) were seen in DISH patients with vs. without baseline spondylophytes.

The mean mSASSS increased from 14.3±6.7 to 17.6±7.8 (mean change: 3.2±4.2 units) and from 20.5±14.4 to 24.6±15.9 units (mean change: 4.1±9.5 units) between baseline and follow-up in DISH and AS, respectively.

Conclusions: This study shows that a radiographic differentiation between AS and DISH is possible but syndesmophytes and spondylophytes do occur in both dis-eases. In both diseases, radiographic damage at BL is predictive of further and faster progression. The finding of similar progression rates in AS and DISH is surprising.

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Relationship between Active Inflammatory Lesions in the Spine and Sacroiliac Joints and New Development of Fatty Infiltration on Whole-Body MRI in Early Axial Spondyloarthritis—Results of the ESTHER Trial at Week 48. In-Ho Song[1], Kay-Geert Hermann[2], Hildrun Haibel[1], Christian Althoff[2], Joachim Listing[3], Bruce Freundlich[4], Martin Rudwaleit[1] and Joachim Sieper[1]. [1]Charite Campus Benjamin-Franklin, Medical Clinic I, Rheumatology, Berlin, Germany, [2]Charite Campus Mitte, Radiology, Berlin, Germany, [3]German Rheumatism Research Center, Berlin, Germany, [4]Wyeth/Pfizer Inc., Collegeville, PA

Purpose: To investigate the relationship between resolution of active inflammatory lesions on whole-body magnetic resonance imaging (wb-MRI) and new development of fatty infiltration in early axial spondyloarthritis (SpA) treated either with etanercept (ETA) or sulfasalazine (SSZ).

Method: Axial SpA patients enrolled in a randomized controlled trial (1) were treated with ETA (n= 40) vs. SSZ (n= 36) over 48 weeks. All patients showed active inflammatory lesions (bone marrow edema) on wb-MRI in either the sacroiliac joints (SIJ) and/or the spine at baseline (BL). Wb-MRIs were performed at weeks 0, 24 and 48 and were scored for active inflammation and fatty infiltration in the four quadrants of each SIJ and the 23 vertebral units (VUs) of the spine. Scoring was performed by two radiologists, blinded for treatment arm and MRI time point. Generalized estimation equations were used to calculate confidence intervals by taking repeated measurements within individual patients into account.

Results: There was a very low rate of new fatty infiltration of about 1% (0.8% for SIJ quadrants and 1.7% for VUs) if there was no previous inflammation in the bone (see table). There was a good relationship between disappearance of inflammation and the appearance of fatty infiltration: if inflammation resolved fatty infiltration occurred in 17.3% (SIJ quadrants) and 19.1% (VUs). If inflammation did not resolve fatty infiltration occurred much less frequently: 8.4% (SIJ quadrants) and 5.8% (VUs) (p= 0.0001 for SIJ and p= 0.1 for VUs for the difference between resolved and persistent inflammation group, see table). Interestingly, new fatty infiltration occurred more frequently in the ETA group (26 VU sites and 33 SIJ sites) compared to the SSZ group (8 VU sites and 12 SIJ quadrant sites). This was in concordance with the significantly higher increase of the mean fatty infiltration score in the ETA (mean fat infiltration score 1.86 at baseline vs. 2.56 at week 24 for the SIJ, and 3.88 vs. 4.60 for the spine) compared to the SSZ (mean fat infiltration score 1.73 at baseline vs. 1.76 at week 24 for the SIJ, and 3.34 vs. 3.51 for the spine, respectively) group (p= 0.018 and p= 0.006 for the differences).

Conclusion: These data indicate that there is a close interaction between inflammation, TNF-blockade and fatty infiltration of subchondral bone marrow. The higher amount of fatty infiltration in the ETA group is probably due to the effective suppression of active inflammation. The molecular mechanisms of these interactions have to be further investigated.

Table. Development of fatty infiltration at week 48 according in development of active inflammation

		New fatty infiltration at week 48	
Location	Active inflammation	Number	% [95% confidence intervals]
Spine-vertebral units	No active inflammation at any time	13/1555	0.8% [0.4%–1.8%]
	Active lesion at baseline and resolution at week 48	13/75	17.3% [8.5%–32.2%]
	Persistent active inflammation	8/95	8.4% [3.8%–17.5%]
SIJ-Quadrants	No active inflammation at any time	4/241	1.7% [0.4%–7.5%]
	Active lesion at baseline and resolution at week 48	29/152	19.1% [12.4%–28.1%]
	Persistent active inflammation	12/207	5.8% [2.8%–11.3%]

(1) Song I.-H. et al. EULAR 2010, OP 0029

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Growth Differentiation Factor-9 Induced by Insulin-Like Growth Factor Binding Protein-5 May Contribute to Fibrosis in Systemic Sclerosis. Yukie Yamaguchi[2] and Carol A. Feghali-Bostwick[1]. [1]University of Pittsburgh, Pittsburgh, PA, [2]University of Pittsburgh, Yokohama City University, Yokohama, Kanagawa, Japan

Background: We previously described elevated levels of insulin-like growth factor binding protein- 5 (IGFBP- 5) in fibrotic disorders such as systemic sclerosis (SSc). IGFBP- 5 is a pro-fibrotic factor that induces production of extracellular matrix (ECM) components *in vitro*, *in vivo* in lung and skin, and *ex vivo* in human skin. Using microarray analysis of IGFBP-5-expressing fibroblasts, we identified growth differentiation factor- 9 (GDF-9) as a downstream target of IGFBP-5. GDF-9 is a member of the TGF superfamily and was originally described as an oocyte-derived growth factor required for folliclogenesis. We therefore sought to examine the role of GDF-9 in mediating the fibrotic effects of IGFBP-5.

Methods: Induction of GDF-9 by IGFBP-5 was evaluated in IGFBP-5-expressing fibroblasts *in vitro* and in human skin *ex vivo*. Co-localization of IGFBP-5 and GDF-9 was assessed by immunocytostaining and immunoprecipitation in primary human lung fibroblasts. The signaling pathway mediating IGFBP-5 induction of GDF-9 was identified using chemical inhibitors. Furthermore, induction of ECM by GDF-9 was assessed by western blot, and GDF-9 expression was examined in SSc lung tissues using immunohistochemistry. Finally, the effect of overexpressing GDF-9 in human skin in an *ex vivo* organ culture model was assessed.

Results: GDF-9 was induced in IGFBP-5 expressing fibroblasts, fibroblasts stimulated with recombinant IGFBP-5, and in human skin injected with an IGFBP-5-expressing adenovirus. GDF-9 co-localized with and bound to IGFBP-5. Induction of GDF-9 was reduced in the presence of P38b-inhibitor or a BMPRII neutralizing antibody, but not following TGF-b neutralization, suggesting that GDF-9 production was mediated via P38b-dependent, BMPRII-dependent, and TGF-b-independent mechanisms. Recombinant GDF-9 triggered Smad3 phosphorylation and promoted ECM production and deposition. Interestingly, levels of GDF-9 were very high in lung tissues of patients with SSc. Finally, overexpression of GDF-9 in human skin *ex vivo* significantly increased dermal thickness.

Conclusion: GDF-9 is induced by IGFBP-5 and contributes to the development of organ fibrosis via p38b activation. Furthermore, GDF-9's pro-fibrotic effects are mediated, at least in part, via BMPRII.

Disclosure: Y. Yamaguchi: None; **C. A. Feghali-Bostwick:** None.

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Epithelial Cells Undergoing Epithelial Mesenchymal Transition (EMT) in Systemic Sclerosis Lack Caveolin-1 and Modulate WNT Signaling in the Dermis by Secreting SFRP4. Ilaria Tinazzi, Justin Gillespie, Giuseppina Abignano, Chiara Colato, Domenico Biasi, Paul Emery and Francesco Del Galdo. University of Leeds

Background: Systemic Sclerosis is a chronic fibrotic disease highly heterogeneous in clinical outcome, involving autoimmune activation, fibroproliferative vasculopathy and tissue fibrosis of skin and multiple internal organs. The mechanisms linking immune activation and tissue fibrosis are still not fully characterized. A widely accepted model of immune mediated skin fibrosis is chronic Sclerodermatous Graft versus Host Disease (SclGVHD), a form of chronic GVHD with a prevalence of approximately 3–10% in patients receiving allogenic bone marrow transplant. Recent histopathologic studies of cGVHD skin biopsies confirmed the presence of both fibroproliferative vasculopathy and tissue fibrosis in Scl-GVHD.

Purpose: To identify which of the genes differentially expressed in SSc skin biopsies are similarly expressed in the transcriptome of cGVHD skin biopsies and therefore of potential importance in linking the immune activation and the skin fibrosis.

Methods: Metanalysis of the microarray data published in the literature identified a set of 86 genes whose differential expression is highly reproduced in SSc skin biopsies that we defined the SSc signature. The mRNA expression level of these genes was measured in 8 Scl-GVHD, three cGVHD skin biopsies and compared to normal skin mRNA and to their differential expression in SSc. All the genes found to be significantly differentially expressed ($p < 0.05$) in univariate analysis were tested in multivariate analysis. Immunofluorescence studies on skin biopsies were conducted to validate the mRNA findings

Results: 46 genes were differentially expressed in cGVHD biopsies and 34 remained peculiar of Scleroderma. 78.3% of the differentially expressed genes had a similar pattern of regulation in SSc. 25% were similarly expressed in both cGVHD variants, whereas 16.6% were specific of Scl GVHD. Remarkably, this analysis allowed to identify specific chemokines (CCL5, CXCL9–10–11) involved specifically in the fibrotic versus non fibrotic response in GVHD and an increased expression of SFRP4 a potent angiogenesis inhibitor in SSc and SCL-GVHD. Double IF studies followed by confocal laser scanning microscopy allowed to identify as the source of increased SFRP4 expression, cells in the basal layer of the epidermis which lost E-cadherin expression, co-expressed Vimentin and specifically lacked caveolin-1 expression.

Conclusion: About 50% of SSc signature genes presented an altered expression in cGVHD. The further caracterization of the cells that play a role both in the fibrotic process, by undergoing EMT, and in the vasculopathy, by inhibiting angiogenesis through WNT inhibition, may pave the way to understand the link between these two processes in SSc.

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The Notch Pathway Controls Fibroblast Activation and Tissue Fibrosis in Systemic Sclerosis. Clara Dees[2], Pawel Zerr[2], Michal Tomcik[2], Christian Beyer[2], Angelika Horn[2], Alfiya Akhmetshina[2], Katrin Palumbo[2], Nicole Reich[2], Jochen Zwerina[2], Mark P. Mattson[3], Oliver Distler[1], Georg Schett[2] and Joerg H. W. Distler[2]. [1]Center of Experimental Rheumatology and Zurich Center of Integrative Human Physiology, University Hospital Zurich, Switzerland, [2]Department of Internal Medicine 3, University Erlangen-Nuremberg, Germany, [3]Laboratory of Neurosciences, National Institute on Aging Intramural Research Program, Baltimore, MD

Purpose: Tissue fibrosis caused by pathological activation of fibroblasts with increased synthesis of extracellular matrix components is a major hallmark of systemic sclerosis (SSc) and other fibrotic diseases. Pathologic activation of Notch signaling has been implicated in the pathogenesis of human malignancies. The aims of the present study were to investigate whether Notch contributes to the uncontrolled activation of fibroblasts and tissue fibrosis in SSc and to evaluate the therapeutic potential of Notch inhibition for the treatment of fibrosis.

Methods: Activation of the Notch pathway was analyzed by immunohistochemistry in skin sections of SSc patients and healthy volunteers. Dermal fibroblasts were stimulated with recombinant human Jagged-1 (Jag-1) Fc Chimera and incubated with the γ-secretase inhibitor DAPT. Fibroblast activation was determined by staining for α-smooth muscle actin (αSMA) and stress fibers. Inhibition of Notch signaling for the treatment of fibrosis was evaluated in the mouse model of bleomycin-induced dermal fibrosis and in tight-skin-1 (tsk-1) mice.

Results: Notch signaling is activated in skin of SSc patients as analyzed by immunohistochemistry. Moreover, this activation persisted in cultured fibroblasts *in vitro* with significantly elevated levels of activated Notch-1, its ligand Jag-1 and its target gene hes-1. Activation of the Notch pathway by stimulation with recombinant Jag-1 potently induced differentiation of resting fibroblasts into myofibroblasts with increased levels of αSMA and formation of stress fibers. In addition, Jag-1 increased collagen synthesis to 294 ± 37 % ($p < 0.05$) which was prevented upon pre-incubation with DAPT. Consistent with the selective activation of Notch signaling in SSc fibroblasts, incubation of dermal fibroblasts with DAPT decreased the basal collagen synthesis only in SSc but not in healthy dermal fibroblasts. In the mouse model of bleomycin-induced dermal fibrosis, treatment with DAPT completely prevented dermal thickening upon bleomycin-challenge ($p < 0.05$). Inhibition of γ-secretase prevented also hypodermal thickening in tsk-1 mice with a mean reduction of hypodermal thickness by 75 ± 4 % ($p < 0.05$). Overexpression of a Notch-1 antisense construct confirmed the results obtained with the

chemical inhibitor. Bleomycin-induced dermal thickening was reduced by 85 ± 19 % ($p < 0.05$) and hypodermal thickness in tsk-1 mice decreased by 51 ± 11 % ($p < 0.05$). Of note, treatment with DAPT not only prevented fibrosis but induced significant regression of dermal thickening below pre-treatment levels in a modified model of established bleomycin-induced skin fibrosis.

Conclusion: We demonstrate that the Notch pathway is activated in fibrotic skin, induces myofibroblast differentiation and stimulates the release of collagen. Inhibition of Notch signaling exerts potent anti-fibrotic effects in preclinical models suggesting that targeting Notch signaling might be a promising molecular approach for anti-fibrotic therapy.

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Myofibroblast Specific Gene Expression Signature in Systemic Sclerosis, More Than TGF-beta Induced Activation. Giuseppina Abignano[2], Heidi Hermes, Justin Gillespie, Sergio A. Jimenez, Paul Emery and Francesco Del Galdo[1]. [1]Leeds, [2]University of Leeds

The key cellular elements in the pathogenesis of tissue fibrosis are myofibroblasts. It is widely accepted that the number of myofibroblasts is increased in SSc and it correlates with the severity of tissue fibrosis. The mechanisms underlying their increased number and their heterogeneity in SSc are unknown. The heterogeneity in their frequency may explain the inconsistency of some in vitro studies published on SSc fibroblast biology, and may mirror the clinical heterogeneity of SSc patients both in natural history and severity of skin fibrosis. The purpose of this study was to unravel the specific transcriptome of myofibroblasts derived from SSc skin biopsies.

Methods: 4 patients with diffuse rapidly progressive SSc, within 18 months from skin involvement and before any immunosuppression, were enrolled in the study. Skin biopsy on forearm was performed and the fibroblasts subcultured for three passages. 250 acetone fixed alpha-SMA positive cells were isolated by laser capture microdissection (LCM) for mRNA analysis by Affymetrix Gene array and qRT-PCR validation. Pathway analysis was conducted according to David-NIH software. Immunofluorescence (IF) followed by confocal laser scanning microscopy (CLSM) was conducted as well. Normal dermal fibroblasts were utilized to evaluate the effects of TGF-beta stimulation both at mRNA and protein level.

Results: qRT-PCR for a-SMA showed in average 3.7 fold increased expression in a-SMA in the LCM captured cells. Microarray analisis identified 269 genes upregulated more than 2 fold in the myofibroblasts. Of these, 24 were clearly reconducible to profibrotic activation, including a-SMA, Collagens I, VI and XI, Fibronectin, several Integrin genes, FGF7, CD36, IGF and Rho; 16 were ribosomial genes; 14 were mitochondrial genes involved in oxidative phosphorylation, including COX1,2, 3 and 6 ND1 to 6, CYT-b and F-type ATP-ase; 28 genes were involved in cell to cell adhesion including, JAM2, ERM, and MLC and 7 in antigen processing and presentation including RAB13, B2-microgrobiulin, cathepsin, HSPs, calnexin, and calreticulin. The remaining genes were not classifiable in any specific functional pathway and comprised tropomyosin, reticulocalbin 1, caldesmon 1, and 6 members of Neuroblastome Breakpoint Family (NBPF). IF studies followed by CLSM confirmed the expression, never shown before, of NBPF in dermal fibroblasts. Functional studies on normal dermal fibroblalsts indicated that NBPF was not inducible by 24 or 48 h stimulation with 10 ng/ml TGF-beta neither at mRNA or protein level.

IF followed by CLSM of alpha-SMA positive vs negative cells showed a specific expression profile for pro-collagen-1, caveolin-1, beta-catenin and phospho-RB whereas SMAD3, SMAD1, SMAD5, and NF-kB did not differ between alpha-SMA positive or negative cells.

Conclusions: Myofibroblast secretome displayed, besides predictable genes involved in the increased ECM production and TGF-beta pathway activation, genes involved in several pathways not known to be specific of myofibroblasts or inducible by TGF-beta. The specific expression of these genes may reflect either a specific metabolic status or a specific differentiation lineage of myofibroblasts

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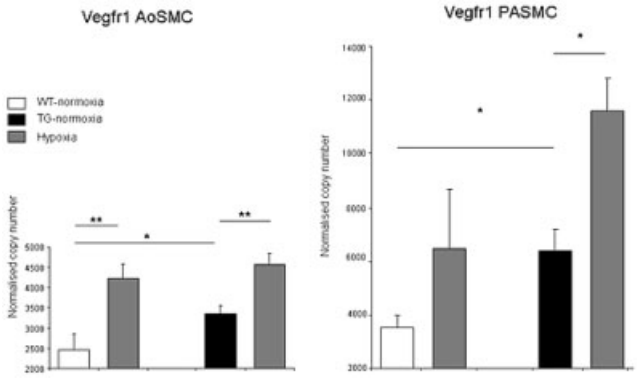
Perturbed VEGF Signalling within the Pulmonary Vasculature of a TGFβ Dependent Mouse Model of Systemic Sclerosis. Emma C. Derrett-Smith[2], Audrey Dooley[2], Reshma Baliga[1], Adrian Hobbs[1], Raymond MacAllister[1], David Abraham[4] and Christopher P. Denton[3]. [1]Centre for Clinical Pharmacology, Rayne Institute, UCL, London, Canada, [2]Centre for Rheumatology and Connective Tissue Diseases, Royal Free Campus, UCL Medical School, London, [3]Royal Free Hospital, London, United Kingdom, [4]University College London, London, United Kingdom

Purpose: Vascular complications of systemic sclerosis (SSc) are a major cause of mortality and morbidity. A role for altered VEGF signaling in PAH-SSc is supported by data that correlate circulating VEGF with mPAP at diagnosis. There is also a trend for VEGF levels to fall after initiation of PAH-specific therapy. High circulating VEGF levels may be a marker of repair in response to vascular injury. We have therefore examined VEGF signaling in a TGFβ-dependent mouse model of SSc with evidence of a constitutive pulmonary vasculopathy.

Methods: The transgenic mouse strain TβRIIΔk-fib expresses a kinase-deficient type II TGFβ receptor driven by a fibroblast-specific promoter leading to balanced ligand-dependent upregulation of TGFβ signalling. Pulmonary vasculopathy was confirmed by histological assessment of vessel architecture, isolated organ bath and *in vivo* haemodynamic studies performed on adult male transgenic and littermate wildtype animals (n=8 in each group). Biochemical analysis of the VEGF and endothelin axes were performed assessing RNA by quantitative PCR and protein by Western blotting using cultured aortic and pulmonary artery smooth muscle cells, and by immunostaining of tissue sections. Results were compared to the same cells cultured under hypoxic conditions.

Results: Within the pulmonary arterial circulation, transgenic vessel wall thickness was increased, particularly in smaller vessels (30–60μm diameter) due to hypertrophy of the smooth muscle layer (mean wildtype vessel thickness:circumference ratio 0.66±0.02, mean transgenic 0.88±0.04, $p<0.05$). Pulmonary arterial ring responses to direct and receptor-mediated contractile stimuli were reduced in the transgenic animals (in response to endothelin contraction at 10^{-5}M wildtype 1.10mN±0.02, transgenic 0.62±0.12, $p<0.05$) and right ventricular pressures were elevated in transgenic animals (wildtype mean 29mmHg±4, transgenic mean 37mmHg±3). Explanted transgenic vascular smooth muscle cells showed upregulation of TGFβ responsive genes including Vegf and Vegfr1 which were further upregulated in the pulmonary arterial circulation (PASMC) when compared to aortic smooth muscle cells (AoSMC) from the same animals.



Endothelin receptor A gene expression was also reduced in transgenic animals. Hypoxic culture resulted in upregulation of Vegf and Vegfr1 in cells from both wildtype and transgenic animals, again more marked in the pulmonary arterial cells.

Conclusions: The pulmonary vascular phenotype of this transgenic mouse model appears to replicate key histological and pathophysiological features of human SSc, and supports a potential role for perturbed TGFβ, endothelin and VEGF activity in the pulmonary circulation in this model.

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The IL13/IL4RA/CCL2 Pathway Drives Sclerodermatous Graft Versus Host Disease in Mice and Correlates with Disease Activity in Scleroderma Patients. Antonios O. Aliprantis[4], Matthew Greenblatt[3], Jennifer Sargent[2], Giuseppina Farina[6], Kelly Tsang[3], Robert A. Lafyatis[1], Michael Whitfield[2] and Laurie Glimcher[5]. [1]Boston University School of Medicine, Arlington, MA, [2]Department of Genetics, Dartmouth Medical School, [3]Department of Immunology and Infectious Diseases, Harvard School of Public Health, [4]Department of Medicine, Division of Rheumatology, Allergy and Immunology, Brigham and Women's Hospital and Harvard Medical School and Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, MA, [5]Department of Medicine, Division of Rheumatology, Allergy and Immunology, Brigham and Women's Hospital and Harvard Medical School and Department of Immunology and Infectious Diseases, Harvard School of Public Health, [6]Rheumatology Section, Boston University School of Medicine

Background: Scleroderma (SSc) is an irreversible autoimmune disease characterized by tissue fibrosis. Agents to treat SSc remain elusive since mechanisms underlying the initiation and propagation of fibrosis are not well understood. We have shown that the gene expression profile of murine sclerodermatous graft-versus-host disease (sclGVHD) approximates an "inflammatory" subset of human SSc patients and that both diseases display activation of the IL13 cytokine pathway. Here, the function of the IL13 pathway and downstream CCL2 expression is defined in the mouse model and SSc patients.

Methods: SclGVHD was induced by injection of splenocytes from allogeneic B10.D2 mice into MHC-matched BALB/c Rag2−/−, BALB/c Rag2−/−IL13−/− or BALB/c Rag2−/−IL4Ra−/− hosts. Control hosts received syngeneic BALB/c splenocytes. Recipient mice were scored biweekly for development of clinical sclGVHD. At 6 weeks, a blinded SSc expert scored back skin histopathology. Explant cultures and experiments on FACS sorted cells isolated from back skin were performed 2 or 3 weeks after cell transfer. Human SSc skin RNA was purified from a cohort of patients with a mean disease duration of 24 months. ELISA or quantitative RT-PCR was used to detect gene expression. Centocor, Inc provided previously published blocking antibodies to CCL2 and CCL12.

Results: Compared to syngeneic controls, explant cultures of back skin from sclGVHD mice displayed robust IL13 production confirming expression of this cytokine at the major site of pathology. Consistent with this, Rag2−/−IL13−/− hosts were partially protected from the development of sclGVHD. Partial protection suggested redundant expression of IL13 by both host and graft sources. Accordingly, both host macrophage and graft T-cell populations were found to produce IL13 in lesional skin. In contrast to Rag2−/−IL13−/− hosts, those lacking the ability to respond to IL13 (Rag2−/−IL4Ra−/−) were nearly completely protected from sclGVHD. Protection was associated with increased production of the anti-inflammatory cytokine IL-10 by graft T-cells isolated from Rag2−/−IL4Ra−/− hosts. Comparative expression profiling of Rag2−/− and Rag2−/−IL4Ra−/− sclGVHD mice also revealed that the latter displayed reduced CCL2 expression in whole skin, as well as in purified macrophage and CD45- stromal cell populations. Parallel exploration of additional datasets, including IL13 stimulated human dermal fibroblasts and IL13 transgenic mice, also suggested CCL2 as a common target of IL13 pathway activation. Confirming the functional significance of this finding, co-treatment with blocking antibodies to CCL2 and its murine homolog CCL12 prevented sclGVHD. Lastly, we show that expression of receptor subunits for IL13 signaling (IL13RA1 and IL4RA) and CCL2 are significantly increased in the skin of SSc patients and correlate with modified Rodnan skin scores, a clinical measure of cutaneous disease.

Conclusions: These data provide evidence that the IL13/IL4Ra/CCL2 axis is important to SSc pathogenesis. Inhibition of this pathway may be a viable therapeutic option for SSc patients exhibiting the inflammatory gene signature.

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Two Year Follow-Up Results from a Randomised Trial of Rituximab Versus Cyclophosphamide for 'Generalized' ANCA-Associated Vasculitis: RITUXVAS. Rachel B. Jones[1], Jan Willem Cohen Tervaert[5], Thomas Hauser[4], Raashid Luqmani[7], Matthew D. Morgan[11], Chen Au Peh[8], Caroline O. Savage[11], Mårten Segelmark[9], Vladimir Tesar[3], Pieter van Paassen[6], Dorothy Walsh[2], Michael Walsh[2], Kerstin Westman[10] and David R. W. Jayne[1]. [1]Addenbrooke's Hospital, Cambridge, United Kingdom, [2]Addenbrooke's Hospital, [3]Charles University, [4]Immunologie-Zentrum Zürich, Zurich, Switzerland, [5]Maastricht University Medical Center, Maastricht, The Netherlands, [6]Maastricht University Medical Center, [7]Nuffield Orthopaedic Centre, Oxford, United Kingdom, [8]Royal Adelaide Hospital, Adelaide, Australia, [9]University Hospital of Skane and Lund University, Lund, [10]University Hospital of Skane and Lund University, [11]University of Birmingham, Birmingham, United Kingdom

Cyclophosphamide based induction regimens are standard therapy for ANCA-associated vasculitis with major organ involvement; however, associated mortality and adverse event rates are high and safer regimens are required. Rituximab based regimens are a potential alternative to cyclophosphamide induction.

We report the two year results of a randomised trial comparing a rituximab based induction regimen with a standard intravenous cyclophosphamide regimen for new ANCA-associated renal vasculitis. All patients had newly diagnosed ANCA-associated vasculitis with active renal disease and ANCA positivity. 44 patients were randomised; 33 to rituximab 4×375mg/m^2 & 2×15mg/kg intravenous cyclophosphamide; and 11 to intravenous cyclophosphamide 6–10×15mg/kg. Both groups received the same intravenous and oral prednisolone regimen.

At entry: median age was 68 years, Wegener's granulomatosis 50%, microscopic polyangiitis 50%; CRP 28; BVAS 18; PR3-ANCA 57%, MPO-ANCA 43%, glomerular filtration rate 18ml/min, 20% required dialysis. At two years, the primary composite outcome of relapse, death or end stage renal failure occurred in 14/33 (42%) Rituximab versus 4/11 (36%) cyclophosphamide (p=1.00). Relapse occurred in 7/33 (21%) rituximab versus 2/11 (18%) cyclophosphamide (p=1.00), death in 6/33 (18%) rituximab versus 3/11 (27%) cyclophosphamide (p=0.67) and end stage renal failure in 2/33 (6%) rituximab versus 0/11 cyclophosphamide (p=0.57). Median estimated glomerular filtration rate was 20 & 44ml/min/m^2 in rituximab patients at 0 and 24 months respectively compared to 12 & 31ml/min/m^2 in cyclophosphamide patients. Serious adverse events occurred in 61% rituximab (50 events, 20/33 patients) versus 36% cyclophosphamide (15 events, 4/11 patients) (incidence rate ratio 1.16; 95% confidence interval 0.64–2.22) (p=0.64).

Rituximab based induction therapy is efficacious but is not superior to intravenous cyclophosphamide at two years in terms of combined relapse, mortality and end stage renal failure outcome. Further strategies to reduce mortality and serious adverse events and prevent relapse should be considered.

Disclosure: R. B. Jones: Roche, 8; **J. W. Cohen Tervaert:** Abbott Laboratories, 5, Roche, 7, 8; **T. Hauser:** CSL Behring Switzerland, 9, Novartis Pharmaceuticals Corporation, 9, Roche, 9; **R. Luqmani:** Abbott Laboratories, 9, Roche, 5, 9, Schering-Plough, 5, Wyeth Pharmaceuticals, 9; **M. D. Morgan:** None; **C. A. Peh:** None; **C. O. Savage:** Biogen Idec, 5, GlaxoSmithKline, 5, 9, Talecris, 2; **M. Segelmark:** None; **V. Tesar:** Roche, 9; **P. van Paassen:** None; **D. Walsh:** None; **M. Walsh:** None; **K. Westman:** None; **D. R. W. Jayne:** Roche, 5, 8.

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Increased Circulating Osteoclast Precursors and Lesional Osteoclast-Like Multinucleated Giant Cells in the Lung of Patients with Wegener's Granulomatosis. Jin Kyun Park[1], Frederic Askin[2], Antony Rosen[3] and Stuart M. Levine[1]. [1]Johns Hopkins University, Baltimore, MD, [2]Johns Hopkins University, [3]The Johns Hopkins University, Baltimore, MD

Background: Tissue-infiltrating multinucleated giant cells (MNGCs) surrounding areas of geographic necrosis are the pathologic hallmarks of Wegener's granulomatosis (WG). However, the origin, phenotype, and function of these cells in WG remain undefined.

Methods: MNGC phenotype was examined by immunohistochemistry in serial paraffin sections of WG lung tissue (N=12) using antibodies recognizing the osteoclast (OC)-lineage markers CD68, cathepsin K and tartrate-resistant-acid-phophatase (TRAP). To examine whether WG patients had an increased propensity toward MNGC formation over healthy control subjects, peripheral blood mononuclear cells (PBMC) obtained from 11 patients (5 with limited and 6 with systemic disease) and 7 healthy controls were cultured in 96- well plates in the presence of RANKL and M-CSF to induce MNGC formation. After 9 days in culture, MNGC morphology and TRAP expression were examined. OC-like giant cells were defined as TRAP (+) cells containing 3 or more nuclei. Mean MNGC values were compared between groups using the Mann-Whitney U test or Student's t-test where appropriate. P-values of < 0.05 were considered statistically significant.

Results: WG lung tissue granulomata contained numerous MNGCs. All tissue-infiltrating MNGCs expressed CD68, indicative of monocytic lineage, and exhibited robust TRAP and cathepsin K staining, a phenotype thought to be unique to bone-resident osteoclasts. After co-incubation with the osteoclastogenic cytokines RANKL and M-CSF, patients with WG formed significantly more MNGCs at Day 9 than healthy controls (109 +/− 112 MNGC/well vs. 18 +/− 16 MNGC/well, p=0.03). Patients with systemic disease produced significantly more MNGC than both controls (167 +/− 114 MNGC/well vs. 18 +/− 16 MNGC/well, p=0.01) and those with a limited disease phenotype (167 +/− 114 MNGC/well vs. 39 +/− 62 MNGC/well, p=0.03). No significant difference in MNGC formation was noted between patients with limited WG and controls (p=0.87).

Conclusion: We demonstrate for the first time that MNGCs in Wegener's granulomata in the lung have osteoclast-like features. We further show that WG patients have a higher propensity to from OC-like MNGC from the peripheral blood than do healthy controls, a feature that might be more pronounced in patients with a systemic disease phenotype. Inhibition of the pathways leading to the enhanced formation and migration of these cells to target tissues in WG might provide a novel therapeutic opportunity in this disease.

Disclosure: J. K. Park: None; **F. Askin:** None; **A. Rosen:** None; **S. M. Levine:** None.

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Protocolised Versus Non-Protocolised Rituximab Treatment for Refractory ANCA-Associated Vasculitis. Rachel B. Jones[1], Rona Smith[2], Mary-Jane Guerry[2], Simona Laurino[2], Fausta Catapano[2], Afzal Chaudhry[2] and David R. W. Jayne[1]. [1]Addenbrooke's Hospital, Cambridge, United Kingdom, [2]Addenbrooke's Hospital

Rituximab is effective new therapy for refractory ANCA-associated vasculitis. However, the majority of patients relapse after rituximab, needing further treatment courses. Relapses occur from six months onwards and are associated with organ damage and high corticosteroid exposure. Relapse avoidance is desirable; however biomarkers that accurately predict relapse are not available.

We performed a single centre cohort study comparing six monthly, protocolised rituximab re-treatment and non-protocolised rituximab re-treatment according to clinical need for refractory ANCA-associated vasculitis.

72 patients received a protocolised rituximab regimen; 1g ×2 followed by 1g ×1 every 6 months for 2 years (5g total) with early immunosuppression and corticosteroid withdrawal. 34 received non-protocolised rituximab; either 1g ×2 or 375mg/m^2 ×4 only repeated if relapse occurred.

Overall 75% patients had Wegener's granulomatosis. At first rituximab median disease duration was 55 months: prior cyclophosphamide exposure was 14g. Rituximab indication was relapsing disease in 82% of protocol and 83% of non-protocol patients; the remainder had grumbling disease whilst receiving continuous high dose corticosteroids or immunosuppression.

Median follow-up was 31 (4–56) months, protocol patients versus 22 (6–84) months, non-protocol patients. Response to rituximab occurred in 70/72 (97%) protocol patients (93% full remission, 4% partial), and 33/34 (97%) non-protocol patients (82% full remission, 15% partial). In protocol patients only 4/72 (6%) were still receiving immunosuppression at 6 months and by 24 months 26% had withdrawn from prednisolone (4.75mg/day median). At 2 years relapse had occurred in 16/72 (22%) protocol patients versus 24/34 (71%) non-protocol patients and by the end of follow-up 21/72 (29%) protocol patients, 26/34 (76%) non-protocol patients (p<0.01). Serious infections occurred in 10/72 (31%) protocol patients and 6/34 (26%) non-protocol patients.

Six monthly protocolised rituximab re-treatment is effective for relapse prevention, allows immunosuppression withdrawal and appears safe in refractory ANCA-associated vasculitis.

Disclosure: R. B. Jones: Roche, 8; **R. Smith:** None; **M.-J. Guerry:** None; **S. Laurino:** None; **F. Catapano:** None; **A. Chaudhry:** Astellas Pharma, 5, 8, Roche, 5, 8; **D. R. W. Jayne:** Roche, 5, 8.

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Xenografted Nasal Mucosa from Wegener's Granulomatosis Patients Induces Destruction of Human Cartilage in Immunodeficient Mice. Nina Kesel[2], Dorothee Köhler[2], Martin Laudien[5], Konstanze Holl-Ulrich[3], Astrid Jüngel[1], Michel Neidhart[1], Steffen Gay[1], Renate E. Gay[1], Elena Csernok[6], Wolfgang L. Gross[6], Udo Schumacher[4] and Sebastian Ullrich[4]. [1]Center of Experimental Rheumatology, University Hospital Zurich, Switzerland, [2]Dept. of Anatomy II: Experimental Morphology, University Medical Center Hamburg, Hamburg, Germany, [3]Dept. of Pathology, University Hospital of Schleswig-Holstein, Campus Lübeck, Lübeck, Germany, [4]University Medical Center Hamburg, [5]University of Kiel, Dept. of Otorhinolaryngology, Head and Neck Surgery, Kiel, Germany, [6]University of Lübeck, Dept. For Rheumatology, Vasculitis Center UKSH & Clinical Center Bad Bramstedt, Lübeck, Germany

Background: One of the hallmarks of Wegener's Granulomatosis (WG) is a destructive chronic granulomatous inflammation of the respiratory tract whose pathogenic mechanisms remain enigmatic.

Aims: The aim was to establish a xenograft model of nasal cartilage destruction in WG, to analyze the mechanisms of tissue damage and to evaluate the effect of systemic steroid treatment upon the inflammatory process.

Methods: Nasal mucosa biopsies from active and destructive WG (n=10) and active sinusitis patients were subcutaneously co-implanted in collagen sponges with healthy human nasal cartilage as aggregates (overall 36 WG vs. 48 controls), into 25 (WG) and 24 (controls) immunodeficient pfp/rag2 −/− mice. Three mice with WG transplants were treated with systemic steroids. Transplants were removed after 21 days and examined histologically. In addition, nasal fibroblasts isolated from tissue specimens from WG patients (n=8) and healthy controls were cultured and cells proliferation and apoptosis were quantified. Furthermore, mRNA and protein levels of MMP's and cytokines were evaluated at baseline and after stimulation with TNF-alpha and IL1-beta.

Results: All untreated WG aggregates showed areas of human fibroblasts invading the human cartilage 21 days after transplantation, whereas cartilage destruction was only marginal in control samples. The destructed nasal cartilage in WG samples was replaced by proliferating human fibroblasts. Systemic steroid treatment suppressed this tissue destruction completely. The human origin of the cells was confirmed by anti-human vimentin and anti-human mitochondrial antibody staining. The tissue organization of transplanted tissues (fibroblasts, T- and B- lymphocytes, follicular dendritic cells (FDC), monocytes) remained almost identical to the tissue at the time of sampling as demonstrated by immunohistochemistry. An up-regulated production of MMP 1, 3 and 13 was found in areas of tissue destruction. Stimulation of fibroblasts in cell culture with TNF-alpha and IL-1 beta resulted in a significant up-regulation of MMPs 1, 3, 13. While proliferation of isolated fibroblasts was comparable between WG and controls, WG samples showed a significant delay of apoptosis.

Discussion: These findings show for the first time that nasal tissue destruction in WG results from local mucosal inflammation and strongly relates to the local activation of fibroblasts and locally residing inflammatory cells. As in WG patients, systemic steroid treatment of the mice impaired cartilage destruction. The delay of apoptosis may explain the invasive character of granulomatous tissue. Because of its similarity with the clinical situation, this model offers new possibilities to study novel treatments in WG in a clinically relevant xenograft model.

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Rituximab for Remission Induction and Maintenance in ANCA-Associated Vasculitis: A Single-Center Ten-Year Experience in 108 Patients. Rodrigo Cartin-Ceba[3], Jason Golbin[1], Karina A. Keogh[3], Tobias Peikert[3], Fernando C. Fervenza[3], Steven R. Ytterberg[2] and Ulrich Specks[3]. [1]Long Island Lung Center, [2]Mayo Clinic, Rochester, MN, [3]Mayo Clinic

Rationale: B-cell depletion with Rituximab (RTX) and glucocorticoids has been used successfully to induce sustained remission in patients with severe refractory ANCA-associated vasculitis (AAV). The need for repeated treatments as well as the efficacy and safety of repeated and prolonged B-cell depletion for long-term remission maintenance is less clear.

Objectives: To evaluate the efficacy and safety of rituximab for remission induction and long-term maintenance in patients with chronically relapsing AAV.

Methods: Single-center observational study of all patients with AAV treated with RTX between January 2000 and May 2010. Four weekly infusions at 375 mg/m^2 were used for remission induction and maintenance. More recently, 2 weekly infusions of 1000 mg were used for remission maintenance in some patients. Patients were identified from a cohort of 637 patients with AAV followed at our institution. Participants in the RAVE trial were excluded from this analysis. Treatment response, indications for retreatment, frequency and type of clinical relapse, duration of peripheral blood B cell depletion, ANCA levels, infusion-related adverse events, and infections were abstracted from electronic medical records. Disease activity was measured using the BVAS/WG score. Data are expressed as median (interquartile range, IQR) and percentages.

Results: 108 patients with refractory AAV received glucocorticoids and at least one course of RTX therapy for remission induction; all achieved remission as measured by a BVAS/WG = 0. Fifty three patients (median age 46, IQR 28–61; 53% women) received subsequent courses of RTX for relapses or to maintain remission. All but one patient were PR3/ANCA positive. These 53 patients received a median of 4 (IQR 3–5) courses of RTX (a total of 200 courses of four weekly infusions at 375 mg/m^2, and 10 courses of two weekly infusions of 1000 mg). All patients had depletion of B cells and the median time to return of B cells was 7 months (IQR 6–11 months). All observed relapses occurred after reconstitution of B cells and were accompanied or preceded by an increase in ANCA levels except in one patient. A total of 72 (34%) courses of RTX were given due to relapse (achieving remission in all individuals) and 138 (66%) courses were given preemptively due to either B cell reconstitution or following the increase of both B cells and ANCA levels. Infusion related adverse events occurred in 7 patients and none precluded completion of treatment. During the period of B cell depletion, 8 infectious complications were observed (5 upper respiratory tract infections, 2 pneumonias, and 1 skin infection; only one patient with pneumonia required hospitalization).

Conclusion: RTX is effective and safe for induction and maintenance of remission in patients with relapsing AAV. Prolonged B cell depletion seems to be associated with a low risk of infections. Timing of retreatment can be individualized based on B cell counts and ANCA levels in these patients and the use of this treatment modality for long-term remission maintenance merits further formal investigation.

Disclosure: R. Cartin-Ceba: None; **J. Golbin:** None; **K. A. Keogh:** None; **T. Peikert:** None; **F. C. Fervenza:** None; **S. R. Ytterberg:** None; **U. Specks:** Dynavax, 5.

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Hsp60 Proteolysis by Proteinase 3 Induces Neutrophil Degranulation: Implications for Amplification of Injury in Wegener's Granulomatosis. Shinji Sato[4], Jin Kyun Park[1], Frederic Askin[3], Antony Rosen[2] and Stuart M. Levine[1]. [1]Johns Hopkins University, Baltimore, MD, [2]The Johns Hopkins University, Baltimore, MD, [3]The Johns Hopkins University, [4]Tokai University, Kamakura, Japan

Background: Extracellular proteolytic processing by proteinase 3 (PR3) released from activated neutrophils has recently been implicated in several important biological processes. Heat shock proteins are induced in response to a variety of inflammatory stimuli, and some, such as Hsp60, can be released into the extracellular environment, where they can exert pro-inflammatory functions. Whether PR3-mediated proteolysis of Hsp60 released in the WG microenvironment contributes to the inflammatory response is unknown.

Methods: Human recombinant Hsp60 was incubated for varying times with increasing concentrations of PR3, and cleaved products were detected by SDS-PAGE and immunoblotting. Polymorphonuclear cells (PMNs) were isolated from heparinized peripheral venous blood by density gradient centrifugation. Following co-incubation with intact or PR3-cleaved Hsp60, PMN degranulation was quantified using the β-glucuronidase release assay at baseline and after 90 minutes. Activity units (U) were calculated for each experiment from the observed fluorescent intensities using a standard curve obtained from serial concentrations of a dye standard. The supernatants of TNF-primed PMNs were similarly assessed for Hsp60 proteolytic activity, and the effects of PR3 inhibition using α1-antitrypsin were examined. Hsp60 expression in WG tissue was examined by immunohistochemistry.

Results: Hsp60 was efficiently cleaved by purified PR3 *in vitro* with a k_{cat}/K_m of 7.5×10^4 M $^{-1}$ S $^{-1}$. PR3-cleaved HSP60 caused significant β-glucuronidase release from PMNs at 90 minutes compared to intact Hsp60 (73.7 U +/− 22.7 vs. 30.3 U +/− 19.1, p=0.01). Upon PMN priming with TNF-α, small amounts of PR3 released in the supernatants were detected by immunoblotting. Co-incubation of these TNF-primed supernatants with Hsp60 led to Hsp60 processing that was inhibited by the PR3 inhibitor α1-antitrypsin. Subsequent incubation of fresh, non-primed PMNs with this PR3-processed Hsp60 caused significant degranulation compared to those incubated with supernatants from non-TNF-primed PMNs (51.7 U +/− 9.9 vs. 23.5 U +/− 16.7, p=0.005), demonstrating that the PR3 released by primed PMNs can cleave exogenous Hsp60 to further amplify fresh PMN degranulation. Finally, an analysis of WG lung tissues reveals that Hsp60 is highly expressed in the giant cells of WG granulomata.

Conclusions: These studies identify multinucleated giant cells in the WG granuloma as a rich source of Hsp60. TNF-primed PMNs release PR3, and PR3-cleaved Hsp60 induces further degranulation of fresh PMNs, suggesting a novel mechanism whereby PR3 participates in amplification of the local inflammatory response in WG. This reinforcing interaction of target tissue and inflammatory cells in the local WG microenvironment may be useful for disease monitoring and therapy.

Disclosure: S. Sato: None; **J. K. Park:** None; **F. Askin:** None; **A. Rosen:** None; **S. M. Levine:** None.

ACR/ARHP Combined Abstract Session
ACR/ARHP Combined Epidemiology and Health Services Research: Impact on Osteoarthritis
Monday, November 8, 2010, 2:30 PM–4:00 PM

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Unpredictability of Intermittent Knee OA Pain – Impact on Pain, Function and Mood. Gillian A. Hawker[2], Melissa R. French[3], Joy G. Elkayam[3] and Aileen M. Davis[1]. [1]Toronto Western Research Insti, Toronto, ON, Canada, [2]Women's College Hospital, Toronto, ON, Canada, [3]Women's College Hospital, Toronto, Canada

Purpose: In people with painful knee osteoarthritis (OA), focus groups identified the predictability of the pain as a key determinant of the pain impact. This study evaluated the effects of unpredictable knee pain (without warning) and pain after a trigger on the pain experience, physical functioning and mood in people with knee OA. We hypothesized that unpredictable knee pain would be associated with greater pain, worse physical functioning and more depressed mood than would predictable knee pain.

Methods: In a cohort with hip and knee OA, participants completed the OARSI-OMERACT Intermittent and Constant Osteoarthritis Pain (ICOAP) measure, WOMAC, and a measure of depressed mood (CES-D). For *each* symptomatic knee, those with intermittent knee pain were asked how often their pain occurs 'without warning' (*unpredictable* pain) or 'after a specific trigger', e.g. an activity (*predictable* pain) (0, never, to 4, very often). For those without hip complaints, the proportions with each type of intermittent pain were calculated (at least sometimes versus never/rarely). The relationships between type of intermittent pain and ICOAP and WOMAC scores were evaluated using linear regression. For each type of intermittent pain, we examined the relationship between the number of knees affected (0, 1 or 2) and ICOAP and WOMAC scores using Wilcoxon Rank Sum tests. We examined the relationship between each type of intermittent pain and depressed mood (CES-D scores), controlling for age, sex and arthritis severity (WOMAC summary score).

Results: The mean age of the 116 knee OA participants was 79.7 years (64.0 to 93.2); 74.1% were female and 23.4% had < high school education. 103 subjects (88.8%) reported intermittent knee pain in at least one knee; of these, 18.1% (n=21) had pain only after a trigger, 12.9% (n=15) had only unpredictable pain, while 44.0% (n=51) had both types of intermittent pain. Controlling for age and sex, unpredictable knee pain in one or both knees was independently associated with higher ICOAP and WOMAC scores ($p<0.05$ for all). Controlling for unpredictable knee pain, knee pain after a trigger was independently associated only with higher scores on the ICOAP intermittent scale (p=0.01). A greater number of knees with unpredictable pain was associated with higher ICOAP intermittent ($p<0.0001$) and WOMAC summary (p=0.01) scores. For pain after a trigger, this relationship was found

only with ICOAP intermittent scores ($p<0.0001$). Controlling for age, sex and arthritis severity, unpredictable knee pain, but not knee pain after a trigger, was independently associated with higher scores for depressed mood ($p=0.005$).

Conclusions: Both unpredictable pain and pain following a trigger occur commonly in people with chronic symptomatic knee OA. Compared with pain following a trigger, unpredictable knee pain is associated with greater pain and functional disability, and more depressed mood. Studies are needed to identify potentially modifiable risk factors for unpredictable knee OA pain in order to develop and test interventions to relieve this complaint.

Disclosure: G. A. Hawker: None; **M. R. French:** None; **J. G. Elkayam:** None; **A. M. Davis:** None.

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Low Positive Affect Predicts the Development of Disability over 30-Months: The MOST Study. Julie J. Keysor[1], Lisa Fredman[4], Bin Zhang[2], Daniel K. White[3], James C. Torner[8], Cora E. Lewis[6], Irina Tolstykh[7] and David T. Felson[5]. [1]Boston Univ Sargent College, Boston, MA, [2]Boston Univ Schl of Medicine, Boston, MA, [3]Boston Univ School of Med, Boston, MA, [4]Boston University, [5]Boston University School of Medicine, Boston, MA, [6]University of Alabama-Birmingham, Birmingham, AL, [7]University of California and San Francisco, San Francisco, CA, [8]University of Iowa, Iowa City, IA

Low positive affect above and beyond high depressive symptoms is linked to incident frailty among older adults. The impact positive affect has on functional outcomes is not known. Cross sectional studies have the potential flaw that good functional outcomes may make people happy, making cause and effect impossible to disentangle. We propose a longitudinal study to examine whether low positive affect predicted incident disability among adults at risk of developing disabilities.

Methods: Baseline and 30-month longitudinal data from the Multicenter Osteoarthritis (MOST) Study, a prospective cohort study of progressive and incident symptomatic knee osteoarthritis, were used for these analyses. A three-category variable representing "high positive affect", "low positive affect" and "high depressive symptoms (depressed)" was computed from the Center of Epidemiological Study-Depression Scale (CES-D). Respondents who scored less than 16 on the CES-D and who scored "most of the time" on 4 positive affect questions of the CES-D were categorized as high positive affect; whereas, those reporting anything less than most of the time on the 4 items were classified as low positive affect. Respondents whose overall CES-D score was 16 or greater were classified as depressed. Disability was ascertained using the of the Late Life Disability Instrument-Instrumental Limitation subscale (LLDI-IL). The LLDI-IL was dichotomized into no/mild disability (no disability) and moderate/severe disability (disability) based on previously established cutpoints. Age, sex, education, race, body mass index (BMI), knee pain (max score of right or left knee visual analog scale), and gait speed (m/sec) were taken from baseline data and were used as covariates. Among persons with no disability at baseline, we examined the associations between baseline positive affect and depression and the development of disability at 30-follow-up using logistic regression.

Results: 2054 subjects had no disability at baseline. The mean age of the sample was 63 years. 58% were female and 89% were white. 1381 (67%) had high positive affect; 531 (26%) had low positive affect; 141 (7%) were depressed at baseline. 260 (13%) developed disability at 30-months. Subjects who reported low positive affect and those who were depressed were more likely to report disability at 30-months compared to persons with high positive affect after adjusting for covariates. As expected, high depressive symptoms was also associated with incident disability. (Table 1)

Discussion: Compared with high positive, low positive affect increased people's risk of developing disability over a 30-month time period, even above and beyond the risk associated with depressive symptoms. Further research is needed to elicit the role positive psychological factors play in disablement.

Table 1. Unadjusted and adjusted odds ratio of low positive affect and "depressed" status compared to high positive affect.

	Event/Subjects (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
High Positive Affect	140/1381 (10%)	1.0	1.0
Low Positive Affect	79/531 (15 %)	1.5 (1.2–2.1)	1.5 (1.1–2.1)
Depressed (High Depressive Symptoms)	41/141 (29 %)	3.6 (2.4–5.4)	2.7 (1.7, 4.1)

Disclosure: J. J. Keysor: None; **L. Fredman:** None; **B. Zhang:** None; **D. K. White:** None; **J. C. Torner:** None; **C. E. Lewis:** None; **I. Tolstykh:** None; **D. T. Felson:** None.

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Potential Gender Effect on the Association between Knee Osteoarthritis and Risk of Indoor and Outdoor Falls in Elderly Men and Women. Uyen-Sa D. T. Nguyen[4], Marian T. Hannan[5], Robert H. Shmerling[2], Douglas P. Kiel[7], Suzanne G. Leveille[8], Carol A. Oatis[1], Lien Quach[6] and Yuqing Zhang[3]. [1]Arcadia University, Glenside, PA, [2]Beth Israel Deaconess Med Ctr., Boston, MA, [3]Boston Univ School of Medicine, Boston, MA, [4]Boston University School of Medicine, Boston, MA, [5]Hebrew SL & Harvard Med Sch, Boston, MA, [6]Institute for Aging Research, Hebrew SeniorLife, [7]Institute for Aging Research, Hebrew SeniorLife and Harvard Medical School, Boston, MA, [8]University of Massachusetts-Boston

Purpose: Knee osteoarthritis (OA) and falls are common in older adults and limit mobility. A few studies have linked knee OA and risk of falls. Recent research, however, suggests that some factors increased risk for indoor falls while decreased risk for outdoor falls; thus, grouping falls together may mask the true effect of a particular risk factor. Also, older men and women may differ in factors related to falls such as gait, balance, and physical activity that may modify the association between knee OA and risk of falls. To date, no study has examined the relation of knee OA with the risk of indoor vs. outdoor falls and explored whether such association differs by sex.

Methods: This analysis included 764 participants from the MOBILIZE Boston Study, a population-based cohort of elderly men and women. Knee OA was assessed at baseline using the ACR criteria. Falls data were prospectively collected using monthly calendars, with phone follow-up assessment of location of falls, and were adjudicated. Fall rate was calculated separately for indoor and outdoor falls (falls/follow-up year). We used negative binomial regression to estimate the effect of knee OA on rate of indoor and outdoor falls separately, adjusting for age, sex, BMI, medications, number of comorbidities, and history of falls. We repeated the analyses for men and women separately, and tested whether the effect of knee OA on outdoor and on indoor falls was modified by sex by adding an interaction term (i.e., knee OA*sex) in the model.

Results: Of 486 women and 278 men (mean age: 78 years, mean BMI: 27.3), 25% had ACR-defined clinical knee OA. Over an average of 2.2 years of follow-up, 60% of participants had at least 1 fall. Rates of *outdoor* falls were 49 and 34 per 100 person-years for participants with and without knee OA, respectively. The corresponding *indoor* falls rates were 53 and 39 per 100 person-years. Compared with those without knee OA, the adjusted rate ratio (RR) for outdoor falls among participants with knee OA was 1.35 (95% CI: 1.04–1.77); the corresponding RR for indoor falls was 1.21 (95% CI: 0.94–1.57). However, the effect of knee OA on risk of indoor and outdoor falls was modified by sex. In women, knee OA was strongly associated with an increased risk of outdoor falls; no such effect was observed in men (p-value for interaction=0.04). Although the interaction term was not statistically significant for indoor falls, the association of knee OA with the risk of indoor falls was stronger in men, albeit at borderline significance, than that in women (Table).

Table. The Association between Knee Osteoarthritis and Rate of Outdoor and Indoor Falls in Men and Women

	Knee OA Rate of Falls (per 100 P-Y[1])	No Knee OA Rate of Falls (per 100 P-Y)	RR (95% CI)[2]	P-Value for Interaction
Outdoor Falls				
Men	47	45	0.91 (0.60, 1.38)	0.04
Women	50	27	1.70 (1.21, 2.40)	
Indoor Falls				
Men	60	35	1.58 (0.99, 2.32)	0.22
Women	49	41	1.11 (0.82. 1.50)	

[1]Person-Years.
[2]Adjusted for age, BMI, fall-inducing medications (anti-depressants, anti-psychotics, anti-hypertensives, and sedatives), no. of co-morbidities (high blood pressure, stroke, heart disease, diabetes, ulcer/stomach disease, kidney disease, anemia, cancer/skin cancer, rheumatoid arthritis), and history of falls.

Conclusions: Knee OA was associated with an increased risk of outdoor falls, and such an association was limited to women. Knee OA also appeared to be more strongly associated with indoor falls in men. Future studies should examine specific mechanisms such as balance, gait speed, and physical activity that may explain why knee OA on the risk of outdoor vs. indoor fall are different in women from that in men.

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Increasing Prevalence of Knee Pain and Symptomatic Knee Osteoarthritis. Uyen-Sa D. T. Nguyen[5], Yuqing Zhang[2], Jingbo Niu[3], Bin Zhang[1] and David T. Felson[4]. [1]Boston Univ Schl of Medicine, Boston, MA, [2]Boston Univ School of Medicine, Boston, MA, [3]Boston University Schol of Medicine, Boston, MA, [4]Boston University School of Medicine, Boston, MA, [5]Boston University School of Medicine, Boston, MA

Purpose: Knee pain, a common complaint in older adults, limits function and mobility and is a major reason for knee replacement among those with knee osteoarthritis (OA). Obesity is a strong risk factor for knee pain and knee OA. Given the recent epidemic of obesity in the U.S., the prevalence of knee pain is projected to rise. We examined the secular trend of knee pain and knee OA prevalence and determined whether any increase in prevalence is accounted by changes in body mass index (BMI).

Methods: Data were from the Framingham OA Study (FOA) and NHANES, a nationwide population based study. Knee pain was assessed in the FOA at three exams roughly 10 years apart, in subject groups that varied from exam to exam but which were all population based, using a questionnaire that asked about pain in or around the knee lasting at least 1 month in the past 12 months. Knee pain data were also collected in the NHANES I, II, III in addition to three later surveys. In NHANES, subjects were asked about pain in or around the knee on most days for at least 1 month or 6 weeks. Starting in 1999, NHANES also specified knee pain in the past 12 months. Weight bearing anteroposterior x-rays were obtained in the FOA to define radiographic knee OA (ROA)--Kellgren Lawrence grade $\geq$ 2, and knees with both ROA and knee pain were considered as having symptomatic OA (SxOA). We estimated race- and sex-specific prevalence for each outcome by 5-year age groups, and standardized to the sex-specific, age-appropriate, 2000-census US White population distribution. We estimated prevalence ratios (PR) and 95% confidence intervals (CI) adjusting for age (years) and BMI (Kg/M^2) using Poisson regression.

Results: Included in the analyses were 3,306 participants from FOA (57% women, mean age $\pm$ SD: 70.2 $\pm$ 7.1 years) and 10,383 from NHANES (51% women, mean age $\pm$ SD: 66.6 $\pm$ 4.3). The age-adjusted prevalence of knee pain in the FOA almost tripled in a 20-year period in women, and more than tripled in men (Figure 1a). The age-adjusted prevalence of knee pain more than doubled in NHANES from 1974–1994 among White people, and continued to increase from 1999 to 2004 (Figures 1b). Similar results were found in a smaller sample of African Americans in NHANES. In FOA, there were no substantial changes in the prevalence of ROA over the period studied: 31.7%, 30.3%, and 29.0% in men; 32.7%, 34.6%, and 32.9% in women. The age-adjusted prevalence of SxOA did increase substantially over time: 5.3%, 8.2%, and 17.9% in men; 8.8%, 12.7%, and 22.6% in women. BMI adjustment explained about 25% of the increasing age adjusted prevalence of knee pain for men and women (Table).

Figure 1a. **Sex-Specific Prevalence of Knee Pain in Framingham Osteoarthritis Study**

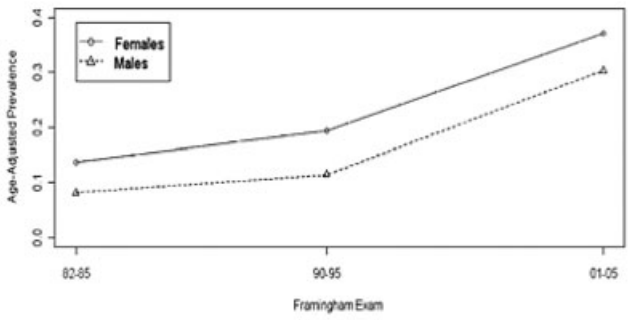

Figure 1b. **Sex-Specific Prevalence of Knee Pain in NHANES**

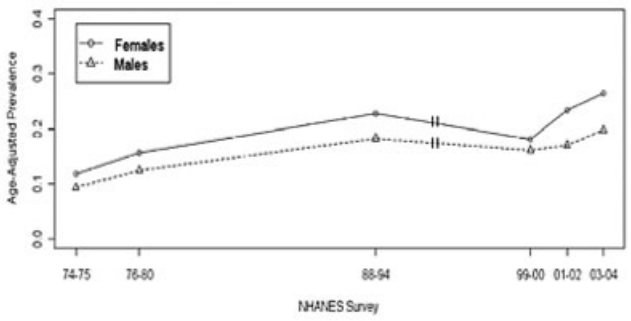

Table. Temporal Trend of knee Pain and Knee Osteoarthritis in the Framingham Osteoarthritis Study and NHANES

	Males		Females	
	Time 2 vs. 1 PR (95% CI)	Time 3 vs. 1 PR (95% CI)	Time 2 vs. 1 PR (95% CI)	Time 3 vs. 1 PR (95% CI)
Knee Pain				
Framingham OA Study 1982–2005[a]				
Adjusted for Age	1.48 (0.92, 2.34)	3.87 (2.62, 5.71)	1.22 (0.95, 1.58)	239 (1.86, 3.06)
Adjusted for Age, BMI	1.34 (0.83, 2.14)	3.16 (2.11, 4.73)	1.17 (0.91, 1.51)	2.07 (1.60, 2.67)
NHANES 1971–1994[b]				
Adjusted for Age	1.37 (1.03, 1.81)	2.00 (1.52, 2.64)	1.30 (1.02, 1.64)	1.90 (1.50, 2.39)
Adjusted for Age, BMI	1.31 (1.01, 1.78)	1.79 (1.35, 2.37)	131 (1.04, 1.66)	1.76 (1.39, 2.22)
NHANES 1999–2004[c]				
Adjusted for Age	1.09 (0.81, 1.49)	1.22 (0.91, 1.63)	1.29 (0.99, 1.69)	1.45 (1.12, 1.88)
Adjusted for Age, BMI	1.04 (0.76, 1.41)	1.10 (0.83, 1.47)	1.21 (0.91, 1.61)	1.50 (1.16, 1.95)
Knee SxOA (1982–2005)[a]				
Adjusted for Age	1.48 (0.82, 2.68)	3.52 (2.14, 5.81)	1.21 (0.87, 1.67)	2.05 (1.46, 2.88)
Adjusted for Age, BMI	1.37 (0.76, 2.48)	2.73 (1.63, 4.56)	1.12 (0.81, 1.55)	1.54 (1.08, 2.20)

[a] Framingham OA Study 1982–2005: Time 1 = 1982–1985, Time 2 = 1990–1995, Time 3 = 2001–2005.
[b] NHANES 1971–1994: Time 1 = 1974–1975, Time 2 = 1976–1980, Time 3 = 1988–1994.
[c] NHANES 1999–2004: Time 1 = 1999–2000, Time 2 = 2001–2002, Time 3 = 2003–2004.

Conclusions: Independent of age, the prevalence of knee pain has increased markedly over the last 20 years with a commensurate increase in SxOA but no evident increase in x-ray OA. While obesity has become more prevalent, it accounted for only part of this increase.

Disclosure: U.-S. D. T. Nguyen: None; **Y. Zhang:** None; **J. Niu:** None; **B. Zhang:** None; **D. T. Felson:** None.

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Community Mobility Barriers Predict the Development of 30-Month Disability: The MOST Study. Julie J. Keysor[1], Bin Zhang[2], James C. Torner[6], Cora E. Lewis[4], Irina Tolstykh[5] and David T. Felson[3]. [1]Boston Univ Sargent College, Boston, MA, [2]Boston Univ Schl of Medicine, Boston, MA, [3]Boston University School of Medicine, Boston, MA, [4]University of Alabama-Birmingham, Birmingham, AL, [5]University of California at San Francisco, San Francisco, CA, [6]University of Iowa, Iowa City, IA

Longitudinal studies linking the physical environment to incident disability are scarce. The purpose of this study is to examine whether mobility-related factors in the community environment are associated with the development of 30-month disability among older adults with functional limitations.

Methods: Data from the Multicenter Osteoarthritis (MOST) Study, a cohort study of persons with or at high risk of developing symptomatic knee OA, and the MOST-Knee Pain and Disability (MOST-KPAD), a MOST sub-cohort study of older adults with functional limitations were used. Community mobility barriers (BAR) (e.g., uneven sidewalks or other walking areas, parks and walking areas that are easy to get to and easy to use, places to sit and rest) and transportation facilitators (FAC) (e.g., public transportation close to home, public transportation with adaptations for people with disabilities, handicap parking, and car available) were ascertained at baseline using the Home and Community Environment scale. Disability was ascertained at baseline and 30-months using the Late Life Disability Instrument-Instrumental Limitation subscale and was dichotomized into no/mild disability and moderate/severe disability (disability) based on previously established cut-points. Among persons with no/mild disability at baseline, we examined the associations between baseline BAR and FAC dichotomized scores and development of disability at follow-up using logistic regression and adjusting for age, sex, race, education, body mass index, pain, walking speed, and site.

Results: Among 302 subjects who had baseline scores of no/mild disability and 30-month follow-up disability data, 50 (17%) developed disability at follow-up. The mean age of the sample at baseline was 70.3 (SD=3.9) years. 69% were women; 94% were white; 67% completed at least some college education. Overall the sample had mild pain (mean=28, SD=20, range 0–98) and functional limitation (gait speed: mean =1.2m/sec, SD=0.2, range 0.6–1.6). Subjects who reported high BAR at baseline were twice as likely to develop moderate/severe disability at 30-month follow-up compared to persons who reported low community barriers after adjusting for covariates. Report of high FAC was modestly protective of incident disability though this did not reach statistical significance. (Table 1)

Table 1. Odds of Developing Moderate/Severe Disability Over 30-Months by Features of the Community Environment

	Number of Subjects (%) Developing Moderate/ Severe LLDI-IL	Crude OR (95% CI)	Adjusted OR* (95% CI)
Community Mobility Barriers (BAR)			
Low BAR	27/219 (12)	1.0	1.0
High BAR	23/83 (28)	2.7 (1.5–5.1)	2.4 (1.2, 4.6)
Transportation Facilitators (FAC)			
Low FAC	23/112 (21)	1.0	1.0
High FAC	27/190 (14)	0.6 (0.3–1.2)	0.7 (0.3–1.3)

* Adjusted for age, sex, race, education, body mass, index, pain, walking speed, and site

Discussion: Mobility-related features of the environment may have an impact on development of disability over a 30-month time period.

Disclosure: J. J. Keysor: None; **B. Zhang:** None; **J. C. Torner:** None; **C. E. Lewis:** None; **I. Tolstykh:** None; **D. T. Felson:** None.

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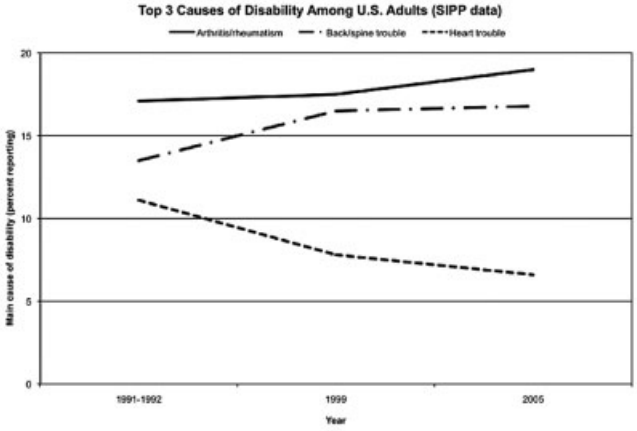
When 1st Is Worst: Musculoskeletal Conditions Maintain 15 Year Reign as the Most Common Cause of Disability in US Adults. Kristina Theis[4], Jennifer M. Hootman[3], Charles G. Helmick[2] and Matthew Brault[1]. [1]Bureau of the Census, [2]CDC, Atlanta, GA, [3]Centers for Disease Control, Kennesaw, GA, [4]Centers for Disease Control and Prevention

Background: As the population ages and arthritis and related disability become more prevalent, the documented rheumatology workforce shortage and need to expand evidence-based public health interventions will be even more important. We describe the prevalence, causes of, and trends in disability among US adults.

Methods: The Survey of Income and Program Participation (SIPP) is a longitudinal panel survey fielded by the US Census Bureau representing the civilian, non-institutionalized US population. Panel members undergo in-person interviews at 4-month intervals for a period of 2.5–4 years. In 1991/1992 (T1), 1996 (T2), and, most-recently, 2005 (T3) a cross-sectional disability topic module was administered to panel adults to identify the prevalence and causes of self-reported disability (difficulty with ≥1 specified functional activities, activities of daily living, instrumental activities of daily living, selected impairments, use of an assistive aid, or limitation in ability to work around the house or at a job or business (1996 and 2005 only)). Analyses weighted to population controls and incorporating sampling weights produced estimates of disability prevalence and cause, from each disability module.

Results: The number of US adults reporting disability has increased from 42 million (T1) to 44.1 (T2) to 47.5 million (T3). Overall, the most common causes of disability at all 3 time-points were arthritis/rheumatism, back or spine problems, and heart trouble. Women report twice the prevalence of disability due to arthritis/rheumatism (26.9% T1; 22% T2; 24% T3) compared with men (13.7% T1; 11% T2; 11.5% T3) making it the most common cause of disability among women. Although women and men have similar prevalence of disability due to back/spine problems at all time points (15.3% T1; 16.6% T2; 16.3%T3 vs. 16.0% T1; 16.8% T2; 16.9% T3), back/spine problems are the most common cause of disability among men and the 2nd most common cause of disability among women. The number and percent of adults reporting disability due to musculoskeletal conditions (MSK) (arthritis/rheumatism and back or spine problems) has risen consistently from T1 to T3, while heart trouble, the next most common cause of disability, has decreased in absolute number and % prevalence. In fact, six of the 10 most common causes of disability have either declined or remained level from T1 to T3, while MSK have increased.

Conclusion: Medical and public health providers must prepare for greater demands on the healthcare and public health systems with the aging population, including training more providers in the diagnosis and management of MSK and increasing reach of evidence-based programs that address modifiable lifestyle characteristics (e.g., physical inactivity and obesity) that contribute to disability, particularly among those with MSK.



Disclosure: K. Theis: None; **J. M. Hootman:** None; **C. G. Helmick:** None; **M. Brault:** None.

ARHP Concurrent Abstract Sessions
Physical Activity: Just "Move It"
Monday, November 8, 2010, 2:30 PM–4:00 PM

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Does Physical Activity Dose Predict Physical and Mental Health-Related Quality of Life in People with Arthritis? Dina L. Jones, Ruoxin Zhang, Melissa Himes and Jennifer L. Eicher. Morgantown, WV

Background: Little is known about the relationship between health-related quality of life (HRQOL) and physical activity (PA) dose in people with arthritis (PWA). A prior survey indicated that PWA who met national PA recommendations had fewer unhealthy days per month due to physical or mental health. To further explore this relationship, we analyzed baseline data in PWA in an exercise intervention to determine if HRQOL improved over increasing increments of PA dose.

Methods: Sedentary adults with self-reported physician-diagnosed arthritis were enrolled in a 12-week, community-based, exercise intervention using the EnhanceFitness® program. Baseline data were collected on demographics, comorbidities, arthritis symptoms, performance-based physical function (Senior Fitness Test), body mass index (BMI), self-efficacy, outcome expectations, self-reported PA, and HRQOL. The CHAMPS Activities Questionnaire for Older Adults assessed the typical weekly frequency and duration of participation in 41 leisure/daily activities. Dose was the number of hours spent per week in moderate- or vigorous-intensity leisure activity: 1) inactive (0 mins), 2) insufficiently active (1–149 mins), and 3) meeting recommendations (≥ 150 mins). The SF-12 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores were used to measure HRQOL. Two stepwise multiple linear regression procedures, with dose forced into each model, were performed to determine if dose predicted the PCS or MCS after adjusting for other covariates.

Results: The study included 173 participants (83% female) with a mean age of 69 ± 10.4 years. Univariate predictors of the PCS included dose ($p = 0.01$) and comorbidities ($r = -.36$), pain ($r = -.38$), stiffness ($r = -.47$), fatigue ($r = -.33$), BMI ($r = -.36$), number of chair stands in 30 secs ($r = .43$), number of seconds to walk 8 feet ($r = -.37$), number of steps marched in 2 mins ($r = .36$), self-efficacy ($r = .38$), outcome expectations ($r = .35$), and arthritis limitations (all $p < 0.001$). The best set of predictors in the PCS model were dose ($\beta = 2.7–2.9$, $p = 0.1$), stiffness ($\beta = -.68$, $p = 0.03$), chair stands ($\beta = .70$, $p = 0.003$), BMI ($\beta = -.24$, $p = 0.01$); pain ($\beta = -.83$, $p = 0.02$), and number of steps ($\beta = .08$, $p = 0.04$) ($R^2 = .47$). Univariate predictors of the MCS included dose ($p = 0.04$); employment ($p = 0.001$); outcome expectations ($r = .19$, $p = 0.02$); and age ($r = .36$), pain ($r = -.29$), stiffness ($r = -.23$), fatigue ($r = -.42$), comorbidities ($r = -.42$), and self-efficacy ($r = .34$) (all $p < 0.001$). The best set of predictors in the MCS model were dose ($\beta = 2.3–2.6$, $p = 0.25$), comorbidities ($\beta = -.26$, $p = 0.01$), age ($\beta = .38$, $p < 0.001$), and fatigue ($\beta = -1.37$, $p < 0.001$) ($R^2 = .36$).

Conclusion: Although PA dose predicted mental and physical HRQOL when considered alone, the relationship did not remain after adjusting for other factors. After controlling for dose, physical HRQOL was better in PWA with less pain and stiffness, a lower BMI, and better performance on physical

function tests. Mental HRQOL was better in PWA with fewer comorbid conditions, lower fatigue, and older age, after adjusting for dose. Future research could further investigate this relationship longitudinally by examining changes in dose and HRQOL over time.

Disclosure: D. L. Jones: None; **R. Zhang:** None; **M. Himes:** None; **J. L. Eicher:** None.

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Ready and Waiting: Adults with Arthritis Are Interested in Population-Based Physical Activity Programs. Louise Murphy[2], Teresa J. Brady[2], Kristina A. Theis[2], Julie Bolen[2] and Patience White[1]. [1]Arthritis Foundation, [2]Centers for Disease Control and Prevention

Background: Dissemination of population-based packaged physical activity (PA) programs among people with arthritis has been limited. Our study objective was to identify characteristics of adults with arthritis who are most likely to attend two types of evidence-based PA programs.

Method: We analyzed data from a national U.S. phone survey of white and black adults (n=1,002), ages 40–70 years old, who have doctor diagnosed arthritis ("Have you EVER been told by a doctor or other health professional that you have some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?), and "some" or "many" arthritis attributable activity limitations (AAAL). Participants rated how likely (i.e., very or somewhat likely, or not very or not at all likely) they would be to attend each of a generic and an arthritis-specific PA program. We estimated the percent who reported that they were very likely to attend each type of program and examined correlates (e.g., demographics, symptoms, number of comorbidities) of interest for each using multivariable adjusted logistic regression with odds ratios (ORs) and 95% confidence intervals (CI); CIs that did not overlap OR=1 were statistically significant.

Results: 30% reported being very likely to attend at least one type of PA program; among those who were very likely, 42% were interested in both, 32% in a generic program only, and 26% in arthritis-specific only. In the multivariable analysis, four groups were significantly more likely to have high interest in generic programs: women (OR=1.6), blacks (OR=2.5; ref=whites) and those with ≥3 comorbidities (OR=3.0; ref=no comorbidities) or who were very likely to attend a generic or arthritis-specific self-management education program (SME) (OR=16.5; ref=not very likely to attend either SME). For the arthritis-specific PA program, interest was significantly higher among women (OR=1.7) and respondents with less than a high school education (OR=3.3; ref=completed high school), some AAALs (OR=1.8; ref=many AAALs), who disagreed that there was nothing they could do to manage their arthritis (OR=1.6; ref=agreed), or who were very likely to attend an SME (OR=16.4 respectively; ref=no interest in either SME).

Conclusion: Approximately a third of respondents were very likely to attend at least one type of PA program. Interest was consistently higher among women and those who were very likely to attend an SME. Specific target groups for the two types of programs emerged: whereas blacks and people with multiple comorbidities had a greater interest in generic programs, those with some AAALs or less than a high school education had greater interest in arthritis-specific programs. Our findings indicate a demand for population based PA programs among a select but substantial group of adults with arthritis. The shared interest in SME and PA programs suggest that this group is eager for opportunities to learn self-management strategies. Clinical and public health practitioners can be encouraged that their efforts in program delivery are important. These study findings may help practitioners identify specific subgroups who are most ready for referral to community based PA programs.

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Evaluation of Tai Chi Course Effectiveness for People with Arthritis. Leigh F. Callahan[1], Jack H. Shreffler[3], Betsy S. Hackney[3], Kathryn Remmes Martin[2] and Brian Charnock[3]. [1]Univ of North Carolina, Chapel Hill, NC, [2]University of North Carolina, Chapel Hill, Chapel Hill, NC, [3]University of North Carolina, Chapel Hill

Purpose: To evaluate the effectiveness of the Arthritis Foundation's 6-week Tai Chi course in reducing symptoms, increasing function, and improving psychosocial status in participants with arthritis using a community based randomized control trial (RCT).

Methods: At baseline, 332 participants were registered at 20 sites in North Carolina or New Jersey and randomly assigned to treatment (172) or delayed control (160). All participants received baseline and 6-week follow-up evaluations, after which the control group received the course. No adverse events were noted during the course. Self-report Instruments included pain, fatigue and stiffness visual analog scales (VAS), Health Assessment Questionnaire (HAQ), general health, Rheumatology Attitudes Index (RAI, helplessness), and Arthritis self-efficacy (ASE) for pain and symptoms. Participants also completed the PROMIS™ (PR) Short Form instruments for sleep disturbance and satisfaction with social roles. Physical performance measures were time to complete 3 chair stands, normal and fast gait speed, single leg stance, and reaching ability. The follow-up rate was 75% (120 control; 128 treatment). Regression analyses related the change in score from baseline to 6-week follow-up to the intervention status, with adjustment for baseline value, age, gender, and BMI.

Results: There are no significant differences between treatment and control groups at baseline. The participants were 85% female, with average age of 65 (19–89) and BMI of 28.5. The group was highly educated, 15% with high school diploma and 82% continuing beyond high school. The racial breakdown was 85% Caucasian and 11% African American. Results of the regression analyses showed significant ($p<0.05$) modest improvements in the treatment group for reported pain, fatigue and stiffness VAS (effect sizes ES=0.27, 0.23, 0.29, respectively). Moderate significant improvements were also seen in helplessness (RAI, ES=0.35), self-efficacy (ASE) for pain (ES=0.26) and symptoms (ES=0.35) of arthritis, PR sleep disturbance (ES=0.43), and PR satisfaction with social roles (0.31). Total of four reaching spans (left, right, forward, backward) showed significant improvement after treatment (ES=0.31).

Conclusions: Participants in the AF Tai Chi program showed improvements in pain, fatigue, and stiffness and sense of well-being related to psychosocial variables. The HAQ measure of physical function did not indicate significant change, and the physical performance measures involving chair stands, gait speed and single leg stance were not improved convincingly. The ability to reach while maintaining balance improved, perhaps reflecting the nature of the Tai Chi training and movements.

Disclosure: L. F. Callahan: None; **J. H. Shreffler:** None; **B. S. Hackney:** None; **K. R. Martin:** None; **B. Charnock:** None.

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Walk with Ease Program: One-Year Follow-Up. Leigh F. Callahan[2], Jack H. Shreffler[4], Mary Altpeter[4], Laura O. Houenou[4], Britta Schoster[4], Kathryn Remmes Martin[3], Jennifer M. Hootman[1] and Todd Schwartz[4]. [1]Centers for Disease Control, Kennesaw, GA, [2]Univ of North Carolina, Chapel Hill, NC, [3]University of North Carolina at Chapel Hill, Chapel Hill, NC, [4]University of North Carolina, Chapel Hill

Purpose: One year after completing the Arthritis Foundation's 6-week Walk with Ease (WWE) group or self-directed mode of intervention, participants were evaluated to determine their adherence to the WWE program and to see what improvements in physical function, symptoms and psychosocial variables were noted

Methods: 403 individuals who completed the 6 week follow-up assessment (178 group, 225 self-directed) were mailed a self-report questionnaire designed to assess physical function, arthritis symptoms, psychosocial variables, and continuation of the WWE program at one year after the intervention completion. Repeated measures regression models were used to fit the data from baseline, 6-weeks, and 1-year. Responses were required at all time points for inclusion in the model. An indicator was included for mode of intervention (self-directed or group). Results were adjusted for age, education, gender, race, and BMI.

Results: 158 (89%) group and 204 (91%) self-directed participants completed the 1 year follow-up questionnaire. At 6-weeks, there were significant improvements in nearly all self-report measures and physical performance measures (not included in 1 year follow-up) regardless of the mode of intervention (presented previously). For both the group and self directed intervention modes, 2 measures show significant improvements at one year from baseline: PROMIS satisfaction with social roles (effect sizes ES=0.33/0.27); arthritis self-efficacy (ASE) for handling pain (ES=0.17/0.17). There were 7 outcomes where self-directed participants showed significant improvement from baseline, while the group participants did not: Health Assessment Questionnaire (HAQ) (ES =0.21); pain (ES=0.38) and stiffness (ES=0.31) Visual Analog Scales (VAS); general health (ES=0.17);

Rheumatology Attitudes Index (RAI, helplessness) (ES=0.28); PROMIS depression (ES=0.17); and ASE for dealing with symptoms (ES=0.22). The follow-up rate at 1-yr was similar for both modes, but 60% of group participants continued walking versus 70% of the self-directed participants. The most frequently cited reason for stopping walking for both modes was "pain, stiffness, or fatigue" (42%/36%). The group participants also cited "other health problems" more frequently (33%) than the self-directed (17%).

Conclusions: Both group and self-directed participants maintained some benefits 1 year after the WWE intervention. However, self-directed participants were more likely to continue walking and retained improvement in more self-reported physical function, symptoms, and psychosocial outcomes. Two factors could influence this finding. First, the self-directed participants were on average about 5.7 years younger than those in the group sessions. Second, the self-directed have chosen a mode of intervention that suited their proclivity to act alone, while the group participants may be stimulated by group instruction but have less inclination to continue after the course ended.

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Fit and Strong!: Bolstering Maintenance of Physical Activity among Older Adults with Lower-Extremity Osteoarthritis. Susan L. Hughes[4], Rachel B. Seymour[4], Richard T. Campbell[3], Pankaja Desai[3], Gail Huber[2] and Justina Chang[1]. [1]JAMA, [2]Northwestern University, [3]University of Illinois Chicago, [4]University of Illinois Chicago, Chicago, IL

Osteoarthritis (OA) is the most common condition affecting older people today. Lower extremity joint impairment caused by osteoarthritis has been shown to be a risk factor for future disability. Physical activity (PA) has been shown to play a critical role in the amelioration of symptoms and progress of the disease. However, little is known about effective ways of motivating older adults to maintain PA after a formal training program ends. Fit and Strong! is an award winning, evidence-based multiple-component PA/behavior change program for older adults with lower-extremity (LE) OA. This study used a multi-site comparative effectiveness trial (N=486) with repeated measures to compare the impact of negotiated vs. mainstreamed follow-up with and without telephone reinforcement (TR) on maintenance of PA after the 8-week Fit and Strong! program ends. Random effects analyses for the total sample showed significant pre-post improvements at 2,6,12, and 18 months on PA maintenance that were accompanied by significant improvements in LE pain and stiffness, LE function, sit-stand, and 6-minute distance walk and anxiety and anxiety/depression. Analyses by treatment condition showed that persons in the negotiated group who received TR maintained a 21% increase in caloric expenditures over baseline, with lesser benefits seen in the negotiated only, mainstreamed with TR, and mainstreamed only groups. Significant benefits of telephone dose were also seen on lower-extremity joint stiffness, pain, and function as well as anxiety and anxiety/depression. The negotiated follow-up contract that Fit and Strong! uses, bolstered by TR, is associated with enhanced long-term PA maintenance and associated health outcomes. While TR was effective, it is not inexpensive, which may impede its translation and dissemination into community-based settings. Other forms of reinforcement, like participant and instructor videos will also be important to test if we are to maximize the successful translation of evidence-based programs in the future.

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Characteristics of Persons with or at High Risk of Knee OA Achieving Recommended Physical Activity Levels: The MOST Study. Daniel K. White[1], Tuhina Neogi[2], Jingbo Niu[2], Michael Nevitt[3], C. Elizabeth Lewis[4], James Torner[5] and Doug Gross[2]. [1]Boston University, Boston, MA, [2]Boston University, [3]University California San Francisco, [4]University of Alabama, [5]University of Iowa

The CDC recommends physical activity for multiple health benefits with walking being the most common means of obtaining physical activity. However, as few as 24% for persons with self reported arthritis meet these guidelines. Among persons with radiographic knee osteoarthritis (ROA), it is not known how many satisfy these guidelines, nor which factors are associated with meeting them. Hence, we examined the characteristics of persons with or at high risk of ROA that meet activity guidelines as measured by an accelerometer-enabled monitor.

The Multicenter Osteoarthritis Study (MOST) is a NIH funded longitudinal study of people who have or are at high risk for knee OA. Subjects at the 60 month visit wore an accelerometer-enabled monitor to record walking activity over 7 days. Using a disablement model framework, we evaluated pathology, impairment, functional limitation, and psychosocial characteristics associated with meeting CDC guidelines. Specifically, we examined ROA and total knee replacement (TKR) (pathology), knee pain (impairment), self reported difficulty walking and walking at a pedestrian speed (>1.2 m/s) in the clinic (functional limitation), and depressive symptoms (psychosocial). We defined meeting CDC guidelines as walking at least 80 steps per minute for 150 minutes over 7 days. We compared disablement characteristics among persons meeting and not meeting activity guidelines using prevalence ratios adjusted for age, sex, BMI, race, number of comorbidities, and presence of widespread pain.

Of 806 subjects (Age 62 ± 8 yrs, BMI 31 ± 6 kg/m2, female 69%), 174 (22%) met CDC guidelines for physical activity. These persons were more often male with a lower mean age and BMI, and did not have widespread pain. In adjusted models pathology was not associated with meeting CDC guidelines, however persons with bilateral knee pain, self reported difficulty walking, and those who could not walk at a pedestrian speed were 40% to 80% less likely to meet CDC guidelines than their counterparts (see table).

Pathology-related characteristics (ROA and TKR) were not associated with meeting CDC guidelines, whereas pain and functional limitation characteristics were associated. These findings may be encouraging to providers given that these latter factors are potentially modifiable.

		% meeting CDC Guidelines (number meeting guidelines/all subjects)		
Age	50–59 years	28 (86/303)		
	60–69 years	19 (62/330)		
	70–79 years	15 (26/173)		
Sex	Male	25 (63/251)		
	Female	20 (111/555)		
BMI	<30	31 (40/129)		
	30–34	19 (46/245)		
	>35	10 (16/157)		
Comorbidities	None	25 (140/550)		
	≥1	13 (34/252)		
Widespread pain	Absent	25 (118/478)		
	Present	17 (56/324)		
		% meeting CDC guidelines	Adjusted Prevalence Ratio*	95% CI
ROA	None	28 (90/321)	1.0	Ref
	Unilateral	24 (41/168)	0.9	0.6, 1.4
	Bilateral	17 (32/193)	0.8	0.5, 1.3
TKR	None	24 (164/699)	1.0	Ref
	Present	9 (10/107)	0.6	0.3, 1.3
Knee pain	None	31 (94/298)	1.0	Ref
	Mild unilateral	25 (39/157)	0.9	0.6, 1.4
	Mild bilateral	13 (4/30)	0.5	0.3, 0.8
	Mod/Sev unilateral	16 (31/196)	0.4	0.1, 1.7
	Mod/Sev bilateral	5 (6/122)	0.2	0.1, 0.6
Depressive symptoms	CES_D <16	22 (160/715)	1.0	Ref
	CES_D≥16	16 (14/87)	0.8	0.4, 1.5
Difficulty walking	No	29 (135/467)	1.0	Ref
	Yes	5 (39/336)	0.6	0.4, 0.9
Walking speed	≥1.2 m/s	33 (127/389)	1.0	Ref
	1.2 m/s	11 (45/394)	0.4	0.1, 1.0

* Adjusted few age, sex BMI, race, the number of comorbities, and widespread pain.

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Parvovirus B19 Non-Structural Protein NS1 Forms Adducts with Cellular DNA, Induces Apoptosis, and Is Condensed in Apoptotic Bodies: A Model for Viral Induction of Autoantibodies and Systemic Lupus Erythematosus. Leona Gilbert[3], Pavan K. Dhanyamraju[3], Eoin Wallace[3], Elina Dadu[3], Liping Wang[3], Harry J. Whitlow[3], Violetta Kivovich[1] and Stanley J. Naides[2]. [1]Pennsylvania State University, Milton S. Hershey Medical Center, [2]Quest Diagnostics Nichols Institute, San Juan Capistrano, CA, [3]University of Jyväskylä, Finland

Background: Human parvovirus B19 causes acute illness with many features of systemic lupus erythematosus (SLE) including transient antinuclear, anti-dsDNA and antiphospholipid antibodies. B19 may persist in various tissues, e.g. in liver, where it may cause a "restricted" infection with expression of the viral non-structural protein NS1, but little or no capsid protein. NS1 is a superfamily 3 (SF3) helicase typical of DNA viruses. Our group previously reported that expression of enhanced green fluorescent protein-NS1 (eGFP-NS1) fusion protein induced NS1 bulky adduct formation and single strand nicks in hepatocyte DNA leading to caspase 9 mediated apoptosis. Excess nucleosomes and apoptotic bodies are seen in the blood in SLE patients.

Objective: In order to construct a model for B19 induced abrogation of tolerance to self-DNA, we determined whether NS1-DNA adducts survived apoptosis by examining surface blebs and extruded apoptotic bodies for B19 NS1, DNA and proteins known to be autoantigens in SLE.

Methods: The liver-derived cell line, HepG2, was transduced with recombinant baculovirus hosting eGFP, eGFP-NS1 or eGFP-NS1 with a mutation in the NS1 putative metal coordination site. At 48 hours post-transduction, apoptotic cells and bodies were evaluated by scanning electron microscopy (SEM), comet assay, flow cytometry and confocal microscopy.

Results: eGFP-NS1, but not eGFP, transduced cells showed increased surface blebs post-transduction. An eGFP-NS1 mutant with a deletion in the putative metal coordination site, dMetal, showed decreased blebbing. eGFP-NS1, but not eGFP, induced DNA damage as demonstrated by comet formation, while a site directed mutant, Metal 1, and dMetal constructs where intermediate. Of purified apoptotic bodies, 87% induced by eGFP-NS1 fluoresced compared to only 28% in eGFP transduced cultures. Confocal imaging of apoptotic cells showed surface blebs containing NS1, dsDNA, and histone H4. Purified apoptotic bodies showed surface phosphotidylserine by Annexin V staining, internal DNA by DAPI staining, eGFP-NS1, histone 4, proliferating cell nuclear antigen, and lysosomal antigen Lamp2, but not histone H2B.

Conclusions: B19 NS1 expression damages host cell DNA and induces apoptosis. NS1 bulky adduct modified self-DNA is condensed into apoptotic bodies in the presence of nuclear and cytoplasmic self-proteins. Antigen presenting cells could ingest these apoptotic bodies, present NS1 peptides, and activate NS1 specific T cells. The last could provide costimulatory signals to anergized anti-DNA B cells presenting NS1 peptides processed after surface Ig mediated uptake of NS1-modified nucleosomal DNA. Epitope spreading would allow expansion of autoantibody specificities. The presence of similar SF3 helicases in other DNA viruses, e.g. Epstein Barr nuclear antigen 1, EBNA1, suggests that this model may more broadly explain viral induction of DNA autoantibodies and SLE disease.

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Occurrence of Rheumatoid Arthritis-Associated Autoantibodies in Leishmania Donovani Infection. Erik Åhlin[1], Amir Elshafie[2], Musa A. M. Nur[4], Sayda Hassan El Safi[3] and Johan Rönnelid[1]. [1]Clinical Immunology Unit, Uppsala University, Uppsala, Sweden, [2]Clinical Immunology Unit, Uppsala University, Uppsala, Sweden. Department of Pathology and Microbiology, Alribat University Hospital, Khartoum, Sudan, [3]Department of Microbiology and Parasitology, Faculty of Medicine, University of Khartoum, Sudan, [4]Unit of Rheumatology, Alribat University Hospital, Khartoum, Sudan

Background: The presence of antibodies against citrullinated peptides (anti-CCP) and rheumatoid factors (RF) are closely associated with rheumatic diseases but are also seen in a number of infectious diseases. Our aim with this investigation was to evaluate the occurrence of anti-CCP, RF and circulating immune complexes (CIC) in Sudanese patients infected with the Leishmania donovani parasite. The infection causes an internal disease called visceral leishmaniasis (VL) with an immunopathology characterised by a strong humoral immune response with high production of antileishmanial antibodies, CIC, and polyclonal activation of B-lymphocytes, all factors that could give rise to rheumatic-like manifestations.

Methods: Serum samples were collected from 136 Leishmania infected patients and 85 healthy Sudanese controls. Twenty-one Sudanese anti-CCP positive RA patients diagnosed following the 1987 ACR criteria were also included in the study. Levels of CIC were measured by a solid-phase C1q assay. Anti-CCP was measured using a commercial ELISA-test kit. A control plate with cyclic peptides containing arginine instead of citrulline as the antigen was used to evaluate citrulline specific reactivity. Rheumatoid factor was measured by nephelometry.

Results: Among both Leishmania-infected patients and anti-CCP positive RA patients the majority (86% in both groups) were RF positive while the frequency of CIC positivity was higher among VL patients (VL: 38%, CCP pos. RA: 24%). When anti-CCP reactivity was analysed, 11% of VL patients were found to be positive. The levels of anti-CCP among VL patients correlated well to the CIC levels found (rho: 0.59, $p<0.001$). In the RA group no association was found between CIC and anti-CCP. To rule out the possibility that anti-CCP positivity was due to cross reactions with CIC, we adsorbed C1q binding CIC from sera and evaluated CCP reactivity afterwards. This procedure did not diminish the anti-CCP reactivity in either the VL group or among anti-CCP positive RA patients. We then went on to analyse the citrulline specificity among anti-CCP positive patients. All anti-CCP-positive VL patients showed equivalent reactivity towards CCP and the non citrullinated control peptide. This was in strict contrast to the anti-CCP positive Sudanese RA patients among whom anti-CCP was restricted to CCP ($p<0.0001$).

Conclusions: In this study we found that sera from Leishmania infected patients were often RF positive, had elevated CIC levels and that a substantial amount showed reactivity towards CCP. However, contrary to what was seen in RA sera, the CCP reactivity was not restricted to citrulline. This argues that this is an effect of extensive inflammation and immune activation more than a sign of shared pathogenic characteristics with anti-CCP positive arthritis. Furthermore, our findings stress the importance to interpret a positive CCP test carefully.

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IL-12p70 Alteration in Antibiotic Treatment of *Chlamydia*-Induced Reactive Arthritis (ReA). Robert D. Inman[1], Basil Chiu, Alan P. Hudson[3] and John D. Carter[2]. [1]Toronto Western Hospital, Toronto, ON, Canada, [2]Univ of South Florida, Tampa, FL, [3]Wayne State Univ Schl of Med, Detroit, MI

Background: A recent study of combination antibiotics has proved to be effective for the treatment of *Chlamydia*-induced ReA, but the immune events underlying clinical response with this treatment have not been defined. In the present study we examine the cytokine signatures of patients enrolled in that randomized controlled trial.

Methods: Patients with chronic *Chlamydia*-induced ReA were randomized to a 6-month course of Rifampin + Azithromycin (AR), Rifampin + Doxycycline (DR), or placebo (PCB). Serum samples were obtained at baseline, 6 months, and 9 months after the start of treatment. The assay system was a multi-analyte ELISA, which quantitatively assays serum levels of 42 cytokines.

Results: Analysis of covariance (ANCOVA) was used to test whether treatment has an effect on cytokine values at second time point after removing the variance account of the cytokine values at the first time point. P-values were utilized to determine if the difference in means were significant for [DR vs. Placebo], [AR vs. Placebo], [global p-values for previous two tests] and [DR or AR vs. Placebo] respectively. Using a univariate analysis, the following cytokines showed significant ($p<0.05$) treatment effects: EGF (AR *vs* PCB), GM.CSF (DR *vs* PCB), IFN-γ (DR *vs* PCB), IL-1ra (AR *vs* PCB), TGF-α (AR *vs* PCB) and VEGF (AR *vs* PCB) and IL-12p70 (DR *vs* PCB and AR *vs* PCB). IL-12p70 demonstrated the most significant treatment effect ($p<0.001$ for both AR and DR). After Bonferroni adjustment for multiple test

correction, treatment effect only remains significant for IL-12p70 (at both 6 months and 9 months).

Conclusion: IL-12p70 is required for optimal host IFN-γ T cell response against intracellular pathogens and endocervical IL-12 expression has previously been shown to decline with clearance of *Chlamydia*. The distinctive changes in serum levels of IL-12p70 following antibiotic treatment of *Chlamydia*-induced ReA point toward changing host cytokine responses concurrent with clinical improvement, and highlight the importance of IFN-γ in this process.

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The Efficacy and Safety of Vaccination Against H1N1 in Patients with Rheumatoid Arthritis, Systemic Lupus Erythematosus, Psoriatic Arthritis and Ankylosing Spondylitis. Ori Elkayam[2], Sharon Amir[2], Michal Mandelboim[1], Ella Mendelson[1], Jonathan Wollman[2], Uri Arad[2], Daphna Paran[2], David Levartovsky[2], Irena Wigler[2] and Dan Caspi[2]. [1]Center of Virology, Sheba Medical Center, [2]Department of Rheumatology, Tel Aviv Medical Center

Background: In spring 2009, a new swine-origin influenza virus A (H1N1) quickly spread worldwide prompting the development of pandemic H1N1 influenza vaccine launched by the end of 2009.

Purpose: To assess the efficacy and clinical safety of vaccination against H1N1 in patients suffering from Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), Psoriatic Arthritis (PsA) and Ankylosing Spondylitis (AS) in comparison with healthy controls.

Patients and Methods: The study population comprised 4 groups of patients and healthy controls: 41RA patients: 56% female, age: 52.6±14.5, disease duration: 9 years;21SLE patients: 66% female, age: 41.7±11.5, disease duration: 11 years;17 PsA: 35% female, age: 48.5±11.8, disease duration: 12 years; 15 AS: 20% female, age: 47.2±13.3, disease duration: 14 years; 17 healthy controls: 60% female, age: 47.3±11.3. All the subjects were vaccinated against H1N1 using the Novartis MF59-adjuvanted H1N1v monovalent influenza vaccine, Focetria®. Each 0.5 ml dose contained 7.5 μg H1N1 HA antigen and the full dose of the oil-in water emulsion adjuvant, MF59®, containing 9.75 mg squalene. The immunogenicity of the vaccine was assessed on day 1 and 4 weeks after by hemagglutination inhibition (HI) assay. Geometric mean titers (GMT) and seroconversion rates were calculated for each group. Seroconversion rates were calculated as the percentages of each group that displayed seroconversion in initially seronegative subjects or a significant increase in titer in initially seropositive subjects (a four-fold increase in titer in those < 40 prevaccination).The safety of the vaccine was evaluated using Disease activity score (DAS) for RA and PsA, Systemic Lupus Index disease activity (SLEDAI) for SLE and BASDAI for AS.

Results: The proportion of baseline protective levels of antibodies against H1N1 was similar in most groups, except for AS patients: RA: 23%, SLE: 24%, PsA: 29%, AS: 7% and healthy controls: 29%.A significant increase in GMT was observed in the 5 groups. A substantial proportion of patients and controls responded to the vaccine, Healthy controls demonstrating a better response (Table 1). Multivariate logistic regression analysis identified RA and PsA as parameters of significant lower response. Treatment with Infliximab and Leflunomide was associated with a lower response.DAS, BASDAI and SLEDAI remained unchanged after vaccination.

Table 1

	Healthy controls (n = 17)	RA (n = 41)	SLE (n = 21)	PsA (n = 17)	AS (n = 15)
GMT0	4.38	5.72	6.91	5.6	2.33
GMT1	85.67	64.29	70.93	55.5	57.04
Proportion of responders	82%	56%	67%	59%	53%
%seroprotection 0	29%	23%	24%	29%	7%
%seroprotection 1	88%	71%	76%	76%	60%

0 - Baseline 1–4 weeks after vaccination.

Conclusions: Vaccination against H1N1 using an adjuvanted H1N1v monovalent influenza induced an appropriate response in patients with RA, SLE, PsA and AS. The vaccine was found to be safe in this cohort of patients.

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Serious Infection in Rheumatoid Arthritis Patients Switching Anti-Tumor Necrosis Factor Drugs. Bao-Anh Nguyen-Khoa[2], Earl L. Goehring, Jr[2], Kimberly Alexander[1], Wei Dong[1], Pavel Napalkov[1] and Judith K. Jones[2]. [1]Genentech, South San Francisco, CA, [2]The Degge Group Ltd, Arlington, VA

Purpose: Rheumatoid arthritis (RA) patients commonly change drug therapy for reasons of safety or effectiveness. This study describes rates of first serious infection among RA patients who switch from one anti-Tumor Necrosis Factor (aTNF) drug to another aTNF compared to those who do not switch.

Methods: Subjects with RA who received only an aTNF drug (infliximab, etanercept, or adalimumab) were observed in a large health claims database from 1/1/2001 to 12/31/2007. Non-switchers (NS) remained on one aTNF during the study period, Switchers (S) had at least one change to another aTNF. Index dates were defined as the day of the first aTNF claim for NS, and the day of the treatment switch for S. Baseline data were collected for the 365 days of enrollment prior to the index date. Serious infections included those which required IV antibiotics or hospitalization; only the first event was included in incidence rate estimates. Two attributable risk periods were used: 1) infection occurring ≤ 90 days from a prior claim for an aTNF (90-Day) and 2) any infection occurring after the index date (Ever-Treated). Data were stratified by 1-year and ≥ 2 years post-index. Cox regression was used to compare serious infection rates, adjusting for age, gender, selected comorbidities, Charlson comorbidity score, hospitalizations, and other RA treatments.

Results: There were 13,752 RA patients in the NS cohort, and 2,293 in the S cohort. In the 90-Day model, unadjusted rates of first serious infection was nonsignificantly lower for NS vs S (6.31/100 PY, 95% CI: 6.01–6.62 vs. 6.78/100 PY, 95% CI: 5.95–7.67). Rates of first serious infections declined from 8.59/100 PY and 8.72/100 PY in the first year post-index for NS and S, to 2.66/100 PY and 2.64/100 PY ≥ 2 years post-index.

In the Ever-Treated model, NS also had nonsignificantly lower unadjusted first infection rates than S (8.45/100 PY 95% CI: 8.10–8.80 vs. 9.10/100 PY, 95% CI: 8.15–10.12). Rates of first serious infection declined from 10.15/100 PY and 10.11/100 PY in the first year post-index for NS and S, to 4.18/100 PY and 4.44/100 PY ≥ 2 years post-index.

Regression analysis showed no significant difference between NS and S cohorts in the risk of serious infection for either attribution model (90-Day HR=0.93, 95CI: 0.74–1.17; Ever Treated HR=0.94, 95CI: 0.78–1.15). First and second year rates were not different between NS and S. Significant predictors for increased risk of serious infection included: age ≥ 50 years; positive history of serious or opportunistic infection, diabetes, respiratory disease; baseline Charlson score ≥ 2, or increasing number of hospitalizations. The effect of methotrexate on infection was conditionally related to several other risk factors.

Conclusions The risk of a serious infection was not different between RA patients that switched aTNF drugs and those who did not. Indications for switching an aTNF drug could not be captured in this study. Rates in the Ever-Treated model were generally higher than the 90-Day model for overall, 1-year, and ≥ 2 years post-index. Regardless of switching status, the rate of first infection 1-year post-index was up to 3 times greater than 2+ years post-index.

Disclosure: B.-A. Nguyen-Khoa: None; **E. L. Goehring, Jr:** None; **K. Alexander:** Genentech and Biogen IDEC Inc, 3; **W. Dong:** Genentech and Biogen IDEC Inc, 3; **P. Napalkov:** Genentech and Biogen IDEC Inc, 3; **J. K. Jones:** None.

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Defining Latent and/or Disseminated Active Tuberculous Infection with TST, Quantiferon Gold and Multisite Cultures in TNFi Exposed Individuals. Dilrukshie Cooray[2], James S. Louie[4], Rosalinda C. Moran[1] and George A. Karpouzas[3]. [1]Harbor- UCLA Medical Center, Carson, CA, [2]Harbor-UCLA Medical Center, Torrance, CA, [3]Harbor-UCLA Medical Center, Long Beach, CA, [4]University of California Los Angeles, Los Angeles, CA

Background: Patients (pts) receiving Tumor Necrosis Factor-α inhibitors (TNFi) are at increased risk for developing granulomatous infections with Mycobacterium tuberculosis (MTB) or non-tuberculous mycobacteria (NTM). Prior to starting TNFi, baseline screening for latent MTB includes tuberculin skin testing (TST) and/or ex vivo cellular responses to mycobacterial antigens [Quantiferon (QFN)] in addition to chest x-ray (CXR).

Clinically asymptomatic pts who have mycobacterial reactivity [TST or QFN positive (+)] and a negative (-) CXR are treated with Isoniazid (INH) for 9 mos. High risk pts on continued TNFi are still prone to subsequent infection and seroconversion and thus should be regularly monitored; however, the frequency and/or sequence of these screening schedules have not yet been standardized. The use of QFN assays in pts receiving TNFi has not yet been proven and more data is needed in this area. We found that the combination of TST and QFN testing may be a prudent strategy in monitoring pts on TNFi.

Methods: We report on 483 pts treated with TNFi between 11/1/2000 and 6/1/2010 in a single institution. Pts received at least one month (mo) of adalimumab (ADA), etanercept (ETN), Golimumab (GO), or loading dose of infliximab (IFX) 3mg/kg at 0,2, and 6 weeks. Screening TST and/or QFN assay plus CXR were obtained at baseline and (-) pts were serially re-screened yearly while on TNFi. Induration of > 5mm was considered a (+) TST. Those who were asymptomatic with a new (+) TST and/or QFN were tested for disseminated active disease with cultures and polymerase chain reaction (PCR) of sputum, urine, and stool (for MTB and NTM), along with CXR and chest CT.

Results: Of 481 pts exposed to TNFi, 447 pts received baseline TST; 127 (28%) had baseline (+) TST and 35/127 (28%) had old granulomatous disease (OGD) on CXR but were clinically asymptomatic. All 127 pts were treated as LTBI with INH for 9 mos. One pt developed active TB while on TNFi despite completion of LTBI treatment. The remaining 320 TST (-) pts had sequential annual TST re-screens, and 56 also underwent QFN testing. Thirty-seven of 320 (11%) pts developed a (+) TST (15.28±5.74 mm) while on TNFi. Of 56 QFN tested pts, 9 were (+) overall: 2 at baseline prior toTNFi and 7 after TNFi exposure. Two pts were QFN and TST (+); 5 had (+) QFN and (-) TST. Although clinically asymptomatic, all 41 pts with (+) TST and/or (+) QFN were assessed for dissemination as above; 9/41 (22%) pts had (+) cultures (2 with MTB, 7 with NTM). 3 of these pts were treated with multidrug anti-TB therapy and the rest were treated with INH. All patients continued TNFi without adverse outcomes to date (1589 PT-Years).

Conclusion: In high risk populations with rheumatic conditions, there is a high prevalence of LTBI both at baseline and upon subsequent rescreens while on TNFi. Our expanded cohort has combined yearly testing of TST with QFN assay. We propose conducting combined annual TST and QNF testing in all high risk individuals on TNFi and consider (+) pts for Chest CT, multisite cultures and PCR to evaluate for active disseminated disease.

Disclosure: D. Cooray: Amgen Inc., 8; **J. S. Louie:** Abbott Immunology Pharmaceuticals, 5, 8, Amgen Inc., 5, 8, Genentech and Biogen IDEC Inc, 5, Pfizer Inc, 5, 8, UCB, Inc., 5; **R. C. Moran:** None; **G. A. Karpouzas:** Abbott Immunology Pharmaceuticals, 8, Centocor, Inc., 8.

ACR Concurrent Abstract Sessions
Miscellaneous Rheumatic and Inflammatory Diseases
Monday, November 8, 2010, 4:30 PM–6:00 PM

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Progressive Multifocal Leukoencephalopathy Associated with Biologic and Synthetic DMARD Therapy in Rheumatic Diseases: An Analysis of the FDA Adverse Event Reporting System Database. Eamonn S. Molloy[2] and Leonard H. Calabrese[1]. [1]Cleveland Clinic Foundation, Cleveland, OH, [2]St Vincent's University Hospital, Dublin, Ireland

Background: PML is a rare and often fatal opportunistic infection recently associated with several biologic therapies. Unfortunately the general understanding of PML is poor and ascribing risk to individual therapies has been problematic. This study examined the aggregate experience of PML reported in association with autoimmune disorders and biologic DMARD exposure in the FDA Adverse Event Reporting System (AERS) database through review of MedWatch forms.

Method: A Freedom of Information Act request was submitted for all cases of PML and/or JC virus infection within the FDA AERS database from November 1, 1997 to March 31, 2009. All MedWatch forms received at the time of this analysis were reviewed; those with identified autoimmune diseases and/or exposure to rituximab, anti-TNF antagonists, anakinra, or abatacept were selected for further analysis. PML was classified as confirmed, possible or unconfirmed. Other data collected from the forms included demographics, critical clinical and lab features and disease association cofactors of PML.

Results: A total of 473 cases were received and analyzed. Among all cases, 114 (24%) were found to have one or more autoimmune diseases, 40 of which were categorized as autoimmune rheumatic diseases (15 RA, 15 SLE, 6 vasculitis, 4 other).Of these 40 cases, 18 were considered 'confirmed' cases of PML based on the available information. Of these, 6 were treated with biologic agents (5 rituximab, 2 infliximab – 1 patient received both). Neither case associated with infliximab could clearly be attributed to the use of this agent – 1 subsequently received rituximab for dermatomyositis and the other was treated with cyclophosphamide for rheumatoid vasculitis. No confirmed cases were reported in association with the use of other biologic DMARDs such as other anti-TNF agents, anakinra or abatacept. The remaining 12 non-confounded, confirmed cases of PML among autoimmune rheumatic disease patients were treated with synthetic DMARDs only (7 cyclophosphamide (5 of whom subsequently received mycophenolate mofetil) and 5 others). Of 12 autoimmune rheumatic disease cases of 'possible' PML, 7 were associated with biologic therapies (5 anti-TNF therapy, 2 rituximab, 2 abatacept – 1 patient received adalimumab prior to rituximab, 1 received anti-TNF therapy prior to abatacept).

Conclusion: PML is a reported complication of a variety of disease states and associated with both synthetic and biologic immunosuppressive therapies. While the small numbers of cases involved precludes attribution of causality, two points deserve emphasis. The relative paucity of confirmed cases in patients treated with anti-TNF therapy, despite their widespread use, suggests that a causal relationship is unlikely. In contrast, there is a concerning, albeit rare, signal emerging regarding use of rituximab, especially considering that 5 cases of PML among rituximab-treated RA patients, in addition to those reported in this analysis, have been reported to Genentech. Nevertheless, until greater clarity can be achieved, all patients treated with immunosuppressive therapies for autoimmune disease should be considered at risk for PML.

Disclosure: E. S. Molloy: Genentech and Biogen IDEC Inc, 5; **L. H. Calabrese:** Abbott Laboratories, 5, Amgen Inc., 5, Centocor, Inc., 5, Elan, 5, Genentech and Biogen IDEC Inc, 5, Roche, 5.

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Tocilizumab in Refractory Adult Still's Disease: A Cohort Study. Xavier Puéchal, Michel de Bandt, Jean-Marie Berthelot, Maxime Breban, Jean-Jacques Dubost, Olivier Fain, Jean-Emmanuel Kahn, Laurence Lequen, Maïté Longy-Boursier, Aleth Perdriger, Thierry Schaeverbeke, Eric Toussirot, Jean Sibilia and The CRI. Center for Rare Systemic and Auto-immune Diseases, Department of Rheumatology, Le Mans, France

Background: Interleukin-6 (IL-6) is thought to play a role in the pathogenesis of Still's disease. We report the first series of patients with adult Still's disease (ASD) treated with tocilizumab (TCZ), a humanized anti-IL-6 receptor antibody.

Objectives: To assess the efficacy and tolerance of TCZ in adult patients with refractory ASD.

Methods: Cohort study of all patients with ASD treated in France with off-label TCZ between July 2006 and July 2009 and enrolled in a specific French Agency for the Safety of Health Products (AFSSAPS) protocol.

Main Outcome Measures: European League of Associations for Rheumatology (EULAR) improvement criteria and resolution of systemic symptoms at 3 and 6-month follow-up.

Results: Fourteen patients were included in this study. At the start of TCZ treatment, despite a mean prednisone dose of 23.3 mg/day, mean tender joint count was 10.5/28, swollen joint count was 7.9/28 and mean DAS28 was 5.61. Recurrent systemic involvement, including fever and rash, was present in seven patients. TCZ was administered at 5 to 8 mg/kg every two or four weeks (8 mg/kg/month, n=9). Eleven patients successfully completed the six-month study; one withdrew due to necrotizing angiodermatitis, another due to thoracic oppression at each TCZ infusion and a third due to systemic flare. A good EULAR arthritis response was observed in 64% (9/14) of patients at three months and EULAR arthritis remission in 57% (8/14) at six months. Systemic symptoms were resolved in 86% (6/7) of patients. Moreover, corticosteroid dose was reduced by 56%. No other severe adverse effects occurred.

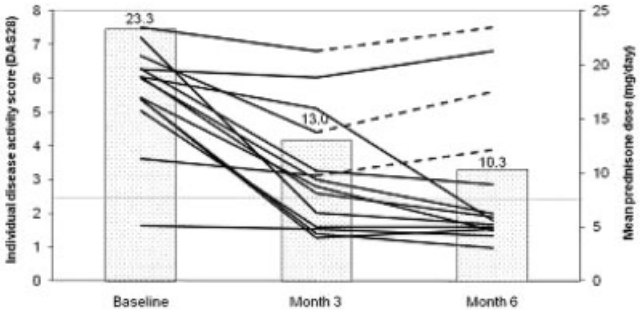

Figure. Individual disease activity score and mean prednisone dose before and after tocilizumab therapy in adult Still's disease.

Conclusions: In this cohort of patients with intractable refractory ASD, TCZ was effective against systemic involvement of the disease in almost all patients and led to arthritis remission in half the patients, showing a marked corticosteroid-sparing effect and an acceptable tolerance profile. TCZ is a promising new treatment for ASD.

Disclosure: X. Puéchal: None; **M. de Bandt:** None; **J.-M. Berthelot:** None; **M. Breban:** None; **J.-J. Dubost:** None; **O. Fain:** None; **J.-E. Kahn:** None; **L. Lequen:** None; **M. Longy-Boursier:** None; **A. Perdriger:** None; **T. Schaeverbeke:** None; **E. Toussirot:** None; **J. Sibilia:** None; **The CRI:** None.

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Clinical Implications of the NMO-IgG Antibody and Overlapping Neuromyelitis Optica Spectrum Disorder in Patients with Connective Tissue Disease and Myelitis. Jason R. Kolfenbach[1], Brian J. Horner[3] and Sterling G. West[2]. [1]Division of Rheumatology, University of Colorado at Denver, Aurora, CO, [2]University of Colorado at Denver, Aurora, CO, [3]University of Colorado Denver School of Medicine

Objective: To identify the presence of neuromyelitis optica spectrum disorders (NMOSD) in patients with acute myelitis and suspected connective tissue disease (CTD), and to determine if the presence of NMOSD or the NMO-IgG antibody is associated with poor clinical outcomes

Methods: Seventeen patients with myelitis were identified from a university-based rheumatology clinic and prospectively followed. Clinical follow-up extended from July 1998 to February 2010. The diagnosis of myelitis was based on fulfillment of criteria established by the Transverse Myelitis Consortium Working Group, and/or diagnosis by a board-certified neurologist. Longitudinal myelitis (LM) was defined as T2 enhancement on spinal MRI of $\geq$ 3 contiguous vertebral segments. Inflammatory myelitis not meeting the criteria for LM was classified as transverse myelitis (TM). Optic neuritis (ON) was diagnosed by a board-certified neurologist or neuro-ophthalmologist. Clinical data and serologic profile were used to determine the presence of neuromyelitis optica (NMO) or NMOSD according to established criteria. Disease course and response to treatment were recorded. Statistical comparisons were calculated using Fishers exact testing.

Results: Eight of 15 (53%) patients diagnosed with a CTD and acute myelitis met criteria for NMOSD. Additionally, two patients had full-spectrum NMO without evidence of co-existent CTD. Optic neuritis was more commonly seen in Sjogren's syndrome (SS) than in systemic lupus erythematosus (SLE) (83% vs. 0%; p = 0.02), as was the serum NMO-IgG antibody (67% vs. 0%; p = 0.06). Full-spectrum NMO was diagnosed in four of six patients with primary SS, one of four with Sjogren's-associated overlap syndrome, and none of the five with SLE alone [Table]. Among patients with follow-up data (N= 15), all six with NMO-IgG positivity suffered relapse compared to 3/9 patients that were NMO-IgG negative (p = 0.03). Furthermore, patients who were positive for the NMO-IgG antibody suffered a total of 20 relapses (51 patient-years of follow-up) compared to four total relapses among 3/9 patients that were negative for the NMO-IgG antibody (114.5 patient-years of follow-up). Five of six patients with the NMO-IgG antibody were treated with rituximab in our series; evidence of clinical benefit included relapse cessation in some patients as well as prevention of LM and ON in a patient with transverse myelitis and the NMO-IgG antibody.

Table. Serologic profile & clinical characteristics of patients with CTD and myelitis

	SS (N = 6)	SLE (N = 5)	SS/SLE (N = 2)	MS/SS (N = 2)
Autoantibodies				
NMO-IgG	4/6 (67%)	0/5 (0%)	1/2 (50%)	0/2 (0%)
ANA	5/6 (83%)	5/5 (100%)	2/2 (100%)	2/2 (100%)
SS-A	5/6 (83%)	1/5 (20%)	0/2 (0%)	2/2 (100%)
SS-B	1/6 (17%)	0/5 (0%)	0/2 (0%)	1/2 (50%)
RF^+	3/5 (60%)	0/4 (0%)	0/1 (0%)	1/2 (50%)
Clinical features:				
LM	3/6 (50%)	2/5 (40%)	1/2 (50%)	0/2 (0%)
ON	5/6 (83%)	0/5 (0%)	1/2 (50%)	0/2 (0%)
Presence of NMO				
NMO	4/6 (67%)	0/5 (0%)	1/2 (50%)	0/2 (0%)
NMOSD	5/6 (83%)	2/5 (40%)	1/2 (50%)	0/2 (0%)

+: Some patients did not have RF testing performed; denominator represents patients with available results.
Abbreviations: NMO: Neuromyelitis optica; NMOSD: Neuromyelitis optica spectrum disorder; LM: longitudinal myelitis; ON: optic neuritis; MS/SS: overlap multiple sclerosis & Sjogren's syndrome.

Conclusion: NMOSD was common in our patients with CTD and autoimmune myelitis. Full-spectrum NMO and presence of the NMO-IgG antibody was more common among patients with SS than SLE. The presence of the NMO-IgG antibody was associated with disease relapse and may suggest the need for prolonged immunosuppressive therapy, supporting current recommendations for the treatment of NMO.

Disclosure: J. R. Kolfenbach: None; **B. J. Horner:** None; **S. G. West:** None.

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Diagnostic Significance of Serum Interleukin-18 Level in Adult-Onset Still's Disease. Junko Maruyama[3], Shigeko Inokuma[1] and Noboru Hagino[2]. [1]Japanese Red Cross Medical Center, [2]The University of Tokyo Hospital, [3]Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

Purpose: To investigate the diagnostic significance and a cut-off value of serum interleukin-18 (IL-18) in adult-onset Still's disease (AOSD) patients.

Methods: We retrospectively analyzed serum IL-18 levels in 41 febrile patients with ferritin level elevation (>1,000 ng/mL) in our hospital from 2000 to 2008. They were compared between 16 patients who were finally diagnosed with AOSD and 25 patients with other diseases. Serum IL-18 levels were also compared between 16 AOSD patients and 5 hemophagocytic syndrome (HPS) patients associated with other diseases among the 25.

Results: The median levels of serum IL-18 were 99,106 pg/mL (interquartile range [IQR] 145,484) in patients with AOSD, 1,365 pg/mL (IQR 1,899) in other febrile patients ($p<0.000005$, vs. AOSD), and 2,709 pg/mL (IQR 4,408) in HPS patients with other diseases ($p=0.0017$, vs. AOSD). According to the receiver operating characteristic curve analysis, a cut-off IL-18 level of >20,000 pg/mL had a sensitivity of 93.8% and a specificity of 96.0% for diagnosing AOSD. There was no difference in serum ferritin levels among the groups.

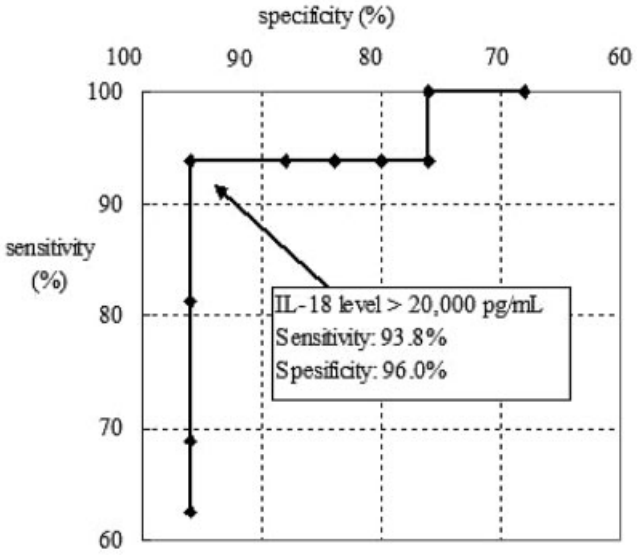

Figure. ROC curve analysis of serum IL-18 level for diagnosing AOSD.

Conclusions: Serum IL-18 level is a powerful diagnostic test for AOSD.

Disclosure: J. Maruyama: None; **S. Inokuma:** None; **N. Hagino:** None.

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Extrapulmonary Course of Connective Tissue Disease and Survival after Lung Transplant. Troy K. Takagishi, Iffat Ahmed and Rodney Tehrani. Loyola University Medical Center

Purpose: Interstitial lung disease (ILD) is a common cause of morbidity and mortality in patients with connective tissue diseases (CTD). Lung transplants (LT) are becoming an increasingly viable option for the management of these patients. A review of the literature revealed no studies evaluating for extrapulmonary flares of the primary CTD following LT. Very few studies have documented the survival outcomes of this group of patients. We hypothesize that extrapulmonary disease flares rarely occur following LT and also that survival (%) is similar in patients with LT for CTD as compared to LT for COPD.

Methods: We performed an observational and retrospective chart review of all patients in a large tertiary care medical center that had a LT for CTD (LT/CTD) between 1999 and 2010 and evaluated for any extrapulmonary flares of the primary CTD following LT. Also, we compared their survival outcomes to those who underwent LT for COPD (LT/COPD). COPD was chosen as the control group because it comprises the largest group of patients undergoing LT nationally. From 1995–2008 there had been 8,417 LT due to COPD documented in the UNOS national registry which is compared to 181 for CTD during the same time period.

Results: From 1999–2010 at a large tertiary care medical center, 15 patients underwent LT for ILD secondary to their CTD: 5 with dermatomyositis or polymyositis (33%), 5 with rheumatoid arthritis (33%), 3 with lupus (20%), and 2 with mixed connective tissue disease (13%). 4/15 (27%) of the patients had an extrapulmonary flare of their primary CTD following LT. All episodes were arthritic flares (3 monoarticular and 1 polyarticular) and each occurred in a different patient (3 with RA and 1 with SLE). This data equates to 1 flare/15.71 patient years. The Kaplan-Meier survival curves for LT/CTD and LT/COPD respectively at 3 mo was 93% and 93%; at 1 yr was 92% and 93%; at 5 yrs was 75% and 77%.

Conclusion: There is no published literature on the extrapulmonary manifesations of CTD following LT. There is only scarce data on the survival outcome of this patient population. We found that extrapulmonary flares of the primary CTD are extremely rare following LT likely due to the use of immunosuppressants for LT. In addition, survival following LT for CTD was found to be equivalent to that for LT for COPD. LT appears to be a viable option in a select group of patients with end stage ILD secondary to CTD.

Disclosure: T. K. Takagishi: None; **I. Ahmed:** None; **R. Tehrani:** None.

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Idiopathic Retroperitoneal Fibrosis: Treatment-Related Outcomes and Predictors of Clinical Response. Tanaz A. Kermani[1], Cynthia S. Crowson[2], Sara Achenbach[2] and Harvinder S. Luthra[1]. [1]Mayo Clinic, Rochester, MN, [2]Mayo Clinic

Purpose: 1) To compare outcomes by treatment type, and 2) to determine baseline variables associated with treatment response, in 151 patients with retroperitoneal fibrosis (RF) followed at a single tertiary-care center.

Methods: In this retrospective study, incident cases of RF diagnosed between 1/1/1996 and 12/31/2006 were included. RF was defined by compatible imaging findings. Medical records were reviewed and treatment and outcomes were abstracted.

We defined 4 response types: partial response (stabilization/improvement in imaging findings on stable medical regimen for 1 year), complete response (stabilization/improvement in imaging findings on a stable medical regimen with discontinuation of prednisone for 1 year), remission (stabilization/improvement in imaging findings off all therapy for 1 year), and relapse (worsening imaging findings 1 year after an initial response). Patients were followed until last contact, death or December 31, 2009. Kaplan-Meier methods were used to compare outcomes by treatment group. Cox proportional hazard models were used to evaluate the association between baseline variables and treatment response.

Results: We identified 185 patients with RF, mean age at diagnosis 57.6 (±11.8) years. Follow-up was available in 151 patients which included 87 men (58%) and 64 women (42%); median length of follow-up 4.0 years (total 671 person-years).

Forty-seven patients (31%) were treated with medications only (Group 1), 67 patients (44%) received medications and ureteral stenting (Group 2) and 20 patients (13%) were treated with medications and ureterolysis (Group 3). Commonly prescribed medications were prednisone (96 patients), tamoxifen (107 patients) and methotrexate (46 patients). Five patients (3%) who received no treatment and 12 patients (8%) treated only with stenting or ureterolysis were not analyzed due to small numbers.

At baseline, all 3 treatment groups were similar in age at diagnosis, ethnicity, sex, smoking status, anemia, ESR and CRP ($p>0.05$). However, baseline creatinine (Cr) was elevated in 2 patients (4.4%) in Group 1 compared to 39 patients (62%) in Group 2 and 11 patients (55%) in Group 3 ($p<0.001$). Also, more patients in Groups 2 and 3 had hydronephrosis compared to Group 1 ($p<0.001$).

Kaplan-Meier curves for the 3 groups were similar for all response types ($p>0.05$). At 2 years from diagnosis, 59% of all patients achieved at least partial response. Relapses occurred in 18 patients. There were no differences in relapse rates by treatment group ($p=0.198$). Age at diagnosis, ethnicity, sex, smoking status, anemia, ESR, CRP, elevated Cr, or hydronephrosis did not predict any response type.

Conclusions: This is the largest series to systematically evaluate treatment outcomes and predictors of response in RF. We defined 4 response types. While patients with baseline renal insufficiency or hydronephrosis were more likely to undergo a urologic procedure, the outcomes for all treatment groups analyzed were similar. No baseline variables were associated any response type. Our findings suggest that regardless of baseline Cr, with close follow-up and appropriate treatment (medical and surgical), the overall outcomes were good.

Disclosure: T. A. Kermani: None; **C. S. Crowson:** None; **S. Achenbach:** None; **H. S. Luthra:** None.

ACR Concurrent Abstract Sessions

Osteoarthritis - Clinical Aspects: Genetics, Novel approaches, and Therapy

Monday, November 8, 2010, 4:30 PM–6:00 PM

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Clinical Trial of Vitamin D To Reduce Pain and Structural Progression of Knee Osteoarthritis (OA). Timothy E. McAlindon[3], Bess Dawson-Hughes[5], Jeffrey Driban[4], Michael LaValley[2], Ji Yeon Lee[4], Grace H. Lo[1], Melynn Nuite[4] and Lori Lyn Price[4]. [1]Baylor College of Medicine, [2]Boston University School of Public Health, [3]Tufts Medical Center, Boston, MA, [4]Tufts Medical Center, [5]USDA HNRC; Tufts University

Background: Observational epidemiologic studies suggest that vitamin D may reduce the structural progression of knee OA, an effect that could be mediated through bone or chondrocyte mechanisms. The aim of this study was to test for disease-modifying effects of a vitamin D intervention strategy for knee OA.

Methods: This was a 2-year, NIH-funded, double–blind, placebo-controlled clinical trial among individuals with symptomatic knee OA (ACR criteria). Randomization was blocked and stratified by disease severity (Kellgren Lawrence (KL) grade). The intervention consisted of vitamin D3 2000 IU daily (Tishcon Corp, NY), which was escalated in increments of 2000 IU as needed at 3,6, and 9 months, for a target serum vitamin D level of >30 ng/ml. Blinding was maintained by the use of a dummy escalation protocol in the placebo group. Assessments included the WOMAC questionnaire at each visit, physical function tests; annual MRI (Siemens Avanto 1.5T; sagittal and coronal IW FS and DESS sequences); and standardized semi-flexed knee radiography at the beginning and end of study. Cartilage volume and thickness, and bone marrow lesion (BML) volume, in the index tibial and femoral compartments, were determined by manual segmentation of registered images using Analyze©. Intra-tester reliability ICCs were .96 & .90 for cartilage volume and volume loss, and.87-.98 for BML volume. Minimal radiographic joint space width was measured using a semi-automated computer program. Primary outcomes were WOMAC pain and cartilage volume loss. To test for differences we used mixed effects regression for repeated measures with linear, or linear and quadratic time trends, with adjustment for KL grade, knee alignment, and body mass index (BMI).

Results: Out of 282 screened, 146 subjects were randomized (mean age 62.4 [s.d. 8.5]; 57% female; 79% Caucasian; mean BMI 30.7 kgm-2 [5.7]; 56% taking supplements; mean vitamin D level 22.3 ngml-1 [10.0]; femoral neck BMD 0.95 gcm-2 [0.14]). 50% had KL grade 2, 29% grade 3 and 21% grade 4. The groups were evenly balanced for these characteristics and outcome measures (Table). 124 (85%) completed the study. Mean serum vit D level increased by 15.0 ng/ml in vitamin D compared to 1.8 in the placebo group ($p<0.0001$). There were no substantial or significant between-group

differences in any the outcome measures (Table). In the repeated measures analyses, neither treatment assignment nor increase in serum vitamin D level had any influence on the outcomes. There were 28 serious adverse events in the vitamin D and 23 in the placebo group, all classified as unrelated except one 'possibly related' (hip fracture).

	Vitamin D Group		Placebo Group	
	Baseline	Δ*	Baseline	Δ*
WOMAC Pain	6.86 (3.78)	−2.14 (3.79)	5.81 (3.41)	−1.20 (4.00)
Chair Stand Time (s)	19.8 (7.2)	−1.06 (5.56)	18.6 (5.8)	−1.30 (6.67)
Tibia				
cartilage volume (mm^3)	1010 (437)	−39.2 (36.5)	1148 (473)	−42.5 (32.5)
cartilage thickness (mm)	1.17 (0.39)	−0.06 (0.06)	1.21 (0.36)	−0.05 (0.04)
BML volume (cm^3)	15.8 (28.0)	0.17 (14.5)	13.6 (19.4)	−1.71 (18.2)
Femur				
cartilage volume	4212 (1349)	−167 (118)	4740 (1273)	−182 (131)
cartilage thickness	1.77 (0.36)	−0.06 (0.04)	1.84 (0.30)	−0.06 (0.05)
BML volume	8.5 (15.0)	0.34 (14.37)	9.4 (14.2)	−3.52 (9.88)
Minimum JSW (mm)	3.25 (1.64)	−0.20 (0.73)	3.39 (1.67)	−0.16 (0.72)

All between-group p-values >0.05.

Conclusions: Vitamin D supplementation at a dose sufficient to elevate serum levels above 30 ng/ml does not appear to have any symptom or structure-modifying benefits for knee OA.

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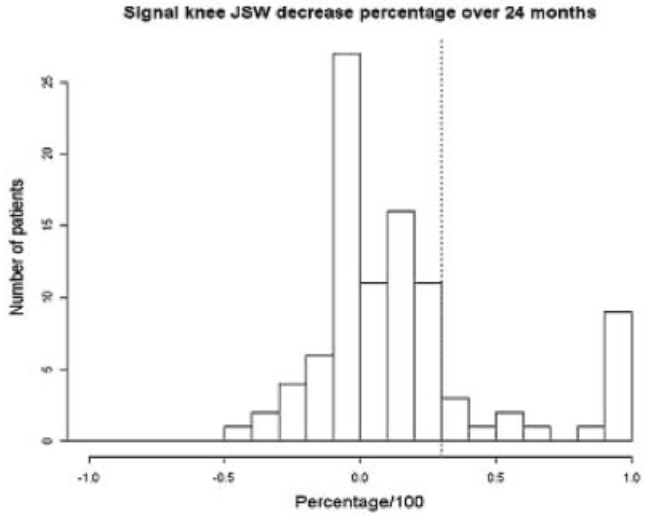
Interleukin-1 Receptor Antagonist (IL-1RN) Gene Variations Predict the Severity and Progression of Knee Osteoarthritis. Mukundan Attur[8], Cheongun Oh[7], Svetlana Krasnokutsky[6], Jonathan Samuels[5], Leon Rybak[9], Jenny Bencardino[9], Jeffrey D. Greenberg[1], Virginia Kraus[2], Kenneth Kornman[4] and Steven B. Abramson[3]. [1]Millburn, NJ, [2]Duke University Medical Center, Durham, NC, [3]Hospital for Joint Dis/NYU, New York, NY, [4]Interleukin Genetics, [5]New York University Hospital for Joint Disease, New York, NY, [6]NYU Hospital for Joint Disease, New York, NY, [7]NYU-Hospital for Joint Diseases, [8]NYU-Hospital for Joint Diseases, New York, NY, [9]NYU-Hospital for Joint Diseases Radiology Dept.

Purpose: We have previously shown that carriage of an IL1RN haplotype (CTA) was associated with substantially lower odds of radiographic severity (KL score, joint space width [JSW]) (Ann Rheum Dis. 2010). In this 24 month prospective study we assessed whether IL1-RN haplotypes predicted disease progression in patients with symptomatic knee OA.

Methods: Ninety-seven (N=97) patients from NYUHJD who met ACR criteria for symptomatic knee OA were genotyped for single nucleotide polymorphisms (SNPs) in the IL-1b and IL-1RN genes. Standardized fixed-flexion radiographs were taken on all patients at baseline and 24 months. Radiographic progression of signal (more painful) knee OA was determined by change in JSW over 24 months. To account for variations in baseline JSW, we defined progression as greater than 30% joint space narrowing (JSN) of the diseased compartment over 24 months, rather than in change in absolute JSW in millimeters.

Results: Decreases in JSW ranged from zero to 3.7 mm over the 24 months; 19 of 97 patients exhibited > 30% JSN.



Patients with the IL-1RN (rs419598/rs315952/9005) TTG haplotype exhibited increased radiographic knee OA severity at baseline compared to those without TTG ($p<0.08$). These TTG patients exhibited increased risk for radiographic progression at 24 months that approached significance based on ≥30% JSN [OR = 2.85; 95%CI=0.68–11.67; $p<0.15$]. In contrast, OA patients with IL-1RN CTA haplotype showed decreased risk for JSN over 24 months in the signal knee [OR= 0.33; 95%CI=0.170–1.014; $p<0.05$]. Differences in reported VAS pain between the CTA and TTG group were significant at 24 months ($p< 0.01$), indicating that while these patients were not distinguishable by radiograph or symptoms at onset, IL1RN haplotype predicted symptomatic differences at two years. Finally, the TTG haplotype group of patients expressed relatively increased IL-1b gene expression [15.683 ± 9.407 ($p<0.0001$)] as assessed by TaqMan QPCR in peripheral blood leukocytes. The TTG patients also exhibited decreased sIL-1Ra [283.64 ± 36.4 pg/ml ($p<0.001$) in plasma samples compared to IL-1RN CTA haplotype protective groups [IL-1b (fold change), 5.444 ± 10.083; sIL-1Ra, 370.35 ± 43.3pg/ml] of patients respectively.

Conclusion: IL-1RN gene family polymorphisms, which appear to affect host production of IL-1Ra, merit evaluation as biomarkers that predict the risk of progression in patients with symptomatic knee OA.

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Hand Osteoarthritis (OA) a Predictor of Accelerated Progression in Knee OA? Jonathan Samuels[3], Catherine Petchprapa[6], Elizabeth L. Carpenter[6], Svetlana Krasnokutsky[4], Mukundan Attur[2], Leon Rybak[5], Jenny Bencardino[5], Cheongeun Oh[6] and Steven B. Abramson[1]. [1]Hospital for Joint Dis/NYU, New York, NY, [2]Hospital for Joint Dis/NYU Langone Medical Center, [3]New York University Hospital for Joint Disease, New York, NY, [4]NYU Hospital for Joint Disease, New York, NY, [5]NYU Hospital for Joint Diseases, [6]NYU Langone Medical Center

Purpose: There is insufficient understanding regarding how generalized OA involving the hand and knee differs from isolated knee OA, which may result from other factors such as obesity or trauma. The purpose of these studies is to determine whether the presence of hand OA involving interphalangeal (IP) and first carpometacarpal (CMC) joints, alone or in combination, predicts progression of patients with symptomatic knee OA.

Methods: Hand radiographs were obtained on 94 patients at NYUHJD who met ACR criteria for symptomatic knee OA, and who were enrolled in a two-year NIH-sponsored prospective study. The patients completed standardized fixed-flexion knee radiographs at baseline and 24 months, with progression the signal (more painful) knee OA determined by change in joint space width (JSW) and KL score. For these analyses, the patients were separated into two groups by results on their signal knee: 17 progressors, defined by at least 30% decreased JSW over 24 months, and 77 non-progressors. For each set of hand x-rays, 2 radiologists evaluated 18 IP joints and 2 CMC joints for joint space narrowing and/or osteophytes, and whether or not there was erosive change at the IP joints; we averaged the scores from the two readers.

Results: Kappa scores between the two scoring radiologists for the IP and CMC joints, and for the presence of erosive IP disease, were 0.79, 0.87 and 0.96, respectively. The overall mean IP score was 5.6 and 1st CMC score was 0.9, while medians were 5 and 1.0, respectively. The 17 progressors had a higher average IP (but not CMC) score than the non-progressors, 7.2± 5.4 vs. 5.0±4.6, p=0.13. Since the IP scores were not normally distributed, we further analyzed data by dichotomizing the study populations into two groups using the median IP total (5) as the cutoff point. When so analyzed, the presence of "hand OA" increased the odds ratio of knee OA progression to 2.8 (p=0.096). Of interest, the severity of knee OA correlated with hand OA scores: the average total hand OA scores (out of 20 joints) increased with baseline KL score, with mean scores of 3.8±5.5, 6.1±6.1 and 7.2±5.6 for KL 1 to 3 (p=0.06). There is also an increasing trend of total hand OA joint scores by KL score (p=0.042) when dichotomized around the median (5 joints), and with IP scores alone (p=0.026). The 8 patients with radiographic evidence of erosive IP disease, as compared with the 31 non-erosive IP OA patients (>5 IP joints) and the 54 without IP OA, demonstrated faster knee OA progression over 2 years by average KL increases (1.00, 0.35, 0.30) and decreases in joint space width (0.65, 0.56, 0.36), although perhaps given small numbers, this was not statistically significant (p=0.839).

Conclusions: In cross-sectional analysis, the quantitative "burden" of hand OA correlates with the radiographic severity of knee OA (KL).

Moreover, radiographic hand OA at the IP joints, but not at the 1st CMC joint, predicts more rapid progression of knee OA. Erosive IP disease may be an even stronger predictor than non-erosive IP disease of accelerated progression of knee OA.

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Bone Marrow Lesions (BMLs) Are Strongly Associated with Increased Bone Volume Fraction; "Virtual Bone Biopsy" Using MRI. Anna M. Tassinari[3], Grace H. Lo[1], Jeffrey Driban[3], Lori Lyn Price[3], Erika Schneider[2] and Timothy E. McAlindon[3]. [1]Baylor College of Medicine, Houston, TX, [2]The Cleveland Clinic, Cleveland, OH, [3]Tufts Medical Center, Boston, MA

Introduction: BMLs are a common MRI feature of knee osteoarthritis (KOA) that associate with symptoms and predict structural progression. In a recent study, we have observed that worse radiographic KOA is associated with higher periarticular bone volume fraction (aBVF).

While BMLs are probably associated with trabecular damage, their pathological basis remains poorly understood and has not been evaluated in-vivo. Our aim was to evaluate trabecular structure changes within KOA BMLs using MR trabecular morphometry.

Methods: The sample comprised 158 participants in the Osteoarthritis Initiative (OAI) who had 3T MRIs (Trio, Siemens) that included coronal 3D FISP trabecular sequences for morphometry and sagittal intermediate-weighted TSE, fat-suppressed images for BML scoring.

We used a trabecular morphometry program with a modified algorithm (*calcDCN, UCSF*) to evaluate aBVF and explore additional trabecular features, such as number, spacing and thickness. The four measures were calculated for 20 consecutive central slices, within a 15 mm × 3.75 mm ROI placed periarticular in the medial tibia, and then averaged. Intra-rater reproducibility was high (*ICC* = 0.99). We validated the modified *calcDCN* algorithm for aBVF against aBVF values from images segmented manually in Analyze® (*ICC* = 0.99).

We defined BMLs as areas of increased signal intensity visible on ≥ 2 consecutive sagittal slices, and situated adjacent to the articular cartilage. Based on estimated volume of the BML within the medial tibia, we classified knees as having *none*, *small* or *large* BMLs.

We performed Analyses of Variance (ANOVA) to evaluate whether mean aBVF, trabecular number, spacing or thickness differed by BML score. We also assessed their associations using linear regression, adjusting for age, gender, ethnicity, body mass index (BMI) and hip bone mineral density (BMD).

Results: One hundred fifty eight subjects were included; 52% were female; 13.3% were Black, 3.2% Hispanic; mean age was 69.0 ± 8.9 yrs, BMI = 29.22 ± 5.0 kg/m2, hip BMD = 0.944 ± 0.16 gm/cm2; 79% with no BMLs, 15% with small BML and 6% with large BML.

BMLs were significantly associated with higher aBVF, trabecular number and thickness and lower trabecular spacing (Table). After adjusting for confounders, BML score remained significantly and independently associated with all four measures.

Table. Trabecular bone changes in BMLs

BML score	Mean aBVF ± SD	Mean Trabecular Number ± SD (mm^{-1})	Mean Trabecular Spacing ± SD (mm)	Mean Trabecular Thickness ± SD (mm)
none (n = 124)	0.122 ± 0.077	0.87 ± 0.39	1.51 ± 1.3	0.131 ± 0.023
small (n = 24)	0.183 ± 0.095	1.13 ± 0.39	0.93 ± 0.57	0.152 ± 0.028
large (n = 10)	0.221 ± 0.094	1.35 ± 0.33	0.73 ± 0.31	0.163 ± 0.032
Overall (n = 158)	0.138 ± 0.09	0.94 ± 0.4	1.37 ± 1.2	0.14 ± 0.03
Overall model p-value	**p < 0.0001**	**p < 0.0001**	**p = 0.02**	**p < 0.0001**

Conclusion: Bone volume appears increased in BMLs. The exploratory trabecular measures suggest that as BMLs are associated with higher trabecular number and thickness, but lower separation. These findings could represent locally increased bone turnover or compression and suggest that treatments targeting bone that could influence these pathologies should be explored.

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REGN475/SAR164877, a Nerve Growth Factor Inhibitor, in Osteoarthritis Patients with Moderate to Severe Knee Pain: Results of a Phase 2, Randomized, Double-Blind, Placebo-Controlled Study. Paul Tiseo[4], Alan J. Kivitz[1], John E. Ervin[2], Scott J. Mellis[3], Haobo Ren[4], Damir Skific[4], Richard Wu[4] and Peter Powchik[4]. [1]Altoona Arthritis & Osteo Ctr, Duncansville, PA, [2]Center for Pharmaceutical Res, Kansas City, MO, [3]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [4]Regeneron Pharmaceuticals, Inc.

Purpose: To evaluate the safety and efficacy of REGN475/SAR164877 (R/S), a fully human monoclonal antibody with highly selective binding affinity for nerve growth factor (NGF), in the treatment of osteoarthritis (OA) pain.

Methods: This phase 2, double-blind, placebo-controlled, parallel-group, repeat-dose study enrolled patients aged 40–75 y with physician-confirmed diagnosis of active, moderate to severe OA (ACR criteria + subjective pain + Kellgren-Lawrence G2-G3 radiographic severity). Other eligibility requirements included walking knee pain (WKP) levels ≥ 4 at baseline [11-pt numerical rating scale (NRS)] and washout of any current pain medications prior to baseline visit (Day 1). Rescue medication with acetaminophen (up to 4g per day; no more than 4 consecutive days) was permitted. Patients (N=217) were randomized to receive intravenous (IV) R/S 0.03, 0.1, or 0.3 mg/kg or IV placebo (Pbo) on Day 1 and Day 57, with a 16-wk follow-up period after the second dose. Safety/tolerability [frequency of treatment emergent adverse events (TEAEs)] was the primary endpoint. Key efficacy variables included change from baseline on WKP and Western Ontario and McMaster Osteoarthritis (WOMAC) Index.

Results: Baseline characteristics were similar among treatment groups: mean (SD) age 59.3±8.7 yrs; 31.2% male; and 78.1% white. After 24 weeks, the incidence of TEAEs ranged from 66.1–75.0% in the R/S groups vs 63.6% for placebo. The most common TEAEs included headache (R/S range 7.1–7.7% vs Pbo 7.3%), hypoaesthesia (3.8–7.7% vs 0%), musculoskeletal pain (3.6–19.2% vs 5.5%), paraesthesia (0–5.8% vs 5.5%), peripheral edema/joint swelling (3.6–9.6% vs 0–1.8%), and respiratory infections (1.9–8.9% vs 1.8–7.3%). 5.6% of R/S patients and 3.7% of Pbo patients withdrew due to TEAEs; serious TEAEs were infrequent and the incidence was similar between active treatment groups and Pbo. Evidence of treatment effect was reported in the individual R/S dosing groups vs Pbo; results of the key efficacy evaluations are summarized in the table below. At Week 16, a consistent dose-response relationship was demonstrated in the WOMAC pain and function subscales.

Treatment Differences from Baseline at Weeks 8 and 16

Key Efficacy Variables	Placebo (n = 55)	REGN475/SAR164877 0.03 mg/kg (n = 53)	0.1 mg/kg (n = 53)	0.3 mg/kg (n = 54)
Walking Knee Pain (NRS)				
Mean Change (SD) from Baseline at Wk 8	−2.01 (2.08)	−2.8 (2.29)	−3.3 (2.61)*	−3.6 (2.48)*
Mean Change (SD) from Baseline at Wk 16	−2.5 (2.15)	−3.4 (2.24)*	−3.4 (2.58)*	−3.3 (2.55)
WOMAC Pain Score				
Mean Change (SD) from Baseline at Wk 8	−1.9 (1.74)	−2.6 (2.01)*	−3.4 (2.54)*	−3.5 (2.42)
Mean Change (SD) from Baseline at Wk 16	−2.4 (2.18)	−2.7 (1.89)	−3.4 (2.53)*	−3.2 (2.24)*
WOMAC Function Score				
Mean Change (SD) from Baseline at Wk 8	−1.8 (1.95)	−2.8 (2.07)*	−3.4 (2.32)*	−3.4 (2.57)
Mean Change (SD) from Baseline at Wk 16	−2.3 (2.30)	−2.9 (1.78)	−3.4 (2.28)*	−3.1 (2.18)*

* P ≤ 0.05 (difference vs Pbo).

Conclusions: REGN475/SAR164877 was generally well-tolerated; incidence and type of TEAEs were similar to those previously reported with NGF inhibition. Preliminary data suggest that neurosensory TEAEs were more frequent at higher doses. Efficacy assessments indicate that anti-NGF therapy may be associated with a significant reduction in OA knee pain for up to 8 weeks, with dropouts at the highest dose possibly accounting for the reduced efficacy at 16 weeks.

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Novel Biomarkers of Knee Osteoarthritis Identified Using a Non-Targeted Metabolomic Approach. Guangju Zhai, Karsten Suhre, Deborah Hart, Christian Gieger, Nicole Soranzo and Tim D. Spector. King's College London, London, United Kingdom

Objectives: There is a pressing need to develop reliable molecular biomarkers that can inform on the process of joint destruction in osteoarthritis (OA). Such biomarkers could aid in drug development by identifying fast progressors and early response to therapy. Recent advance in metabolomics (the quantitative analysis of all metabolites present within a biological sample) has opened new avenues for biomarker identification. Using targeted metabolomic profiling approach, we have identified that serum branched chain amino acid to histidine ratio is associated with knee OA (Zhai G, et al Ann Rheum Dis 2010). To identify additional novel metabolic biomarkers for OA, we carried out this study using a non-targeted metabolomics approach.

Methods and Subjects: An available fasting serum sample derived from the TwinsUK cohort was utilized. 1052 Caucasian females were profiled metabolomically using non-targeted approach with LC-MS/MS. Among them, 891 individuals with mean age of 58±10.7 years had knee OA data available. 158 were knee OA cases defined as either having total knee joint replacement due to primary OA (n=22), radiographic knee OA if Kellgren-Lawrence score >=2 (n=72), or self-reported clinical diagnosed knee OA (n=64). 733 were controls with none of these three case definitions. We examined the association between knee OA and the serum metabolomic profile using robust linear regression. Their abundance in each individual's serum sample was measured by the area counts under the MS spectral peak. The area counts were then transformed by natural logarithm to approximate the normal distribution and used in the subsequent analysis after correcting for multiple testing with Bonferroni method.

Results: A total of 275 serum metabolites were identified. We examined the association between each of the 275 serum metabolites and knee OA with adjustment for age, and identified four metabolites associated with knee OA ($p < 0.00018$). γ-glutmyl valine was increased in knee OA patients ($\beta=0.42$ SD, $p=0.00017$), which is a confirmation of our previous findings. In addition, we found that α-tocopherol and bilirubin were negatively associated with knee OA ($\beta=-0.47$ SD, $p=0.00004$, and $\beta=-0.43$ SD, $p=0.0001$, respectively), and hyodeoxycholate was positively associated with knee OA ($\beta=0.46$ SD, $p=0.0001$).

Conclusion: This novel study using high-throughput metabolomics confirms our previous findings of valine as a marker of OA and identified an additional three novel serum metabolic biomarkers for knee OA, which could have potential clinical utility.

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ACR Concurrent Abstract Sessions

Rheumatoid Arthritis - Animal Models: Insight in Pathogenesis and Novel Therapeutic Targets

Monday, November 8, 2010, 4:30 PM–6:00 PM

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Anti-CD20 Therapy Inhibits the Progression of Synovitis and Focal Erosion in the Knee Joints but Not in the Ankle Joints of TNF-Tg Mice. Jie Li, Igor Kuzin, Christopher Ritchlin, Ignacio Sanz, Andrea Bottaro, Lianping Xing and Edward Schwarz. University of Rochester, Rochester, NY

Purpose: B cell depletion therapy (BCDT) is effective for some RA patients. However, its mechanism of action and variable efficacy remains an enigma. Previously we utilized contrast enhanced (CE) MRI, micro-CT and near infrared-indocyanine green (NIR-ICG) lymphatic imaging to evaluate arthritis in TNF-Tg mice, and demonstrated that disease commences in the ankle, which is consistent with reports defining tenosynovitis in the foot as the initiating pathology. We also found that arthritic progression occurs following a sudden decrease in lymphatic flow from the lower limb to the popliteal lymph node (PLN). This decrease leads to a "collapsed" phenotype characterized by the translocation of CD23+/CD21hi B cells from the follicles into the sinus space, resulting in "clogging" lymphatic flow of the PLN. Thus, we hypothesize that BCDT ameliorates TNF-induced arthritis by increasing lymphatic flow through the depletion of these B cells, and tested this in our murine model.

Methods: TNF-Tg mice with collapsed PLNs and ankle synovitis were identified by CE-MRI and followed with scans every two weeks. NIR-ICG footpad clearance (T-clearance) and micro-CT scans were performed before and after treatment with anti-CD20 (n=8; 16 knees) (10mg/kg/i.v. every two weeks) or placebo (n=4; 4 knees) for 6 weeks. PLNs were harvested for flow cytometry or immunohistochemistry (IHC). Ankle and knee joints were harvested for H&E and TRAP stained histology.

Results: 1) Anti-CD20 significantly decreased knee synovial volume ($SynVol=4.55+/-2.39mm^3$, $p=0.002$) and synovitis progression ($p=0003$) vs. placebo ($SynVol=8.98+/-4.16mm^3$), and PLN B cells (80–95% depletion). 2) Anti-CD20 significantly increased T-clearance from 82.3+/−0.16% to 90.4+/−0.08% ($p=0.02$). 3) Anti-CD20 protected the knee from focal erosions, as there was no significant change in patellar bone volume ($p=0.1$). However, it failed to prevent bone erosion in the ankle joint, as the talus volume dramatically decreased from $0.64+/-0.32mm^3$ to $0.30+/-0.27mm^3$ ($p=2\times10^{-6}$) during the 6-week treatment.

Conclusion: Our results show BCDT effectively inhibits progression of arthritis in knee, but not in the ankle, suggesting distinct etiologies for large and small joint pathogenesis. The lack of efficacy observed in the foot is consistent with unabated tenosynovitis in which B cells play little if any role, as evidenced by arthritis in the ankles of TNF-TgxRAG1−/− mice. In contrast, the absence of tendon insertions proximal to synovium in large joints precludes tenosynovitis as a mechanism of inflammatory-erosive arthritis in the knee. Our observations that draining lymph function and the location of B cells in PLNs correlates with disease in the adjacent knee of TNF-Tg mice is consistent with a novel mechanism of action for BCDT in which removal of the B cells that are "clogging" the lymphatic vessels restores draining function to ameliorate synovitis. Our current clinical pilot to test this hypothesis in anti-TNF refractory RA patients receiving BCDT will be discussed.

Disclosure: J. Li: None; **I. Kuzin:** None; **C. Ritchlin:** None; **I. Sanz:** None; **A. Bottaro:** None; **L. Xing:** None; **E. Schwarz:** None.

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Identifying the TLR4 Bearing Target Cell in Experimental Arthritis. Ben T. van den Brand, Shahla Abdollahi-Roodsaz, Miranda B. Bennink, Onno J. Arntz, Wim B. van den Berg and Fons A. J. van de Loo. Radboud University Nijmegen Medical Centre

Purpose: The IL-1 receptor antagonist (IL-1Ra) knockout mice spontaneously develop T-cell driven arthritis due to excessive IL-1 signalling. Joint destruction is accompanied by increased Th17 cells and elevated IL-17 levels compared to wild type (Balb/c) mice. When cross bred with TLR4 knock out (TLR4−/−) these animals showed reduced inflammation, joint destruction, and diminished IL-17 levels. To reduce adverse effects of TLR4 inhibition a cell specific targeted therapy of arthritis is desired. Therefore, we set out to identify the TLR4 bearing cells in experimental arthritis responsible for increased IL-17 production and arthritis severity.

Method: A reciprocal sex-mismatched bone marrow transplantation was performed with TLR4−/− and TLR4+/+ mice in the IL-1Ra−/− background and Balb/c bone marrow as control. Y-chromosome staining of bone marrow was performed to assess engraftment. Clinical manifestation of disease was assessed macroscopically over time. Spleen and lymph node cells were isolated and subjected to T-helper subset analysis.

Results: Engraftment of bone marrow was near 100% successful as determined by Y-chromosome staining of the bone marrow, which indicates a successful reconstitution. Lack of TLR4 on either the engrafted bone marrow cells or the radio-resistant cells in the joint did not affect disease incidence. However, animals that lacked TLR4 on the engrafted bone marrow derived cells, radio-resistant cells, or both showed reduced macroscopic arthritis scores. In mesenteric lymph nodes there were no differences observed in percentage of IFNγ and IL-17 producing cells. Neither was there a difference in Th1 cells in the spleen. However, decreased Th17 levels were observed in the spleen when radio-resistant cells lack TLR4.

Conclusion: These data suggest that TLR4 plays a role on both the bone marrow derived and local resident cells in aggravating experimental arthritis. TLR4 plays a role locally on the synovial fibroblasts by creating a more aggressive inflammatory environment in the joint cavity and thereby increas-

ing joint destruction. Conversely, TLR4 activation on the bone marrow derived cells could increase T-cell activation by antigen presenting cells and thereby promoting a more aggressive Th17 phenotype and increase joint swelling.

Disclosure: B. T. van den Brand: None; **S. Abdollahi-Roodsaz:** None; **M. B. Bennink:** None; **O. J. Arntz:** None; **W. B. van den Berg:** None; **F. A. J. van de Loo:** None.

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Local Expression of IL-27 Reduces Collagen Induced Arthritis through Reduction of Monocyte Migration and Vascularization. Sarah R. Pickens[4], Michael V. Volin[1], Arthur M. Mandelin[2] and Shiva Shahrara[3]. [1]Midwestern University, [2]Northwester University, Chicago, IL, [3]Northwestern Univ Feinberg, Chicago, IL, [4]Northwestern University

Introduction: To determine the effect and potential mechanism of IL-27 treatment in rheumatoid arthritis (RA), local expression of IL-27 was studied in ankle joints of collagen induced arthritis (CIA) mice compared to control animals.

Methods: Adenovirus containing IL-27 transcript (Ad-IL-27) was constructed and was locally delivered into the ankles of CIA mice. Clinical parameters were assessed histologically and by measuring ankle circumference. IL-17 and its downstream targets, as well as cytokines promoting TH-17 cell differentiation, were quantified by ELISA from CIA tissue homogenates locally expressing IL-27 or Ad-control. Ankles from both treatment groups were immunostained for neutrophil and monocyte abundance and vascularization was determined by quantifying ankle hemoglobin levels and PECAM expression by real-time RT-PCR.

Results: The joint circumference of Ad-IL-27 injected animals was significantly smaller than control animals throughout the study. Histological analysis of ankles from day 41 confirmed that local expression of IL-27 resulted in significantly less inflammation compared to the control group. Further histological studies demonstrated that local expression of IL-27 resulted in a significant decrease ($p<0.05$) of synovial lining thickness and bone erosion. Next, we found that the cytokines which induce TH-17 cell differentiation (IL-1β and IL-6) and the downstream targets of IL-17 (CXCL1, CXCL5 and CCL2) were significantly decreased in ankle homogenates by local expression of IL-27 compared to control treatment. CIA ankles immunostained for neutrophils and monocytes showed that the local expression of IL-27 greatly decreased the infiltration of these cells into the ankle joints compared to control group. In order to quantify the vascularization changes in the Ad-IL-27 group, ankle hemoglobin and PECAM levels were quantified and compared to control group. Ad-IL-27 treated CIA ankle joints had significantly reduced hemoglobin and PECAM levels compared to control joints.

Conclusion: Our results suggest that increased IL-27 levels relieved arthritis in CIA ankles. This amelioration of arthritis involved a reduction of IL-27-induced TH-17 cell differentiation and resulted in decreased IL-17-mediated monocyte recruitment and angiogenesis. Hence, IL-27 may be a therapeutic target in RA.

Disclosure: S. R. Pickens: None; **M. V. Volin:** None; **A. M. Mandelin:** None; **S. Shahrara:** None.

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Impaired B Cell Immunity in IL-22 Knock-Out Mice in Collagen Induced Arthritis. Odilia Corneth[1], Anne-Marie Mus[2], Patrick Asmawidjaja[2], Laurens Kil[2], Wenjun Ouyang[3], Rudi Hendriks[2] and Erik Lubberts[2]. [1]Erasmus MC, University Medical Center, Rotterdam, ZH, The Netherlands, [2]Erasmus MC, University Medical Center, [3]Genentech

Background: The role of IL-22, a cytokine produced by Th17 cells, in autoimmunity is not fully understood. Previous research has shown that IL-22 is important in the development of collagen induced arthritis (CIA). However, the mechanism behind the apparent protection in IL-22 knock-out mice against CIA remains unclear.

Objective: To investigate the mechanisms by which IL-22 knock-out mice are protected against collagen induced arthritis.

Materials and Methods: For CIA, IL-22 knock-out and wild type mice were immunized with chicken collagen type II (CII) and complete Freud's adjuvant (CFA) and boosted 21 days later. Antigen specific serum IgG levels were measured by ELISA. Mice were sacrificed 50 days after immunization. Splenocytes were analyzed by flow cytometry and immunohistochemistry (IHC). Functional assays were performed with splenic Th17 cells sorted from mice ten days after immunization. For antigen induced arthritis (AIA), mice were immunized with methylated bovine serum albumin (mBSA) and CFA and triggered seven days later by intra-articular mBSA injection.

Results: In IL-22 knock-out mice, the severity of CIA was lower compared to wild type controls. No significant difference in disease incidence was observed between wild type and IL-22 knock-out mice. This prompted us to study the pathogenicity of Th17 cells from these mice. Synovial fibroblasts produced higher levels of IL-6 when co-cultured with Th17 cells from IL-22 knock-out mice compared to wild type Th17 cells. To study the pathogenicity of these cells in vivo, we made use of the Th17 mediated AIA model. IL-22 knock-out mice developed AIA similarly to wild type controls, showing that Th17 cells function normally in vivo. As CIA is strongly driven by B cells and immune complexes, we investigated whether B cell immunity is normal in IL-22 knock-out mice. Antigen specific serum IgG2a levels were significantly lower in IL-22 knock-out mice at early onset of disease. Flow cytometric analysis of splenic B cells showed no significant differences in B cell numbers or activation. However, IHC slides of spleens from IL-22 knock-out mice show no or very small germinal centers and fewer IgG2a plasma cells compared to wild type controls.

Discussion: Here we show that lack of IL-22 production affects B cell immunity in CIA. We show that Th17 cells in IL-22 knock-out mice function normally in vitro in a functional assay and in vivo in antigen induced arthritis (AIA). This indicates that the lack of IL-22 production does not affect the pathogenicity of Th17 cells. However, germinal center formation, plasma cell formation and IgG2a antibody production are lower in IL-22 knock-out mice in CIA, suggesting that IL-22 has a role in further differentiation of B cells in autoimmunity.

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Repair of Bone Erosions in Inflammatory Arthritis Occurs as Inflammation Resolves, Accompanied by Alterations in the Wnt Signaling Pathway. M. M. Matzelle[4], M. A. Gallant[3], K. W. Condon[2], N. C. Walsh[5], C. A. Manning[1], J. B. Lian[1], D. B. Burr[2] and Ellen M. Gravallese[1]. [1]Worcester, MA, [2]Indianapolis, IN, [3]Department of Anatomy and Cell Biology, Indiana University School of Medicine, Indianapolis, IN, [4]Department of Medicine and Department of Cell Biology, University of Massachusetts Medical School, Worcester, MA, [5]St. Vincent's Institute, Fitzroy, VIC, Australia

Background: Rheumatoid arthritis (RA) is characterized by chronic synovial inflammation and invasive pannus that drives osteoclast-mediated articular bone erosion. While effective therapies can slow the progression of bone erosion, repair occurs in only a small percentage of RA patients and generally correlates with control of disease.

Methods: To examine the potential for erosion repair and mechanisms driving this process, inflammatory arthritis was induced by transfer of arthritogenic K/BxN serum to 12-week old C57BL/6J mice and arthritis was subsequently allowed to resolve. Clinical inflammation peaked at day 10 after initial serum injection and full resolution of clinical inflammation occurred between days 28 and 38. Forefoot bones of the hind paws were evaluated by histology, microCT, and histomorphometry, and quantitative RT-PCR (qPCR) was performed on synovial tissue.

Results: qPCR of synovial tissue confirmed resolution of inflammation, with a 20-fold induction of IL-1β mRNA, 1.5-fold induction of TNF, and 40-fold induction of MMP-13 at day 10, all of which returned to non-arthritic levels by day 28. RANKL/OPG mRNA ratios in synovium also correlated with inflammation, favoring osteoclast-mediated resorption at day 10 and protection from resorption beginning as early as day 15. Serial microCT and histologic analysis of the forefoot bones were consistent with repair of previously established erosions. To quantify bone formation occurring with the resolution of inflammation, dynamic histomorphometric analyses of fluorochrome incorporation at sites of erosion were performed on days 10, 28, 38, 48 and 58. Inflammation at the bone interface (day 10) was accompanied by a low bone formation rate (BFR), similar to rates in non-arthritic mice, as we previously reported. In this study, we found that resolution of inflammation from days 28 to 48 was accompanied by a significant increase in BFR and mineral apposition rate (MAR) in arthritic compared to non-arthritic mice, contributing to repair at sites of erosion. Reduction of inflammation was accompanied by striking changes in the expression of modulators of the Wnt/β-catenin pathway, a pathway responsible for bone formation. qPCR revealed that inflammation induced expression of the Wnt antagonist sFRP1,

whereas resolution of inflammation reversed this induction. Correlating with the increase in osteoblast-mediated bone formation, we found an increase in the expression of Wnt10b and the Wnt antagonist DKK2, which are both required for bone matrix synthesis and mineralization. In addition, inflammation induced expression of Wnt7b, which has been shown to exhibit a negative relationship with DKK2 (Li et al., Nature Genetics, 2005; 37: 945).

Conclusions: Resolution of inflammation promotes osteoblast-mediated repair of articular bone erosions in this murine RA model. These data provide further rationale for aggressive treatment of inflammation in RA, which not only inhibits bone erosion, but may also promote bone formation and repair of existing bone erosions. Finally, these data demonstrate that there is a complex relationship between inflammation and regulation of components of the Wnt signaling pathway.

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SB1578, a Novel Selective JAK2 Inhibitor, Is Highly Efficacious in Rodent Models of Rheumatoid Arthritis. Kee Chuan Goh, Stefan Hart, Yung Kiang Loh, Yong Cheng Tan, Chithra Amalini, Ramesh Jayaraman, Kantharaj Ethirajulu and Jeanette Wood. S*BIO Pte Ltd

Background: JAK2, a member of the Janus kinase family, is a key component in the signaling pathways elicited by pro-inflammatory cytokines such as interferon-g, interleukin-6, interleukin-12 and interleukin-23. These cytokines, in different sequence and combinations with other factors, initiate and/or sustain the T-helper cell subsets activated during autoimmune inflammatory diseases. The JAK2 kinase may therefore serve as a useful target for pharmacological intervention in some of these diseases, including rheumatoid arthritis (RA). We report here SB1578, a novel JAK2 inhibitor which demonstrates a unique kinase spectrum, activity on cellular biomarkers, favorable pharmacokinetic and *in vitro* safety profile, and promising activity in 2 rodent models of rheumatoid arthritis.

Methods: *In vitro* potency of SB1578 against a diverse panel of kinases was evaluated using recombinant enzymes with synthetic substrates. Potency on intracellular signaling pathways was assessed by Western blot analyses of the phosphorylated substrates in cell lysates. Viability assays were performed on tumor cell lines to investigate potential anti-proliferative activity. *In vivo* efficacy was tested in a rat model of adjuvant-induced arthritis and a mouse model of collagen-induced arthritis.

Results: SB1578 was shown to be a potent inhibitor of JAK2 (IC_{50} = 46 nM) as well as two other kinases reported to be implicated in human rheumatoid arthritis, namely FLT3 and CSF-1R (IC_{50} = 62 nM and 69 nM respectively). In a panel of 25 cell lines, SB1578 selectively inhibits proliferation in cell lines with a known dependence on JAK2 or FLT3 signaling, whether wild-type or mutated. These include MV4–11, Molm13, 32D, and BaF3 cells with transfected wild-type or mutant JAK2 (IC_{50} from 39 to 500 nM). Phosphoblot analysis in these cells showed that FLT3 or JAK2 signaling pathways are blocked in a dose-dependent manner. In a Lewis rat model of adjuvant-induced arthritis, administration of SB1578 (20 and 40 mg/kg BID, *i.p.*) led to dose-related reductions toward normal for histopathologic bone resorption, paw inflammation, ankle measurements, and splenic inflammation. In a B10RIII murine model of collagen-induced arthritis, oral administration of SB1578 (100, 200 and 300 mg/kg BID) led to dose-dependent reductions of clinical arthritis scores and hallmarks of mouse CIA model, including pannus formation and histological joint damage. The highest dose of 300 mg/kg BID led to zero disease incidence in terms of paw inflammation and histological parameters. Analyses of terminal serum samples showed that two cytokines, IL-6 and the chemokine KC, were significantly elevated in diseased compared with normal mice, and levels of these two cytokines were normalized by treatment with SB1578. Studies on primary PBMCs to illustrate the effects of SB1578 on Th1 and Th17 pathways will also be reported.

Conclusions: SB1578, a novel and selective JAK2 inhibitor, has demonstrated promising on-target activities in JAK2-dependent cell lines and is highly efficacious in two rodent models of rheumatoid arthritis. It is currently undergoing final preclinical development activities to prepare it for clinical studies.

Disclosure: K. C. Goh: S*BIO, 3; **S. Hart:** S*BIO, 3; **Y. K. Loh:** S*BIO, 3; **Y. C. Tan:** S*BIO, 3; **C. Amalini:** S*BIO, 3; **R. Jayaraman:** S*BIO, 3; **K. Ethirajulu:** S*BIO, 3; **J. Wood:** S*BIO, 3.

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Certolizumab Pegol Use in Pregnancy: Low Levels Detected in Cord Blood. Douglas Wolf[1] and Uma Mahadevan[2]. [1]Atlanta Gastroenterology Associates, Atlanta, GA, [2]UCSF Center for Colitis and Crohn's Disease, San Francisco, CA

Introduction: Infliximab is an IgG1 antibody against TNF alpha. Although its pregnancy classification is B, infliximab is detected in cord blood and newborns. Because IgG1 is actively transferred across the placenta during the third trimester, newborn serum infliximab levels are higher than maternal serum levels at birth.[1] Adalimumab is also an IgG1 antibody and is assumed to have similar transfer characteristics but commercial assays for measurement are not available. Certolizumab pegol (CZP), a Fab' fragment against TNF-alpha, has been shown to have low placental transfer levels in a rat model.[2] The transfer in humans is not known.

Methods: CZP levels were measured in women with IBD receiving therapy during pregnancy. Serum levels were measured by ELISA; 0.41 μg/ml is the lowest limit of detection. On the day of birth, levels were measured in the mother, the infant and in the cord blood.

Results: Ten mothers were enrolled. There were 2 sets of twins for a total of 12 infants. The table lists the time of last dose prior to delivery and the levels of CZP in mother, infant and cord blood on the day of birth. For patient 2, levels were again checked 1 month after birth and mother was 22.93 μg/ml, infant was 0.84 μg/ml and 5 samples of breast milk at varying times from CZP dose had levels <0.41 μg/ml.

Conclusions: CZP does not appear to be actively transferred across the placenta in the third trimester of pregnancy, unlike infliximab. These results are consistent with animal studies and may impact the choice of anti-TNF agent in the pregnant patient.

Table.

		Birth (μg/ml)		
Mother #	Last Dose (days)	Mother	Cord	Infant (DOB)
01	14	18.83	1.65	–
02	7	59.57	0.94	1.02
03	28	4.87	1.19	1.22
04	17	20.13	0.57	0.44
05	21	16.49	<0.41	<0.41
06	24	34.65	1.66	1.58
07	28	1.87	<0.41	<0.41
08-A	42	6.32	<0.41	0.58
B			<0.41	<0.41
09-A	6	42.7	1.28	1.34
B			1.16	1.18
10	5	37.83	0.55	0.6

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Disclosure: D. Wolf: Abbott Laboratories, 2, 5, 8, Centocor, Inc., 2, 5, 8, Elan, 2, 5, Millenium Pharmaceuticals, 2, 5, Prometheus Laboratories, 2, 5, 8, UCB, Inc., 2, 5, 8; **U. Mahadevan:** Abbott Laboratories, 2, 5, Centocor, Inc., 5, Takeda Pharmaceuticals North America, 2, UCB, Inc., 5.

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Anti-TNF Therapy Reduces Adipocytokine Levels and Improves the Lipid Profile in Patients with Rheumatoid Arthritis: A Possible Mechanism Contributing to Lowered Cardiovascular Risk. Marieke Herenius[2], Ruth Klaasen[2], Wilco de Jager[4], Berent Prakken[4], Daniëlle Gerlag[3] and Paul P. Tak[1]. [1]Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, [2]Department of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [3]Department of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, The Netherlands, [4]Department of Pediatric Immunology, University Medical Center Utrecht, Wilhelmina Children's Hospital, Utrecht, The Netherlands

Background: The atherosclerotic process is accelerated in patients with rheumatoid arthritis (RA), contributing to higher mortality rates than those found in the general population. Recently, treatment with TNF-blockers has been associated with a lower risk of first-ever CVD events. However the mechanisms by which TNF-blockers exert this effect is unclear. Adipocytokines have been linked to obesity, insulin resistance, inflammation, and coronary heart disease in the general population and their serum levels are elevated in RA. To explore the relationship between inflammation and atherogenesis, we investigated the effects of anti-TNF therapy on serum adipocytokine levels (adiponectin, resistin, leptin and visfatin) and known risk factors such as C-reactive protein levels and lipid profile in RA patients.

Methods: 49 patients with active disease (disease activity score evaluated in 28 joints (DAS28)) ≥3.2) were started on adalimumab therapy (40 mg subcutaneously every other week). Blood was drawn from patients while fasting at baseline and 16 weeks after the initiation of therapy. Lipid profiles (total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides (TG), lipoprotein (a) (Lp(a)), ApoA- I and Apo B levels), CRP and ESR were determined. Adiponectin, resistin and leptin levels were measured using multiplex analysis and visfatin levels were measured by ELISA.

Results: After 16 weeks of treatment, there was a significant reduction in DAS28 ($p<0.001$), ESR ($p<0.001$), and CRP ($p<0.001$) levels. Of interest, we found a decrease in serum concentrations of resistin (19,2%, $p=0.02$) and visfatin (17.2%, $p=0.09$). There were not clear cut changes in serum levels of adiponectin ($p= 0.91$) and leptin ($p=0.55$). Furthermore, a significant improvement was seen of the TC/HDL ratio ($p=0.047$**),** the apoB/apo A-I ratio ($p=0.013$) and lp(a) levels ($p<0.001$). Baseline visfatin levels correlated with BMI, TC/HDL ratio and LDL/HDL ratio. In addition, the decrease in visfatin levels was related to improvements in LDL/HDL ratio ($r=0.32$, $p=0.05$) and TC/HDL ratio ($r=0.35$, $p=0.03$)

Conclusions: These data support the downregulation of visfatin as a potential new mechanism by which anti-TNF therapy might reduce vascular inflammation, and as such cardiovascular morbidity in RA patients. These data are in line with recent observations that elevated visfatin levels are related to abnormalities in lipid metabolism.

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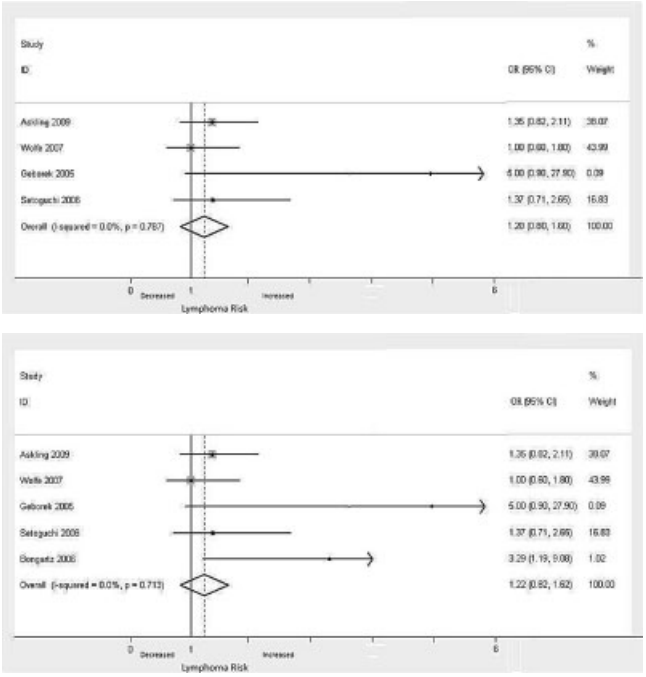
Biologics and Risk of Lymphoma in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. Lindsay C. Burns[1], Mary De Vera[1], Vidula Bhole[1], Yanyan Zhu[3], Peter Grayson[2], Devyani Misra[3] and Hyon K. Choi[4]. [1]Arthritis Research Centre of Canada, [2]Boston University, [3]Boston University School of Medicine, [4]Univ of British Columbia, Vancouver, BC, Canada

Purpose: A previous meta-analysis of biologics trials has reported a three-fold increased risk of malignancies (including lymphoma) (Bongatz et al JAMA 2006), but trials are not designed to capture long-term safety outcomes. To this end, we conducted a systematic review and meta-analysis to determine whether biologic use among RA is associated with risk of lymphoma.

Methods: We searched MEDLINE, EMBASE, and INTERNATIONAL PHARMACEUTICAL ABSTRACTS databases from Jan 1990 to May 2010 for studies that evaluated adverse effects of biologics or evaluated efficacy of biologics with reporting of adverse events. Eligibility criteria were: a) use of an RCT or observational study design (case control, cohort study), b) a study duration of ≥12 weeks, c) sample size of ≥100 for observational studies, d) RA population, or if mixed population, reporting of RA-specific results, e) evaluation of a biologic therapy as mono-therapy or in combination with other RA therapies, f) clearly defined lymphoma outcomes, and g) information on relative risk (RR), odds ratio (OR), and 95% confidence intervals (95% CI). We calculated weighted-pooled summary estimates for lymphoma risk using a random effects model. Then, we combined our results with the previous meta-analysis assuming the reported cancer risk (OR=3.3) as the lymphoma risk. We used the Q statistic to test for heterogeneity and the Egger's test the possibility of publication bias.

Results: We reviewed 11 articles that evaluated lymphoma outcomes associated with biologic use in RA, including 2 RCTs and 9 cohort studies. Of these, 7 articles were excluded from subsequent pooling because they failed to report risk estimates for lymphoma (n=5) or were earlier studies on the same study sample (n=2). The remaining 4 articles were large cohort studies that reported risks of lymphomas associated with infliximab, etanercept, adalimumab, and anakinra, with sample sizes ranging from 757 to 7815 and average RA duration ranging from 127 to 158 months. A total of 19,323 patients contributed 119,433 person years of follow up, and 129 lymphomas were identified. Using adjusted values, the pooled risk estimate for lymphoma was 1.20 (95% CI, 0.80–1.60) (Figure). Heterogeneity was small (I2-statistic $p=0.79$) and we did not detect publication bias (Egger test $p=0.26$). Combining results with recent meta-analysis did not change the pooled risk estimate (1.22; 95% CI, 082–1.62) materially.



Conclusions: Our meta-analysis of the current literature does not support an increased risk of lymphoma with biologic use in RA. The differences between the previous meta-analysis of trials and the current study include study type (trial vs. observational study), durations, and sample sizes.

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The Comparative Incidence of Serious Infections among Rheumatoid Arthritis Patients Who Switch Biologic Agents. Jeffrey R. Curtis[3], Fenglong Xie[2], Lang Chen[2], John Baddley[2], Timothy Beukelman[4], Kenneth G. Saag[5], Kevin Winthrop[1] and Elizabeth Delzell[2]. [1]OHSU, [2]Univ of Alabama at Birmingham, Birmingham, [3]University of Alabama– Birmingham, Birmingham, AL, [4]University of Alabama-Birmingham, Birmingham, AL, [5]University of Alabama-Birmingham, Birmingham, AL

Background: The safety profile of the anti-TNF agents has been well characterized. However, it is unclear whether the comparative safety of newer biologics with different mechanisms of action is similar to the anti-TNF agents. Our objective was to evaluate the incidence of hospitalized infections among rheumatoid arthritis (RA) patients switching to a new biologic.

Methods: Using the administrative databases of a large U.S. healthcare organization from 1/2005-8/2009, we identified enrollees with RA based on having at least 1 physician visit for RA (ICD9 714.X). To control for confounding related to characteristics that cause patients to switch from one biologic to another, eligible patients were those switching to a new biologic who had been treated with a different biologic in the preceding 6 months, defined as the baseline period. Observation time began on the switch date. To further control for confounding, we created pair-wise propensity scores (PS) for each drug contrast using covariates measured at baseline. PS were categorized into quintiles; non-overlapping regions of the PS distributions were trimmed. Exposure was defined as current use of the biologic, allowing for an extension of 90 days. Outcomes of interest were hospitalized infections identified using previously-validated algorithms. Cox proportional hazards models evaluated the incidence rate of hospitalized infections, comparing each biologic to infliximab, selected as a convenient reference standard for

uniform comparison. Observation time was censored at the first hospitalized infection, end of study, or lack of current exposure.

Results: Among a total of 101,906 unique RA patients enrolled in the health plan, 1923 switched to a new biologic and contributed 1915 person-years (py) of observation. Characteristics of these eligible patients were mean ± SD age 49.3 ± 11.2 years, 78% women. A total of 82 first hospitalized infections were identified; the rate of hospitalized infections ranged from a low of 1.8 (switch to etanercept) to a high of 6.2 (switch to rituximab) per 100py. There was insufficient use of golimumab or certolizumab to evaluate these agents. Referent to infliximab, there were no significant differences between the rates of infection for any biologic after adjusting for age, sex, and PS quintile (Table). There were no cases of active tuberculosis or of hospitalized progressive multifocal leukoencephalocathy (PML).

Conclusion: The rate of all hospitalized infections among RA patients switching to a new biologic varies across a relatively small range and was not significantly different between agents.

Hazard Ratio Comparing the Rate of Serious Infections for Persons Switching to Various Biologies

Drug Switching To	Incidence Rate (per 100 pt-years)	Crude Hazard Ratio	Adjusted for age, sex, propensity score
Abatacept	5.8	1.08 (0.57, 2.04)	0.87 (0.45, 1.70)
Adalimumab	3.8	0.73 (0.40, 1.34)	0.68 (0.36, 1.29)
Etanercept	1.8	0.44 (0.19, 1.05)	0.46 (0.19, 1.12)
Infliximab	4.8	1.0 (ref)	1.0 (ref)
Rituximab	6.2	1.07 (0.56, 2.05)	0.89 (0.43, 1.82)

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Characteristics of Cases of PML among Patients with Selected Rheumatic and Autoimmune Diseases. Timothy Beukelman[5], Fenglong Xie[3], Lang Chen[3], John Baddley[3], Elizabeth Delzell[3], Carlos G. Grijalva[7], Nivedita M. Patkar[2], Kenneth G. Saag[6], Kevin Winthrop[1] and Jeffrey R. Curtis[4]. [1]OHSU, [2]Univ of AL at Birmingham, Birmingham, AL, [3]Univ of AL at Birmingham, [4]University of Alabama - Brimingham, Birmingham, AL, [5]University of Alabama-Birmingham, Birmingham, AL, [6]University of Alabama-Birmingham, Birmingham, AL, [7]Vanderbilt

Background: The incidence and antecedent risk factors for infection with progressive multifocal leukoencephalopathy (PML) infection have been minimally characterized in patients with rheumatic diseases.

Methods: Using individually-identifiable, person-level administrative data from the entire United States from the Center for Medicare and Medicaid Services (CMS) from 2000–2006, we identified both Medicaid-only and also 'dual-eligible' (Medicare + Medicaid) individuals with at least one diagnosis of rheumatoid arthritis (RA), psoriatic arthritis (PsA), psoriasis (PsA), juvenile idiopathic arthritis (JIA), inflammatory bowel disease (IBD), and anklylosing spondylitis (AS) claim at any time. PML was identified using hospital discharge diagnosis codes (ICD9 046.3), and the 'case date' was assigned as the date of hospital admission. Risk factors for PML were evaluated in the 6 months prior to the case date, and separately using all data prior to the case date. During these assessment periods, patients must also have had full insurance coverage (e.g. Medicare Part A+B, not enrolled in Medicare Advantage). 4 month mortality following the case date was described. Data Use Agreement restrictions from the Center for Medicare and Medicaid Services (CMS) required collapsing categories with individual cell sizes < 11.

Results: Among 712,708 unique individuals with RA, PsA, PsO, JIA, IBD, or AS, a total of 55 hospitalizations for PML were identified (7.7 per 100,000 individuals). Of these cases, 29 had insurance coverage for at least 6 months prior to the PML case date and had one or more physician diagnoses of a rheumatic disease that occurred before the PML case date. Characteristics of these 29 PML cases include mean ± SD age 46.8 ± 8.18 years, 41% women. There was at least 1 case of PML that occurred among patients with each rheumatic disease studied except for JIA. The most prevalent concomitant comorbidity was HIV (83% of patients). Additional comorbidities present with low prevalence among PML cases included malignancy and concomitant systemic lupus erythematosus. At least one individual with PML had none of these comorbidities nor HIV but was a current user of infliximab.

Among all PML cases, more than 1 patient had antecedent exposure to infliximab in the 6 months prior to the PML case date; the median time from the most recent exposure to infliximab to hospitalization for PML was between 1 and 2 months. No other PML patients had any prior exposure to any other biologic agent. Fewer than 10 patients were using glucocorticoids in the 6 months prior to the PML infection. More than 1/3 of patients died in the 4 months following the PML case date.

Conclusion: PML is a rare infection that has been observed to occur among patients with inflammatory and autoimmune conditions, even in the absence of recent biologic drug exposure or other risk factors such as HIV disease. A better understanding of the epidemiology of PML infections and associated risk factors may be useful to inform patients regarding this rare but serious adverse event.

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Consequence of Remission Misclassification Due to Reduced Joint Counts Omitting the Forefeet. Lilian H. D. van Tuyl[8], Karin Britsemmer[3], David T. Felson[2], George A. Wells[6], Josef S. Smolen[4], Bin Zhang[1], Julia Funovits[5], Dirkjan van Schaardenburg[3] and Maarten Boers[7]. [1]Boston Univ Schl of Medicine, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]Jan van Breemen Institute, [4]Krankenhaus Lainz, Vienna, Austria, [5]Medical University of Vienna, [6]Univ of Ottawa Faculty of Med, Ottawa, ON, Canada, [7]VU University Medical Center, Amsterdam, The Netherlands, [8]VU University Medical Center, Amsterdam

Introduction: With remission in rheumatoid arthritis (RA) a realistic outcome of treatment, the ACR, EULAR and OMERACT have joined forces to develop a new definition for remission in RA to be used in clinical trials. One of the issues on the research agenda is the consequence of using a 28- vs a more complete joint count. Several studies report residual disease activity in the feet in patients with a 28-joint count of zero, although this might not be a problem in defining remission if such patients fail to classify because of activity in other measures within the definition.

In an observational early disease cohort we studied the consequences of misclassification due to residual disease activity in the feet of patients in remission by 28-joint counts.

Methods: All patients fulfilling the '87 ACR criteria for RA at inclusion or at 1 year follow up in the early arthritis cohort of the Jan van Breemen Institute (Amsterdam, The Netherlands), not using biologicals were included.

Boolean as well as index-based candidate remission definitions were calculated using the 28- and 38 joint count that includes the 10 metatarsophalangeal joints. Disease stability was defined as stable x-ray scores over 1 year (change ≤0 in van der Heijde/Sharp scores) AND stable and low scores on the Health Assessment Questionnaire (HAQ change ≤0 AND HAQ score consistently ≤0.5), all during the 2nd year after inclusion.

Analyses comprised: 1) residual disease activity (swollen or tender joints>0) in the feet of patients that fulfilled the candidate remission criteria using a 28 joint count; 2) likelihood ratio's of remission definitions to predict disease stability.

Results: Of a total of 423 RA patients 8 to 30% reached remission at 1 year using a 28 joint count (Table 1).

Table 1. Count(%) of patients in remission with active feet

Remission definition	Total in remission	Subset with TJC or SJC > 0 in feet
TJC+SJC+CRP+		
PtGA≤1*	38 (9)	10 (2)
PtGA+PhGA ≤1	36 (9)	10 (2)
PhGA+pain ≤1	38 (9)	13 (3)
PtGA+pain≤1	34 (8)	10 (2)
PtGA+pain+PhGA ≤1	32 (8)	10 (2)
SDAI ≤3.3*	61 (14)	22 (5)
CDAI ≤2.8	63 (15)	25 (6)
DAS28 < 2.6	128 (30)	56 (13)

*New ACR/EULAR preliminary remission definitions in RA

The 6-measure Boolean definition is most strict, the DAS28<2.6 most relaxed. Of these, 26 to 44% showed activity in the feet, ~70% being due to both swelling and tenderness. Misclassification due to reduced joint counts was observed in 2 to 3 % of patients measured with a Boolean definition.

A state of remission increased the likelihood of stability of both x-ray and HAQ, with slightly higher LRs for definitions using 38 joint counts vs definitions using 28 joint counts.

Table 2. Likelihood ratio's of remission definitions with 28 vs 38 joint counts to predict disease stability

Remission definition	Joint counts	Total in remission	Stable and: in remission	Stable and: not in remission	LR	P
TJC+SJC+CRP+						
PtGA ≤1	28	38	15	70	2.6	*
PtGA ≤1	38	29	12	73	2.8	*
PtGA+PhGA ≤1	28	36	15	70	2.8	**
PtGA+PhGA ≤1	38	27	12	73	3.2	**
PhGA+pain ≤1	28	38	19	66	4.0	**
PhGA+pain ≤1	38	26	14	71	4.6	**
PtGA+pain ≤1	28	34	14	71	2.8	**
PtGA+pain ≤1	38	25	11	74	3.1	*
PtGA+pain+PhGA ≤1	28	32	14	71	3.1	**
PtGA+pain+PhGA ≤1	38	23	11	74	3.7	**

*P-value <0.01; **P-value ≤0.001

Conclusion: A substantial proportion of patients in remission according to 28 joint counts show activity in the feet. Actual misclassification occurs in 2–3% of the total population studied. The ability of remission definitions with 28 vs 38 joint counts to predict long term good radiological and functional outcome is highly similar.

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ACR Concurrent Abstract Sessions

Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's - Clinical Aspects and Therapeutics

Monday, November 8, 2010, 4:30 PM–6:00 PM

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Use of Serum Clara Cell 16-kDa (CC16) Levels as a Potential Indicator of Active Pulmonary Fibrosis in Systemic Sclerosis. Minoru Hasegawa, Manabu Fujimoto and Kazuhiko Takehara. Kanazawa University

Background: Pulmonary fibrosis (PF) is one of the major systemic sclerosis (SSc) -related causes of death. Krebs von den Lungen-6 (KL-6) and surfactant protein-D (SP-D) are currently considered the best serum markers of PF in patients with SSc. However, these markers are not perfect and an additional serum marker may be helpful for reliable monitoring of PF. Clara cell 16-kDa (CC16, previously named CC10) is a pneumoprotein secreted from along the tracheobronchial tree, specifically in the terminal bronchioles where Clara cells are localized.

Objective: To clarify the clinical significance of serum CC16 protein levels in the diagnosis and monitoring of PF in patients with SSc, and to compare CC16 levels with levels of KL-6 and SP-D.

Methods: Serum CC16 levels were determined by competitive enzyme-linked immunosorbent assay (ELISA) and serum levels of KL-6 and SP-D were measured by sandwich ELISA in 92 SSc patients, 20 systemic lupus erythematosus (SLE) patients, and 20 healthy controls. In a retrospective longitudinal study, correlation of serum CC16 levels with the progress of PF was assessed in 16 SSc patients with elevated serum CC16 levels at their first visit.

Results: Although CC16 levels at the first visit were higher in patients with SSc than in SLE patients or healthy controls, the difference was not significant. Serum levels of CC16 were comparable in limited cutaneous SSc and diffuse cutaneous SSc patients (60.8 ± 109.5 vs. 78.3 ± 124.3 ng/ml) and significantly elevated in SSc patients with PF compared with SSc patients without PF (90.8 ± 110.7 vs. 42.1 ± 80.7 ng/ml, $p<0.05$). Furthermore, SSc patients with active PF showed significantly elevated serum CC16 levels compared to patients with inactive PF (168.8.8 ± 161.5 vs. 53.8 ± 95.0 ng/ml, $p<0.01$). Serum CC16 levels were significantly associated with SP-D ($r=0.39$, $p< 0.01$), but not with KL-6 ($r=0.19$, $p=0.15$). In a longitudinal study, reduced serum CC16 levels were associated with the stabilization of PF activity. Although the serum CC16 levels were less useful for the evaluation of PF severity, CC16 levels were likely as effective for the monitoring of PF activity as KL-6 or SP-D.

Conclusions: Our findings suggest that CC16 levels can be used as a potential serum biomarker for active PF in SSc. Use of this marker in combination with KL-6 and SP-D may be a more valuable as an indicator of PF activity in SSc patients than KL-6 and SP-D alone. Further prospective and comparative studies in larger populations will be needed to confirm these studies.

Disclosure: M. Hasegawa: None; **M. Fujimoto:** None; **K. Takehara:** None.

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HLA DRB1*0407 and *1304 Are Predictive Biomarkers for Scleroderma Renal Crisis. Binh Y. Nguyen[1], Maureen D. Mayes[6], Frank C. Arnett[7], Deborah J. del Junco[2], Emilio B. Gonzalez[4], Hilda T. Draeger[3], Marilyn Perry[2], Amir Hendiani[2], John D. Reveille[5] and Shervin Assassi[1]. [1]Univ of Texas Health Science Center Houston, Houston, TX, [2]Univ of Texas Health Science Center Houston, [3]Univ of Texas Health Science Center San Antonio, San Antonio, TX, [4]Univ of Texas Medical Branch, Galveston, TX, [5]Univ Texas Health Sci Ctr, Houston, TX, [6]University of Texas-Houston, Houston, TX, [7]UT Medical School, Houston, TX

Background: Scleroderma Renal Crisis (SRC) is a life-threatening complication of systemic sclerosis (SSc). The Major Histocompatibility Region (MHC) showed the strongest association with SSc in a recently published large genome-wide association study, raising the possibility that this gene locus might be also important for biomarker development. The predictive significance of MHC genetic markers for SRC has not been previously investigated. The goal of the current study was to examine the predictive role of MHC genetic markers for the SRC beyond the known clinical correlates in a large population of patients with SSc.

Methods: SSc patients from the Scleroderma Family Registry and DNA Repository, Genetics versus Environment in Scleroderma Outcomes Study (GENISOS) and divisional registry at the University of Texas Health Science Center at Houston were included in the study. Patients, enrolled in more than one of the above mentioned sources, were identified and duplicate entries were omitted. ANA, anticentromere (ACA), anti-topoisomerase (ATA), and anti-RNA polymerase III (ARA) antibodies were detected utilizing commercially available kits. Furthermore, HLA Class II genotyping (DRB1, DQA1, DPB1) was performed on extracted and purified genomic DNA. Multivariate models were constructed following a purposeful variable selection method. First, we evaluated the demographic and clinical variables without genetic risk factors for their multivariable associations with SRC. Subsequently, we conducted a separate purposeful model building analysis after addition of the MHC genetic data. Ethnicities were included in all univariate and multivariable genetic analysis models.

Results: Overall, 1519 patients with SSc were included in this study, from which 90 patients (5.9%) had developed SRC. Of the 90 patients with SRC, diffuse cutaneous subtypes were found in 76%, ATA in 9%, ACA in 2%, and ARA in 50%. ARA and diffuse disease type were independent risk factors for presence of SRC, whereas ACA and ATA were protective in the multivariate model of clinical variables. In the final multivariable analysis after inclusion of HLA allotypes, we identified HLA-DRB1*0407 (OR=3.21, 95% CI 1.27–8.08; P=0.013) and *1304 (OR=4.51, 95% CI 1.30–15.68; P=0.018) as independent risk factors for SRC. Only 3 clinical characteristics, ARA, diffuse disease type and ACA remained statistically significant in the final model.

Conclusion: This study suggests that HLA DRB1*0407 and *1304 can be used as biomarkers for identification of SSc patients at risk for developing SRC beyond the information provided by known clinical predictors.

Disclosure: B. Y. Nguyen: None; **M. D. Mayes:** None; **F. C. Arnett:** None; **D. J. del Junco:** None; **E. B. Gonzalez:** None; **H. T. Draeger:** None; **M. Perry:** None; **A. Hendiani:** None; **J. D. Reveille:** None; **S. Assassi:** None.

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GAVE (Gastric Antral Vascular Ectasia) in Early Diffuse SSc: Updated Report from the SCOT (Scleroderma Cyclophosphamide or Transplant) Trial. Emily W. Hung[9], Maureen D. Mayes[10], Lynette Keyes-Elstein[5], Leslie J. Crofford[6], Mary Ellen Csuka[3], Daniel E. Furst[8], Ellen Goldmuntz[4], Peter McSweeney[11], Richard Nash[2], Victor Machicao[7] and Keith Sullivan[1]. [1]Duke University Medical Center, for the SCOT Trial Investigators, Durham, NC, [2]Fred Hutchinson Cancer Research Center, [3]Medical College of Wisconsin, Milwaukee, WI, [4]NIAID, [5]Rho Federal Systems Inc., [6]Univ of KY, Lexington, KY, [7]Univ of Texas Health Science Center at Houston, [8]University of California Los Angeles Medical School, Los Angeles, CA, [9]University of Texas at Houston, Houston, TX, [10]University of Texas-Houston, Houston, TX, [11]US Oncology

Objective: To identify the prevalence of, and predictors for, clinically silent GAVE in early diffuse SSc.

Introduction: Also known as watermelon stomach, GAVE is an endoscopic finding consisting of dilated sub-mucosal vessels radiating in a spoke-like fashion from pylorus to antrum. It is usually associated with chronic anemia. The prevalence of clinically silent GAVE (ie no anemia or evident GI bleeding) in SSc has not been previously reported. The SCOT (Scleroderma: Cyclophosphamide or Transplant) study is a pivotal randomized, NIH supported trial of monthly IV cyclophosphamide for 12 months versus immunoablation followed by CD34 selected autologous stem cell rescue in early, diffuse scleroderma with internal organ involvement. The presence of active GAVE, as defined by evidence of bleeding on endoscopy, is an exclusion criterion for SCOT due to the risk of gastric hemorrhage in the thrombocytopenic period for the stem cell arm. Complete inclusion/exclusion criteria and trial description are at www.sclerodermatrial.org.

Methods: 103 subjects without overt GI bleeding were screened for participation in the SCOT trial and had an upper endoscopy. All subjects had diffuse cutaneous systemic sclerosis with ≤ 5 years of disease duration from the first non-Raynaud's phenomenon symptom.

Results: Twenty three of 103 (22.3%) individuals were found to have GAVE (all inactive). Table 1 provides a comparison of demographic and disease-related features for those with GAVE and those without this characteristic. Not all subjects had results for all parameters.

Feature	GAVE = Present (n = 23)	GAVE = Absent (n = 80)
Age in years, mean ± sd	48.2 ± 7.45	45.99 ± 11.52
% Female	73.7%	75.0%
Race/ethnicity		
Caucasian	85.0%	79.7%
African-American	0	6.2%
Other/Not given	15.0%	14.1%
*BMI (kg/m^2), mean ± sd	27.44 ± 5.56	24.75 ± 4.00
Hemoglobin (g/dl), mean ± sd	11.76 ± 1.78	12.41 ± 1.50
Mean corpuscular volume, mean ± sd	85.19 ± 6.72	86.94 ± 6.09
mRSS (modified Rodnan Skin Score) Mean ± sd	30.5 ± 9.3	29.2 ± 9.4
% predicted FVC, mean ± sd	78.4 ± 13.92	75.64 ± 15.75
% predicted DLCO, Adjusted for Hb Mean ± sd	53.04 ± 7.65	58.86 ± 17.10
RVSP (right ventricle systolic pressure) Mean ± sd	31.33 ± 7.87	31.17 ± 7.43
Creatinine Clearance, mean ± sd	105.12 ± 37.60	110.55 ± 43.49

*This comparison was statistically significant (p = 0.0112)

The only clinical feature that distinguished those with versus those without GAVE was the BMI, which was marginally higher in the group with GAVE by simple t-test (uncorrected). The clinical significance of this finding is uncertain. All other demographic and clinical features were not statistically significant between groups. Other abnormal findings on upper endoscopy were common and expected, consisting of esophagitis and/or gastritis of varying degrees of severity.

Conclusion: In this study, 22.3% of subjects with early diffuse SSc, without overt GI blood loss, had characteristic findings of GAVE on screening EGD. This was a somewhat surprising finding and suggests that upper endoscopy should be performed prior to initiation of therapies that increase the risk of bleeding.

Disclosure: E. W. Hung: None; **M. D. Mayes:** None; **L. Keyes-Elstein:** None; **L. J. Crofford:** None; **M. E. Csuka:** None; **D. E. Furst:** None; **E. Goldmuntz:** None; **P. McSweeney:** None; **R. Nash:** None; **V. Machicao:** None; **K. Sullivan:** None.

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A Formula To Predict Mean Pulmonary Artery Pressures in Patients with Connective Tissue Disease Based on Echocardiography, NTproBNP and O_2 Saturation. Benjamin E. Schreiber[3], Christopher J. Valerio[3], Clive Handler[3], Greg Keir[1], Athol U. Wells[1], Christopher P. Denton[2] and J. Gerry Coghlan[3]. [1]Royal Brompton Hospital, London, [2]Royal Free Hospital, London, United Kingdom, [3]Royal Free Hospital, London, London, United Kingdom

Introduction: Pulmonary Hypertension (PH) is an important complication of connective tissue disease (CTD). Diagnosis is confirmed by right heart catheter (RHC) but no single non-invasive test accurately predicts PH. To improve selection of patients for RHC, we analysed the relationship between non-invasive tests and mean pulmonary artery pressure (mPAP) at RHC and derived a new formula to predict PAP.

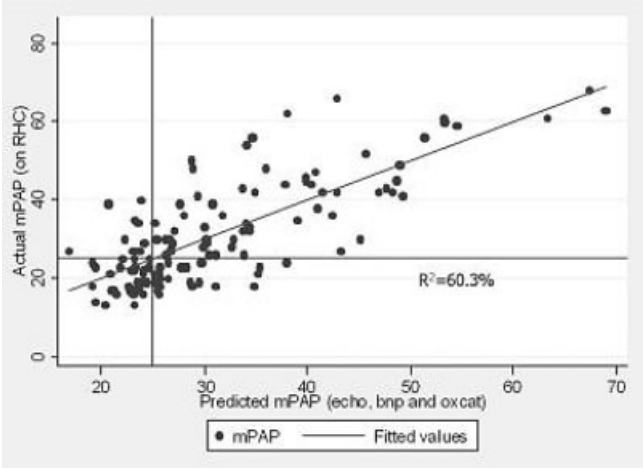
Methods: Retrospective analysis of patients with CTD undergoing a first RHC. In our database we have 968 patients (811 SSc, 53 SLE, 15 RA, 42 UCTD, 8 MCTD, 12 DM, 7 PM, 6 Sjogrens, 3 antiphospholipid syndrome, 3 vasculitis). We included for analysis NTproBNP and echocardiography if performed within 3 months of RHC and pulmonary function tests if done within 6 months. Pulse oximetry was measured at the time of the RHC.

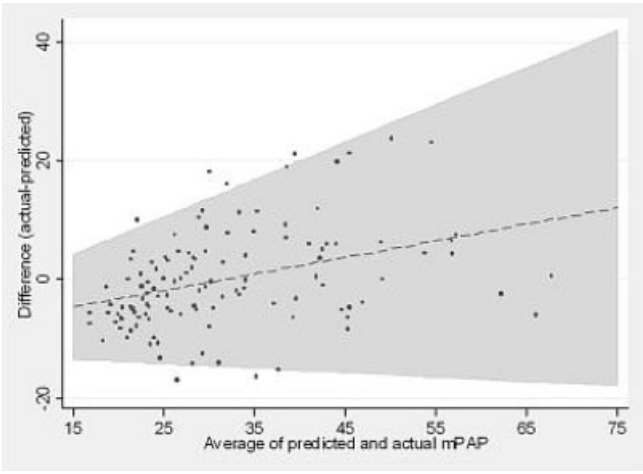
Results: Regression analysis of these variables individually against mPAP at RHC gave the following results: DL_{CO} (n=469) gave R^2=8.7, AUC=0.68; NTproBNP (capped at 300 pmol/litre to reduce the skewing effect of large values) with n=380, gave R^2=31.5, AUC=0.74 and echo derived tricuspid valve gradient (n=165) gave R^2=48.9, AUC=0.81. Capping NTproBNP gave similar results to a log transformation.

Multivariable linear regression showed significant correlation with mPAP for Echo derived TV gradient (p<0.0005), capped NTproBNP and Oxygen (p=0.004). Addition of predicted DL_{CO}, K_{CO}, FVC, weight or height did not improve the fit. To reduce heteroskedasticity, oxygen was used categorically (1 if SpO_2 >94%, 2 if 90–94%, 3 if <90%). Based on all 123 patients for whom we had NTproBNP, echo and SpO_2 data, the derived formula is:

Predicted mPAP = 8.37
+3.83 × Oxygen category
+ 0.328 × Echo derived Tricuspid Valve gradient
+ 0.032 × NTproBNP (capped)

This formula had R^2 of 60.3%.





The area under the curve was 0.84 (95% CI 0.77–0.91). Using a threshold predicted mPAP of 25 it has a sensitivity of 87.3%, specificity of 55.8%, positive LR of 2.0 and negative LR of 0.2. Using a threshold predicted mPAP of 30, it has a sensitivity of 66.2%, specificity of 90.4%, positive LR of 6.9, negative LR of 0.4.

Bland-Altman analysis showed a mean agreement of −0.6 (95% CI −16.4, 16.3) for difference between predicted and actual mPAP, although as seen in the figure, the 95% CI are tighter at lower predicted values.

This compares favourably with echocardiography done within 1 hour of the RHC (Fisher MR et al, Am J Respir Crit Care Med. 2009).

Conclusions: This formula may help identify CTD patients requiring RHC. Patients with a formula predicted mPAP under 25 are unlikely to have PH, and those patients with predicted mPAP above 30 are very likely to have PH.

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Predictive Factors of Hand Radiographic Lesions in Systemic Sclerosis: A Prospective Study. Jerome Avouac[4], Giulia Mogavero[1], Henri Guérini[2], Jean-Luc Drapé[2], Alessandro Mathieu[1], Andre Kahan[3] and Yannick Allanore[3]. [1]2nd Chair of Rheumatology, University of Cagliari, Cagliari, Italy, [2]Paris Descartes University, Radiology B Department, Cochin Hospital, APHP, Paris, France, [3]Paris Descartes University, Rheumatology A Department, Cochin Hospital, APHP, Paris, France, [4]Paris Descartes University, Rheumatology A Department, Cochin Hospital, APHP, Paris, France

Background: Joint, bone and soft tissue involvement has been shown to strongly contribute to impaired hand function in systemic sclerosis (SSc). We previously showed in a cross-sectional study performed on 120 SSc patients the prominent level of hand radiographic involvement in SSc (1). However, this study had no longitudinal follow-up, precluding the identification of predictors of hand radiographic progression in SSc.

Objective: To examine the outcomes of hand radiographic X-Rays in patients with SSc and identify risk factors for the progression of hand radiographic lesions in a prospective cohort.

Patients and Methods: Subsequently to our initial cross-sectional study, dual time-point X-Rays with standard posteroanterior views of the hands and wrists were systematically performed after a median interval of 5 years (range: 4–7 years) in 103 SSc patients consecutively recruited. Univariate and multivariate Cox proportional hazards models evaluated predictors of progression of hand radiographic lesions (incident or worsened involvements) for three radiographic patterns of abnormalities of joints (erosive arthritis, defined by the presence of both erosion and joint space narrowing), bone (acro-osteolysis) and soft tissue (calcifications, flexion contracture). SSc patients (81% women) were 61±12 years old and had mean disease duration of 12±8 years.

Results: Incidences of erosive arthritis, acro-osteolysis, calcinosis and flexion contracture were 10%, 9% 14% and 8% respectively. The worsening of already known erosive arthritis, acro-osteolysis, calcinosis and flexion contracture occurred respectively in 13.5%, 12.5%, 11.5% and 10% of SSc patients. Cox regression analysis did not identify any predictor of the progression of erosive arthritis. Digital ulcers were shown to independently predict the progression of acro-osteolysis and calcinosis (Hazard Ratio, HR:12.43, 95% confidence interval, CI:1.97–88.40 and HR:3.16, 95%CI: 1.22–9.43, respectively). The diffuse cutaneous subset was shown to be an independent predictor of the progression of flexion contracture (HR:7.52, 95%CI:1.21–43.93).

Conclusion: This is the first prospective study to determine the outcomes and identify predictors of hand radiographic lesions in patients with SSc. This systematic examination highlights the striking level of incident and worsened hand radiographic lesions in SSc after a median interval of 5 years. Our data suggest a close monitoring of patients with the diffuse cutaneous subset with the need of early therapeutic intervention for prevention flexion contracture. Our results also show that severe peripheral vascular involvement predict both acro-osteolysis and calcinosis, highlighting their vascular background and suggesting that the impact of vascular treatments on these severe complications need to be addressed.

(1) Avouac J et al, Ann Rheum Dis 2006

Disclosure: J. Avouac: None; **G. Mogavero:** None; **H. Guérini:** None; **J.-L. Drapé:** None; **A. Mathieu:** None; **A. Kahan:** None; **Y. Allanore:** None.

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Predictive Value of Non-Invasive Tests for the Diagnosis of Scleroderma-Associated Pulmonary Hypertension: PHAROS Registry. Dinesh Khanna[4], Rajeev Saggar[4], Daniel E. Furst[4], Yannick Allanore[3], James R. Seibold[5], Philip J. Clements[4], Rajan Saggar[4], Chi-hong Tseng[4], Paul Maranian[4], Monique Hinchcliff[2], Virginia Steen[1] and PHAROS Investigators. [1]Georgetown University, [2]Northwestern Univ, [3]Paris Descartes University, [4]UCLA, [5]Univ of Connecticut

Background: Pulmonary hypertension (PH) is a major cause of death in systemic sclerosis (SSc). The Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) is a prospective longitudinal study of patients at risk of developing PH and those who have definite PH.

Objective: Our objective was to assess the performance of non-invasive tests (echo RVSP, PFTs, serum BNP) for the diagnosis of PH (defined as mPAP≥25 mmHg on right heart catheterization [RHC]; includes WHO Groups1–3) in SSc patients.

Methods: Entry criteria for patients "at risk" for PH included a DLCO≤55% predicted, a FVC%/DLCO% ≥1.6 or a PASP on echo ≥ 40 mmHg. RHC are performed based on the clinical judgment of the physician. We performed 3 analyses: 1) assessed individual positive (PPV) and negative predictive value (NPV) for echo RVSP, FVC/DLCO, DLCO% predicted, and serum BNP compared to initial RHC mPA; 2) analyzed discriminatory power of echo RVSP, FVC%/DLCO%, DLCO% predicted, and BNP using classification and regression tree (CART) analysis; and 3) calculated what proportion of patients are captured by serum BNP and PFTs who were missed by different RVSP cut offs.

Results: We analyzed 209 SSc patients who underwent RHC after enrollment into PHAROS; 177 had the cath done at visit#1 and 32 had it done during follow-up visits. 143 (68%) had PH on RHC. PPV for RVSP (35 –50 mmHg) ranged from 0.78 to 0.91; FVC%/DLCO% (1.4 to 2.0) ranged from 0.67 to 0.78; and DLCO% cut offs (50%–70%) ranged from 0.68 to 0.73, and serum BNP (>100) was 0.94. Combination of RVSP >50 mmHg and DLCO< 50% had greatest PPV (0.95). CART analysis showed that RVSP >50 mmHg had greatest discrimination for diagnosing PH followed by serum BNP >100 units (Figure). However, 10% to 40% (Echo cutoff>50 mmHg) of patients with PH were missed with RVSP > 35 and > 50mmHg respectively (Table). In those missed, 2–5% were captured by serum BNP> 100, 5–29% by DLCO< 60% and 3–23% by FVC/DLCO ≤ 1.6. (Table).

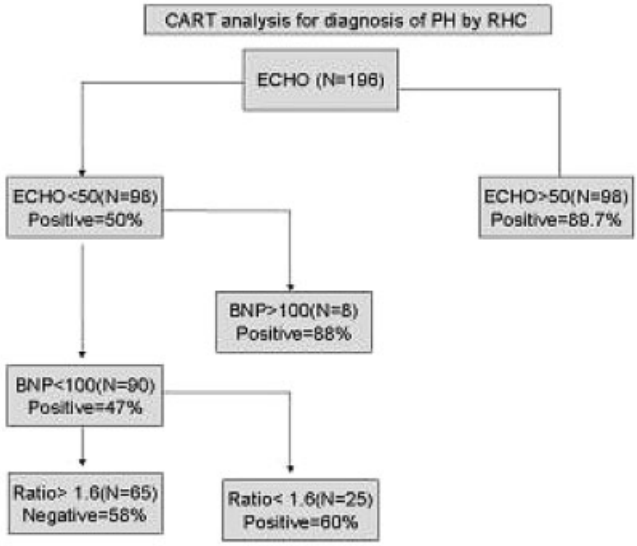

Table. Performance of various non-invasive tests

Echo cut off	PH missed by Echo RSVP	Additional patients captured with RHC-defined PH: Serum BNP >100*	DLCO <60%	FVC/DLCO ≥1.6
Echo >35 mm Hg	10%	2%	5%	3%
Echo >40 mm Hg	20%	3%	14%	10%
Echo >45 mm Hg	30%	4%	22%	16%
Echo >50 mm Hg	40%	5%	29%	22%

*only 67 patients had serum BNP reported

Conclusion: Echo RVSP > 50 mmHg has the greatest discriminatory power to detect PH in SSc in this enriched cohort. However, at this cut-off, serum BNP and PFT captures additional 27% of patients with PH. Serum BNP and PFTs complement Echo RVSP and should be included as part of work up of PH in SSc. This data needs to be confirmed in another real-life cohort.

Disclosure: D. Khanna: Actelion Pharmaceuticals US, 2, 8, Gilead Sciences, Inc., 2, 8, NIAMS-NIH, 2, United Therapeutics, 8; **R. Saggar:** None; **D. E. Furst:** Actelion Pharmaceuticals US, 9, Gilead Sciences, Inc., 9, NIH, 9; **Y. Allanore:** Actelion Pharmaceuticals US, 2, Pfizer Inc, 2; **J. R. Seibold:** Actelion Pharmaceuticals US, 5, Gilead Sciences, Inc., 5, Pfizer Inc, 5, United Therapeutics, 5; **P. J. Clements:** Gilead Sciences, Inc., 5; **R. Saggar:** None; **C.-h. Tseng:** None; **P. Maranian:** None; **M. Hinchcliff:** Arthritis Foundation, 2, NIAMS-NIH, 2; **V. Steen:** Actelion Pharmaceuticals US, 9, Gilead Sciences, Inc., 9, United Therapeutics, 9; **PHAROS Investigators:** None.

ACR REF Special Session

REF Edmond L. Dubois, MD Memorial Lectureship: The Path from Gene to Function: Analysis of a Lupus Susceptibility Gene

Monday, November 8, 2010, 4:30 PM–6:00 PM

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Single-Nucleotide Polymorphisms Associated with Systemic Lupus Erythematosus (SLE) Skew Alternative Splicing of Human Complement Receptor 2 (CR2/CD21) towards an Isoform with Increased Ligand Binding Ability. Kara M. Lough[3], Katherine B. Douglas[3], Carissa L. Homme[3], Daniela Ulgiati[1], Betty P. Tsao[2] and Susan A. Boackle[3]. [1]School of Biomedical, Biomolecular and Chemical Sciences, University of Western Australia, [2]University of California, Los Angeles, [3]University of Colorado Denver School of Medicine

Background: Human complement receptor 2 (CR2/CD21) exists as two known isoforms consisting of 15 or 16 extracellular repeating subunits termed short consensus repeats (SCRs) that result from alternative splicing of exon 11 in the primary mRNA transcript. The major alleles of three lupus-associated single-nucleotide polymorphisms (SNPs) in the CR2 gene (rs1048971 and rs17615 in exon 10 and the rs4308977 in exon 11) and a closely linked fourth SNP in exon 11 (rs17616) increase the splicing efficiency of exon 11 in vitro and ex vivo. The differential function of the two isoforms generated by this process and the factors controlling it are not known.

Methods: The cDNA for each isoform was amplified from Raji B cell RNA, cloned into the pcDNA5-FRT-V5-His TOPO TA expression vector (Invitrogen), and transfected into Flp-In CHO cells (Invitrogen). Stable clones were incubated with recombinant C3dg (rC3dg) tetramers prepared with biotiylated rC3dg and PE-streptavidin and binding was determined by flow cytometry. To identify the specific SNP(s) influencing splicing efficiency of exon 11, an exon-trapping vector (pL53In) containing genomic DNA spanning introns 9 to 12 of CR2 was modified by site-directed mutagenesis to generate vectors containing various allelic combinations of these SNPs. After transient transfection into Raji B cell and HK FDC lines, the relative amount of vector-derived mRNA transcripts including or excluding exon 11 was measured by quantitative RT-PCR.

Results: CHO cells expressing the long CR2 isoform bound up to two-fold higher levels of tetramers than CHO cells expressing equivalent amounts of the short isoform. In the Raji cell line, the presence of the minor allele at both rs17615 and rs17616 reduced splicing efficiency of exon 11 to the same extent as when all four SNPs were minor, whereas in the HK cell line, the presence of the minor allele at only rs17616 was sufficient to reduce the splicing efficiency of exon 11 to that seen in the all minor allele construct.

Conclusions: These data demonstrate that the long isoform of human CR2 is better able to bind C3d-opsonized ligands, suggesting that the introduction of SCR11 alters the structure and function of the receptor. The data also suggest that the minor alleles at rs17615 and rs17616 modify the secondary structure of the CR2 pre-mRNA, interfering with splice site recognition by regulatory proteins. Variations in the relative amounts of these splice isoforms of CR2 on the surface of B cells or follicular dendritic cells may influence susceptibility to lupus, and the regulatory proteins that determine this process could serve as future targets for therapeutic intervention.

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Further Defining Cancer Risk in Systemic Lupus: Updated Results in an Expanded International Multi-Centre Cohort. Sasha R. Bernatsky[4], Ann E. Clarke[7], Michelle A. Petri[1], Murray B. Urowitz[14], Paul R. Fortin[15], Dafna D. Gladman[16], Søren Jacobsen[12], Susan Manzi[20], Graciela S. Alarcon[2], Ellen M. Ginzler[13], Christine A. Peschken[18], Mary Anne Dooley[3], John G. Hanly[10], Ola Nived[19], Gunnar K. Sturfelt[17], Jean-Luc Senecal[9], Jeremy Labrecque[5], Elizabeth M. Turnbull[6], Jennifer L. F. Lee[11] and Rosalind Ramsey-Goldman[8]. [1]Timonium, MD, [2]Oakland, CA, [3]Capital Health and Dalhousie University, Chapel Hill, NC, [4]McGill UHC/RVH, Montreal, QC, Canada, [5]McGill University, Montreal, Canada, [6]McGill University Health Ctr, Montreal, QC, Canada, [7]Montreal General Hospital, Montreal, QC, Canada, [8]Northwestern University, Chicago, IL, [9]Notre-Dame Hospital, M-4243, Montreal, QC, Canada, [10]Queen Elizabeth II Health Services Center, Halifax, NS, Canada, [11]RI McGill Univ Health Ctr, Montreal, QC, Canada, [12]Rigshospitalet - 4242, Copenhagen, Denmark, [13]SUNY-Downstate Medical Center, Brooklyn, NY, [14]The Toronto Western Hospital, Toronto, ON, Canada, [15]Toronto Western Hospital, Toronto, ON, Canada, [16]Toronto Western Hospital, Toronto, ON, Canada, [17]UCL Div of Medicine, Room 331, 3rd Floor, Lund, Sweden, [18]Univ of Manitoba, Winnipeg, MB, Canada, [19]University Hospital, Lund, Sweden, [20]West Penn Allegheny Health System, Pittsburgh, PA

Purpose: Our previous collaborative effort demonstrated an association between systemic lupus (SLE) and cancer, driven primarily by lymphoma risk. We aimed to more precisely estimate cancer incidence rates in SLE, compared to the general population. We also present results stratified by age group.

Methods: We assembled an expanded multi-centre international cohort of clinically confirmed SLE patients. Patients at each center were linked to regional tumor registries to determine cancer occurrence. Standardized incidence ratios (SIRs) were calculated as the ratio of observed to expected cancers. Cancers expected were determined by multiplying person-years in the cohort by the geographically matched age, sex, and calendar year-specific cancer rates, and summing over all person-years.

Results: The 13,492 patients from 24 centers were observed for a total of 118,359 patient-years, with an average follow-up of 9 years. Within the observation interval, 632 cancers occurred. The data confirmed an increased risk of cancer among patients with SLE. For all cancers combined, the SIR estimate was 1.15 (95% confidence interval, 95% CI, 1.06–1.24), and for all hematologic malignancies combined, the SIR was 2.53 (95% CI 2.05–3.07). Regarding specific types of hematological malignancies, increased risk was demonstrated for all lymphomas (SIR 3.21, 95% CI 2.48–4.07) as well non-Hodgkin's lymphoma specifically (SIR 3.41, 95% CI 2.61–4.39), and for leukemia (1.69, 95% CI 1.00–2.67). We also demonstrated an increased risk of lung cancer (SIR 1.24; 95% CI 1.00–1.53), cervical cancer (SIR 1.65, 95% CI 1.09–2.41), vulvo-vaginal cancers (SIR 2.80, 95% CI 1.12–5.77), and hepatic cancer (SIR 2.18, 95% CI 1.16–3.73). Meanwhile, a significant decreased risk was seen for hormone-sensitive cancers, including breast cancer (SIR 0.70, 95% CI 0.58, 0.85), endometrial cancer (SIR 0.49, 95% CI 0.27, 0.83), and ovarian cancer (0.56, 95% CI 0.28, 0.97). When SIR estimates were stratified by age, SLE patients in the youngest age group (<40) appeared to have a particularly high relative cancer risk (compared to the general population), with an over-all cancer SIR of 1.70 (95% CI 1.34, 2.12)

Conclusion: These results more precisely define cancer risk in SLE, highlighting a higher risk of hematological malignancies, both lymphoma and leukemia; these are being further studied in case-cohort analyses of drugs and disease activity. One additional hypothesis for the higher risk of certain events, such as cervical and vulvo-vaginal cancers, is the possibility of altered clearance of viruses (e.g. HPV). On the other hand, the lower risk of several hormone-sensitive cancers may invoke the possibility of alterations in the metabolism of estrogen and/or other hormones. Although cancers in general are more common with age, younger SLE patients have a particularly high relative cancer risk (compared to the general population).

Table: Cancer Risk in Systemic Lupus

Cancer Type	Observed	Expected	SIR	95% CI	
Hematological	99	39.2	2.53	2.05	3.07
Non-Hodgkin Lymphoma	61	17.9	3.41	2.61	4.39
All lymphoma	67	20.9	3.21	2.48	4.07
Multiple Myeloma	8	5.6	1.41	0.61	2.79
Leukemia	18	10.6	1.69	1.00	2.67
Breast	112	159.2	0.70	0.58	0.85
Ovarian	12	21.4	0.56	0.28	0.97
Cervical	27	16.3	1.65	1.09	2.41
Vulvo - Vaginal	7	2.5	2.80	1.12	5.77
Endometrial	14	28.2	0.49	0.27	0.83
Lung	89	71.7	1.24	1.00	1.53
Hepatic	13	5.9	2.18	1.16	3.73
Pancreatic	13	12.1	1.07	0.57	1.84
Gastric	11	11.3	0.96	0.48	1.73
Colorectal	60	62.5	0.95	0.73	1.23
Thyroid	17	11.7	1.45	0.84	2.32
Bladder	21	15.3	1.37	0.84	2.09
Prostate	12	18.3	0.65	0.33	1.14
Melanoma	13	16.8	0.77	0.41	1.32

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Hydroxychloroquine and Prevention of Anti-SSA/Ro Associated Cardiac Disease in Mothers with a Previous Child with Neonatal Lupus. Peter M. Izmirly[4], Cecilia Pisoni[2], Mimi Y. Kim[1], Deborah Friedman[3], Carolina Llanos[5], Nathalie Costedoat-Chalumeau[7], Munther A. Khamashta[6] and Jill P. Buyon[4]. [1]Albert Einstein College of Medicine, [2]King's College of London, [3]New York Medical College, [4]NYU School of Medicine, New York, NY, [5]Pontificia Universidad Catolica de Chile, [6]The Rayne Institute, London, United Kingdom, [7]Universite Paris VI Pierre et Marie Curie

Purpose: Despite weekly monitoring of fetuses exposed to maternal anti-SSA/Ro antibodies, immediate treatment has never permanently reversed complete heart block. This irreversibility strongly supports an emphasis on preventative strategies. A recent case-control study revealed that fetal exposure to Hydroxychloroquine (HCQ), which prevents endosomal acidification and Toll-Like Receptor ligation (proposed pathway involved in cardiac inflammation and scarring), decreases the risk of cardiac manifestations of neonatal lupus (cardiac-NL) in Systemic Lupus Erythematosus (SLE) mothers with anti-SSA/Ro antibodies. That study did not address the effect of HCQ on the recurrence rate in subsequent pregnancies which is nearly 10 fold the frequency in anti-SSA/Ro positive women who have not had an affected child. Accordingly, this study explores whether HCQ prevents the development of cardiac-NL in these highest risk pregnancies.

Methods: Twenty-four pregnancies of 22 mothers satisfied the inclusion criterion: exposure to HCQ in a pregnancy of a mother whose previous child had either cardiac or cutaneous-NL. Exposure was defined as the sustained use of HCQ throughout pregnancy with initiation prior to 6 weeks gestation. In 19 of these 22 families the previous child had cardiac-NL (1- isolated cardiomyopathy and 18- advanced congenital heart block (CHB) 8 of whom died from complications of the disease) and in 3 families the prior child had cutaneous-NL. Of these 22 previous NL pregnancies, 15 were unexposed to HCQ (13 CHB, 1 cardiomyopathy and 1 rash), 6 were exposed to HCQ (4 CHB and 2 rash) and in 1 CHB child, exposure to HCQ was unknown.

Results: Sixty-eight percent of the mothers were Caucasian. The maternal health status was SLE in 41%, Sjogren's Syndrome (SS) in 32%, SLE with secondary SS in 18%, and Undifferentiated Autoimmune Syndrome in 9%. Sixty-four percent (14/22) of the mothers were positive for both anti-SSA/Ro and anti-SSB/La antibodies. The mean daily dose of HCQ was 352.6 mg. Using prospective data from the Research Registry for Neonatal Lupus, the recurrence rate of cardiac-NL following a child with cardiac-NL is 18% (based on 161 pregnancies following a previous child with CHB) and the occurrence rate of cardiac-NL following a child with cutaneous-NL is 13% (based on 39 pregnancies following a previous child with cutaneous-NL). These data suggest that the expected rate of cardiac-NL in this cohort should be approximately 17.2%. Of the 24 subsequent pregnancies exposed to HCQ in this study only one fetus developed cardiac-NL (3rd degree) and this mother's previous child had cutaneous-NL. Thus, the recurrence/occurrence rate was 4.2% (95% CI:(0.11% - 21.1%), a reduction of 75.7%. In addition to HCQ, 25% (6/24) of the mothers received intermittent low dose IVIG, 75% (18/24) non-fluorinated steroids, 17 of whom were on $\leq$ 10 mg of Prednisone, and 8.3% (2/24) fluorinated steroids, one after the diagnosis of CHB.

Conclusion: This case series suggests that in mothers with anti-SSA/Ro antibodies and a previous child with NL, exposure to HCQ during a subsequent pregnancy may decrease the risk for fetal development of cardiac-NL.

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A Systems Biology Approach to Understanding SLE Complexity. John Jung[5], Jennifer Hossler[5], Youqun Huang[5], Elise Palmer[5], Elides Marin[5], Tracy Sanford[5], Ehtisham Akhter[2], Michelle A. Petri[1], Alex Rosenberg[5], Jennifer H. Anolik[3], Chungwen Wei[5] and Ignacio Sanz[4]. [1]Timonium, MD, [2]John Hopkin University School of Medicine, Baltimore, MD, [3]University of Rochester, Rochester, NY, [4]University of Rochester Medical Center, Rochester, NY, [5]University of Rochester Medical Center, Rochester, NY

Background: B cell involvement in SLE has been demonstrated as a significant contributing determinant to disease pathogenesis. However, phenotypic heterogeneity and physiological importance of B cell subsets remain elusive and pose a challenge to understanding the complex mechanisms resulting in autoimmunity. Therefore, utilizing 3 different 12-color flow cytometry panels we have captured a comprehensive high-resolution footprint of the B cell profile in SLE in order to systematically explore the diverse human B cell repertoire and identify biomarkers of disease activity and prognosis.

Methods: B-cells from Healthy Controls (n=26) and SLE patients (n=127) were analyzed by multi-color flow cytometry for expression of anchor markers that identify larger parental B cell populations. The individual panels also included subset specific markers to further define parental populations: Memory; Transitional and Naive; and Plasma B cells. Multivariate methods were used to seek natural divisions based on the B cell profiles, and to relate them to various clinical parameters. SLE patients met ACR criteria for the classification of SLE, and were sub-categorized based on primary clinical manifestation. Disease activity and flares were measured by SELENA-SLEDAI and physician global assessment.

Results: Preliminary analyses show SLE B cell profiles exhibited a broader spread across different subsets compared to Healthy Control (HC). However, after sub-categorizing SLE patients based on primary clinical manifestations, the SLE sub-categories were revealed to have distinct B cell profiles. Overall, SLE patients had higher transitional populations and lower true naive B cells than HC ($p<0.05$). Nephritis, musculoskeletal/skin, and flaring patients exhibited a CD27- memory B cell expansion ($p<0.05$) with expression of CD95+ ($p<0.05$) and CD21- ($p<0.05$), markers of putative effector memory B cells, compared to HC. Nephritis patients had a unique memory CD27- B cell subset expressing significantly higher B220+ ($p<0.05$) and CD24- ($p<0.0005$). Musculoskeletal/skin patients exhibit CD27- memory that expressed CXCR3+ and high CD27+ memory with CD95+ ($p<0.005$) when compared to HC. Overall, Spearman correlation shows SLE DAI scores correlated with CD27- Memory with phenotypes CD95+($r=0.46$, $p<0.005$), CD21-($r=0.44$, $p<0.005$), and CD24- ($r=0.44$, $p<0.005$). SLE DAI also correlated with plasmablast counts ($r=0.35$,$p<0.05$).

Conclusions: These results indicate that unique B-cell signatures cluster with distinct clinical parameters, indicating a spectrum of disease states in SLE. Moreover, the exploration of multiple B cell subsets by a multi-colored flow-cytometry approach suggests that B cell profiles may serve as biomarkers of disease phenotype, activity, and treatment response. These profiles will be invaluable to understand disease heterogeneity and possibly its genetic basis and should prove of great help in the design of future therapeutic studies, especially with B cell targeting agents. Ongoing studies are exploring longitudinal changes in B cell phenotypes and correlation with T cell abnormalities to create an even more comprehensive picture of SLE disease pathogenesis.

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Antibodies from Antibody-Secreting Cells Following Vaccination in Patients with Systemic Lupus Erythematosus Are Autoreactive and Polyspecific. Kenneth A. Smith[2], Lori Garman[3], Jennifer Morris[3], Linda Thompson[3], Patrick C. Wilson[4] and Judith A. James[1]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Fort Wayne, IN, [3]Oklahoma Medical Research Foundation, [4]University of Chicago

Background: Immunization against *Streptococcus pneumoniae* and influenza is recommended for patients with systemic lupus erythematosus (SLE), but with vaccination comes the risk of inducing or exacerbating an autoimmune response. Several components of vaccines are well known to induce antibodies that are cross-reactive to self-antigens, including tetanus toxiod which has been reported to induce antibodies to cardiolipin (aCL) or DNA and phosphorylcholine (a component of *S. pneumoniae* C polysaccharide) which has been reported to induce antibodies to dsDNA. However, the induction of antibodies specific to other SLE autoantigens after immunization remains unclear. Most of the previous studies on vaccine-induced autoreactivity have been done using patient sera; in our study, we sought to examine the physiological autoantibody response to two implicated vaccinations, the yearly influenza vaccine and the *S. pneumoniae* vaccine (PN), by analyzing the antibody repertoire arising during the immune response through generation of human monoclonal antibodies.

Methods: Two SLE patients were vaccinated, with at least 4 weeks between vaccinations, and PBMCs were isolated seven days after each immunization. Vaccine-specific ASCs were isolated as single cells from bulk PBMCs. The VDJ regions of the heavy and light chains of individual ASCs were cloned into vectors and expressed together in mammalian cells as monoclonal antibodies (mAbs). Vaccine-specific (PN polysaccharides or influenza virion) binding and autoreactivity (Ro, La, Sm, nRNP) ELISAs were performed on each mAb. Cloning of mAbs were also performed in four healthy individuals, two receiving the flu vaccine and two receiving PN.

Results: On average, 27 mAbs were produced per individual, about 14 specific to each vaccine. PN-specific antibodies were much more likely to use VH3 genes (81%) than flu-specific antibodies (50%; $p = 0.007$, Chi-square). Overall, the SLE individuals produced more mAbs reactive against SLE antigens (33% of anti-flu and anti-PN) than control individuals (2.7%). Of the mAbs generated from SLE patients, mAbs specific to PN were more likely to be reactive against the tested SLE antigens (47%) than flu mAbs (12%; $p = 0.008$, Chi-square with Yate's correction). Remarkably, virtually all of these antibodies cross-react with at least two of the autoantigens tested and many mAbs react to all four. Notably, the polysaccharide antibodies were highly serotype specific yet still bound multiple self-antigens, albeit at affinities several orders of magnitude lower than against the immunogen. While pre-incubation with polysaccharide could inhibit mAb binding to SLE antigens, the converse was not true.

Conclusions: These results suggest that *S. pneumoniae* and influenza vaccination are both capable of inducing antibodies which are cross-reactive to both vaccine antigens and SLE antigens and can escape selection in SLE individuals. In addition, these results indicate that antibodies monospecific to SLE antigens, particularly Ro and La, are rare in the SLE memory pool.

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Antibodies to CCP Versus the Unmodified Arginine-Containing Peptide (CAP) as a Serological Marker To Differentiate SLE from RA. Jason Chan[2], Rufus Burlingame[1], Angela Ceribelli[2], Eric S. Sobel[3], Yi Li[3], Westley H. Reeves[3], Edward K. L. Chan[3] and Minoru Satoh[3]. [1]INOVA Diagnostics, Inc., [2]University of Florida, [3]University of Florida, Gainesville, FL

Purpose: Anti-cyclic citrullinated peptide (CCP) ELISA has been established as a serological marker of RA and used extensively in clinical practice. Early studies on anti-CCP emphasized the selective reactivity of sera from patients with RA for CCP but not with the corresponding unmodified peptide containing arginine (CAP); however, reactivity against CAP is not generally considered in clinical practice or in most studies using commercial anti-CCP ELISA. Recent studies reported that anti-CCP reactivity in non-RA patients is often not specific for CCP but also reactive with CAP, indicating the importance of comparing reactivity with CCP vs CAP. In the present study, reactivity against CCP was compared with that to corresponding unmodified peptide containing arginine (CAP3) in RA, SLE, scleroderma (SSc), polymyositis/dermatomyositis (PM/DM), and controls.

Methods: An ELISA kit using a peptide corresponding to CCP3 but containing unmodified arginine (CAP3) was developed. Anti-CCP3 and CAP3 in sera from SLE ($n = 201$), SSc ($n = 105$), PM/DM ($n = 44$), RA ($n = 84$), and healthy individual ($n = 34$) were tested by ELISA. Reactivity of each serum was calculated as units following the manufacturer's protocol. Patients were classified into 4 groups based on their serum reactivity against CCP vs CAP. Clinical information was from a database.

Results: Anti-CCP was positive in 70% of RA (69% were specific for CCP) vs 12% in SLE (7% specific for CCP), 6% in SSc, and 4% PM/DM,

similar to previous studies. All except one anti-CCP positive RA showed CCP selective reactivity but 42% (10/24) of anti-CCP positive SLE sera also reacted strongly with CAP, indicating lack of specificity for citrullinated peptide in SLE. Surprisingly, anti-CAP reactivity without anti-CCP was frequently seen in SLE (45%) but uncommon in other systemic rheumatic diseases or NHS ($P < 0.0001$).

	RA (84)	SLE (201)	SSc (105)	PM/DM (44)	NHS (34)
CCP(+) CAP(−)	**69%**	7%	5%	4%	0%
CCP(+) CAP(+)	1%	5%	1%	0%	0%
CCP(−) CAP (+)	1%	**45%**	5%	0%	3%
CCP(−) CAP(−)	29%	43%	89%	96%	97%

Conclusions: Anti-CAP without CCP was in high prevalence and relatively specific for SLE among systemic rheumatic diseases. When patients with early undiagnosed arthritis are seen at clinic, positive anti-CAP and negative anti-CCP can serve as a useful serological marker to differentiate SLE from RA. RA sera specifically reacted with CCP but not with CAP as previously described. In contrast to CCP specific reactivity in RA, CAP positivity was common in anti-CCP positive SLE sera.

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Apoptotic Cell Bodies and Blebs Stimulate Self Reactive B-Cells Via Engagement of the BCR and Endosomal Toll-Like Receptors. John McCahan[2], Nathanial Green[1] and Ann Marshak-Rothstein[3]. [1]Boston University, Boston, MA, [2]Rheumatology Section, Boston University, [3]The University of Massachusetts Medical School, Worcester MA

Purpose: Apoptosis is a genetically programmed pathway of cell death that results in the condensation of a cell into sub-cellular particles. Under normal circumstances these are removed by surrounding cells and nearby phagocytes with a non-inflammatory effect. However, disruption of pathways involved in the removal of apoptotic cells has been shown to lead to signs of autoimmunity including autoantibody formation and tissue damage. The mechanisms that lead to the induction of auto-antibodies remain unclear. B cells from AM14 transgenic mice are a model of self reactive B-cells. They express an antigen receptor specific for IgG2aa/j and make a class of auto-antibodies known as rheumatoid factor (RF). It has been shown that immune complexes composed of IgG2a-chromatin or IgG2a-RNA can stimulate AM14 B-cells by the synergistic engagement of the antigen receptor and a member of the Toll-like receptor (TLR) family. Our purpose was to determine if apoptotic cells express auto-antigens that can stimulate self-reactive B-cells.

Methods: Keratinocyte and fibroblast cell lines were induced to undergo apoptosis by several methods including ultraviolet light exposure, etoposide, and serum starvation. In some experiments, cell surface proteins were biotinylated prior to the induction of apoptosis to nonspecifically label cell-surface-derived apoptotic debris. Subcellular particles were fractionated by differential centrifugation yielding two populations defined as apoptotic cell bodies and apoptotic blebs. Each fraction was analyzed by flow cytometry for the induction of apoptosis and autoantigen expression including nucleosomes, Ro, Smith antigen, and nucleoli. Immune complexes composed of subcellular particles bound by IgG2a autoantibodies were used to stimulate AM14 B cells. The contribution of TLR7 and TLR9 in this activation process was addressed by using cells from TLR-deficient mice.

Results: A robust proliferative response was induced by immune complexes composed of apoptotic cell bodies and blebs bound by autoantibodies. This effect was enhanced with IFN-β priming and stimulation was mediated by binding of the B-cell receptor and engagement of either TLR7 or TLR9. Biotinylation experiments indicated that the autoantigens were associated with the cell membrane. By comparing the activity of immune complexes formed with the anti-biotin mAb and mAbs specific for defined autoantigens, we have been able to address the differential expression of autoantigens on apoptotic debris derived from diverse cell types.

Conclusion: Our findings suggest that self reactive B-cells can be stimulated by apoptotic cell bodies and blebs through a TLR mediated process.

Disclosure: J. McCahan: None; **N. Green:** None; **A. Marshak-Rothstein:** None.

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B Cell-Dependent Regulation (Breg) of T-Cell Proliferation Is Deficient in Systemic Lupus Erythematosus (SLE). Jacques-Olivier Pers, Sébastien Lemoine, Ahsen Morva, Christophe Jamin and Pierre Youinou. Brest University

Background: Association of B-cell depletion with increased inflammation in murine models suggests that B cells exert regulatory function, through inhibition of T-cell proliferation. The current study was aimed at evaluating the functional aspect of regulatory B cells in humans and specifically in autoimmune disorders.

Methods: B and T lymphocytes were negatively purified from peripheral blood of 9 healthy donors (HDs), 5 primary Sjögren's syndrome (pSS) patients, 5 SLE patients, and 4 rheumatoid arthritis (RA) patients. T cells were induce to proliferate by stimulation with anti-CD3 and anti-CD28 antibodies. The results was measured by flow cytometry analyses of CFSE stained cells. CD40, TLR9 and/or BCR stimulation were evaluated for their ability to activate the B cells and to induce a regulatory effect. Activated B cells were co-cultured with stimulated T cells, and modulation of the T-cell proliferative response assessed by flow cytometry.

Summary of the Results: Resting B cells from HDs did not affect the proliferation of T cells. In contrast, activated B cells exhibited regulatory effects resulting in a decreased T-cell proliferation rate. For B cells to modulate the T-cell response, CD40 activation appeared to be required. Furthermore, TLR9 signals synergized with CD40 to trigger the most efficient down-regulation of the T-cell proliferative response. Activated Breg from pSS and RA patients were all efficient whilst those of SLE were unable to control the T-cell proliferation.

Conclusion: Human Breg are functionally effective when appropriately activated. They can alter the T-cell proliferation. Our results suggest that both population behave as those of HDs in pSS and RA patients. In contrast, Breg properties appear to be defective in SLE patients. Whether this is due to defective Breg function or to T-cell refractory response remains to be determined.

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B Cells Modify Regulatory T Cells in Healthy Individuals but Not in Patients with Systemic Lupus Erythematosus. Mark N. Lazarus, Hardeep S. Kalsi, David A. Isenberg and Michael R. Ehrenstein. UCL Div of Medicine, London, United Kingdom

Background: A number of publications have demonstrated that B cells can modify regulatory T cells (Treg) number indicating that B cells could contribute to the maintenance of tolerance via effects on Treg. B cell depletion therapy is currently used to treat some patients with systemic lupus erythematosus, but conflicting results have been obtained on the effects on Treg. We therefore investigated whether Treg are affected by removal of B cells *in vitro* and *in vivo*.

Methods: Treg were enumerated in healthy individuals and patients with lupus before and after rituximab therapy and correlated with B cell numbers. Intracellular cytokine staining for IL-2 and interferon gamma was performed in some assays. Peripheral blood mononuclear cells (PBMC) from healthy controls and lupus patients were cultured whole or following depletion of B cells by MACS LD™ beads and stimulated with anti-CD3/CD28. CD4, Foxp3 and CD25 expression assayed after 3 days using FACS.

Results: In patients with SLE, Foxp3 expression was significantly increased compared to healthy controls ($p<0.001$). Both CD4+Foxp3+ and CD4Foxp3hi T cells were significantly increased compared to healthy individuals. CD4+Foxp3+ T cells did not produce any IL-2 or interferon gamma suggesting that these are not simply activated T cells. Following B cell depletion, the increased frequency of Treg compared to healthy controls remained unchanged during depletion and repopulation. There was a strong correlation between Treg numbers and the CD19:CD4 ratio in healthy individuals (r2 0.6059, $p<0.005$), but not in lupus patients. Treg numbers were significantly reduced in the PBMC of healthy individuals ($p<0.001$) but not lupus patients following removal of B cells *in vitro*.

Conclusions: B cells partly drive an increase in Treg numbers *in vitro* following activation in healthy individuals. However, this was not observed in PBMC from lupus patients suggesting that this control on Treg is defective. The notion that the increased frequency of Treg in lupus patients is driven by B cell independent mechanisms is supported by our observation that Foxp3

expression remains unchanged following B cell depletion therapy and that a strong correlation between Treg frequency and B:T cell ratio in healthy individuals is lost in patients with SLE.

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BAFF Binding Receptors (BBR) Related To Relapse after Rituximab in Patients with Reumatoid Arthritis (RA). Inmaculada De la Torre[1], Lara Valor[1], Rita Moura[2], Maria J. Leandro[3], Jonathan C. W. Edwards[3] and Geraldine Cambridge[3]. [1]Hospital Gregorio Maranon, Madrid, Spain, [2]Instituto de Biologia Molecular, Lisboa, Portugal, [3]University College London, London, UK

Background: Coordinated expression of BBR (BAFF-R, TACI, BCMA) control differentiation of B cells into immunoglobulin (Ig) secreting cells. We have previously shown that i) BAFF levels increase after B cell depletion with rituximab (rtx) in patients with RA, remaining raised even after B cell return ii) BAFF-R expression in naïve (NB) and memory B (MB) cells is reduced after rtx and related to clinical relapse independently of circulating BAFF levels or time to relapse after B cell return. iii) Class-switch recombination (CSR) and autoantibody production is also related to clinical relapse after rtx. When B cells differentiate into Ig secreting cells, BAFF-R is lost and BCMA up-regulated. TACI is induced upon B cell activation. Although it can be expressed on activated NB cells (<25%) it is related to CSR and memory-plasma cell differentiation.

Aim: To investigate BBR expression in relation to B cell maturation and clinical relapse in RA patients after rtx.

Methods: Phenotypic analysis of BAFF-R, TACI and BCMA expression on PBMC were performed using combinations of CD19, CD27, CD38 and IgD (% and mean fluorescence intensity-MFI) in normal controls (NC) (n: 5) and patients pre (n: 10) and after rtx, classified as concordant ie relapsing at B cell repopulation (C-R, n: 16), or discordant relapsing > 3 months after repopulation (D-R, n: 10) or non-relapsing after B cell return (D-NR, n: 11).

Results: Mean % of NB cell BAFF-R+ was significantly lower only in patients relapsing (C-R: 65.3%, D-R: 89.7%) when compared to NC ($p=0.027$,$p=0.026$). Percentage and MFI of MB cell BAFFR+ was significantly lower in all patients when compared to both NC and pre-rtx (%: $p<0.05$, MFI: $p<0.005$). In patients relapsing, % NB cell TACI+ tended to be higher in C-R than D-R (23.4% vs 9.9%). All patients pre and after rtx had significantly lower % of MB cell TACI+ when compared to NC ($p<0.05$). However % of MB cell TACI+ was significantly higher in D-NR when compared to D-R ($p=0.001$).

	BAFFR Naïve B cells		BAFFR Memory B cells		TACI Naïve B cells		TACI Memory B cells	
	%	MFI	%	MFI	%	MFI	%	MFI
NC (n:5)	98.5	126	95.43	107.6	16.2	206.5	81.5	155.7
Pre (n:10)	93.40	82.8	83.5	79.4	13.5	62.1#	50.4#	65.3#
C-R (n:16)	65.3#/*	45.3#/*	44.6#/*	51.7#/*	23.4	60.4#	43.6#	67.6#
D-R (n:10)	89.7#/**	60.9#	63.2#/*	57.5#/*	9.9	73.2#	38.9#/*	77.2#
D-NR (n:11)	92.03	47.6#	63.8#/*	56.7#/*	18.1	71.4#	49.8#/***	83.5#/***

P < 0.05: # vs NC, *vs Pre, **vs CR, ***vs DR

BAFF-R and BCMA did not always had an inverse correlation in plasma cells population after rtx. Finally, C-R patients had higher % of plasma cells than D-R and D-NR (16.5 vs 2.06 and 1.85; $p=0.03$ and $p=0.06$).

Conclusions: Rises in autoantibody levels have been related to clinical relapse after rtx. Modulation of BBR expression permissive to plasma cell formation in C-R patients with an earlier down regulation of BAFF-R and up regulation of TACI on (presumably activated autoreactive) NB cells may explain clinical relapse closer to B cell return. Normal BAFF-R expression on NB cells from D-NR patients may reduce the chance of becoming Ig-producing cells, allowing a normal maturation process within germinal center reactions. The consequences of disturbed BBR expression on B cell selection and the advancement or inhibition of progression to autoantibody production may explain timing of relapse after rtx.

Disclosure: I. De la Torre: None; **L. Valor:** None; **R. Moura:** None; **M. J. Leandro:** None; **J. C. W. Edwards:** None; **G. Cambridge:** None.

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Cellular and Serological Changes Following B Cell Repopulation after Rituximab Therapy Suggest Antibody-Independent Roles for B Cells in Systemic Lupus Erythematosus. Mark N. Lazarus, Andrew Fester, Tabitha Turner-Stokes, David A. Isenberg and Michael R. Ehrenstein. UCL Div of Medicine, London, United Kingdom

Introduction: For the last ten years B cell depletion therapy (BCDT) has been used in the treatment of systemic lupus erythematosus (SLE). However, the clinical improvements that follow BCDT are not always associated with a reduction in autoantibody titres suggesting that B cells might also induce disease via antibody-independent mechanisms.

Purpose: The aim of this study was to investigate whether B cells exert an effect on other immune cells which are known to be low in the blood of patients with active disease.

Methods: We analysed changes in the titres of anti-dsDNA antibodies, C3 and lymphocyte and monocyte numbers in the blood of 55 patients with SLE during B cell depletion and over a 52 week period following repopulation. PBMCs were obtained from 53 rituximab treated patients and analysed by flow cytometry for the expression of the activation markers CD69 and HLA-DR by CD4+ T cells. Chemokines were measured in the serum of 19 rituximab treated patients using a cytometric bead assay. *In vitro* experiments were carried out using PBMCs from 5 healthy controls and 5 patients with SLE.

Results: Our results showed that in patients with high anti-dsDNA antibody titres (above 100 IU/L) pre BCDT titres only fell in patients who remained in remission at 52 weeks following B cell repopulation ($p<0.05$) but did not change in patients that relapsed, either during the B cell depletion phase or during repopulation. C3 levels rose during B cell depletion and fell again during relapse but only in patients with high anti-dsDNA antibodies pre-BCDT ($p<0.01$; $p=0.07$). Lymphocyte numbers increased during repopulation in all patients ($p<0.05$) but fell during relapse only in patients who had low titres of anti-dsDNA antibody pre-BCDT ($p<0.05$). The fall in lymphocytes was paralleled by an increase in the expression of HLA-DR by CD4+CD49d+ T cells ($p<0.05$). Expression of CD69 was increased in all lupus patients and did not change following B cell depletion. *In vitro* experiments revealed that B cell activation directly led to increased expression of HLA-DR, but not CD69, on CD4+ T cells. Finally, monocyte numbers increased during depletion and fell during relapse in all groups ($p<0.05$). These changes in monocyte numbers coincided with a reduction in the serum levels of the monocyte recruiting chemokine, MCP-1 ($p<0.05$). MCP-1 production increased *in vitro* when PBMCs were stimulated through the B cell receptor ($p<0.05$).

Conclusion: These results demonstrate that changes in anti-dsDNA antibody and C3 correlate with response to BCDT but only in patients with high titres of anti-dsDNA antibody pre-BCDT. In patients with low anti-dsDNA titres pre-BCDT changes in lymphocyte and moncyte numbers may be more important. These changes in lymphocyte and monocyte numbers correlated with changes in HLA-DR expression by CD4+ T cells and MCP-1 levels respectively, suggesting that B cells might also induce the migration of T cells and monocytes to sites of inflammation in addition to producing autoantibodies. In conclusion, these results suggest that responses to rituximab may be partly governed by antibody independent mechanisms providing an explanation for some of the heterogeneous responses to BCDT that have been observed in SLE.

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Elevated Serum BAFF Correlates with Loss of Mature B Cells and Promotes B Cell Recovery in Mice after B Cell Depletion Treatment. Yue Wang[2], Sandra Gallagher[1], Isharat Yusuf[1], Bahija Jallal[1], Anthony Coyle[1] and Ronald Herbst[1]. [1]MedImmune LLC, [2]MedImmune LLC, Gaithersburg, MD

Purpose: B cell depletion therapy with anti-CD20 monoclonal antibody (MAb) is an effective treatment for rheumatoid arthritis. There are ongoing clinical trials for treating autoimmune diseases with new B cell depleting MAb therapies, which may lead to more complete B cell depletion. It is therefore important to compare the outcome of B cell depletion with different MAbs and correlate that with changes of diseases status as well as pharmacodynamic (PD) markers. Previous studies have indicated that following treatment with anti-CD20 MAb in patients, serum BAFF (B cell activating

factor belonging to the TNF family) levels significantly increase. In this study, we used animal models to investigate the relationship of serum BAFF levels with loss of B cells and the contribution of BAFF to B cell depletion and recovery.

Methods: Mice were treated with escalating doses (0.1～10 mg/kg) of B cell depleting MAb. Numbers of B cells in blood and tissues (spleen and bone marrow) were quantified by FACS and serum BAFF levels detected by ELISA. To study whether elevated BAFF levels can affect B cell depletion, mice were dosed with 2ug recombinant BAFF before and during MAb treatment. To investigate the role of BAFF during B cell recovery, mice were treated with BAFF-R-Fc starting at the time when B cell recovery was detected. The biological function of recombinant BAFF and BAFF-R-Fc were confirmed by in vitro assays.

Results: Treatment of mice with B cell depleting MAb led to dose-dependent reduction in B cell numbers. At a dose of 0.5mg/kg or above, more than 90% of B cells were depleted, spanning from pre-B cells in bone marrow to mature B cells in spleens. The duration of B cell depletion is also dose-dependent and followed by reconstitution of B cells in blood and spleens. Changes in serum BAFF levels and B cell numbers were coupled: BAFF levels are elevated only when tissue B cells start to be depleted and, as B cells recover, serum BAFF levels drop back to baseline. The increase in BAFF levels significantly correlated with loss of mature B cells. When BAFF was elevated 5-fold during the treatment of MAb, B cell depletion was not affected. However, treatment with BAFF-R-Fc during B cell reconstitution resulted in a block of mature B cell regeneration. Consequently, spleen mature B cells were 90% lower in the BAFF-R-Fc treated group compared to the control group.

Summary: A newly developed MAb effectively depletes murine B cells even in the presence of high BAFF levels, supporting its use in autoimmune disease settings. Changes in serum BAFF level after MAb treatment reflect the loss of B cells. Lastly, increased BAFF levels promote B cell recovery and maturation, consistent with the known function of BAFF in regulating B cell survival and homeostasis. Future studies of changes in BAFF levels and functions in B cell depletion are warranted in the clinical trials.

Disclosure: Y. Wang: AstraZeneca, 3; **S. Gallagher:** AstraZeneca, 3; **I. Yusuf:** AstraZeneca, 3; **B. Jallal:** AstraZeneca, 3; **A. Coyle:** AstraZeneca, 3; **R. Herbst:** AstraZeneca, 3.

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Elimination of Autoantibody Producing Plasma Cells Using CXCR4 Antagonist AMD3100. Jason Weinstein[4], Yuan Xu[1], Matthew Delano[3], Yi Li[2], Lijun Yang[1], Eric S. Sobel[2], Lyle Moldawer[1] and Westley H. Reeves[2]. [1]University of Florida, [2]University of Florida, Gainesville, FL, [3]Universsity of Florida, [4]Yale University

Background: Autoantibodies cause disease either directly by interacting with target antigens in cells or tissues or by forming immune complexes that cause inflammation. B cell therapy has been only partially successful because autoantibody producing plasma cells do not express surface molecules, such as CD20, that are targets for the therapeutic mAbs. The chemokine CXCL12 (SDF1) retains plasma cells in stromal cell "niches" where they can survive for many years. We asked whether an antagonist of CXCR4, the receptor for SDF1, could be used to eliminate autoreactive plasma cells.

Methods: Anti-Sm/RNP autoantibodies were induced in BALB/c mice using pristane. Serum autoantibodies to the U1A protein were measured by ELISA. Anti-U1A antibody producing cells were detected by ELISPOT assay using recombinant U1A. Anti-U1A memory B cells were detected by culturing B cells with/without LPS for 5 d followed by ELISPOT assay. Ectopic lymphoid tissue (ELT) arising in the peritoneum after pristane injection was transplanted from untreated or AMD3100 pre-treated anti-U1A+ mice into the peritoneum of naïve recipients and serum anti-U1A levels were monitored for 35 d (ELISA).

Results: Numerous anti-U1A cells were found in the bone marrow (BM), spleen, and ELT of mice with serum anti-Sm/RNP autoantibodies induced by pristane. The BM contained memory B cells but few plasma cells, probably due to a striking reduction of SDF1 expression caused by inflammation. In contrast, ELT expressed high levels of SDF1 and contained many anti-U1A plasma cells but no memory cells. When transplanted into naïve recipients, anti-U1A plasma cells in the ELT continued to secrete anti-U1A antibodies, which could be detected in the recipients' serum. However, if the donor mice were pre-treated with AMD3100, plasma cells were absent by flow cytometry and anti-U1A autoantibody production in the recipients was abolished.

Conclusion: The induction of lupus with pristane generates two populations of anti-Sm/RNP B cells: plasma cells accumulate in the ELT, whereas memory cells accumulate in the BM. Using a transplantation system, autoantibody production from anti-Sm/RNP (U1A) plasma cells residing in ELT can be examined in isolation from memory B cells. AMD3100 (plerixafor), a drug approved for cancer therapy, can be used to eliminate these autoantibody-producing plasma cells. In combination with anti-CD20 mAb treatment, complete depletion of both memory B cells and plasma cells producing autoantibodies may be feasible.

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Expression of the Idiotope 9G4 on Autoantibodies and B Cells from Patients with Rheumatoid Arthritis (RA): Description of a New B Cell Phenotype. Inmaculada De la Torre[1], Rita Moura[2], Maria J. Leandro[3], Jonathan C. W. Edwards[3] and Geraldine Cambridge[3]. [1]Hospital Gregorio Maranon, Madrid, Spain, [2]Instituto de Biologia Molecular, Lisbon, Portugal, [3]University College London, London, UK

Background: The rat monoclonal antibody 9G4 recognises an idiotope on V4–34-derived immunoglobulins(Ig). Antibodies encoded by V4–34 region are inherently autoreactive against red blood cell determinants. An estimated 15% of naïve B cells are 9G4+ but <1% of circulating Ig are 9G4+ in healthy controls (HC). In HC, 9G4+ B cells of a mature pre-switch phenotype (IgM+IgD+CD27+) are found in splenic marginal zones (MZ). 9G4+ B cells are also in tonsils from HC but excluded from germinal center (GC) reactions. Whereas in patients with lupus, post-GC memory B cells (IgD−CD27+) are present, suggesting defective B cell censoring (1). In RA, there is also some evidence that B cell tolerance is affected.

Objective: To determine whether RhF from RA and disease controls express 9G4 and to examine the phenotype of 9G4+ B cells in peripheral blood.

Methods: 9G4-expression on RhF and on total serum IgM and IgG were measured by ELISA in 22 seropositive RA and 20 RhF+ve 1o Sjogrens Syndrome (SS). Peripheral blood CD19+ B cells from 24 patients with RA and 7 HC were obtained by negative selection using MACs columns and stained to distinguish 9G4 expression on CD5 and CD27 populations and also within naïve (IgD+CD38+), transitional (IgD+CD38++), memory post-GC (IgD-CD38+), memory resting (IgD−CD38) and plasmablast (IgD−CD38+++) populations. Analyses were by Mann Whitney rank sum test.

Results: RhF levels and expression of 9G4 on total IgM and IgG were minimally higher in RA than SS patients ($p<0.05$). However 9G4 expression on RhF was significantly greater ($p<0.0001$) in RA vs SS patients. Percentages of 9G4+CD19+ B cells in HC and RA patients were similar (mean %: 6.36 vs 6.45) and most had a naïve phenotype (means: 44%, 42% respectively). Post-GC B cells and plasmablasts had means of 14.5% and 3.5% for NC and, for RA, 29.5% and 9.2% respectively. Gating on the 9G4+ population, CD5−CD27− phenotype was the most common in NC and RA (58.7% vs 55.7%). However a distinct population was described with a CD5+CD27+ B cell phenotype with similar proportions in HC and RA (13.1% vs 17.4%). Further, in some RA patients, a negative correlation was found between the percentage of B cells expressing CD5+CD27+ and 9G4 expression on RhF in the same sample.

Conclusions: Although post-GC 9G4+ B cells were not found in RA tonsils, we found 9G4 on RhF in patients with RA but not in SS. As RhF from patients with SS do not utilize V4–34, this suggests breakdown of 9G4 censoring in patients with RA, perhaps in areas outside secondary lymphoid tissue such as in the spleen or inflamed joints. We also found that HC and RA patients had circulating 9G4+ memory B cells and plasmablasts and describe a new B cell phenotype, CD19+CD5+CD27+, which often carries the 9G4 idiotope. CD5 is found on B cells in splenic MZ and is lost from B cells before entry into late stages of a GC. Also, CD27+ B cells have been shown to be predominantly CD5−CD23−. We suggest that retention of CD5 expression on 9G4+CD27+ B cells, whilst allowing development of a mature phenotype may be a self-censoring mechanism preventing access to GCs (perhaps by affecting BCR signaling) and hence antibody production from these potentially 'dangerous' autoreactive cells.

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Expression of ZAP-70 in B-Cell Is a Feature of Peripheral Blood Repopulation after Rituximab Therapy in Rheumatoid Arthritis. Francesca Faustini, Barbara Tolusso, Giusy Peluso, Elisa Gremese, Silvia Canestri, Graziella D'Antona, Antonella Laria and Gianfranco Ferraccioli. Division of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy

Background: The expression of ZAP-70 in B cells derived from synovial fluid of rheumatoid arthritis (RA) patients seems to define a subset of these cells characterized by increased survival and shows a correlation with the inflammatory and autoimmune phenotype. Aim of the study: to evaluate the expression of ZAP-70 by different subsets of peripheral blood B-cells before and after treatment with Rituximab (RTX) in a cohort of RA patients during a 24 months follow-up and, the relationship between ZAP-70 expression in B cells overtime and clinical response.

Methods: B-cell phenotype was analysed in 16 patients at baseline and at T6, T12 and T24 respectively. Flow cytometric analysis was performed by incubating PBMCs with anti-human monoclonal antibodies (CD19, IgD, CD38, CD27, CD5, CD23) as surface markers and intracellular ZAP-70. Demographic and clinical data were collected at baseline and every three months. The response to therapy was assessed through DAS score based on EULAR criteria. 15 healthy controls were enrolled in the study.

Summary of Results: The assessment of B cell subpopulations according to both IgD-CD38 and IgD-CD27 staining did not reveal significant differences in B cell distribution between patients at baseline and controls. We observed a significant decrease of the percentage of CD19+ cells at 6 (3.4±7.2 vs 9.5±3.5% at baseline, $p<0.001$), 12 (1.6±1.9%, $p<0.001$) and 24 months follow-up (2.2±2.9%, $p<0.001$) and an increase of the Bm2+Bm2′/eBm5+Bm5 ratio from baseline (2.4±2.7 vs 8.7±10.0 at 6 months FU, $p=0.08$; 6.9±7.9 at 12 months, $p=0.04$; 7.6±7.2 at 24 months, $p=0.02$). IgD-CD27 staining confirmed these findings by revealing a significant decrease of the percentage of IgD-CD27+ B cells at 6 months FU (19.5±14.8% at baseline vs 9.4±7.8%,$p=0.01$), IgD−CD27− (12.6±5.5% at baseline vs 7.6±5.2% at 6 months, $p=0.02$ and 8.0±6.6% at 12 months, $p=0.01$). In addition, a parallel decrease of CD38+/CD27+% during FU (9.0±5.9 at baseline vs 3.6±2.7% at 6 months, $p=0.005$; 5.0±6.0% at 12 months, $p=0.02$; 3.9±4.2% at 24 months, $p=0.004$) was observed. The percentage of CD19+/ZAP-70+ cells showed a significant increase at 6 months (2.6±3.6% at baseline vs 9.4±12.4%, $p= 0.005$), 12 months (10.6±8.4%, $p=0.001$) and 24 months (15.3±13.6%, $p=0.001$) after RTX treatment The baseline percentage of CD19+/ZAP-70+ was lower in good responders (0.5±0.2%) compared to poor responders at 6 months FU (3.0±1.0%, $p=0.02$) even if the difference was not confirmed at 12 months analysis.

Conclusions: In RA patients, regeneration of B-cells after BCDT is characterized by a significant decrease of the memory subset along with an increase of the percentage of B-cells expressing ZAP-70.

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In Vivo Effects of Tocilizumab on Peripheral B Cells in Patients with Rheumatoid Arthritis. Petra Roll[2], Khalid Muhammad[2], Mathias Schumann[2], Stefan Kleinert[2], Thomas Dörner[1] and Hans-Peter Tony[2]. [1]Rheumatology and Clinical Immunology Charite Universitätsmedizin Berlin and DRFZ Berlin, Berlin, Germany, [2]Rheumatology/Clinical Immunology, University of Würzburg, Würzburg, Germany

Purpose: Interleukin (IL)-6 receptor inhibition by tocilizumab was recently licensed for the therapy of active rheumatoid arthritis (RA). IL-6 has been originally described to induce differentiation of B cells into antibody forming cells. However the in vivo effects of IL-6 inhibition by tocilizumab on the B cell compartment are currently not known.

Methods: 16 patients with active RA were treated with monthly intravenous infusion of 8 mg/kg tocilizumab. Immunphenotyping was performed at baseline, week 12 and 24.

Results: pre-treatment data indicate a higher proportions of pre-(IgD+/CD27+) and post-switch (IgD-/CD27+) memory B cells in RA patients compared to healthy donors(n=21). During tocilizumab treatment, proportion of both memory B cell subsets declined significantly at week 24 compared to baseline. In detail, pre-switch memory B cells decreased from median 19.6% (range: 3.4–39.0%) to 12.3% (5.5–38.1%, $p=0.04$) and post-switch memory B cells declined from 18.6% (7.1–32.2%) to 15.0% at week 24 (6.7–24.5%, $p=0.04$) respectively. The proportion of IgG+ B cells declined significantly from 6.7% to 4.9% ($p=0.02$) and 2.8% ($p=0.006$) at week 24. The proportion of IgA expressing B cells fell from 9.7% to 4.8% at week 12 ($p=0.03$) and to 2.7% at week 24 ($p=0.004$). Absolute numbers of IgA+ B cells also showed a significant decrease at week 12 ($p=0.01$) and at week 24 ($p<0.001$). In accordance with these results the levels of serum immunoglobulins IgA and IgG were also diminished at week 24 ($p<0.05$). In the naïve B cell compartment a significant increase in relative and absolute numbers of CD38hi/IgD+/CD10+ transitional type B cells is observed indicating that the B cell regeneration capacity is not altered under IL-6 receptor inhibition.

Conclusion: Our results indicate that IL-6 receptor inhibition by tocilizumab alters B cell homeostasis by significantly reducing peripheral pre- and post-switch memory B cells in rheumatoid arthritis. A marked reduction of CD19+/IgA+ and CD19+/IgG+ B cells parallels the significant decline of serum immunoglobulin IgA und IgG levels. The results indicate a reduction of B cell hyperactivity in RA by therapeutic IL-6 receptor inhibition.

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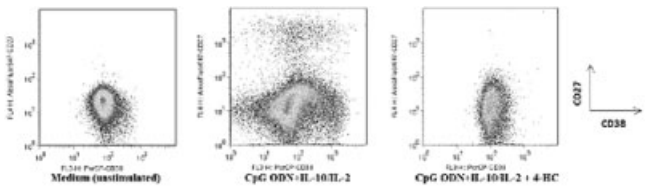
Predominant Suppression of Plasmablasts by Cyclophosphamide in Patients with Systemic Lupus Erythematosus: A Possible Therapeutic Mechanism. Yuko Okamoto[1], Yasuhiro Katsumata[5], Yasushi Kawaguchi[2], Manabu Kawamoto[5], Sayumi Baba[5], Kae Takagi[5], Takahisa Gono[5], Yuko Ota[5], Masako Hara[4] and Hisashi Yamanaka[3]. [1]Tokyo Women's Medical University, Tokyo, Japan, [2]Tokyo Women's Medical University, Tokyo, Japan, [3]Tokyo Women's Medical University, Shinjuku-ku, Tokyo, Japan, [4]Tokyo Women's Medical University, Kamakura Kanagawa, Japan, [5]Tokyo Women's Medical University

Purpose: Cyclophosphamide (CY) has remained the treatment of choice for major organ involvement in systemic lupus erythematosus (SLE). Although CY is generally considered to nonspecifically inhibit the inflammatory immune response, its precise therapeutic mechanism in SLE remains to be elucidated. We aimed to clarify the effect of CY on human B cell subsets *in vivo* and *in vitro*.

Methods: We analyzed 6 patients with recent onset of SLE without prior treatment and 6 normal healthy controls (NHCs). Peripheral blood mononuclear cells (PBMCs) were isolated from heparinized whole blood of these subjects by density gradient centrifugation. Immunofluorescence staining of PBMC for flow cytometry was performed using anti-CD19, anti-CD27, and anti-CD38 antibodies. Multi-color analyses were performed using FACSCalibur and FlowJo software. For *in vitro* assays, $CD19^+$ B cells were positively selected form PBMCs of normal healthy donors by MACS. To mimic B cell homeostasis in active SLE *in vivo*, B cells were cultured with CpG ODN 2006 plus IL-10/IL-2 in the presence or absence of 4-hydroperoxycyclophosphamide (4-HC), activated congener to CY. B cell proliferation, differentiation, and antibody secretion were determined as described below.

Results: The frequencies of plasmablasts ($CD19^+/CD27^{high}/CD38^{high}$) were significantly higher in active untreated SLE patients than in NHCs (13±8% and 1.4±1.2%, respectively; $p = 0.01$) whereas the frequencies of memory B cells ($CD19^+/CD27^+/CD38^{low}$) were significantly lower in active SLE patients than in NHCs (20±11% and 38±9%, respectively; $p = 0.01$). The frequencies of plasmablasts in active SLE patients significantly decreased when re-analyzed 2 weeks after the initiation of IV CY (0.5 g/m^2 of body surface bolus; oral prednisolone was also administered several days ahead) than those before treatment (2.2±1.7% and 12±7%, respectively; $p = 0.006$). In the B cell proliferation assay using tetrazolium salt as a chromogenic indicator for NADH, the O.D. values of the stimulated cells were significantly higher than in those of the unstimulated cells and this proliferation was significantly inhibited by 4-HC (0.66, 0.13, 0.11, respectively). The frequencies of plasmablasts were significantly lower in the unstimulated cells and the 4-HC-treated cells than in the stimulated cells.



The production of IgM and IgG in the culture supernatants were also significantly inhibited by 4-HC: the mean concentrations of IgM and IgG were 62.0 μg/ml and 18.8 μg/ml, respectively in the culture supernatants of the stimulated cells whereas those of the unstimulated cells and the 4-HC-treated cells were under the assay ranges by ELISA.

Conclusions: This study shows that administration of CY predominantly suppresses activation and viability of plasmablasts *in vivo* and *in vitro*. These findings may indicate that therapeutic effect of CY on SLE is at least partly exerted through this mechanism.

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Progesterone Receptors Regulate Humoral Immunity. Alan Wong, Chang Li, Ed Clark and Grant Hughes. University of Washington

The immunological mechanisms linking female reproduction and autoimmune diseases like systemic lupus erythematosus are poorly understood. In humans and genetically susceptible mice, estrogen increases disease development. In the same settings, progesterone (Pg) appears to decrease the risk of disease. How this occurs is unknown but likely involves differential regulation of IFN-α, Th1-related signals and B cell differentiation. Under physiologic conditions, Pg's immunomodulatory effects are thought to be mediated by two Pg receptor types expressed in mouse and human leukocytes: intracellular Pg receptors (PRs) that are ligand-activated transcription factors, and membrane-bound Pg receptors (mPRs) that are linked to inhibitory G proteins and unrelated to PRs. Very little is known about the differential immune functions of PRs vs. mPRs. Recently, Pauklin and Petersen-Mahrt (J Immunol, 2009) demonstrated that Pg, via PR, inhibits B cell class switch recombination (CSR) through transcriptional repression of the activation-induced deaminase (AID) gene in vitro. Here, we show the first genetic evidence linking Pg and PR signaling to adaptive humoral immunity in vivo.

To investigate the role of PRs in antibody (Ab) responses, we used mice in which signaling through PR was genetically ablated (PRKO) by targeted disruption. Female PRKO mice are infertile due to reproductive organ abnormalities. Male PRKO mice are fertile. To assess a role for PR in Ab responses, we measured primary thymus-dependent (TD) Ab responses to alum-adsorbed DNP-KLH and primary thymus-independent type 2 (TI-2) responses to DNP-Ficoll. Female PRKO mice generated significantly more (up to 5 fold) anti-DNP IgM, IgG1, and IgG2a compared to their wild type (WT) female littermates after immunization with DNP-KLH in alum. Thus, PR regulates T cell-dependent humoral immune responses in vivo. Interestingly, these differences were more pronounced in male mice, indicating that PR regulates humoral immunity regardless of sex. PRKO and WT mice did not differ in total serum Ig levels and or numbers of spleen B cells, T cells, and DCs before immunization, and thus differences in Ab responses were not simply due to underlying differences in lymphocyte/DC development. We also observed no differences in anti-DNP Ab responses after TI-2 immunization, suggesting that Pg, via PR, may regulate T cells, B cells or responses to alum. We detected no consistent differences in the ability of PRKO vs. WT purified spleen B cells to undergo CSR in vitro, either to T-cell associated signals (anti-CD40) or LPS. However, CD4+ T cells from PRKO mice produced more IFN-γ, but not IL-4, in response to anti-CD3/CD28 stimulus compared to WT T cells. Thus, the elevated IgG2a responses in PRKO mice may be due to dysregulated Th1 differentiation. This work supported by NIH grant AI073739 and an ARRA supplement to AI073739.

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SLAP Deficiency Alters Both Central and Peripheral B Cell Tolerance Leading to Decreased Autoantibody Production. Lisa K. Peterson[2], Laura A. Shaw[2], Luke F. Pennington[1] and Leonard L. Dragone[2]. [1]Denver, CO, [2]National Jewish Health, Denver, CO

Background: Intrinsic defects in lymphocyte signaling have been implicated in the pathogenesis of autoimmunity. Manipulation of B cell function by altering BCR complex-mediated signaling could be a viable strategy to treat autoimmune disease. Src-like adaptor protein (SLAP) has been shown to influence BCR levels and signaling in developing B cells. We hypothesized that SLAP deficiency through increasing BCR levels and strength of signal through the BCR complex can enhance receptor editing, anergy and/or the negative selection of autoreactive B cells and prevent the development of autoimmune disease.

Methods: To test this hypothesis we utilized two models of autoantibody production. First, we bred the 3H9H/E56R (56R) mice, which express an anti-dsDNA reactive BCR heavy chain that leads to BCR editing and anergy induction, to SLAP-deficient mice to examine the effects of SLAP deficiency on central tolerance. Second, we immunized SLAP-deficient and wild-type BALB/c mice with a peptide mimetope for dsDNA that causes the development of a germinal center dependent anti-dsDNA antibody response that leads to a lupus-like autoimmune disease to examine the effects of SLAP deficiency on peripheral B-cell tolerance mechanisms.

Results: SLAP deficiency (SLAP−/−) led to a significant decrease in serum levels of dsDNA in E56R mice. Compositional analysis of bone marrow revealed a decrease in kappa usage by pre-B cells in SLAP−/− 56R mice, suggesting increased receptor editing. However, splenic B cell subsets and kappa vs. lambda light chain usage were similar between 56R and SLAP−/− 56R mice, indicating that anergy could also be responsible for the decreased production of autoantibodies. To determine if SLAP deficiency leads to enhanced receptor editing verse anergy, hybridomas were generated. Consistent with enhanced receptor editing, less of the SLAP−/− 56R hybridomas produced antibodies reactive with dsDNA compared to the 56R hybridomas. The decreased number of hybridomas secreting anti-dsDNA was due to a qualitative change in light chain repertoire in SLAP−/− 56R mice. The light chain repertoire of SLAP−/− 56R hybridomas was biased toward Vκ21D, an efficient editor of anti-dsDNA reactivity. In contrast, incomplete editors of anti-dsDNA reactivity, Vκ38C and Vκ20, predominated in 56R hybridomas. In the mimetope model of lupus-like autoimmunity, despite the production of an equivalent level of anti-peptide antibodies compared to BALB/c controls, SLAP-deficient mice did not produce anti-dsDNA antibodies upon immunization with a peptide mimitope of dsDNA.

Conclusions: These data show that enhanced signaling through the BCR complex could be a general strategy to treat autoimmune disease by eliminating autoreactive B cells that are either maintained as a result of inefficient receptor editing or failed negative selection upon germinal center formation. Our studies are the first step in defining signaling networks downstream of the BCR signaling complex that can be targeted to enhance the negative selection of autoreactive B cells and possibly prevent or treat antibody-mediated systemic autoimmune disease.

Disclosure: L. K. Peterson: None; **L. A. Shaw:** None; **L. F. Pennington:** None; **L. L. Dragone:** None.

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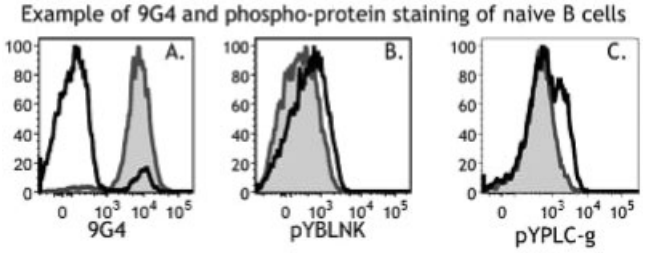
SLE Anti-CD45/B220 9G4 Autoantibodies Induce Attenuated BCR Signaling: Implication for Disease Pathogenesis. Scott A. Jenks[2], Anna E. Schroeder[1] and Ignacio Sanz[2]. [1]Duke University, Durham, NC, [2]Univ of Rochester, Rochester, NY

Background and Purpose: It has long been known that anti-lymphocyte autoantibodies (ALA) are frequently present in SLE patients. One well characterized and prevalent group of ALA are VH4.34-encoded antibodies recognized by the rat anti-human idiotype antibody 9G4 (9G4+ antibodies). In addition to recognition of I/i blood group antigens, these antibodies also bind the glycosylation isoforms of CD45 (B220+) found predominately on naive B cells. In a subset of SLE patients, close to 100% of *ex vivo* naive B cells are positive for the 9G4 idiotype and when naive B cells from healthy controls are incubated with serum from these patients they also become positive for 9G4. Since CD45 is a phosphatase that can alter signaling, binding of 9G4 antibodies to naive B cells may directly change signaling in these cells. Supporting this idea, we have observed that B cells from an SLE patient with strong *ex vivo* 9G4 binding showed poor B cell receptor (BCR) induced phosphorylation as compared to healthy control B cells. The goal of this study was to directly test the hypothesis that binding of 9G4+ antibodies to CD45/B220 will decrease BCR signaling in naive B cells.

Methods: Lymphocytes from healthy control donors were incubated with serum from SLE patients with strong *ex vivo* 9G4 staining on the majority of naive B cells (shaded histogram), SLE patients without strong 9G4 staining (open histogram), and healthy control serum. These cells were then stimulated through the BCR with antibodies against IgM. After fixation and permeabilization, 9G4 staining was measured flow cytometrically (Fig A) and BCR signaling was quantified by measuring induced phosphorylation of BLNK (pY84,) (Fig B) and pPLC-γ2 (pY759) (Fig C).

Results: Anti-IgM induced phosphorylation in naive B cells was substantially reduced in cells incubated with serum from SLE patients with *ex vivo*

9G4 binding, as compared to healthy control serum, or serum from SLE patients without strong 9G4 staining. The reduction in signaling correlated with the degree of 9G4 binding detected. Furthermore this attenuation was dependent on 9G4 immunoglobulin, since purified immunoglobulin was sufficient to reduce phosphorylation and serum depleted of 9G4 no longer had this effect.



Conclusions: Several alterations in BCR signaling have been described in human SLE. While some of these changes are likely due to genetic alterations of signaling molecule expression or function, others may be a direct result of the disease process. These findings describe a novel mechanism by which SLE ALA can directly modulate signaling. These changes in signaling may alter B cell, proliferation, survival, and differentiation and thus help explain some of the abnormalities in B cell homeostasis observed in SLE. Reduced BCR signaling may also result in impaired clonal deletion and reduced RAG upregulation and receptor editing thereby contributing to the increased generation of auto-antibodies.

Disclosure: S. A. Jenks: None; **A. E. Schroeder:** None; **I. Sanz:** None.

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Specific Histone Deacetylase (HDAC2) Inhibition in B Cells May Protect Lupus. Nilamadhab Mishra[1], Kristen Delany[3] and Issac Snowhite[2]. [1]Wake Forest Univ Health Scienc, Winston-Salem, NC, [2]Wake Forest Univ Health Science, [3]Wake Forest Univ Health Sciences

Background: Systemic lupus erythematosus (SLE) is characterized by polyclonal B cell activation, autoantibody production, and glomerulonephritis. The mechanisms how autoreactive B cells are produced in lupus are incompletely understood. Using genome wide mass spectrometry analysis, we have recently demonstrated that there exists histone hypoacetylation in splenocytes from MRL/lpr mice compared to controls. Based upon these findings, we hypothesize that environmental factors trigger epigenetic alternations such as histone modifications to induces autoreactive B cells by up regulating epigenetic modulators histone deacetylases (HDAC).

Material and Methods: Naive B cells isolated from either MRL/lpr or C57BL6(B6) mice (6–7 wk) spleens by CD43+ depletion with MACs beads followed by separation with a non-continuous percoll gradient. The cells were incubated with TLR agonist: TLR-3 poly I:C (5mg) TLR4-LPS (E.coli 111:B4) 25mg/ml, TLR-7,imiquimod (1mg/ml) TLR-9 CpG (3mM) or CpC control, anti-IgM, anti-Cd40, IL-4 etc. Cells were harvested for RNA and protein at six hours post-stimulation. Western blot were performed for different histone deacetylases. MRL/lpr mice were treated with valproic acid that selectively affects HDAC2.

Results: Stimulation of naïve B-cells with agonist for TLR 3, 4, 7 or 9 results in increased mRNA and protein expression of HDAC2 among the HDAC tested. We confirmed the activation status of B cells by measuring IL6 and IL-10. We also examine the major transcriptional regulators MTA3, MITF, XBP1 and IRF4, which are systematically down regulated or up-regulated upon activation. The levels of these proteins were overexpressed in MRL/lpr mice compared to C57/Bl6 mice splenocytes. All mice in the valproic acid treatment group did not develop skin disease whereas all mice in the placebo group developed skin disease. Ninety percent of mice on the treatment arm had grade I proteinuria compared to 20 percent in the vehicle group. The mean renal activity score was 4.833 $\pm$0.654 in the treatment group compared to 8.00 $\pm$0.00 in the vehicle group. The serum anti-dsDNA autoantibodies levels were decreased in valproic acid treatment group. There was no change in serum Ig subtype between vehicle vs treatment group.NZB/W F1 mice treated with valproic acid have decreased proteiuria, kidney disease and autoantibody production In vivo treatment with valproic acid decreased HDAC2 in spleen. Genetic knock down of HDAC2 in B cells by using mice MB1 and CD19 cre trasgenic mice demonstrated that HDAC2 is required for early B cell development. HDAC2 deficient mice have decreaed Pro-B cells in bone marrow and decreased follicular and marginal zone B cells in spleen.

Conclusion: These data suggest that isoform specific histone deacetylase inhibitors may be beneficial for lupus by blocking B cell development.

Disclosure: N. Mishra: None; **K. Delany:** None; **I. Snowhite:** None.

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The Effects of the Anti-CD22 Monoclonal Antibody Epratuzumab on B-Cell Surface Proteins. Anthony Shock[1], Derek Brown[2], Kenneth Crook[2] and Timothy Bourne[2]. [1]UCB, Slough, Berkshire, Slough, United Kingdom, [2]UCB, Slough, Berkshire, UK

Background: Epratuzumab is a humanized monoclonal antibody against CD22 that is currently being evaluated clinically in systemic lupus erythematosus (SLE). Epratuzumab treatment of SLE patients has been shown to reduce CD22 cell surface expression on B cells (Jacobi A, et al. Ann Rheum Dis 2008;67:450–457). The aim of the current study was to investigate the kinetics of internalization on B cells from healthy volunteers in vitro and to look at a range of other cell surface proteins.

Methods: In vitro studies used B cells that were purified by negative selection from human blood and incubated with a concentration range of epratuzumab or an isotype control antibody over time, washed and then stained with fluorescently-labeled antibodies specific to a range of B-cell surface proteins and analyzed by flow cytometry. In order to assess the expression of CD22 in the presence of epratuzumab, a non-competing anti-CD22 antibody (S-HCL-1-PE) was employed. CD22 internalization was also evaluated in a qualitative manner in confocal microscopy experiments employing Alexa488-labeled epratuzumab. Whole blood flow cytometry was used to assess CD22 levels on B cells from SLE patients dosed with epratuzumab.

Results: Epratuzumab caused rapid internalization of B-cell surface CD22 in a range of in vitro experiments. Maximal internalization occurred in 30–60 min at concentrations above 1–2 μg/mL but the level of internalization typically did not exceed 50–70%, even at higher antibody concentrations, suggesting that some B-cell surface CD22 is resistant to epratuzumab-induced internalization. Internalization was prevented by prior cell fixation with paraformaldehyde and was reduced at a lower temperature. Internalization of CD22 on B cells in response to epratuzumab treatment was also confirmed using confocal microscopy. Although epratuzumab was capable of modulating the expression of CD22 in B-cell cultures, it had no consistent effect on several other B-cell markers including IgM, IgD, CD19, CD20, CD27, CD32, CD38, CD69, CD79b, CD95, and HLA-DR Class II measured at a variety of time points up to 6 days. Internalization of CD22 was observed on a number of B-cell subsets following treatment of SLE patients with epratuzumab.

Conclusions: Epratuzumab stimulated rapid internalization of its target, CD22, on human peripheral blood B cells in vitro and in vivo but had no consistent effect on a range of other B-cell markers. This could lead to modulation of B-cell functional responses that are regulated specifically by CD22, which may be relevant in the context of SLE.

Disclosure: A. Shock: UCB, Inc., 3; **D. Brown:** UCB, Inc., 3; **K. Crook:** UCB, Inc., 3; **T. Bourne:** UCB, Inc., 3.

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The Effects of the Anti-CD22 Monoclonal Antibody Epratuzumab on Peripheral Blood B Cells and Immune Responses In Vivo, and Immunoglobulin Production In Vitro. Anthony Shock[1], Derek Brown[2], Kenneth Crook[2], Stevan Shaw[2], Timothy Bourne[2], Roland Foulkes[2] and Geoffrey Rose[2]. [1]UCB, Slough, Berkshire, Slough, United Kingdom, [2]UCB, Slough, Berkshire, UK

Background: Epratuzumab is a humanized monoclonal antibody against CD22 currently being evaluated clinically in patients with systemic lupus erythematosus (SLE). The aim of the current study in cynomolgus monkeys was to investigate the effects of epratuzumab on circulating B cell numbers and on the immune response to the challenge antigens keyhole limpet hemocyanin (KLH) and tetanus toxoid (TT). Additionally, the effect of epratuzumab on immunoglobulin production from human B cells in culture was assessed.

Methods: In one study, cynomolgus monkeys received 4 weekly doses of epratuzumab at 10, 60, or 160 mg/kg and peripheral blood CD20+ B cell numbers were enumerated by flow cytometry. In a second study, cynomolgus monkeys received epratuzumab at 3 different dose levels (1 $\times$ 60 mg/kg, 1 $\times$

10 mg/kg or 4 × 60 mg/kg), or saline. The primary immune response to administered KLH and the secondary immune response to TT were then monitored over time using ELISAs to measure anti-TT and anti-KLH titers in serum. Human peripheral blood mononuclear cells (PBMC) or purified B cells from human tonsils were cultured in vitro with a range of stimuli and the effect of epratuzumab on IgG and IgM production, assessed by ELISA, was monitored after 5 days in culture.

Results: There was a 50–60% reduction in the numbers of circulating B cells in cynomolgus monkeys after treatment with epratuzumab at all doses tested, which occurred within 24 hours of dosing. Animals treated with saline showed a primary anti-KLH response, with an increase in both IgG and IgM antibody levels. Epratuzumab did not inhibit this response at any dose tested, and there was no significant difference between the groups when area under the curve of the response over time for each animal was assessed. A robust IgG anti-TT was demonstrated but, again, no significant difference was observed between the differently dosed groups and saline controls. The production of IgG and IgM from human PBMC or tonsil B cells in culture was unaffected by incubation with a range of concentrations of epratuzumab.

Conclusions: Epratuzumab treatment caused a reduction in B cells but had no effect on the capacity to raise an antibody response to challenge antigens in cynomolgus monkeys in vivo. The production of immunoglobulin by B cells in culture was also unaffected by epratuzumab. This might indicate that the efficacy of epratuzumab in SLE patients is unlikely to be accompanied by a gross effect on the capacity to generate an adaptive immune response.

Disclosure: A. Shock: UCB, Inc., 3; **D. Brown:** UCB, Inc., 3; **K. Crook:** UCB, Inc., 3; **S. Shaw:** UCB, Inc., 3; **T. Bourne:** UCB, Inc., 3; **R. Foulkes:** UCB, Inc., 3; **G. Rose:** UCB, Inc., 3.

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TNF Blockade Impairs the Induction of T-Cell Dependent Antibody Responses. Gabriela Franco Salinas[1], Leen De Rycke[2], Sophie Brouard[4], Vojislav Jovanovic[4], Frederique Moizant[4], Tineke Cantaert[2], Mirjam van der Burg[3], Barbara Barendregt[3], Paul Peter Tak[2], Jean-Paul Soulillou[4] and Dominique Baeten[2]. [1]Academisch Medisch Centrum, University of Amsterdam, Amsterdam, Noord Holland, The Netherlands, [2]Academisch Medisch Centrum, University of Amsterdam, Amsterdam, The Netherlands, [3]Immunology, Erasmus Medical Center, Rotterdam, Netherlands, [4]Institut de Transplantation et Recherche en Transplantation, INSERM U643, Nantes, France

Objectives: TNFα blockade induces anti-nuclear antibodies in patients with Spondylarthritis (SpA) and Rheumatoid Arthritis. These antibodies are related to increased levels of circulating nuclear antigens, restricted to IgM autoantibodies and directed to T cell independent (TI) but not T cell dependent (TD) antigens. Based on this observation, we tested in experimental models and in arthritis patients whether TNF blockade impairs the maturation of TD humoral responses.

Methods: Cardiac allografts from LEW.1W rats were transplanted to LEW.1A rats treated with either anti-TNF or control antibody. Alloantibodies and graft rejection were monitored for 25 days. Transplanted hearts were assessed by histology, immunohistochemistry, and qPCR. In humans, PBMCs from SpA patients treated with TNF blockade or NSAIDs were collected for analysis of somatic hypermutation, lymphocyte phenotype, expression of costimulatory molecules and in vitro assays. After 12 weeks of treatment, both patient groups were vaccinated with a TD vaccine to Hepatitis B and a TI vaccine to S. Pneumoniae. Vaccine-specific antibody titers were determined in serum.

Results: In the rat allotransplantation model, anti-TNF treatment at the day of transplantation inhibited the induction of IgM ($p=0.004$) and IgG ($p=0.020$) alloantibodies as well as IgG deposition in the graft ($p=0.015$). Accordingly, leucocyte infiltration was decreased and graft architecture was better preserved in treated animals ($p=0.015$), resulting in prolonged graft survival ($p=0.020$). In this model, TNF blockade did not affect the Th1/Th2 balance, TLR expression nor the expression of regulatory molecules like TGF-beta, IDO and FoxP3, suggesting that the beneficial clinical effects may be primarily related to the inhibition of the humoral response.

In human arthritis, the antibody response against the TD vaccine was almost completely blocked ($p=0.010$) during TNF blockade in SpA patients whereas TI responses were less affected. An effect on the germinal center (GC) reaction was suggested by a decreased degree of somatic hypermutation of peripheral B cells in SpA patients treated with anti-TNFα blockers versus controls ($p=0.040$). In addition, we observed an increased number of circulating memory B cells ($p=0.001$) but a decrease in plasmablasts ($p=0.039$) in anti-TNF treated patients. This was not due to an intrinsic B cell defect as B cells obtained after TNF blockade in vivo did not display defective differentiation towards plasma cells in vitro. Neither could we evidence a defective B cell activation as the post-GC B lymphocytes of anti-TNF treated patients displayed an increased expression of CD40 and HLA-DR ex vivo and a normal expression of CD80 and CD86 after TD stimulation in vitro. Further studies on the underlying mechanisms will focus on extra-follicular B cells as well as B cell migration.

Conclusion: TNF blockade impairs the induction of humoral responses in rodents and humans, with the most pronounced effect on TD responses. Whereas the exact mechanism is currently under investigation, these data reveal a novel mechanism of action of anti-TNF with potential relevance for several fields of clinical immunology.

Disclosure: G. Franco Salinas: None; **L. De Rycke:** None; **S. Brouard:** None; **V. Jovanovic:** None; **F. Moizant:** None; **T. Cantaert:** None; **M. van der Burg:** None; **B. Barendregt:** None; **P. P. Tak:** None; **J.-P. Soulillou:** None; **D. Baeten:** None.

ACR Poster Session B
Epidemiology and Health Services Research: MSK, CTD and SLE Focus
Tuesday, November 9, 2010, 9:00 AM–6:00 PM

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A Systematic Literature Review of the Direct Costs of Systemic Lupus Erythematosus (SLE) in the United States (US). Katherine A. Slawsky[1], Ancilla Fernandes[2], Susan Manzi[3], Lauren Fusfeld[1] and Thomas F. Goss[1]. [1]Boston Healthcare Associates, Inc., Boston MA and Washington DC, [2]MedImmune LLC, Gaithersburg, MD, [3]West Penn Allegheny Health System, Pittsburgh, PA

Background: SLE is a chronic autoimmune disorder characterized by acute flares and remissions. Patients are generally managed with multiple medications depending on disease severity, tolerance, and organ system affected. SLE is thought to be associated with high symptom and economic burden; here, we review annual direct medical costs associated with SLE among adults in the US.

Methods: English-language studies published between 01/2000 and 04/2010 were systematically reviewed from both MEDLINE PubMed and the Cochrane databases. Studies were included if they reported direct medical costs of SLE among adults in the US.

Results: Nine studies reporting direct costs associated with SLE in the US and published since 01/2000 were identified, Five were excluded: one focused on a pediatric population, a review with no pooled- or meta-analyses, one study that reported no actual cost estimates and two studies that applied Canadian costs to US patients. A summary of the selected four studies is presented in **Table 1** below.

Table 1. Results Summary

Data Source	Study 1: Commercial Claims	Study 2: Commercial Claims	Study 3: Medicaid Claims	Study 4: Patient Self-reported Resource Utilization
Sample size	6,269	15,590	2,298	815
Year of data analysis*	2005	2006	2006	2004
Mean annual direct cost per SLE patient (all patients) (SD)	$20,926 ($45,093)	N/A	$17,009 ($27,531)	$13,735 ($25,792)
Mean annual direct cost per SLE patient without nephritis (SD)	$16,575 ($29,300)	$12,273 ($27,096)	$13,758	N/A
Mean annual direct cost per SLE patient with nephritis (SD)	$62,651 ($106,745)	$31,274 ($52,800)	$29,034 ($41,876)	N/A
Mean annual direct cost per control patient (SD)	$7,794 ($22,014)	N/A	$9,788 ($18,078)	N/A

*All costs included to 2009 values using the GDP calculator, available http:GDP.html

Studies examined main cost categories of inpatient, outpatient, and pharmacy services, all of which contributed substantially to total costs, although the relative contribution of each main cost category varied. Median costs were consistently lower than means reported, suggesting outliers may skew overall mean costs. With the exception of study 4, all studies examined annual costs of newly diagnosed or newly active patients. No identified studies explicitly examined costs of specific treatments or disease manifestations (other than nephritis), or disease severity. Methodologies varied across studies, with patient self-reported resource

utilization generating the lowest estimates vs. claims analyses; Medicaid claims analyses generated lower incremental cost estimates for SLE patients vs. control patients compared to commercial claims analysis.

Conclusions: SLE is associated with substantial annual direct cost burden in the US; however, little research has been done examining costs associated with specific treatments, cost variation by disease severity, and disease manifestations. It is important to investigate the variation in costs due to disease severity and manifestations as newer and more expensive biologic therapies continue to emerge.

Disclosure: K. A. Slawsky: MedImmune, LLC, 2; **A. Fernandes:** AstraZeneca, 1, MedImmune, LLC, 3; **S. Manzi:** MedImmune, LLC, 9; **L. Fusfeld:** MedImmune, LLC, 2; **T. F. Goss:** MedImmune, LLC, 2.

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A Systematic Review To Appraise the Quality of Cost-Effectiveness Studies of Biologic Agents for the Treatment of Rheumatoid Arthritis. Maria A. Lopez-Olivo[1], Yomei Shaw[2] and Maria E. Suarez-Almazor[3]. [1]The University of Texas M.D. Anderson Cancer Center, Houston, TX, [2]The University of Texas M.D. Anderson Cancer Center, [3]University of Texas, MD Anderson Cancer Center, Houston, TX

Background: Recently, evidence has shown outstanding advances in the therapeutic approach of rheumatic diseases. The use of cost effectiveness (CE) analyses in this area has increased rapidly due to the elevated costs of the newer agents. We conducted a systematic literature review to describe the methodology reported and integrate findings from publications concerning CE in the treatment of rheumatoid arthritis with biologic agents.

Methods: We searched for cost effectiveness studies (including cost-utility) on the use of infliximab, etanercept, adalimumab, golimumab, certolizumab, tocilizumab, rituximab, abatacept and anakinra for the treatment of rheumatoid arthritis, published through September, 2009. Sources included electronic databases (MEDLINE, EMBASE, BIOSIS, etc.) and pertinent websites. Review of 2957 citations revealed 29 CE analyses. Two independent reviewers evaluated development methods of selected studies using the Quality of Health Economic Studies (QHES) tool, which was adapted using the OMERACT criteria for economic evaluations in RA.

Results: Of the 29 publications, 14 reported CE in etanercept, 12 in infliximab, 7 in adalimumab, 3 in abatacept, 2 in rituximab and 1 anakinra. Dates of publication ranged from 2002 to 2009. The studies varied in the clinical trials they cited as evidence for their models (1 to 9 RCTs) and with respect to the costs reported. There was also disparity in how studies were modeled and reported. 82% of the included studies fulfilled 75% or more of the quality of reporting criteria obtaining a "good" quality score. Studies failed to report perspective of the analysis (76%), discounting rate (35%), and pre-specification of groups at the beginning of the study -if estimates came from a subgroup analysis (72%). Studies published after 2006 scored higher in most quality domains than those published before (55%) and also those studies evaluating RA over a time period of >1 year (83%). Studies funded by industry tend to score lower (<75%) than those conducted by agencies (NS). Only 1 study did not specify the source of funding (QHES 81.5%). Figure 1 shows that 80% of the studies funded by industry concluded a cost-effective intervention versus 54% of those funded by agencies (NS).Overall, treatments included in the studies were consider cost-effective (ICERs reported in the studies were within or below 50,000 USD, even after adjusting for inflation and differences in currencies).

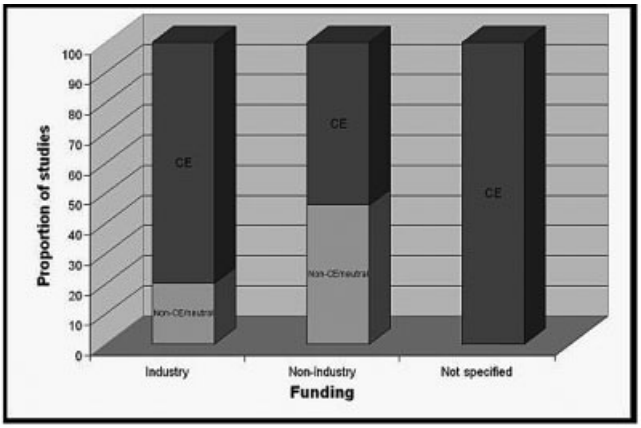

Figure 1. CE* per source of funding.
*as described by the authors

Conclusion: Quality scores of CE articles published were rated acceptable. However, several differences in the design, key assumptions, and model structure were observed among studies. There is a need for more uniformity and transparency in the methodology reported in economic evaluations of biologic agents for the treatment of rheumatoid arthritis to help decision makers make better informed decisions.

Disclosure: M. A. Lopez-Olivo: None; **Y. Shaw:** None; **M. E. Suarez-Almazor:** AHRQ, 2, Amgen Inc., 8, Bristol-Myers Squibb, 8, NIH, 2, Roche, 8.

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Agreement between Tuberculin Skin Test and Interferon-γ Assay in Korean Patients with Rheumatoid Arthritis and Ankylosing Spondylitis before Initiation of Anti-Tumor Necrosis Factor Therapy. Yong-Geun Jeong[1], Ji-Min Kim[3], Su-Jin Moon[3], Seung-Ki Kwok[3], Ji-Hyeon Ju[3], Kyung-Su Park[3], Sung-Hwan Park[2] and Ho-Youn Kim[1]. [1]Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea, [2]Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea, Republic of, [3]Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea

Purpose: To evaluate the responsiveness to tuberculin skin test (TST) in patients with rheumatoid arthritisis (RA) and ankylosing spondylitis (AS) before initiating tumor necrosis factor α blockade (TNF-blocker) therapy, and assess its association with clinical feature and interferon-γ (IFN-γ) assay result.

Method: We retrospectively reviewed the medical records of 483 patients (251 RA, 227 AS, 5 Psoriatic arthritis, PsA) who were treated with TNF-blockers in the department of rheumatology in Seoul St. Mary's Hospital between January 2003 and April 2009 and then analyzed the clinical characteristic and the result of TST and IFN-γ assay.

Results: TST results of 483 patients (251 RA, 227 AS, 5 PsA) were examined. The mean diameter of induration was smaller in RA patients than in AS patients (3.88mm±6.24 versus 7.52mm±8.24, $p< 0.001$). TST positive rate was higher in AS compared to RA (41.4% vs 20.7%; $p<0.001$). Both in RA patients and AS patients, there were no significant difference between positive TST group and negative TST group in terms of disease activity, age, past history of tuberculosis and steroid usage. The positive rate of IFN-γ assay was comparable between RA and AS (41.3% versus 45.8%, $P=0.768$). The agreement rate between TST and IFN-γ assay was 71.9% (kappa=0.422) in the whole group, 68.3% (kappa=0.319) in RA, and 76.2% (kappa=0.533) in AS. IFN-γ assay was positive in 26.2% of RA patients and 4.5% of AS patients in whom TST result was negative. Tuberculosis prophylaxis was done in 22.0% of RA patients and 39.1% of AS patients ($p < 0.001$).

Conclusion: There was difference in the TST positive rates between Korean patients with RA and AS. In RA patients, lower TST positive rate gave rise to the low rate of tuberculosis prophylaxis before TNF-blocker therapy compared to AS patients. Interferon-γ assay could identify patients with latent tuberculosis despite negative TST result and should be performed with TST for diagnosis of latent tuberculosis before TNF-blocker therapy, especially in RA patients.

Disclosure: Y.-G. Jeong: None; **J.-M. Kim:** None; **S.-J. Moon:** None; **S.-K. Kwok:** None; **J.-H. Ju:** None; **K.-S. Park:** None; **S.-H. Park:** None; **H.-Y. Kim:** None.

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Assessing Systemic Lupus Erythematosus Disease Severity and Disease Flares: Development of a Claims-Based Algorithm. Cindy P. Garris[2], Priti M. Jhingran[2], Nicole M. Engel-Nitz[4], Aylin A. Riedel[5], George Goldberg[4], Damon L. Bass[1] and Gregory J. Dennis[3]. [1]GlaxoSmithKline, King of Prussia, PA, [2]GlaxoSmithKline, Research Triangle Park, NC, [3]Human Genome Sciences, Rockville, MD, [4]i3 Innovus, Eden Prarie, MN, [5]i3 Innovus, Eden Prarie, NC

Background: Disease severity and disease flares are based primarily on clinical presentation in patients with systemic lupus erythematosus (SLE). Disease severity is not clearly defined but physicians often describe it as a relationship between disease activity and the organs involved. In clinical trials, disease activity and disease flares are usually assessed by composite scores which integrate both clinical and serologic variables. The ability to describe and evaluate populations of SLE patients in real-world settings has been limited due to the lack of validated methodology to identify disease severity or flares in administrative claims data.

Objective: To develop and validate algorithms to identify SLE disease

severity and the occurrence and severity of SLE flares using administrative claims.

Methods: This retrospective, observational study (BLM001HO) used medical and pharmacy data (1/1/2004 to 12/31/2008) from a large managed care health plan. Patients meeting the following criteria were included in the analysis: at least 3 years of continuous enrollment in the health plan (1 year pre-index baseline period and 2 years follow up period); were between the ages of 18 and 64; and evidence of SLE. Evidence of SLE during the study period was based upon a combination of diagnosis code (ICD-9 code 710.0x), visits to rheumatologists, and filled prescriptions for lupus treatment medications (corticosteroids, antimalarials, and immunosuppressives).

Results: A total of 2990 SLE patients were identified in the claims database (92% female, mean age 44 years). Initial algorithms for identifying SLE disease severity and flare severity were developed based upon the literature and clinical consultation with 2 rheumatologists and 1 internal medicine physician. Medical and pharmacy claims for a random sample of SLE patients were reviewed to understand the patients' profile of health services utilization, conditions diagnosed, use of services, types of providers visited, and medication use. Following evaluation of these patient profiles, the initial algorithms were further refined. The resulting disease severity and flare algorithms were applied to the SLE patients identified in the claims database.

SLE Disease Severity Algorithm

Mild	**Not Moderate or High Severity**
Moderate	**Moderate Rx OR Moderate Medical Condition**
Rx	• Oral corticosteroid dose ≥7.5 mg/day to <60 mg/day • Immunosuppressive agent (excluding cyclophosphamide)
Medical Condition:	• *Cardiorespiratory:* myocarditis, pericarditis, pleurisy/ pleural effusion, vasculitis (excluding aortitis) • *Constitutional:* hepatitis (non-viral) • *Gastrointestinal:* acute pancreatitis, lupus enteritis/colitis • *Hematology:* hemolytic anemia • *Musculoskeletal:* ischemic necrosis of bone • *Neuropsychiatric:* demyelinating syndrome/acute inflammatory demyelinating polyradiculoneuropathy, mononeuropathy/polyneuropathy, myelopathy, pseudotumor cerebri, seizure
High	**Intensive RX OR Severe Medical Condition**
Rx:	• Oral corticosteroid dose ≥60 mg/day • Cyclophosphamide • Rituximab
Medical Condition:	• *Cardiorespiratory:* aortitis, arterial/ venous thrombosis, cardiac tamponade, pulmonary hemorrhage, stroke/TIA • *Gastrointestinal:* intestinal pseudo-obstruction • *Neuropsychiatric:* acute confusional state/psychosis, aseptic meningitis, cranial neuropathy • *Ophthalmic:* optic neuritis • *Renal:* end stage renal disease (ESRD)

SLE Flare Severity Algorithm

Mild	
RX Initiation	• Hydroxychloroquine or other antimalarial • Oral corticosteroid with prednisone-equivalent dose of ≤7.5 mg/day • Non-immunosuppressive therapy (NSAIDS, androgens)
Moderate	
RX Initiation	• Oral corticosteroid with prednisone-equivalent dose >7.5 mg/day & ≤ 40 mg/day • Immunosuppressive therapy (excluding cyclophosphamide)
Medical	• ER visit with primary diagnosis of SLE (710.0x) or SLE-related condition • Office visit for new SLE-related condition*
Severe	
RX Initiation	• Oral corticosteroid with prednisone-equivalent dose >40 mg/day • Cyclophosphamide
Medical	• Hospital stay with primary diagnosis of SLE (710.0x) or SLE-related condition*

***SLE-related conditions:** disease severity conditions above or any of following: arthritis/arthralgia, dry eye/tear film insufficiency, rash, low white blood cell count (leukopenia, neutropenia, lymphocytopenia), lymph node enlargement, myalgia/ myositis, urticaria

Applying the algorithm, 26% of patients were classified as mild, 52% were moderate and 22% had high disease severity over the 2 year follow-up period. Over the 2-year period, 71% of patients had at least one mild flare, 86% had at least one moderate flare and 20% had one or more severe flares.

Conclusions: This study has identified an algorithm that may be used to identify SLE disease severity and the occurrence and severity of SLE flares, using a combination of medical and pharmacy administrative claims. Applying this clinically-based algorithm to other claims-based studies of patients with SLE may enable an improved evaluation of SLE patients in real-world populations.

Disclosure: C. P. Garris: GlaxoSmithKline, 3; **P. M. Jhingran:** GlaxoSmithKline, 3; **N. M. Engel-Nitz:** i3 Innovus, 3; **A. A. Riedel:** i3 Innovus, 3; **G. Goldberg:** I3 Innovus, 3; **D. L. Bass:** GlaxoSmithKline, 3; **G. J. Dennis:** Human Genome Sciences, Inc., 3.

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Colonization and Infection by Staphylococcus Aureus among Those Using Biologic Therapy. Cara Varley[1], Atul A. Deodhar[1], Benjamin Ehst[1], Antony Bakke[1], Andrew Blauvelt[1], Robert Vega[2] and Kevin Winthrop[1]. [1]Oregon Health & Science University, Portland, OR, [2]Oregon State Public Health Laboratory, Hillsboro, OR

Purpose: While much emphasis has been placed on preventing opportunistic infections in patients with inflammatory arthritis on biologic therapy, it is clear that most serious infections are due to "routine" organisms like Staphylococcal aureus. In an ongoing prospective study we investigated the relationship between rates of new and persistent colonization, new infections with S. aureus, use of biologics and underlying disorder.

Methods: We prospectively enrolled patients with autoimmune inflammatory diseases from the rheumatology and dermatology clinics of our University. Patients receiving or being considered for biologic therapy (etanercept, infliximab, adalimumab, rituximab, abatacept) were surveyed for the presence of S. aureus infection risk factors and assessed for S. aureus colonization. Specimens collected from the bilateral nares and inguinal folds were cultured using standardized laboratory isolation procedures and screened for the presence of methicillin-resistant S aureus (MRSA) utilizing Spectra™ MRSA test media (Remel Scientific®) and mannitol salt agar containing 4 mcgs of oxacillin (MSAO, Remel Scientific). We actively sought to follow up patients to assess persistence of colonization, new colonization, or infections with S. aureus, and their relationship with underlying disease and therapy.

Results: We enrolled a total of 392 patients (rheumatoid arthritis n=103 (26.3%), psoriasis or psoriatic arthritis n=205 (52.3%), ankylosing spondylitis n=29 (7.4%), combination of two or more n=15 (3.8%), other n=40 (10.2%). At baseline, 156 (39.8%) were colonized with S. aureus, of which 19 (12.2%) had MRSA. Our baseline colonization rates of S. aureus (39.8%) and MRSA (4.8%) were significantly higher than previously reported for the general population (30.8% and 0.8%, $p<0.01$ for both). Colonization rates were similar between biologic users and non-users (40.1% and 39.5%, $p=0.90$) but were significantly higher for psoriasis patients compared to those with RA (43.4% and 30.1%, $p=0.02$). 184 patients, of which 122 (66.3%) were on biologic therapy, completed follow up (mean 1 year, range 0.2–2.3 years). Biologic agents did not increase the risk of persistent (colonized at baseline and follow up) or new colonization (see table). Self reported infections were more common in persistently colonized patients compared to those newly, transiently or never colonized (RR=4.25, 95% CI 0.99–18.25, $p=0.05$).

Conclusion: Inflammatory arthritis patients at our center have higher rates of S. aureus colonization than the general population, and the risk of new colonization is not modified by biologic therapy. Prospective follow up shows a trend towards increased risk of subsequent infections in those with persistent S aureus colonization.

Colonization and Self Reported Staph Infections at Follow-up, N = 184

	Persistent Staph Colonization	No Staph Colonization	Self Reported Staph Infection
Anti-TNF Exposure Between Enrollment and Follow-up	33∞	62	5*
	27.05%	50.82%	4.20%
No Anti-TNF Exposure Between Enrollment and Follow-up	10∞	34	2*
	16.13%	54.84%	3.28%
Rheumatoid Arthritis	11	31	0
	22.92%	64.58%	0.00%
Psoriasis and/or Psoriatic Arthritis	22	49	5
	22.00%	49.00%	5.05%
Ankylosing Spondylitis	5	4	0
	38.46%	30.77%	0.00%
Other$^{\nu}$	3	8	0
	18.75%	50.00%	0.00%
Two or More	2	4	2#
	28.57%	57.14%	28.57%

∞ No statistically significant association between anti-TNF exposure and persistent staph colonization, p = 0.15
* No statistically significant association between anti-TNF exposure and self reported staph infections, p = 1.00
ν Includes Crohn's Disease, Ulcerative Colitis, Uveitis
Both patients had a psoriasis diagnosis

Disclosure: C. Varley: None; **A. A. Deodhar:** Amgen Inc., 2, Centocor Ortho Biotech Inc., 2, 5, 8, Genentech and Biogen IDEC Inc, 2, 5; **B. Ehst:** None; **A. Bakke:** None; **A. Blauvelt:** None; **R. Vega:** None; **K. Winthrop:** Pfizer Inc, 2, 5.

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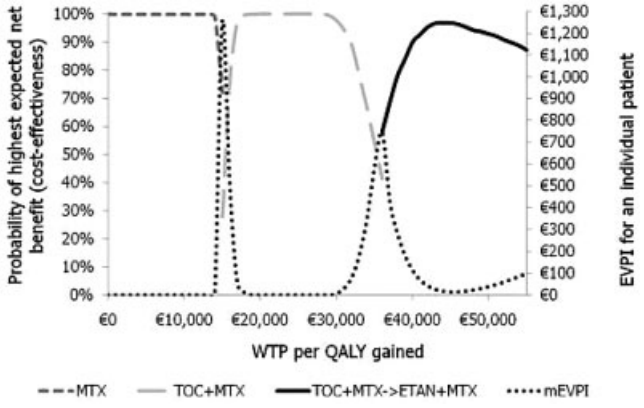
Comprehensive Health Economic Assessment of Sequenced Treatment with Biologics in Moderate-to-Severe Rheumatoid Arthritis: Analysis Based on ACR50 and ACR70 Responses. Erkki J. O. Soini[1], Taru A. Hallinen[1], Markku J. Kauppi[3], Ville Vihervaara[4] and Kari Puolakka[2]. [1]ESiOR Oy, Kuopio, Finland, [2]Lappeenranta Central Hospital, Lappeenranta, Finland, [3]Päijät-Häme Central Hospital, Lahti, Finland, [4]Roche Oy, Espoo, Finland

Purpose: To assess the cost-utility and multinomial expected value of perfect information (mEVPI) of sequenced treatment with biologics in moderate-to-severe rheumatoid arthritis (msRA) after failure of traditional disease modifying antirheumatic drug(s) (tDMARD).

Methods: A probabilistic, individual sampling (microsimulation) model was developed to compare ten different treatment sequences among 3,000 hypothetical Finnish msRA patients in a lifetime scenario. Adalimumab+methotrexate (MTX), etanercept+MTX or tocilizumab+MTX were used as first biologics followed by up to three other biologics. Best supportive care including tDMARDs was assumed to be used after exhaustion of treatment options with biologics. Treatment with MTX alone was added as further comparator. The clinical outcomes (no ACR50, ACR50 and ACR70 responses conditional to the use of biologic drugs) were obtained from a recently published mixed treatment comparison and quality-adjusted life-years (QALY) were estimated based on the Health Assessment Questionnaire (HAQ) scores using a nonlinear equation: $EQ5D = 0.82 - 0.11*HAQ - 0.07*HAQ^2$. Resource use was estimated based on HAQ scores from published references and valued with Finnish unit costs (euro, year 2009). Analyses were performed from payer perspective (productivity losses were excluded) using 3% annual discount rate.

Results: Compared to MTX alone, treatment with tocilizumab+MTX was more cost-effective than treatment with etanercept+MTX. Both tocilizumab+MTX and etanercept+MTX dominated adalimumab+MTX. An additional QALY gained with tocilizumab+MTX costs euro15,478 (mEVPI euro1,258/patient) compared with MTX alone. An additional QALY gained with tocilizumab+MTX followed by etanercept+MTX costs euro35,543 (mEVPI euro748/patient) compared with tocilizumab+MTX. According to cost-effectiveness acceptability frontier (Figure, which presents the optimal treatment options, their probabilities of cost-effectiveness and mEVPI), only MTX alone, tocilizumab+MTX or tocilizumab+MTX followed by etanercept+MTX should be considered, if willingness to pay is euro0–50,000 per QALY gained.



With euro30,000 per QALY gained, tocilizumab+MTX had 97.6% probability of being cost-effective. The results were relatively robust in sensitivity analyses. mEVPI indicated that the value of additional research information is relatively low.

Conclusions: After tDMARD failure, tocilizumab+MTX or tocilizumab+MTX followed by etanercept+MTX were the most cost-effective biologics for patients with msRA.

Disclosure: E. J. O. Soini: ESiOR Oy, 1, 3, 4; **T. A. Hallinen:** ESiOR Oy, 1, 3, 4; **M. J. Kauppi:** Abbott, 5, Bristol-Myers Squibb, 5, MSD, 5, Pfizer, 5, Roche, 5, UCB, 5; **V. Vihervaara:** Roche, 3; **K. Puolakka:** Abbott, 5, Bristol-Myers Squibb, 5, MSD, 5, Pfizer, 5, Roche, 5, UCB, 5.

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Correlations between 3 Work-Related Patient-Reported Outcome Instruments for Patients with Ankylosing Spondylitis. Annelies Boonen[2], Walter P. Maksymowych[3], Sumati Rao[1], Naijun Chen[1] and Mary Cifaldi[1]. [1]Abbott Laboratories, Abbott Park, IL, [2]University Hospital Maastricht, Maastricht, Netherlands, [3]University of Alberta, Edmonton, AB

Background: Several instruments have been proposed to measure work productivity but comparative studies of these instruments for rheumatic diseases are lacking. We assessed correlations between 3 work-related patient-reported outcome (PRO) instruments and the Bath Ankylosing Spondylitis Functional Index (BASFI) for patients with ankylosing spondylitis (AS). We further evaluated the percentage of productivity loss and the impact on cost between the 3 PRO measures of presenteeism, defined as the impact of disease on a patient's ability to perform at work.

Methods: Data were obtained from the Patient-Reported Outcomes Survey in Employment (PROSE) study, a longitudinal, observational study of AS and work productivity. Participants diagnosed with AS completed an online patient survey that included 3 measures of work productivity: 1) the Work Productivity and Activity Impairment Questionnaire (WPAI), 2) the Work Limitations Questionnaire (WLQ), and 3) the Quality-Quantity Method (QQ). The WPAI measures absenteeism, presenteeism, overall work productivity impairment, and activity impairment related to AS, whereas the WLQ has 4 subscales (time management, physical demands, mental–interpersonal demands, and output demands) that assess effects of health problems on job performance (ie, presenteeism) and are combined into an overall productivity loss score. The QQ measures overall quantity and quality of work. Spearman correlation coefficients between mean scores for the WPAI components and the WLQ and QQ scores were calculated at baseline.

Results: Mean changes in WPAI presenteeism and WLQ productivity loss scores represented 22% and 5.5% work productivity loss, respectively. WPAI presenteeism was significantly correlated with WLQ time management ($r=0.59$; $p<0.0001$) and mental–interpersonal demands ($r=0.59$; $p<0.0002$) subscales as well as the overall productivity loss score ($r=0.63$; $p<0.0001$). BASFI was correlated with WPAI absenteeism ($r=0.29$, $p<0.0005$), presenteeism ($r=0.63$, $p<0.0001$), overall impairment ($r=0.65$, $p<0.0001$), and WPAI activity impairment ($r=0.69$, $p<0.0001$); WLQ time management ($r=0.50$, $p<0.0001$), mental–interpersonal demands ($r=0.49$, $p<0.0001$), output demands ($r=0.55$, $p<0.0001$), and productivity loss ($r=0.58$, $p<0.0001$); and QQ quality ($r=-0.44$, $p<0.0001$) and quantity ($r=-0.45$, $p<0.0001$). BASFI was not correlated with the WLQ physical demands subscale. Using the more sensitive, disease-specific 22% reduction in WPAI presenteeism (assuming a 40-hour work week at $18/hr),[1] potential work productivity loss for patients with AS could result in loss of $158/wk per patient with AS.

Conclusion: Although the 3 work-related PRO instruments are highly correlated with each other, there are important differences between the absolute values used to estimate productivity loss. Independent of the approach, loss of work productivity is strongly correlated with BASFI. Further research is required to assess full aspects of validity between the 3 work-related PRO instruments.

Reference:

[1]US Dept of Labor. Available at: http://www.dol.gov/. Accessed June 24, 2010.

Disclosure: A. Boonen: None; **W. P. Maksymowych:** Abbott Laboratories, 5, 8; **S. Rao:** Abbott Laboratories, 3; **N. Chen:** Abbott Laboratories, 3; **M. Cifaldi:** Abbott Laboratories, 1, 3.

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Costs for Health Care, Prescribed Drugs, and Sick Leave Differ for Patients with Different Types of Spondylarthropathy. Ann B. I. Bremander[1], Aleksandra Turkiewicz[2], Martin Englund[2], Emma Haglund[3], Gisela Kobelt[2], Ingemar F. Petersson[2] and Britta Strömbeck[2]. [1]Musculoskeletal Research Center, Dept. of Orthopedics, Clinical Sciences, Lund University, Lund, Research and Development Cente at Spenshult Hospital for Rheumatic Diseases, Oskarstrom, Sweden, [2]Musculoskeletal Research Center, Dept. of Orthopedics, Clinical Sciences, Lund University, Lund, Sweden, [3]Musculoskeletal Research Center, Dept. of Orthopedics, Clinical Sciences, Lund University, Lund, Sweden, Research and Development Cente at Spenshult Hospital for Rheumatic Diseases, Halmstad, Sweden

Background: The spondylarthropathy (SpA) group includes ankylosing spondylitis (AS), psoriatic arthritis (PsA), SpA associated with inflammatory bowel disease (IBD), undifferentiated SpA (USpA), and reactive arthritis

(ReA). It has earlier been established that patients with AS have increased costs for health care and sick leave compared with the background population, but data for other types of SpA are scarce.

Objectives: To estimate the costs for health care, prescribed drugs, and sick leave for the different SpA diagnoses.

Methods: The Skåne Health Care Register (SHCR) in southern Sweden is a legislative, mandatory register based on physicians ICD-10 diagnoses and covers all in- and outpatient health care (total population 1.2 million). We identified all subjects having received a diagnosis of SpA during the years 2003–2007. To increase specificity we required all cases to be diagnosed at least once by a rheumatologist/internist or having had at least two clinic visits with the diagnosis by any other physician. Costs due to health care consumption, prescribed drugs and sick leave were retrieved from the SHCR, the Prescribed Drug Register, and the Swedish Social Insurance Agency for the years 2006–2007, including all patients 15 to 65 years of age.

Results: 3 561 patients with SpA (1 758 men and 1 803 women), mean age (SD) 47 (12) years were identified. The IBD patients had the highest costs for health care (mean €8 057, SD €10 545), prescribed drugs (mean €4 360, SD €6 610), and sick leave (mean € 11 570, SD €10 415) whereas PsA patients had the lowest cost for health care (€4 757, SD €7 080) but the second highest for prescribed drugs (mean €2 986, SD €6 391) and sick leave (mean € 9 224, SD €11 222) (Table).

Table. Cost is Euro (€) for health care, prescribed drugs, and sick leave per patient with Spondylarthropathy (SpA) over 2 years.

	N	Age Mean (SD)	Sex Men/ Women	Cost for health care Mean (SD) Median (range)	Cost for prescribed drugs Mean (SD) Median (range)	Cost for sick leave Mean (SD) Median (range)
All SpA	3.561	47 (12)	1.758/1803	5.234 (9.350)	2.557 (5.917)	8.542 (11.130)
				2.510 (0–158.830)	178 (0–58244)	1188 (0–47595)
AS	793	48 (11)	532/261	5547 (9765)	2872 (6021)	9191 (11535)
				2627 (0–140359)	187 (0–38587)	1751 (0–47.595)
PsA	1.578	49 (12)	704/874	4757 (70)	2986 (6.391)	9.224 (11.222)
				2.477 (0–77.428)	301 (0–58.244)	1.974 (0–455)
IBD	84	49 (11)	24/60	8.057 (10.545)	4.360 (6.610)	11.570 (10.415)
				4.079 (263–58.057)	1.251 (0–25.761)	10.837 (0–36851)
USpA	613	44 (11)	251/362	5.371 (9.120)	2.018 (5.511)	7.740 (10.827)
				2.445 (0–83.805)	97 (0–45.449)	503 (0–42.145)
ReA	493	43 (14)	247/246	5.604 (12.436)	1.044 (3.871)	5.791 (10.108)
				2.346 (0–158.831)	23 (0–53.395)	0 (0–39.348)

Conclusion: The different clinical forms of SpA are also seen as different cost patterns for health care, prescribed drugs, and sick leave due to disease consequences and treatment traditions.

Disclosure: A. B. I. Bremander: None; **A. Turkiewicz:** None; **M. Englund:** None; **E. Haglund:** None; **G. Kobelt:** None; **I. F. Petersson:** None; **B. Strömbeck:** None.

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Dietary Intake of Vitamin D during Adolescence and Risk of Adult Onset Systemic Lupus Erythematosus and Rheumatoid Arthritis. Linda T. Hiraki[3], Karen H. Costenbader[1], Kassandra Munger[4] and Elizabeth W. Karlson[2]. [1]Brigham & Women, Boston, MA, [2]Brigham and Womens Hospital, Boston, MA, [3]Harvard School of Public Health, Boston, MA, [4]Harvard School of Public Health

Introduction: Early life exposures have been implicated in the etiology of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Vitamin D has immunomodulatory effects with implications as an etiologic and therapeutic factor in several autoimmune diseases including SLE and RA. There are no studies on vitamin D intake during adolescence and the risk of adult onset SLE and RA.

Objectives: We examined the relationship between reported vitamin D intake during adolescence and incidence of adult onset RA and SLE in two prospective cohort studies, the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII).

Methods: Previously validated food frequency questionnaires (FFQ) on high school diet, completed by 75,458 NHS participants in 1986 and 45,948 NHSII participants in 1998 (maximum recall of 47 and 35 years respectively), were used to calculate nutrient intakes during adolescence. Incident RA and SLE cases were confirmed by medical record review. Cox-proportional hazards regression relative risks (RR) and 95% CI were calculated for quintiles of adolescent dietary vitamin D intake and incident RA, incident SLE. Calorie adjusted and multivariate adjusted analyses were completed, with adjustment for demographic, dietary and sun-exposure related factors. Random effects models were used to obtain a single combined estimate of association across the two cohorts.

Results: Incident RA was confirmed in 652 NHS and 126 NHSII participants (total 778), and incident SLE was confirmed in 122 NHS and 52 NHSII participants (total 174) over a mean followup of 329 and 207 months for NHS and NHSII respectively. Calorie-adjusted and multivariate-adjusted models did not show significant associations between adolescent vitamin D intake and risk of adult onset RA and SLE when comparing the 5th quintile of vitamin D intake to the 1st quintile (Table 1).

Table 1. Estimated Hazard Ratios and 95% CI of Association between adolescent vitamin D intake and incident RA and SLE

	NHS	NHSH	Pooled
Number of RA cases	652	126	778
HR (95% CI) Energy adjusted Total Vitamin D	1.03 (0.8, 1.32)	1.06 (0.62, 1.82)	1.03 (0.82, 1.3)
HR (95% CI) Multivariate adjusted Total Vitamin D	0.87 (0.6, 1.26)	0.96 (0.51, 1.81)	0.87 (0.64, 1.13)
Number of SLE cases	122	52	174
HR (95% CI) Energy adjusted Total Vitamin D	1.09 (0.62, 1.95)	1.08 (0.47, 2.45)	1.03 (0.65, 1.63)
HR (95% CI) Multivariate adjusted Total Vitamin D	1.16 (0.52, 2.56)	0.69 (0.25, 1.88)	0.87 (0.5, 1.46)

Conclusions: We did not find associations between reported dietary intake of vitamin D during adolescence and risk of RA or SLE in adulthood. This may be due to inaccurate reporting of adolescent diet, focus on a short time period of exposure, unavailable serum vitamin D levels during this exposure period of interest or lack of effect of dietary intake of vitamin D. Small numbers of incident cases also reduced our power to detect an association if one existed.

Disclosure: L. T. Hiraki: None; **K. H. Costenbader:** None; **K. Munger:** None; **E. W. Karlson:** None.

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Direct and Indirect Costs of Spondlyoarthritis Patients Pre- and Post-Diagnosis. Noam Kirson[2], Howard Birnbaum[2], Sumati Rao[1], Elyse Swallow[2], Tracy Waldman[2], Elias Dayoub[2] and Mary Cifaldi[1]. [1]Abbott Laboratories, Abbott Park, IL, [2]Analysis Group, Inc., Boston, MA

Background: Spondyloarthritis (SpA) includes 5 related clinical conditions: ankylosing spondylitis (AS), psoriatic arthritis (PsA), undifferentiated SpA (uSpA), reactive arthritis (ReA), and enteropathic arthritis (EA). Prior research reports significant economic burden associated with subtypes of SpA, but little is known about the profile of direct (medical and prescription drug) and indirect (work loss) costs over time. This study examines direct and indirect costs of SpA patients in the US during a 3-year period starting 2 years before SpA diagnosis.

Methods: Patients aged 18–64 years with ≥2 diagnoses for a subtype of SpA (ICD-9-CM: 720.0, AS; 696.0, PsA; 720.9, uSpA; 099.3 or 711.1x, ReA; or 713.1, EA) were identified in a private insurance claims database (covering 40 employers; ~9,000,000 lives) in the US (1999–2007). Patients had continuous enrollment 24 months before and 12 months after first (index) SpA diagnosis, and no claims for rheumatoid arthritis unless diagnosed with PsA. SpA patients were demographically matched to controls with no history of SpA. Per-patient direct costs for all SpA patients (N=2,194) and indirect costs (absenteeism and disability) for an employee subset (N=737) were compared with controls for 12 consecutive 3-month periods. Bootstrapping was used to compare excess costs (SpA vs. controls) within periods.

Results: Mean excess direct (medical plus drug) costs for SpA patients ranged from \$781 ($P<0.01$) to \$2,565 ($P<0.01$). Mean excess medical costs increased during the year prior to index, peaked at \$1,890 ($P<0.01$) in the 3 months after diagnosis, and decreased approximately 60% in months 4–12 post-index. Increased rheumatologist costs persisted in the post index period (excess \$176 to \$132, $P<0.01$), while total outpatient and inpatient costs fell approximately 40% and 70%, respectively, 3 months after diagnosis. Mean excess drug costs accelerated sharply post index, peaking at \$786 ($P<0.01$), driven largely by an increase in TNFα inhibitor costs (excess \$490, $P<0.01$, 9–12 months post-index). Mean excess indirect costs rose during the year prior to index, peaked in the 3 months following diagnosis (\$789, $P<0.01$), but fell during the subsequent year to levels similar to those 6 months pre-index (\$388, $P<0.01$). A decline in absenteeism accounts for >90% of the fall in indirect costs post index.

Conclusion: Despite post-index increases in costs associated with SpA-targeted treatment (e.g., TNFα inhibitors, rheumatologist visits), total direct

and indirect costs decline considerably 3 months after diagnosis and return to pre-index levels. Further research is necessary to determine the causal relationship between treatment and potential direct and indirect cost savings.

Disclosure: N. Kirson: Analysis Group, Inc., under contract with Abbott, 3; **H. Birnbaum:** Analysis Group, Inc., under contract with Abbott, 3; **S. Rao:** Abbott Laboratories, 3; **E. Swallow:** Analysis Group, Inc., under contract with Abbott, 3; **T. Waldman:** Analysis Group, Inc., under contract with Abbott, 3; **E. Dayoub:** Analysis Group, Inc., under contract with Abbott, 3; **M. Cifaldi:** Analysis Group, Inc., under contract with Abbott, 3.

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Distinguishing Levels of Disease Flare in Patients with Systemic Lupus Erythematosus Using Administrative Claims Data. Nicole Engel-Nitz[5], James Burke[5], Cindy P. Garris[3], Priti Jhingran[1], Damon L. Bass[2] and Gregory J. Dennis[4]. [1]GlaxoSmithKline, [2]GlaxoSmithKline, King of Prussia, PA, [3]GlaxoSmithKline, RTP, NC, [4]Human Genome Sciences, [5]i3 Innovus

Background: Systemic lupus erythematosus (SLE) is a chronic, autoimmune disorder affecting multiple organ systems of the body, characterized by acute exacerbations (flares) and remissions. Disease activity indices have been shown to be reliable when used in clinical trials but have limited application with claims data.

Objective: To differentiate between patients with mild, moderate, and severe SLE flares using a claims-based flare severity algorithm.

Methods: This retrospective observational study used administrative claims from a large managed care health plan (1/2004 - 12/2008). SLE patients 18–64 years of age were included in the analysis if they had continuous enrollment in the health plan for at least 3 years with medical and pharmacy benefits. A diagnosis of SLE was defined by any of the following criteria: a) 3 or more rheumatologist visits on separate dates (no time requirement) with a diagnostic code for SLE (ICD-9 code 710.0x); b) 2 or more rheumatologist visits ≥60 days apart with a diagnostic code for SLE; or c) 2 or more rheumatologist visits on separate dates with a diagnostic code for SLE AND 1 or more filled prescriptions for a medication typically used for the treatment of SLE. Claims-based algorithms consisting of disease activity and medications prescribed were developed and used to identify and classify disease severity (mild, moderate, high) and flares by severity (mild, moderate, severe) for each patient over a 2-year period. Patients with multiple flares could be counted more than once in each flare severity group during the period of observation. Cost of a flare episode was analyzed by flare severity.

Results: A total of 2,990 patients met the inclusion criteria of which 22% were classified as having high severity, 52% with moderate and 26% with mild disease severity. Over the 2 year period, 86%, 99% and 99.5% of patients with high, moderate, and disease severity, respectively, had at least 1 flare ($p<0.001$). Of patients in the high disease severity group, 61% experienced at least 1 severe flare, compared to 13% of patients with moderate and 1% of patients with mild disease severity ($p<0.001$) over the 2 year period. Mean number of flares over 2 years was 4.1, 7.0 and 8.0 for patients with mild, moderate and high disease severity, respectively ($p<0.001$). The cost of a severe flare is approximately 18 times higher than a mild flare and 11 times higher than a moderate flare.

Conclusions: Nearly all patients with SLE had at least one flare identified in the claims data. The mean number of flares was higher for patients with moderate and severe disease compared with mild disease. The cost of a severe flare is substantially higher than moderate or mild flares. Averting a severe flare may be associated with significant cost savings.

Disclosure: N. Engel-Nitz: i3 Innovus, 3; **J. Burke:** i3 Innovus, 3; **C. P. Garris:** GlaxoSmithKline, 3; **P. Jhingran:** GlaxoSmithKline, 3; **D. L. Bass:** GlaxoSmithKline, 3; **G. J. Dennis:** Human Genome Sciences, Inc., 3.

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Does Cigarette Smoking Affect Disease Phenotype in Systemic Lupus Erythematosus. Meenakshi Jolly[2], Rachel A. Mikolaitis[4], Joel A. Block[4] and Michelle Petri[1]. [1]John Hopkins University, [2]Rush University Medical Center, Chicago, IL, [3]Rush University Medical Center, Chicago, IL, [4]Rush University Medical Center

Purpose: We previously reported a greater prevalence of cutaneous activity and damage among smokers than nonsmokers, in a predominantly African American cohort of patients with Systemic Lupus Erythematosus (SLE). We now present the results from a larger SLE cohort comprised of the HOPKINS Lupus Database and PROSE Database (Patient Reported Outcomes in Systemic Lupus Erythematosus). We aimed at determining if any differences in disease activity and/or damage were observed based on patients current smoking status in this large ethnically heterogeneous SLE cohort.

Methods: Cross sectional data from 1,467 SLE patients meeting the ACR criteria were analyzed based on their self report of current smoking status (Yes/No). Variables tested included demographics (age, gender, ethnicity, marital status), auto-antibodies, disease activity (SELENA-SLEDAI) and damage score (SDI). Two independent sample t tests or Mann Whitney test were used to compare continuous variables based on data distribution. Chi square test were used to compare discrete data. Odds ratio was obtained using Mantel-Haenszel method. A p value of ≤ 0.05 was considered significant on two tailed test.

Results: 94% of SLE patients were women. 41% were African American, 53% Caucasian, 1% Hispanics and 6% others. 366/1,467 reported currently smoking status. Age was similar in both groups; however ethnicity and marital status (OR 0.45 for married, 95% CO 0.36, 0.57) were associated with smoking status. There were no significant differences in the total SLEDAI scores. On comparison of itemized disease activity in the past 10 days, we found mucosal ulcers (OR1.8, 95% CI 1.2, 2.6, $p=0.002$) and pleurisy OR 1.6, 95% CI 1.1, 2.1, $p=0.01$) to be more prevalent among smokers and than nonsmokers. Thrombocytopenia was less prevalent among smokers as compared to nonsmokers (OR 0.35, 95% CI 0.14, 0.89, $p=0.02$).

Nonsmokers had a significantly lower total damage score (mean$\pm$ SD, median) as compared to smokers: 2.05 ± 2.43, 1 vs. 2.34 ± 2.45, 2, $p=0.008$. Pulmonary fibrosis was more prevalent among nonsmokers (OR 0.56, 95% CI 0.32, 0.96), while myocardial infarction was more prevalent among current smokers (OR 2.4, 95%CI 1.4, 4.2, $p=0.001$). Skin damage was more prevalent among smokers (scarring/alopecia OR 3.2, 95% CI 2.0, 5.0; extensive scarring/panniculum OR 5.4, 95% CI 3.1, 9.5, $p=0.001$). A trend towards greater peripheral vascular disease among smokers was also noted (OR 2.4, 95% CI 0.8, 6.4, $p=0.07$).

Conclusions: This is the largest study thus far on smoking and its association with disease manifestations in SLE. Smoking is strongly associated with disease activity related mucosal ulceration and pleurisy. A strong association with overall disease damage and especially pulmonary, cardiac and cutaneous damage exists. This study was possible through data sharing between institutions.

Disclosure: M. Jolly: None; **R. A. Mikolaitis:** None; **J. A. Block:** None; **M. Petri:** None.

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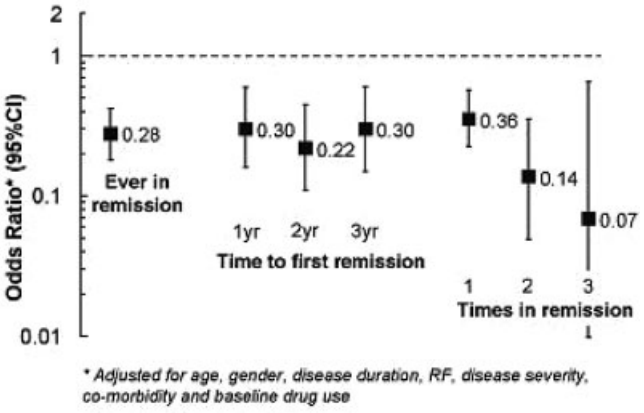
Early and Persistent Clinical Remission Reduces Long-Term Disability in Inflammatory Polyarthritis: Results from the Norfolk Arthritis Register. Carlo Alberto Scirè[2], Suzanne M. Verstappen[1], Hoda Mjriafari[1], Diane Bunn[3], Mark Lunt[1], Ian Bruce[1], Carlomaurizio Montecucco[2] and Deborah P. Symmons[4]. [1]Arthritis Research UK Epidemiology Unit, Stopford Building, The University of Manchester, Manchester, United Kingdom, [2]Department of Rheumatology, IRCCS Policlinico San Matteo Foundation, University of Pavia, Pavia, Italy, [3]Norfolk Arthritis Register, Norfolk and Norwich University Hospital, Norwich, United Kingdom., [4]Univ of Manchester, Manchester, United Kingdom

Background: Remission is an increasingly achievable objective when treating patients with inflammatory arthritis (IP) and its subset rheumatoid arthritis (RA). Although achieving the state of remission is thought to prevent long-term detrimental outcomes, the effect of remission on long-term disability has not yet been systematically investigated. In this study we have tested the predictive validity of a pragmatic definition of remission in terms of long-term disability in patients with IP.

Methods: Consecutive patients with early IP from a primary-care based inception cohort, recruited between 1990 and 1994 (first cohort) and between 2000 and 2004 (second cohort), were included this study. The 51- and 28-tender and swollen joint counts (JC) were assessed at 1, 2 and 3 yr after registration in these cohorts. Remission was defined as the absence of clinically detectable joint inflammation (swollen 51-JC = 0 and tender 51-JC = 0) at each of these time points. Less stringent definitions of remission were based on 28-JC. A 5 yr HAQ-score ≥1 (moderate disability) was chosen as the primary outcome measure. The effect of remission on subsequent disability was analysed by logistic regression. The results are shown as odds ratios (OR) and 95%CI. All analyses were adjusted by baseline confounders and missing data were imputed applying multiple imputations.

Summary of the Results: A total of 1,366 patients, 847 from the first cohort and 519 from the second cohort completed 5 yrs of follow-up. At 5 yrs, 336 (39%) and 248 (48%) of subjects from the first and second cohort respectively had developed moderate disability; 193 (24%) and 202 (36%)

fulfilled the predefined 51-JC remission criteria at least once within the first 3 yrs. In the first cohort, patients with at least one episode of remission were less likely to become disabled compared to patients who never experienced remission (OR 0.28 95%CI 0.18, 0.42) (see Figure 1).



The number of times in remission resulted proportionally decreased odds of disability, with a mean decrease in the probability of disability of about 62% for each time point in remission (OR 0.38 95%CI 0.28, 0.52). The time to the first remission within the first 3 yrs did not discriminate between patients with moderate functional disability and those with no functional disability. Similar results were observed in the second cohort. The association between the less stringent criteria of remission and future disability was weaker.

Conclusions: Patients with IP who achieve a state of remission early in their disease process are less likely to show long-term deterioration of function compared to patients who never achieve remission. Patients with the most persistent remission and under the more stringent definition of remission, have the lowest probability of long-term disability.

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Economic Evaluation of Rituximab Versus Alternative Anti-Tumor Necrosis Factor (TNF) Therapy after Failure of Anti-TNF for Treatment of Rheumatoid Arthritis in Mexico. Fernando Carlos[2] and Patricia Clark[1]. [1]Hospital Infantil Federico Gómez México, Mexico City, Mexico, [2]R A C Salud Consultores, S.A. de C.V.

Background: About 30% of rheumatoid arthritis (RA) patients treated with an anti-TNF agent failed to achieve an improvement of 20% in American College of Rheumatology (ACR) response. Recent clinical practice guidelines recommend the use of rituximab after failure of one anti-TNF instead of cycling between these agents. We aimed to evaluate the cost-utility of different treatment strategies in severe RA after anti-TNF failure from the perspective of the public health care system in Mexico.

Methods: A microsimulation Markov model was used to compare life-time costs and quality-adjusted life years (QALY) of 12 different treatment pathways for one million simulated patients aged 40 years (70% women, mean weight 66.67 Kg) with failure to etanercept (ETA) [Model 1], adalimumab (ADA) [Model 2], or infliximab (INF) [Model 3]. Competing interventions included giving rituximab (RTX) first, followed by a sequence of the two alternative anti-TNF agents or to administrate RTX after complete cycling between anti-TNF agents. RTX (1 course, consisting of 2 infusions of 1g each) given 9 months apart; INF 3 mg/Kg weeks 0, 2, 6, 14 and 22, and then 4.5 mg/Kg given 8 weeks apart starting from week 30; ETA 25mg twice a week; and ADA 40mg every other week, were all combined with methothrexate (MTX) 15mg weekly. Baseline Health Assessment Questionnaire (HAQ) score was sampled from a Normal distribution [mean 1.88; S.D. 0.58). Indirect comparison techniques were used to adjust 6-month ACR responses rates found in 9 clinical trials. HAQ scores dropped accordingly to the magnitude of ACR response. Median duration times were taken from published literature. Once treatment stops, the entire initial gain in HAQ is assumed to be lost instantly. Patients are then allocated to the next available treatment option until the sequence is exhausted. At this point, all patients receive single MTX, until they reach 100 years of age or death. Direct costs included acquisition of biologic drugs besides infusion cost for RTX and INF plus medical attention of each health state into the model. Ambulatory resource use was estimated by an experts' panel of 10 specialists. Inpatient days were estimated on the basis of HAQ score. Unit costs were gathered from official sources. Mortality rates were derived from Mexican life tables and a risk multiplier of 1.33^{HAQ}. A quadratic equation was used to link HAQ score with utility weights. Costs and QALY were discounted at an annual rate of 3%. All costs were calculated in 2009 Mexican Pesos and then expressed in US dollars (12.729 MXP per USD).

Results: Starting therapy with RTX was a dominant (both more effective and less costly) option than switching to another anti-TNF agent, leading to cost-savings that ranged from 862 to 1,365 USD per patient and gains of 8.67 to 16.18 QALY per 1,000 patients. If retreatment with RTX is set at 6 months (keeping all other parameters constant), most of estimates for the incremental cost per QALY gained with initial RTX instead of using alternative anti-TNF agents would fall below 50,000 USD.

Conclusions: This study suggests that starting therapy with RTX after previous failure of one anti-TNF agent is a cost-effective strategy compared to cycling between anti-TNF agents.

Disclosure: F. Carlos: Roche, 5; **P. Clark:** None.

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High Level of Disease Activity in Chronic Inflammatory Rheumatisms Increases the Rate of Indeterminate Interferon-Gamma-Release Assay Results for Latent Tuberculosis Infection Detection. Félicie Costantino[2], Gilbert Faure[1], Marcelo De Carvalho[1], Anne-Christine Rat[2], Hervé Dinginger[2], Damien Loeuille[2] and Isabelle Chary-Valckenaere[2]. [1]Immunology (EA RHEM4369) Department, Nancy University Hospital, Vandoeuvre-lès-Nancy, France, [2]Rheumatology department, Nancy University Hospital, Vandoeuvre-lès-Nancy, France

Purpose: Screening for latent tuberculosis infection (LTBI) is mandatory before initiating TNF-alpha blocker treatment. Recent studies established that interferon gamma release assay (IGRA) have better specificity than Tuberculin Skin Test (TST) for LTBI diagnosis. However, little is known about practical use of IGRA in patients with chronic inflammatory arthritis.

The aim of the study was to identify factors that may influence IGRA results in patients with chronic inflammatory conditions and candidates for TNFalpha-blockers.

Patients and Methods: consecutive patients from one Rheumatology department treated for chronic inflammatory arthritis and candidate for biologics were prospectively enrolled over a 5-years period (July 2004 - July 2009). Clinical data (disease diagnosis, duration and activity), biologic parameters (ESR and CRP), treatment and risk factors for LTBI were recorded at inclusion. All patients underwent TST according to Mantoux method (Tubertest® 5 units, SANOFI PASTEUR MSD, SNC, Lyon, France), chest-x-ray (CXR) and IGRA (T-SPOT.TB®,Oxford Immunotec, UK).

Results: 590 patients were included: 294 (49.8%) with rheumatoid arthritis (RA), 271 (45.9%) with spondyloarthritis (SPA) and 25 (4.2%) with other inflammatory diseases. History of BCG vaccination was present in 460 patients (78%). TST was positive (induration $\geq$5 mm) in 201 patients (34.1%), negative in 335 (56.9%) and non available in 54 cases (9%). T-SPOT.TB® assay was positive in 125 patients (21.2%), negative in 372 (63.0%) and indeterminate in 93 (15.8%). A higher age, previous active TB, the absence of BCG vaccination, TST positivity and CXR abnormalities were associated with T-SPOT.TB® positivity as shown in table 1. Among risk factors for LTBI, only the presence of CXR abnormalities was significantly associated with TST positivity ($p=0.031$). A high level of disease activity, whatever the diagnosis, (i.e. DAS28 for RA and BASDAI for SPA) was statistically associated with more frequent indeterminate results (5.4 vs 4.9, $p=0.008$ and 58.5 vs 50.0, $p=0.022$, respectively). Concordance between T-SPOT.TB® and TST was low ($K=0.17$). The negativity of TST, but not that of T-SPOT.TB® results, was significantly associated with female gender ($p=0.003$), rheumatoid arthritis ($p=0.005$), previous TNF-alpha blockers ($p=0.016$), DMARDs ($p=0.012$) and current corticosteroids treatment ($p=0.001$).

Table 1. Factors influencing T-SPOT.TB® results.

	Negative (n = 372)	Positive (n = 125)	p
Age (years), median (Q1–Q3)	49.0 (38.0–57.0)	53.0 (40.0–61.0)	0.0246
Previous active TB, n (%)	4 (33.3)	8 (66.7)	0.0026
No prior BCG vaccination, n (%)	64 (59.3)	44 (40.7)	<0.0001
TST positivity, n (%)	116 (66.3)	59 (33.7)	0.0002
CXR abnormalities, n (%)	8 (38.1)	13 (61.9)	<0.0001

Conclusion: In RA and SPA patients eligible for biologics, high disease activity increased the rate of indeterminate T-SPOT.TB® results and the difficulty of LTBI diagnosis. TNF-alpha blockers, DMARDs and corticosteroids are associated with negative TST but do not seem to affect T-SPOT.TB® results.

Disclosure: F. Costantino: None; **G. Faure:** None; **M. De Carvalho:** None; **A.-C. Rat:** None; **H. Dintinger:** None; **D. Loeuille:** None; **I. Chary-Valckenaere:** None.

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Improving Health-Related Quality of Life in Patients with Systemic Lupus Erythematosus (SLE): The Role of Disease Control, Steroid Reduction and Smoking Cessation. Mark J. Harrison[5], Nicola Dale[1], Sahena Haque[2], Joanna Shelmerdine[6], Lee-Suan Teh[4], Yasmeen Ahmad[3] and Ian N. Bruce[1]. [1]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [2]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [3]Betsi Cadwaladr University Health Board-West, Rheumatology, Llandudno, United Kingdom, [4]Department of Rheumatology, Royal Blackburn Hospital, Blackburn, United Kingdom, [5]Health Sciences Research Group, The University of Manchester, Manchester, UK, [6]The Kellgren Centre for Rheumatology, Central Manchester Foundation Trust, Manchester, UK

Purpose: Longitudinal studies of cohorts of SLE patients have shown that poor HRQoL does not change significantly over time, despite modern manegement. We aimed to describe changes over a 5-year period in a cohort of outpatient SLE patients and compare the clinical characteristics of sub-groups of patients experiencing clinically important improvement or deterioration.

Methods: Female patients with SLE (≥4 ACR criteria) were recruited from routine outpatient clinics at 2 time points 5 years apart. At baseline and 5 years patients had a clinical assessment including the SLEDAI 2000 and SLICC damage index (SDI). Patients also completed the RAND Medical Outcome Study 36-Item Short-Form Survey version 1 (MOS SF-36), which allowed the SF-6D to be calculated, at both time points. The change in SF-6D over 5 years was assessed in relation to the minimum important difference (MID) of the measure (0.024). The characteristics of patients who experienced >MID improvement, >MID deterioration, or no change (ΔSF6D ≤MID), were compared using the t-test and ANOVA or chi-square test as appropriate.

Results: 107 patients had SF-6D scores both at baseline and at 5 years. The mean(SD) age was 49 (9) years and mean (SD) disease duration 13 (10) years. At baseline, 15% were current smokers. The SF-6D score at baseline (n=107) was 0.62. The mean change in SF-6D over the 5-year period for the longitudinal cohort was 0.00 (SD 0.10). 39% (n=42) of patients in the cohort improved (mean 0.10) and 37% (n=40) of patients worsened (mean −0.10) by more than the MID. SLEDAI scores were significantly different across groups (p=0.001); decreasing in improved patients (−1.5), but increasing in unchanged (1.7) or worsened (2.4) patients. A higher proportion of improved patients stopped steroid treatment (27% vs 5%) or stopped smoking (15% vs 1%). Stopping smoking or steroids were both associated with important gains in SF-6D (0.07 vs −0.01, p=0.022) (0.08 vs −0.02, p=0.127) respectively. SDI scores did not differ between the groups.

Conclusions: While the mean SF-6D scores in this SLE cohort did not change over a 5-year follow-up period, there are groups of patients who experience clinically important improvement or deterioration in HRQOL within this population. Better disease control while targeting a reduction/stopping of steroid therapy and smoking cessation all may contribute to large health gains for SLE patients.

Disclosure: M. J. Harrison: None; **N. Dale:** None; **S. Haque:** None; **J. Shelmerdine:** None; **L.-S. Teh:** None; **Y. Ahmad:** None; **I. N. Bruce:** None.

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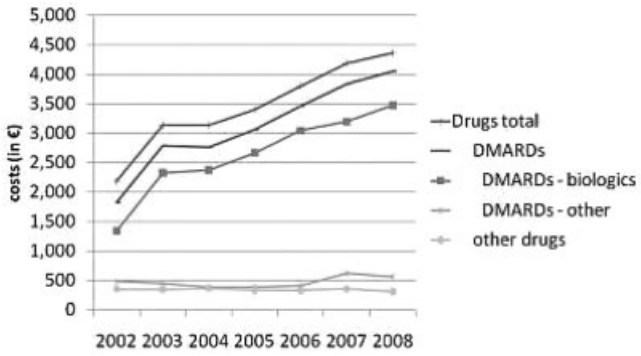
Increase in Direct and Decrease in Indirect Costs of Rheumatoid Arthritis in Germany between 2002 and 2008. Dörte Huscher[2], Katja Thiele[2], Andrea Pfaefflin[2], Sascha Bischoff[2], Rieke Alten[4], Ulrich von Hinueber[3], Matthias K. Schneider[5] and Angela Zink[1]. [1]German Rheumatism Research Centre and Charité University Hospital, Berlin, Germany, [2]German Rheumatism Research Centre, Berlin, Germany, [3]Hildesheim, Germany, [4]Schlosspark-Klinik KG, Department of Internal Medicine II, Rheumatology, Clinical Immunology Osteology, Berlin, Germany, [5]University Hospital Düsseldorf, Duesseldorf, Germany

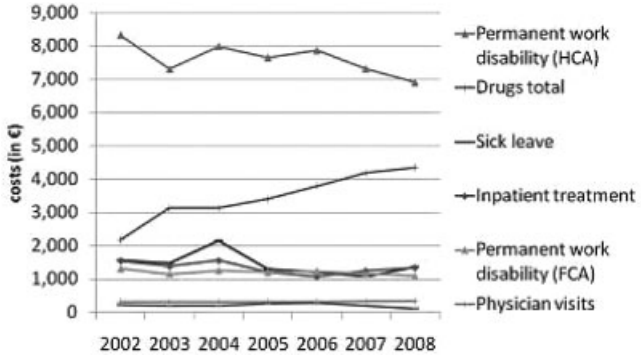
Objective: We recently observed a remarkable reduction in disease activity (DAS28) in patients with RA treated in German rheumatology during the past decade. The frequency and duration of hospitalization and sick leave decreased, whereas the work participation improved. We now analysed how these trends influenced direct and indirect costs.

Methods: We used data from the national database of the German Collaborative Arthritis Centres. An earlier cost analysis used data from the year 2002 which were less detailed than those available now. DMARD and glucocorticoid treatment has been collected now with dosages and exact duration which allows more accuracy in estimating figures of this major cost domain. For the years 2002–2004 these details were not available, and were imputed with median doses and median treatment durations from the following years. Non-pharmacological treatments were calculated for an assumed 9-months period per year. Cost components for hospitalization, sick leave and work disability were calculated by means of the German annual statistical yearbook. For indirect costs, both human capital approach (HCA) and friction cost approach (FCA; 58 days replacement period) were considered. Only those rheumatological units who had participated in all consecutive years were selected for analysis.

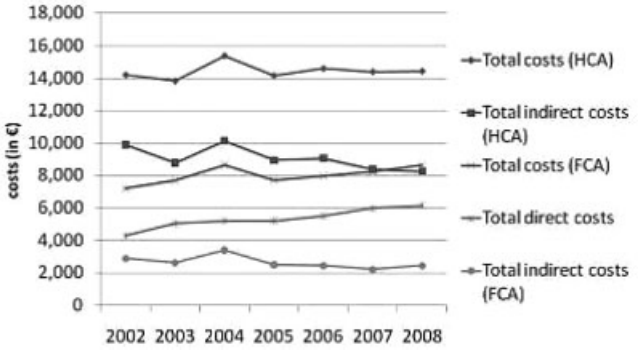
Results: Drug treatment was the cost domain with the highest increase between 2002 and 2008 (Fig. 1). This increase was almost entirely caused by biologic therapies.



Comparing the main cost domains, these risen costs were accompanied by slightly decreasing costs for inpatient treatment and sick leave, and depending on the calculation approach a slight (FCA) or remarkable (HCA) decrease for permanent work disability (Fig. 2).



Accordingly, total costs showed a moderate increase (FCA) or remained almost stable (HCA) (Fig. 3).



Conclusion: We have seen a continuous increase of costs for drug treatment, mainly caused by the growing use of biologics. Depending on the health economic approach for the calculation of indirect costs, these risen direct costs were partially counterbalanced when using the friction cost approach, and were almost entirely compensated when using the human capital approach.

Disclosure: D. Huscher: see study sponsor, 2; **K. Thiele:** see study sponsor, 2; **A. Pfaefflin:** see study sponsor, 2; **S. Bischoff:** see study sponsor, 2; **R. Alten:** see study sponsor, 2; **U. von Hinueber:** see study sponsor, 2; **M. K. Schneider:** see study sponsor, 2; **A. Zink:** see study sponsor, 2.

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Increased Risk of Valvular and Nonvalvular Cardiovascular Disease in Younger Individuals with Ankylosing Spondylitis: A Population-Based Study. Adrian R. Levy[3], Shelagh M. Szabo[3], Sumati Rao[1], Diane V. Lacaille[2], Mary Cifaldi[1] and Walter P. Maksymowych[4]. [1]Abbott, [2]Arthritis Research Ctr Canada, Vancouver, BC, Canada, [3]Oxford Outcomes, [4]University of Alberta, Edmonton, AB, Canada

Background: Increased risk of valvular cardiovascular disease for patients with ankylosing spondylitis (AS) are well-documented. However, data on the association of AS with other types of cardiovascular and cerebrovascular disease are equivocal. While some cross-sectional clinic-based studies report an increased risk of nonvalvular CV disease with long-standing AS, others have concluded that routine cardiologic evaluation is not indicated. No longitudinal population-based data on the risk of CV disease in patients with AS compared with individuals without AS have been presented.The objective was to estimate the population-based prevalence and increased risk of valvular and nonvalvular CV disease among individuals with AS in the Canadian province of Québec.

Methods: A retrospective cohort study was conducted using the population-based administrative physician-billing database maintained by the Régie de l'Assurance Maladie du Québec. The cohort included individuals with at least 1 International Classification of Diseases, 9th Revision, (ICD-9) billing code for AS between 1996 and 2006. A comparison cohort was generated using a 1% random sample of individuals without AS. CV diseases were classified according to ICD-9 code and grouped into 6 categories: valvular (aortic and non-aortic) disease, ischemic heart disease, congestive heart failure, cerebrovascular, and other CV disease. Age- and sex-stratified prevalence, and standardized prevalence ratios, of cardiovascular or cerebrovascular disease in AS compared with the general population were calculated.

Results: There were 8,616 individuals with AS; 55% were male and the median age at diagnosis was 42.5 years. The age-specific prevalence of experiencing any cardiovascular or cerebrovascular disease increased from 18.7 to 81.5 cases per 1,000-person-years among male AS patients aged 20 to 39, to >60 years, over the period. Prevalence was greater with increasing age for all disease subgroups. The prevalence ratios (95% CI) for experiencing any CV disease was greatest for younger AS patients, and ranged from 1.6 (1.5–1.8) for males aged 20 to 39 years to 1.1 (1.1–1.2) for those aged >60 years. These findings were consistent across all CV disease categories, and were similar for females. The standardized prevalence ratios (SPRs) of experiencing cardiovascular or cerebrovascular disease, for patients with AS compared with the general population, was 1.3 (1.3–1.4). SPRs for the disease subgroups ranged from 1.6 (1.4–1.8) for non-aortic valvular disease, to 1.3 (1.2–1.4) for cerebrovascular disease.

Conclusions: Patients with AS are at increased risk for many types of cardiovascular or cerebrovascular disease. The excess risk is greatest for young AS patients. This data supports consideration for cardiovascular risk assessment in the clinical evaluation of patients with AS.

Disclosure: A. R. Levy: None; **S. M. Szabo:** None; **S. Rao:** Abbott Laboratories, 3; **D. V. Lacaille:** Oxford Outcomes, 5; **M. Cifaldi:** Abbott Laboratories, 3; **W. P. Maksymowych:** Oxford Outcomes, 5.

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Is There an Advantage for a Lupus Specific Quality of Life Measure over SF-36? Zahi Touma[2], Dafna D. Gladman[3], Dominique Ibanez[2] and Murray B. Urowitz[1]. [1]The Toronto Western Hospital, Toronto, ON, Canada, [2]Toronto Western Hospital, Toronto, ON, Canada, [3]Toronto Western Hospital, Toronto, ON, Canada

Objective: The LupusQoL questionnaire is a disease-specific instrument for adults with lupus. We aimed to assess whether the LupusQoL contributed additional information not obtained using the SF-36 and to compare the responsiveness of both questionnaires over time in patients in patients who changed clinically.

Methods: 41 patients seen at a single centre were followed at monthly intervals for 12 months. Both questionnaires were co-administered monthly. Lupus activity was determined by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) 30 days. We compared the mean scores for the 4 comparable domains in both questionnaires in all patient-visits. For the 4 non-comparable domains of the LupusQoL we determined the correlation between each domain with the Physical Component Score (PCS) and the Mental Component Score (MCS) of the SF-36.

The effect size (ES) and the standardized response mean (SRM) were used to compare the responsiveness of both questionnaires in patient-visits with lupus flare (SLEDAI-2K≥4), improvement (reduction in SLEDAI-2K >3) and remission (SLEDAI-2K=0) from previous visit.

Results: Among the 41 patients (F 37/M 4), 59% were Caucasian, 17% Black, 7% Asian, and 17% other. The mean age at SLE diagnosis was 30.5±10.3 years. At study visit the mean age was 45.3±13.2 and disease duration 14.8±10.3 years; SLEDAI-2K 2.59±2.41 and SDI 2.12±2.48. 376 patients-visits were recorded. Quality of life assessed by both questionnaires is low among SLE patients. Quality of life assessed by both questionnaires is low among patients. There was no statistically significant difference between the mean scores of comparable domains; Physical Health/Physical Functioning, Emotional Health/Mental Health, Pain/Bodily Pain and Fatigue/Vitality. For the 4 non-comparable domains of the LupusQoL, there was a correlation between Body Image/MCS-SF-36 r=0.61, Planning/MCS-SF-36 r=0.68, Intimate Relationships/PCS-SF-36 r=0.73, and Burden to Others/MCS-SF-36 r=0.70.

Both questionnaires displayed responsiveness as determined by SE and SRM among patients who flared (SF-36: SRM moderate effect 0.64 Role Physical, small effect 0.42 Social Functioning and 0.30 PCS; LupusQoL: SRM moderate effect 0.67 Fatigue and small effect 0.49 Burden to others) and improved (SF-36: SRM moderate effect 0.60 MCS and small effect 0.43 Mental Health, 0.40 General Health, 0.30 Vitality, 0.30 Role Physical, 0.24 Social Functioning and 0.23 Physical Functioning; LupusQoL: SRM moderate effect 0.73 Pain, 0.53 Fatigue and 0.51 Physical Health, and small effect 0.45 Emotional Health, 0.39 Body Image, 0.37 Burden to others and 0.36 Planning) but not among patients in remission when compared to previous visit. There was no significant difference in the responsiveness of both questionnaires in patients with lupus flare and improvement when compared to previous visit.

Conclusions: There is no superiority of LupusQoL over SF-36 in assessing lupus patient's quality of life. Both questionnaires are responsive instruments of lupus quality of life in patients with flare and improvement. The utility of LupusQoL needs to be evaluated in future studies in patients with moderate to severe disease activity.

Disclosure: Z. Touma: None; **D. D. Gladman:** None; **D. Ibanez:** None; **M. B. Urowitz:** None.

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Life Expectancy, Standardized Mortality Ratios and Causes of Deaths of Six Rheumatic Diseases in Hong Kong, China. Chi Chiu Mok[1], Raymond C. L. Kwok[2], Ling Yin Ho[1], Pak To Chan[1] and Paul S. F. Yip[2]. [1]Tuen Mun Hospital, [2]University of Hong Kong

Objectives: To study the life expectancy, standardized mortality ratios (SMRs) and causes of deaths of six rheumatic diseases in Hong Kong

Methods: The number of patients with the International Classification of Disease (ICD)-9 diagnostic codings of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PSA), systemic vasculitides (SV) and systemic sclerosis (SSc) who were followed in our hospital between year 1999 and 2008 were retrieved by the hospital registry called the Clinical Data Analysis and Reporting System (CDARS). The number of patients with these disease codings who died during follow-up was also retrieved by the hospital death registry. The SMRs were calculated by comparing the rate of mortality of each disease entity (observed deaths) with the mortality rate of the general population gathered from the population census and the general death registry (expected deaths). The causes of death were evaluated and compared across these six rheumatic diseases. Life expectancy of each disease was calculated by abridged life table analysis using the prevalence and death data in the CDARS and data reported for the Hong Kong population within the same study period.

Results: The causes of deaths of 348 patients between year 1999 and 2008 were analyzed. The distribution of the underlying diseases was: RA (50%), SLE (23%), SV (14%), AS (7%), SSc (4%) and PSA (1%). The mean age at the time of death was 65.5±17.3 years and 240 patients (69%) were women. The age at death was highest with RA (74.1±12.1 years) and lowest with SLE (49.0±15.7 years). The mean SMR of both sexes and all age groups was highest for SLE (24.3 [22.2–26.4]), followed by SSc (18.3 [15.3–22.1]), SV (11.1 [9.9–12.3]), AS (8.8 [7.6–10.3]), RA (8.3 [7.9–8.8]) and PSA (7.5 [5.7–9.8]). The principle causes of deaths were, in descending order of frequency, infections (34%), cancers (18%), cardiovascular / cerebrovascular complications (16%), renal failure (6%), pulmonary pathologies (4%), liver and gastrointestinal complications (4%), accidents (1%) and suicide (1%). Infections were the commonest cause of death in SLE, RA and AS but not in other three diseases. Cardiovascular death was most frequent in patients with SSc and PSA. Cancer deaths were highest in patients with SV, followed by PSA and AS. Renal failure as a cause of death was reported in SLE and RA only. Cases of suicide occurred exclusively in SLE. In female patients, the loss in life expectancy was greatest with SSc (34.1 years), followed by SV (19.3 years), SLE (19.7 years), RA (6.9 years), PSA (6.5 years) and AS (1.2 years). In male patients, the loss in life expectancy was greatest with SV (28.3 years), followed by SLE (27 years), SSc (16 years), AS (7 years) and RA (5.2 years).

Conclusions: Patients with rheumatic diseases have a higher mortality risk than the general population, leading to a significant loss in life expectancy. Among the six diseases studied, SLE has the highest SMR and female SSc patients had the greatest loss in life expectancy. Infection is the commonest cause of death in SLE, RA and AS; but cancer is the leading cause of death in SV. Cardiovascular deaths are more common in patients with SSc and AS.

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Lower Body Mass Index Is Associated with an Increased Risk of Giant Cell Arteritis. Karin Jakobsson[3], Lennart T. H. Jacobsson[2], Kenneth J. Warrington[1], Eric L. Matteson[1], Kimberly P. Liang[5], Olle Melander[4] and Carl Turesson[3]. [1]Mayo Clinic, Rochester, MN, [2]Skåne University Hospital, Malmo, Sweden, [3]Skåne University Hospital, Malmö, Sweden, [4]Skåne University Hospital, [5]University of Pittsburgh, Pittsburgh, PA

Background: There is limited data on predictors of giant cell arteritis (GCA). In a previous case-control study of women with GCA, a history of smoking, low body mass index (BMI) and several hormonal factors were associated with GCA. Smoking and a low level of formal education have been found to predict other chronic inflammatory disorders, including rheumatoid arthritis.

Objective: To examine potential risk factors of GCA in a nested case-control study based on two prospective health surveys.

Methods: We studied two population based health surveys performed in the same catchment area, the Preventive Medicine Program (PMP) and the Diet Cancer Study (DCS). In the PMP, 33346 subjects (22444 men and 10902 women) were included between 1974 and 1992, and in the DCS, 30447 subjects (12121 men and 18326 women), were included between 1991 and 1996. Information on medical history and life style factors was obtained using standard physical examinations and self-administered questionnaires. From this population, individuals who developed GCA after inclusion were identified by linking the PMP and DCS databases to the local patient administrative register and the national hospital discharge register. A structured review of the medical records of all identified cases was performed. Patients were classified according to the ACR criteria for GCA and the date of diagnosis was noted. Four controls for every confirmed case, matched for sex, year of birth and year of screening, who were alive and free of GCA when the index person was diagnosed with GCA, were selected from the PMP and DCS databases, respectively. For cases who had participated in both surveys, the screening closest preceding the diagnosis of GCA was used. The impact of potential predictors of GCA, including BMI, smoking, and other lifestyle factors, was examined in conditional logistic regression models.

Results: Eighty-three patients (70 % women, 64 % biopsy positive, mean age at diagnosis 71 years) had a confirmed diagnosis of GCA after inclusion in the PMP or the DCS. The median time from screening to GCA diagnosis was 10.6 years (range 0.3–28.2). BMI at screening was lower in GCA cases than in matched controls (mean 24.3 vs 25.6 kg/m^2). In logistic regression analysis, a higher BMI was associated with a significantly reduced risk of subsequent development of GCA [Odds ratio (OR) 0.91 per kg/m^2; 95 % confidence interval (CI) 0.84–0.98]. Individuals who were overweight (BMI>25 kg/m^2) had a lower risk for GCA (OR 0.39, 95 % CI 0.21–0.70) compared to those with a normal or low BMI. There was no significant association between current smoking at screening (OR 1.36; 95 % CI 0.77–2.57) or a history of early menopause (before age 46) (OR 1.76; 95 % CI 0.71–4.39) and GCA. Level of formal education and breast-feeding history did not predict GCA. In multivariate analysis, adjusted for smoking and level of formal education, the association between higher BMI and reduced risk of GCA remained significant (OR 0.91 per kg/m^2; 95% CI 0.85–0.99)

Conclusion: In this study, subsequent development of GCA was predicted by a lower BMI at baseline. Potential explanations include an effect of adipose tissue on hormonal pathways regulating inflammation in the context of GCA.

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Obstetrical and Neonatal Outcomes in Rheumatic Disease. Cheryl C. M. Barnabe, Peter Faris and Hude Quan. University of Calgary, Calgary, AB, Canada

Background: Adverse maternal and neonatal outcomes have been documented in women with rheumatic disease. Our objective was to determine if this situation has improved in the era of better rheumatic disease treatment and prenatal management.

Methods: An inpatient dataset provided obstetrical admission details for a cohort of women with rheumatic disease (including RA, SLE, ankylosing spondylitis, systemic sclerosis, inflammatory myopathies and JIA) and a comparison group matched on maternal age and year of delivery. Maternal outcomes include mean length of stay, and the proportion experiencing pregnancy-related hypertension, instrumentation at delivery or cesarean section, and postpartum infections. Neonatal outcomes include the mean length of stay and the need for special care unit admission. We also examined the proportion of neonates born prematurely, small for gestational age (SGA) or with congenital defects. Conditional logistic regression was used to calculate the crude odds ratio (OR) and the 95% confidence intervals (CI) for the dichotomous outcomes of interest, with adjustments made for known confounders (if occurring in at least 5% of the sample).

Results: 161 singleton pregnancies occurred in 141 women with rheumatic disease, predominantly with RA and SLE. There were a total of 6 stillbirths, 3 in each group. Reasons for readmission particular to rheumatic disease during the first year postpartum included 2 women with flares of SLE, and 1 woman who required 2 arthroscopic procedures. Neonates of women with rheumatic disease were not at increased risk of readmission. There was no evidence of excess congenital defects in babies born to women with rheumatic disease (1.2% vs 2.1%).

Table 1. Summary of Maternal Outcomes

Outcome	Women with Rheumatic Disease n = 161	Women without Rheumatic Disease n = 635
Length of stay (days), mean (SD)	3.7 (4.3)	2.3 (2.0)
Pregnancy-related hypertension, n (%)	27 (16.8)	52 (8.2)
Instrumentation for delivery, n (%)	42 (26.1)	136 (21.4)
Cesarean section, n (%)	70 (43.5)	146 (23.0)
Postpartum infection, n (%)	7 (4.3)	6 (0.9)
1 year readmission, n (%)	22 (13.7)	32 (5.0)

Table 2. Summary of Neonatal Outcomes

Outcome	Neonates of Women with Rheumatic Disease n = 161	Neonates of Women without Rheumatic Disease n = 635
Prematurity, n (%)	44 (27.3)	47 (7.4)
Length of stay (days), mean (SD)	3.6 (4.8)	2.4 (2.0)
Requiring intensive care, n (%)	49 (30.4)	74 (11.7)
Length of stay, intensive care (days), mean (SD)	1.8 (5.1)	0.6 (2.8)
Small for gestational age, n (%)	37 (23.0)	67 (10.6)
1 year readmission, n (%)	14 (8.7)	33 (5.2)

Table 3. Crude and Adjusted Odds Ratios for Maternal and Fetal Outcomes, Comparing Women with Rheumatic Disease to Those Without Rheumatic Disease

Outcome	Crude OR	95% CI	Adjusted OR	95% CI	p value
Maternal					
- Pregnancy-related hypertension	2.25	1.36–3.71	2.33	1.38–3.91	<0.001
- Instrumentation	1.30	0.87–1.95	1.26	0.87–1.93	0.280
- Cesarean section	2.71	1.85–3.95	3.02	1.87–4.86	<0.001
- Postpartum infection	4.47	1.50–13.3	2.99	0.85–10.5	0.087
Neonatal					
- Prematurity	4.51	2.85–7.13	4.38	2.73–7.05	<0.001
- Small for gestational age	2.52	1.60–3.96	2.50	1.59–3.93	<0.001

Conclusions: In our cohort, women with rheumatic disease continue to have increased odds of developing pregnancy-related hypertension, and a large proportion deliver by cesarean section. Neonates of women with rheumatic disease are more likely to be premature, and small for gestational age. These findings are entirely in keeping with the previous literature, and do not appear to have improved over time. Additionally, women with rheumatic disease demonstrate a trend to an increased risk of postpartum infections, which has not been previously documented.

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Patient Perceptions and Access to Resources Influence Patient Decisions To Attend Rheumatology Appointments. Valerie Milne[2], Robin Kearns[1] and Andrew A. Harrison[3]. [1]University of Auckland, New Zealand, New Zealand, [2]University of Otago, Wellington, Wellington, New Zealand, [3]University of Otago, Wellington, New Zealand, New Zealand

Purpose: Patients referred to rheumatology clinics with symptoms of inflammatory arthritis (IA) miss the opportunity for early DMARD treatment when they do not attend their first specialist assessment (FSA). This study aimed, through patient interviews, to understand the social, economic and geographic determinants of FSA attendance at a public rheumatology service.

Method: A purposive sample of 21 people with IA was selected from private clinics, public clinics and the local community. Beliefs about IA and experiences of the condition and its treatment, including the referral process, were elicited in one-on-one interviews. Contradictions and commonalities in patient narrative were thematically coded using QSR Nvivo qualitative software. A narrative approach was informed by the collective lifestyles framework[1], which aims to locate individual health behaviours within a social context.

Results: The context provided by the collective lifestyles framework for discourse about patient circumstance helps explain non-attendance at the FSA. Barriers to attendance revealed by patient interviews were: 1) how patients perceived their symptoms and possible treatment; 2) social support and economic resources 3) the geographic attributes of the residential area and 4) the structure of the rheumatology service. Patients' self-perception and an inaccurate assessment of the risk of DMARDs compared with the benefits of treatment can lead patients to reject rheumatology care. Among people who reported inadequate social and economic resources; childcare, work commitments, and availability of help with impairment and transport were cited as factors affecting attendance. Descriptions of severe pain and impairment associated with long wait time gave some insight as to why patients cancel their public appointment in favour of a private appointment with a shorter wait, despite additional costs.

Conclusion: Patients' narratives suggest that altering the booking procedure from an administrative process to an assessment process to include early assessment of pain, impairment and patient support and co-ordination with the family physician to address these factors could improve non-attendance and cancellation rates. Providing information about the rheumatology service before the FSA could address patients' fears about impairment and reduce negative perceptions of possible treatment options. More general publicity about IA or specifically tailored information to patients with suspected IA may enable patients to make more informed decisions about accepting rheumatology care.

1. Frohlich et al (2001) Sociology of Health and Illness 23(6)776–797

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Patient-Reported Outcome Measures in Patients with Polymyalgia Rheumatica (PMR): Results from an International, Prospective, Multi-Centre Study. ACR – EULAR Study Group for Development of Classification Criteria for PMR. Bhaskar Dasgupta[16], Marco A. Cimmino[10], Hilal Maradit-Kremers[3], Wolfgang A. Schmidt[19], Schirmer Michael[5], Carlo Salvarani[11], Peter Mandl[20], Artur Bachta[4], Maria C. Cid[17], Haner Direskeneli[13], Pierluigi Macchioni[11], Peter V. Balint[1], Christina Duftner[9], Christian Dejaco[14], Hanna Slott-Jensen[18], Zsuzsa Schmidt[20], Gyula Poór[20], Annamaria Iagnocco[24], Victor Martínez-Taboada[28], Elizabeth Nordborg[26], Nicolò Pipitone[11], Pierre Duhaut[27], Carlotta Nannini[25], Georgina Espígol-Frigolé[2], Sibel Z. Aydin[13], Khalid Ahmed[15], Raashid Luqmani[21], Brian Hazelman[12], Colin Pease[22], Richard J. Wakefield[22], Neil Gonter[23], Ralph Marcus[23], Clement J. Michet[7], Mehrdad Mazlumzadeh[8], Andy Abril[6], Cynthia S. Crowson[3] and Eric L. Matteson[7]. [1]3rd Rheumatology Department, National Institute of Rheumatology and Physiotherapy, Budapest, [2]Center for Diagnosis Imaging, Hospital Clínic, Montserrat del Amo, Barcelona, Spain, [3]Department of Health Sciences Research, Mayo Clinic, Rochester, MN, [4]Department of Internal Medicine and Rheumatology, WIM CSK MON, Warszawa, Poland, [5]Department of Internal Medicine I, Medical University Innsbruck, Innsbruck, Austria, [6]Department of Internal Medicine, Division of Rheumatology, Mayo Clinic, Jacksonville, FL, [7]Department of Internal Medicine, Division of Rheumatology, Mayo Clinic, Rochester, MN, [8]Department of Internal Medicine, Division of Rheumatology, Mayo Clinic, Scottsdale, AZ, [9]Department of Internal Medicine, General Hospital of the Elisabethinen, Klagenfurt, Austria, [10]Department of Internal Medicine, University of Genova, Genova, Italy, [11]Department of Rheumatology, Arcispedale S. Maria Nuova, Reggio Emilia, Italy, [12]Department of Rheumatology, Cambridge University, Cambridge, UK, [13]Department of Rheumatology, Marmara University Medical School, Istanbul, Turkey, [14]Department of Rheumatology, Medical University, Graz, Graz, Austria, [15]Department of Rheumatology, Princess Alexandra Hospital, Harlow, United Kingdom, [16]Department of Rheumatology, Southend University Hospital, Essex, United Kingdom, [17]Department of Systemic Autoimmune Hospital Clinic Provincial, Barcelona, Spain, [18]Gentofte Hospital, Rheumatology Division, Hellerup, Denmark, [19]Immanuel Krankenhaus Berlin: Medical Center for Rheumatology Berlin-Buch Berlin, Berlin, Germany, [20]National Institute of Rheumatology and Physiotherapy, Budapest, Hungary, [21]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Oxford University, Oxford, UK, [22]Rheumatology and Rehabilitation Research Unit, University of Leeds, Leeds, UK, [23]Rheumatology Associates of North Jersey, Teaneck, NJ, [24]Rheumatology Unit, Clinica e Terapia Medica Department, Sapienza Università di Roma, Policlinico Umberto I, Rome, Italy, [25]Rheumatology Unit, Ospedale Misericordia e Dolce, Prato, Italy, [26]Sahlgren University Hospital, Department of Rheumatology, Göteborg, Sweden, [27]Service de Medecine Interne, Amiens, France, [28]Servicio de Reumatología, Hospital Universitario Marques de Valdecilla, Facultad de Medicina, Universidad de Cantabria, Santander, Spain

Objective: To evaluate the disease course and performance of patient-reported outcome measures in patients with polymyalgia rheumatica (PMR)

Methods: The study population included 88 patients with new onset PMR who were initially treated with prednisolone/prednisone dose of 15 mg daily

tapered gradually, and assessed at baseline and weeks 1, 4, 12 and 26 following start of steroid therapy. Data were collected on personal and family history, clinical signs and symptoms, laboratory results, treatment details, ultrasound evaluation of shoulders and hip, disability (MHAQ), quality of life (SF36), and patient reported outcomes (PRO) of global pain, PMR pain, shoulder pain and fatigue obtained using visual analog scales (VAS). Complete response to treatment was defined as ≥70% improvement from baseline on patient report of shoulder pain by VAS at each study visit. Spearman methods were used to assess correlations between improvement measures.

Results: At initial presentation, 99% patients had shoulder pain, 70% had hip pain and 96% had abnormal c-reactive protein (CRP) or erythrocyte sedimentation rate (ESR). Median duration of morning stiffness was 120 minutes with median MHAQ 1.1, median global VAS 65, PMR VAS 69 and fatigue VAS 60. Within 4 weeks, all PRO parameters improved dramatically (≥ 70% improvement) in majority of the patients (72% of patients for global VAS, 80% for PMR VAS and 60% for fatigue VAS); median change in MHAQ at 4 weeks was −0.875. Median change at 26 weeks was −0.94. Similarly, 62% of patients had normal CRP/ESR values at 4 weeks. However, few additional patients showed improvement from 4 weeks to 26 weeks. Complete steroid response at 4 weeks was seen in 70% of patients and the response was sustained in 85% of responders at 26 weeks. As planned, the median prednisone dose decreased from 15 mg at baseline to 5.5 mg at 26 weeks. Response to treatment (% improvement in shoulder pain VAS at weeks 4 and 26) was highly correlated with % improvement in other VAS measures (correlation>0.55 and $p<0.001$ at weeks 4 and 26) and % change in ESR ($p<0.001$ at week 4 and $p=0.04$ at week 26), but weakly correlated with % change in CRP ($p=0.07$ at week 4 and $p=0.30$ at week 26) and change in steroid dose ($p=0.39$ at week 4 and $p=0.04$ at week 26).

Conclusions: PRO measures including MHAQ, global, PMR and fatigue VAS, and inflammatory markers performed well in assessing disease activity in patients with PMR. Percent improvement in PRO measures were highly correlated with each other, but ESR and CRP correlated less strongly. We suggest that a minimum set of outcome measures consisting of PROs of shoulder pain and function and an inflammatory marker be used in practice and clinical trials in PMR.

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Psychometric Properties of a Self-Administered Early Inflammatory Arthritis Detection Tool. Mary J. Bell[3], Joel P. Scarf[2] and Ruben Tavares[1]. [1]McMaster University, Hamilton, ON, Canada, [2]Sunnybrook Health Science Ctr, Toronto, ON, Canada, [3]Sunnybrook Health Sciences Ctr, Toronto, ON, Canada

Background: A self-administered tool for the detection of early inflammatory arthritis (EIA) has been developed and is under validation in primary care settings in Canada. The history-based tool consists of 11 questions with binary Yes/No responses, covering dimensions of pain, stiffness and swelling. The objective of this study is to evaluate the discriminant validity, comprehensibility, test-retest reliability and internal consistency of the EIA Detection Tool.

Methods: Of 148 patients (minimum of 37 in each group) planned for recruitment by September 2010, a total of 125 adult English-literate outpatients attending Sunnybrook Health Sciences Centre have participated in one of four study groups: 1.EIA (n=15): A rheumatologist's assessment of, or established diagnosis of either AS, PsA, RA, ReA, other SpA or undifferentiated IA with a symptom duration of six to 52 weeks; 2.Established Inflammatory Arthritis (IA) (n=40): A rheumatologist's assessment of established IA with more than 52 weeks of symptom duration; 3.Musculoskeletal (MSK)/non-IA (n=49): A rheumatologist's established diagnosis of osteoarthritis, osteoporosis, fibromyalgia, arthralgia, bursitis, tendonitis, or other rheumatologist-determined and documented, established non-inflammatory MSK condition; and 4.Non-IA/non-MSK (n=21): Hospital outpatients without bone or joint complaints and no history of arthritis, willing to consult with a study rheumatologist. **Discriminant validity** is reported using a Kruskal-Wallis test for non-parametric differences in total questionnaire Yes responses (Score) between groups including Mean (+/− SD), and Median (+ range). **Comprehensibility** is defined as the percentage of patients who agree or strongly agree with the comprehension of the tool. The EIA Detection Tool is delivered a second time (T2), at one to 2 weeks after the first time (T1) to ascertain **Test-Retest reliability**, (Kappa +/− SD). Patients who report a change in symptoms will be omitted from the assessment of reliability. To measure **Internal Consistency**, one question is repeated within the tool, (Kuder-Richardson-20, binary equivalent to Cronbach Alpha). Study participants will be blinded to the specific purpose of the study.

Results: Discriminant Validity for Group 1.EIA: Mean score 6.7+/−2.8 Median 7 (0–11); 2.Established IA: Mean score 5.2+/−2.3 Median 5 (2–10); 3.MSK/non-IA: Mean score 5.0+/−2.9 Median 5 (0–11); 4. Non-IA/non-MSK: Mean score 2.7+/−3.1 Median 2 (0–9) $p=0.006$. Over all groups Comprehensibility ranged from 94.6%–97.1%, while within Group 1.EIA, Comprehensibility ranged from 91.3%–100.0%. Kappa = 0.85+/−0.08 across all questions for Test-Retest reliability. Finally, Internal Consistency had a value of KR-20=0.990 at T1 and KR-20=0.985 at T2.

Conclusions: The EIA Detection Tool shows very good discriminate validity between the four study groups, and excellent Comprehensibility, Test-Retest reliability and Internal Consistency. Further analyses will be conducted in September 2010 when the dataset is complete to determine if weighting scales and/or decision rules may be imposed on the EIA Detection Tool to improve its discriminative properties.

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Reproductive History and Functional Outcome in Women with Recent-Onset Inflammatory Polyarthritis. Elizabeth M. Camacho[1], Mark Lunt[1], Tracey M. Farragher[1], Mark Harrison[1], Suzanne M. Verstappen[1], Diane K. Bunn[2] and Deborah P. Symmons[3]. [1]Arthritis Research UK Epidemiology Unit, Stopford Building, The University of Manchester, Manchester, United Kingdom, [2]Norfolk Arthritis Register, School of Medicine Health Policiy & Practice, University of East Anglia, Norwich UK, [3]Univ of Manchester, Manchester, United Kingdom

Background: The incidence of rheumatoid arthritis (RA) among women is approximately twice that in men. There have been a number of studies suggesting that female reproductive factors, such as parity or menopause status, may impact upon a woman's likelihood of developing RA and her subsequent disease severity. However little is known about the effects of reproductive factors on long-term disease outcome in women with inflammatory polyarthritis (IP) and its subset RA. Our aim was to investigate the influence of reproductive history before symptom onset on disease outcome over time in a cohort of women with recent onset IP.

Methods: 1873 women, with no subsequent pregnancies, were registered with the Norfolk Arthritis Register (NOAR) between 1990 and 2004, and followed-up for a median of 5 years. Functional disability was assessed using the Stanford Health Assessment Questionnaire (HAQ). At baseline, blood samples were tested for rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA). The number and calendar year of past live births were recorded. Linear random effects models were used to examine differences in HAQ score over time, by parity and time since last live birth (latency), adjusted for age at symptom onset and symptom duration. Results were then stratified for RF and ACPA status.

Results: 1553 (83%) women had at least one pre-symptom-onset live birth, and 319 (17%) women were nulliparous before symptom onset. The median (IQR) latency to symptom onset in parous women was 26 (16–35) years. The median age at symptom onset was comparable in parous (54 years; IQR 44.6–65.2) and nulliparous women (54 years; IQR 36.4–70.0). A marginally higher proportion of nulliparous women who tested positive for RF (34% vs. 29%) or ACPA (33% vs. 30%) compared to parous women. Parous women had significantly lower HAQ scores over time than nulliparous women (−0.19; 95% CI −0.32, −0.06). HAQ score increased by an average of 0.006 (95% CI 0.002, 0.010) per year increase

in time since last pregnancy; the mean HAQ score of women with a latency of approximately 32 years was the same as the mean HAQ score of nulliparous women. The influence of autoantibody status was negligible. The difference in HAQ score by parity in RF- or ACPA-women was the same as for the whole cohort (RF −0.19; 95% CI −0.36, −0.02; ACPA −0.19; 95% CI −0.36, −0.02). Parity was also associated with lower HAQ scores in RF+ and ACPA+ women, although neither reached statistical significance (RF −0.13; 95% CI −0.39, 0.13; ACPA −0.16; 95% CI −0.44, 0.12).

Conclusion: Parous women have better functional outcome over time than nulliparous women. Increasing delay between last live birth and symptom onset (latency) was associated with increasing HAQ score over time, suggesting that the beneficial effect of pregnancy diminishes with time. Autoantibody status did not appear to have an impact on the relationship.

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Rheumatic Diseases among Oklahoma Tribal Populations. Jasmine R. Gaddy[8], Amy B. Dedeke[4], Wendy Klein[3], Fabio Mota[2], Tina Cooper[2], M. Sohail Khan[1], Virginia Roberts[5], Jeremy Levin[5], Scott Stewart[5], Rebecca Stormont[6] and Judith A. James[7]. [1]Cherokee Nation, [2]Chickasaw Nation, [3]Oklahom Research Foundation, OKC, OK, [4]Oklahoma Medical Research Foundation, OKC, OK, [5]Oklahoma Medical Research Foundation, [6]University of Oklahoma HSC, [7]University of Oklahoma HSC, Oklahoma Medical Research Foundation, OKC, OK, [8]University of Oklahoma HSC, Oklahoma Medical Research Foundation, Veteran's Affairs Medical Center, OKC, OK

Background: Rheumatic diseases cause significant morbidity within American Indian populations. Oftentimes, clinical disease presentations overlap and historically associated autoantibodies are not useful in making a diagnosis or assessing prognosis. The purpose of this study is to identify autoantibody associations in Oklahoma tribal populations with rheumatic disease. With this knowledge we seek to create a tailored approach to diagnosing and treating Oklahoma Native American patients which may also translate to the Native American population at large.

Methods: Tribal-based rheumatology clinics were established and staffed with tribal personnel and a consulting rheumatologist. Patients with presentations concerning for rheumatic disease were referred by primary care providers. 220 Oklahoma tribal members were enrolled (110 with rheumatic disease and 110 controls). A rheumatologist assessed patients for clinical features, including disease criteria, activity measures and revised treatment programs. Medical records were reviewed to extract ACR classification criteria for rheumatic disease. Samples were tested for: ANA and anti-dsDNA [IIF]; anti-CCP, rheumatoid factor and aPLs [ELISA] and other lupus autoantibodies (anti-Ro, anti-La, anti-Sm, anti-RNP and anti-Jo) [precipitins]. Statistical analysis was conducted using chi-square and ANOVA methods.

Results: Rheumatic diseases included: 39 (35%) Rheumatoid Arthritis [RA], 17 (15%) Systemic Lupus Erythematosus [SLE], and 8 (7%) Scleroderma [SCL]. Additional diagnoses were comprised of osteoarthritis, Sjogren's Syndrome or fibromyalgia. The remaining patients have rheumatic conditions or symptoms some of which did not meet ACR criteria for disease. Included are inflammatory eye disease (3%), sclerodactyly (1%), undifferentiated connective tissue disease (5%) inflammatory polyarthritis (8%) and polyarthralgia (8%). RA patients were over nineteen times as likely as non-RA patients to be anti-CCP positive (56% vs 2%, $p<0.001$) and almost six times more likely to be RF (by IgM) positive (59% vs 10%, $p<0.001$). Moreover, 18 of 39 patients with RA were both anti-CCP and RF positive. By multivariate logistic regression, together anti-CCP and RF were better predictors of RA than by either test alone ($p=0.007$). Scleroderma patients also exhibited anti-dsDNA, anti-Ro and anti-Jo-1 antibodies which are typically not seen in Scleroderma sera. In addition, anti-Ro, anti-La and anti-dsDNA were also detected in RA patients. Anti-phospholipid antibodies were found across several rheumatic diseases. Finally, autoantibodies against unidentified antigens (UILs) were seen in over 5% of rheumatic patients.

Conclusion: Clinical presentations of rheumatic disease within Oklahoma tribal members are oftentimes overlapping and difficult to define by ACR criteria. Unique autoantibodies were identified in patients meeting ACR criteria for disease. Anti-CCP is a better RA predictor in tribal communities and warrants changes in current diagnostic practices. Other autoantibodies (aPLs and UILs) are found in a variety of American Indian rheumatic disease and clinical significance will need to be established.

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Rheumatoid Arthritis (RA) Impact on Work and RA-Related Indirect Costs during the First Three Years after RA Diagnosis. An Economic Analysis from the ESPOIR Cohort. Sabrina Dadoun[6], Sandy Lucier[2], Marie De Rosa[2], Alain Saraux[3], Francis Berenbaum[4], Isabelle Durand-Zaleski[2], Francis Guillemin[1], Karine Chevreul[7] and Bruno Fautrel[5]. [1]Nancy, France, [2]Paris, France, [3]CHU de la Cavale Blanche, Brest Cedex, France, [4]Faculty of Medicine P&M Curie, Paris, France, [5]Pitie Salpetriere Hospital, Paris, France, [6]Pitie Salpetriere Hospital, Paris, France, [7]URC Eco, Paris, France

Background: Rheumatoid arthritis (RA) has often dramatic impact on work and incur for substantial indirect costs. In this field, only few data are available about patients just starting the disease.

sick leaves, invalidity and job retention.

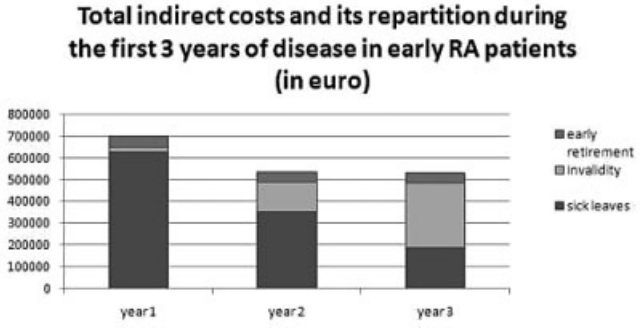
Objective: To assess the impact on work and the indirect costs attributable to RA in early arthritis patients included in the ESPOIR early arthritis cohort and to identify predictors of high indirect costs as soon as the early steps of RA.

Methods: The nationwide ESPOIR cohort included 811 patients with early arthritis (female 77%; mean age 48 years; mean HAQ 1.0; DAS28 5.2; IgM RF+ 47 %; anti-CCP+ 39 %; structural damage on X-ray 22 %; satisfaction of 1987 ACR criteria 71%)[1].

Among this population, people participating on the market place were identified and RA-induced absenteeism was assessed after having defined 4 work states: temporary sick leave, long-term sick leave, permanent disability / invalidity, and early retirement. For each state, the number of patients and the total number of days off work were calculated for every year of follow-up.

The valorization of RA-related absenteeism was estimated from the payer perspective. Daily wages were stratified on patient socio-economic profile and sex. Indirect cost drivers were assessed by using univariate then multivariate analysis in 2 steps: 1) logistic regression to identify predictors of indirect costs versus no indirect costs; then 2) linear regression after log-transformation of indirect costs (skewed cost distribution) to identify predictors of the highest costs.

Results: On the 398 patients participating in the work force at diagnosis, 91% had a paid job and 71% still worked after 3 years of disease. During the first 3 years, 241 patients had at least one temporary sick leave and 54 patients got compensated disability status. Mean number of days in sick leave decreased from 118 days the first year to 71 days the third year, whereas mean number of days in invalidity almost doubled over the three years (figure).



Mean annual cost was €1476 (table). 169 patients had no indirect costs. Predictive factors of indirect costs were disease severity at baseline (DAS28>5.1), HAQ>1, male sex and manual job ($p<0.05$ in the univariate analysis). The linear model showed a significant relation between indirect costs and age at diagnosis, HAQ and DAS28>5.1.

Conclusion: Only a few patients lost their job in the first 3 years of the disease but most of them experienced at least one sick leave (60%). Indirect costs did not show any meaningful decrease during the first 3 years of treatment, mainly because the reduction in sick leave was counterbalanced by an increase in compensated invalidity.

[1]Combe B, *et al*. Joint Bone Spine 2007;74:440–5.

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Screening for Latent Tuberculosis Infection (LTBI)–Performance of Tuberculous Skin Test and Interferon-gamma Release Assays (IGRA) under Real Life Conditions. Stefan Kleinert[7], Hans Peter T. Tony[7], Klaus Krueger[6], Jacqueline Detert[1], Frank Mielke[4], Gerd R. Burmester[2], Roland Diel[3], Martin Feuchtenberger[8] and Christian Kneitz[5]. [1]Charité-Universitätsmedizin Berlin, Dep. of Rheumatology and Clinical Immunology, CC12, [2]Charité Berlin, [3]Department of Pneumology, Medical School (MHH) Hannover, [4]Gemeinschaftspraxis Innere Medizin, Dres. Mielke, Berlin, [5]Klinik für Innere Medizin II (Klinische Immunologie und Rheumatologie, Klinikum Südstadt Rostock), [6]Praxiszentrum St.Bonifatius München, [7]Rheumatology / Clinical Immunology, Med. Klinik 2, University of Wuerzburg, Wuerzburg, Germany, [8]Rheumatology / Clinical Immunology, Med. Klinik 2, University of Wuerzburg

Introduction: Treatment of LTBI has greatly reduced Tb reactivations under anti-TNF therapy. Screening has been based on patient history, chest x-ray, BCG vaccination status and tuberculous skin test (TST). The introduction of IGRAs has improved screening procedures and some national guidelines recently favour IGRA testing over a TST.

This study is a real-life, multicentric approach to compare IGRAs versus TST for detection of LTBI in a large cohort of patients with rheumatic diseases under immunosuppressive therapy.

Methods: 62 centers in Germany evaluated 1529 consecutive patients for LTBI prior to therapy with biologics. TST was performed in all patients. Additionally, an IGRA was performed, either TSPOT.TB assay (TSPOT, n=844) or Quantiferon TB Gold assay (QFT, n=685)), whichever was available in the local laboratory.

Results: Patient distribution was 852 RA, 215 PsA, 294 AS, 92 undiff. SpA, 76 various. 254 patients were previously BCG vaccinated. TST was positive in 173 patients (11.3%), IGRA was positive in 120 patients (7.9 %), 8.3 % (n=70) in the TSPOT group and 7.3% (n=50) in the QFT group. 50 TST positive patients where previously BCG vaccinated. The *prevalence of LTBI defined by a positive TST without previous BCG vaccination* was 8.0% (123 pts) and based on the IGRA 7.9% (120 pts)

The patient group identified by TST (n=123) or IGRA (n=120) predominantly described different patients. Of the 123 TST positive patients only 56 were IGRA positive. Of 120 IGRA positive only 66 were TST positive.

Clinical risk factors for LTBI were found in 122 patients (34 *history* of own Tb, 81 close *contact*, 27 chest x-ray (*cxr*) suggestive of LTBI). A compound risk factor (*rf*) was defined as at least one of these risk factors being present. Uni- and multivariate logistic regression revealed influence of *rf* on TST (OR 6.6; KI 4.41 – 9.96, p<0.001) and BCG status (OR 3.2; KI 2.19 – 4.60, p<0.001). QFT and TSPOT results were influenced by *rf* but not by BCG status (QFT: Rf OR 2.9; KI 1.31– 6.27, p=0.021. BCG OR 0.4, KI 0.17–1.13, p=0.080. TSPOT: Rf OR 8.8; KI 4.93–15.78, p< 0.001. BCG OR 1.69, KI 0.8–3.56, p=0.165).

Conclusion: The study revealed a significant prevalence of LTBI in patients evaluated for biologic therapy in a country with low incidence of Tb. Prevalence for LTBI based on TST was 8%, based on IGRA 7.9 %. Using both test systems, prevalence increased to 11.1% since 40% of TST positive patients were IGRA negative and vice versa. In multivariate analysis TSPOT was strongly influenced by clinical risk factors, followed by TST and QFT. IGRAs were not influenced by prior BCG vaccination, proving its superiority in these patients. Screening procedures based upon TST have been shown to be effective in reducing tuberculosis reactivation by TNF inhibitors. The exclusive use of IGRAs may leave patients at risk.

Disclosure: S. Kleinert: Abbott Immunology Pharmaceuticals, 2, 8, Chugai, 8, Essex, 8, Roche, 5, 8; **H. P. T. Tony:** Abbott Immunology Pharmaceuticals, 8, Chugai, 2, Roche, 5, Wyeth Pharmaceuticals, 8; **K. Krueger:** None; **J. Detert:** None; **F. Mielke:** None; **G. R. Burmester:** Abbott Immunology Pharmaceuticals, 2, 5, 8; **R. Diel:** None; **M. Feuchtenberger:** None; **C. Kneitz:** Abbott Immunology Pharmaceuticals, 5, Essex, 5, Roche, 5, UCB, Inc., 8, Wyeth Pharmaceuticals, 2.

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Seasonal Variation in Vitamin D Levels in Patients with Psoriatic Arthritis from Northern and Southern Latitudes and Its Association with Clinical Outcomes. Zahi Touma[5], Lihi Eder[4], Devy Zisman[1], Joy Field[1], Vinod Chandran[5], Cheryl Rosen[5], Hua Shen[2], Richard Cook[2] and Dafna D. Gladman[3]. [1]"Lin" Medical Centre, Clalit Health Service, Carmel Medical Centre, Haifa, Israel, [2]Division of Biostatistics, University of Waterloo, Waterloo, ON, Canada, [3]Toronto Western Hospital, Toronto, ON, Canada, [4]University of Toronto Psoriatic Arthritis Clinic, Toronto Western Hospital, Torotn, ON, Canada, [5]University of Toronto Psoriatic Arthritis Clinic, Toronto Western Hospital, Toronto, ON, Canada

Background: Vitamin D has emerged as an important factor in the pathogenesis of several autoimmune diseases including psoriasis and inflammatory arthritis. Hypovitaminosis-D seems to be a pandemic problem. Studies showed that it is more common in inhabitants of high latitude compared to low latitude areas.

Objective: We aimed to determine the prevalence of vitamin D deficiency/insufficiency in patients with psoriatic arthritis (PsA), its seasonal and geographic variation, association with demographic and lifestyle characteristics, and with disease activity.

Methods: This study was conducted in a center in a northern geographic area (N;North) and a center in a subtropical region (S;South), from March 2009 to August 2009. Most subjects were assessed in both winter and summer. Patients completed a vitamin D questionnaire developed to assess lifestyle determinants of vitamin D levels. Demographic, clinical data, skin type (Fitzpatrick classification), serum 25(OH) vitamin D, creatinine, calcium, phosphorus and liver enzymes were determined. Vitamin D levels were categorized as deficient < 30, insufficient 30– 74 and adequate >75 ng/ml.

A multivariate linear mixed model that included demographic/lifestyle and clinical variables, latitude, season as covariates, was used to assess the relationship with vitamin D levels.

Results: 302 PsA patients were enrolled: 258 winter (201 in N/57 in S), 214 summer (140 N/74 S). Vitamin D levels (winter/summer) were adequate (N: 41.3/41.4%; S: 42.1/35.1%), insufficient (N: 55.7/58.6%; S: 50.9/62.2%) and deficient (N: 3/0%; S: 3.8/0.9%) among patients (Table 1).

Table 1. Patients' characteristics and vitamin D level distribution

Variables/Sites	North n = 201	South n = 101	Season	Vitamin D	North n = 201	South n = 101	North and South n = 302
Age at visit	51.8 ± 12.5	56.4 ± 13.4	Winter	Adequate	41.3%	42.1%	41.5%
				Insufficient	55.7%	50.9%	54.7%
				Deficient	3%	7%	3.8%
Age at onset of Psoriasis	28.2 ± 14.6	37.1 ± 16.0	Summer	Adequate	41.4%	35.1%	39.3%
				Insufficient	58.6%	62.2%	59.8%
				Deficient	0%	2.7%	0.9%
Age at onset of PsA	36.5 ± 12.9	46.4 ± 14.4					
Sex							
M	128 (63.7%)	59 (58.4%)					
F	73 (36.3%)	42 (41.6%)					
Race							
Caucasians	189 (95.0%)	101 (100%)					
South Asian	1 (0.5%)						
Chinese	4 (2.0%)						
Filipino	2 (1.0%)						
Others	3 (1.5%)						
Skin classification							
1	12 (6.2%)	11 (13.8%)					
2	58 (30.1%)	40 (50.0%)					
3	67 (34.7%)	15 (18.8%)					
4	39 (20.2%)	13 (16.2%)					
5	17 (8.8%)	1 (1.2%)					

Multivariate regression showed that subjects who had suntanned and received phototherapy, in the past three months, has significantly higher vitamin D levels (p=0.012 and p=0.030 respectively). Taking multivitamins increased vitamin D levels (p=0.014) and vitamin D supplementation was independently associated with higher vitamin D levels p<0.001. Fish oil supplementation was also associated with higher levels of vitamin D (p=0.036). Males were more likely to have lower vitamin D levels p=0.02. There was no association between vitamin D levels, geographic and seasonal interaction, race, employment status and skin type, and disease activity as measured by PASI score for psoriasis and active joint count, dactylitis and inflammatory spinal pain for PsA in both seasons. No association between disease activity in summer and vitamin D levels in winter could be found.

Conclusion: A high prevalence of vitamin D insufficiency among PsA patients was found. There is no seasonal variation in vitamin D level among PsA patients in the southern and northern sites. No association could be established between disease activity and vitamin D level. However, lifestyle and demographic determinants such as having a suntan and intake of vitamin D supplements did have an effect on vitamin D level.

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Sedentarity Is an Independent Cardiovascular Risk Factor in Rheumatologic Patients. Marco Antivalle[1], Cecilia Imperio[2], Michele Battellino[2], Alessandra Mutti[2], Maria Chiara Ditto[2], Alberto Batticciotto[2], Fabiola Atzeni[2] and Piercarlo Sarzi-Puttini[2]. [1]Rheumatology Unit, L. Sacco University Hospital Milano, MIlano, Italy, [2]Rheumatology Unit, L. Sacco University Hospital Milano, Italy

Background: There is ample demonstration that physical inactivity is a strong cardiovascular (CV) risk factor in the general population. While several reports suggest that patients with RA and other chronic rheumatic diseases have a reduced level of physical activity (PA) compared with the general population, few studies have evaluated physical activity and the risk of CVD in patients with rheumatic diseases (1).

Aim of the study: To study the relationship between low PA and other cardiovascular risk factors in patients affected by rheumatic diseases.

Methods: PA and CV risk factors were studied in 282 patients with rheumatic diseases (216 Females and 66 Males, mean age 53.5 years). 71.4% of patients had inflammatory diseases. The level of PA was assessed by the IPAQ questionnaire, which allows the estimate of total weekly energy expenditure in MET-minute/week, and the categorization of patients into 3 levels of activity - Low (< 600 MET/m/w), Moderate (< 3000 MET/m/w), and High (=> 3000 MET/m/w)-. Metabolic syndrome (Mets) was assessed by the International Diabetes Federation definition (3).

Results: Average PA energy expenditure was 1654 MET-m/w. Overall, a low level of PA was recorded in 47.3%, MetS in 22.6 %, and smoking in 26.1% of patients. Only 21.8% of patient reported walking at least 30 minutes/5 days/week according to cardiovascular prevention recommendations (4). More than 1 risk factor was present in 24.1% of patients. The distribution of risk factors was different in the 2 sexes, females showing a higher prevalence of LPA and males a higher prevalence of MetS. By logistic regression, MetS prevalence was significantly correlated only to sex (p=0.014) and age (p=0.003), but not to the level of PA (Fig. 1), to the type of rheumatic disease (inflammatory vs non inflammatory), nor to disease duration.

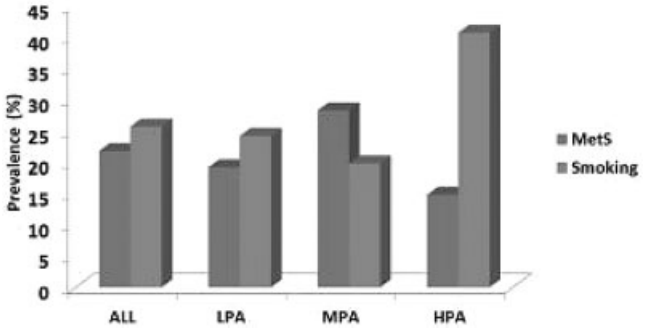

Fig. 1. Prevalence of metabolic syndrome and cigarette smoking according to levels of physical activity.

Conclusions: Sedentarity is very prevalent in rheumatic diseases, and in only 21% of patients weekly exercise meets levels recommended for CV prevention. Low levels of physical activity in this population seem to be unrelated to other cardiovascular risk factors. Preventive strategies to reduce cardiovascular risk in this population should include programs to improve physical fitness.

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Disclosure: M. Antivalle: None; **C. Imperio:** None; **M. Battellino:** None; **A. Mutti:** None; **M. C. Ditto:** None; **A. Batticciotto:** None; **F. Atzeni:** None; **P. Sarzi-Puttini:** None.

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Sex Differences in Pain Level and Location in Inflammatory Arthritis: A Systematic Review and Meta-Analysis. Cheryl C. M. Barnabe[2], Louis Bessette, Cathy Flanagan, Sharon LeClercq[3] and Vivian P. Bykerk[1]. [1]Mt Sinai Hospital, Toronto, ON, Canada, [2]University of Calgary, Calgary, AB, Canada, [3]University of Calgary

Background: Patient sex may influence the disease experience for patients with inflammatory arthritis (including rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA) and spondyloarthropathy (SpA)), with implications for treatment expectations and predicted response. Our objective was to determine if there are differences in the baseline level, location of pain, and the response to treatment, between females and males with inflammatory arthritis.

Methods: A search of PubMed (1950 to April 2010) and EMBASE (1980 to April 2010) was supplemented by manual searches of conference abstracts. We identified studies reporting sex-stratified pain measures (visual analogue scale (VAS), bodily pain component of the 36-item Short Form Health Survey (SF-36BP)) or pain location, in biologic naïve populations. Effects analyzed were a) standardized mean difference (SMD) for pain measures (cross-sectional analyses), b) percentage improvement in pain measure (longitudinal analyses), and c) proportion reporting pain at a particular location. The systematic review for pain measures includes 26 cohorts and 1 randomized controlled trial, and for pain location includes 12 publications. The meta-analysis for pain measures includes 16 cohorts reporting pain by VAS and 3 cohorts reporting pain by SF-36BP.

Results: Meta-analysis revealed a significant difference in the SMD in pain levels measured by VAS in RA (SMD 0.21 (95%CI 0.16–0.26), p<0.001) (Figure 1). This held when stratified by disease duration at measurement (RA < 1 year SMD 0.30 (95%CI 0.15–0.45), established RA SMD 0.20 (95%CI 0.14–0.25)). The SMD for SF-36BP was not significant (SMD −0.14 (95%CI −0.49, 0.20), p=0.411). In longitudinal studies, females improved to a greater degree than males, but still had higher mean pain values at any time point. Males had more inflammatory back pain and females had more peripheral arthritis (Table 1).

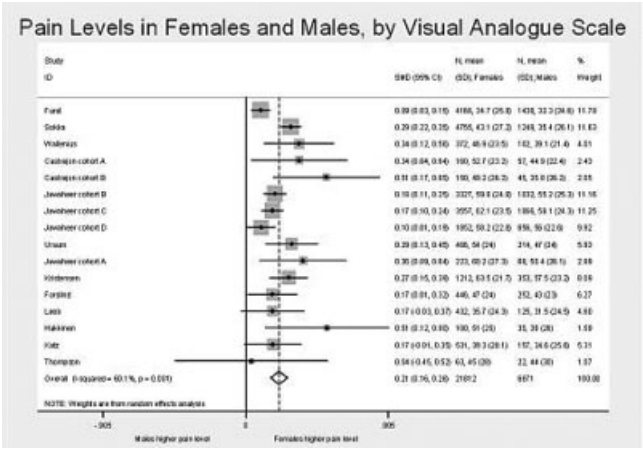

Figure 1. Meta-Analysis of studies reporting sex-stratified VAS pain scores.

Table 1. Studies Reporting Sex-Stratified Pain Location

Author, Year	Disease	Spinal Pain, Females	Spinal Pain, Males	Peripheral Arthritis, Females	Peripheral Arthritis, Males
Marks, 1983	AS	NR	NR	40%	16%
Braunstein, 1982	AS	34%	71%	NR	NR
Coughlan, 1993	AS	37%	69%	42%	17%
Gran, 1985	AS	59%	67%	29%	29%
Jimenez-Balderas, 1993	AS	37%	51%	78%	73%
Kidd, 1988	AS	77%	87%	97%	67%
Maldonado-Cocco, 1985	AS	NR	NR	28%	27%
Mathew, 1989	AS	80%	47%	NR	NR
Resnick, 1976	AS	NR	NR	83%	41%
Queiro, 2001	Ps SpA	43%	49%	24%	11%
Gladman, 1992	Ps SpA	100%	100%	NR	NR
Boyer, 2000	SpA	54%	50%	72%	85%

Conclusions: Females with RA experience higher pain levels than males, but do have a greater degree of improvement with treatment. Although this analysis does not explore confounding factors that may explain sex differences in inflammatory arthritis, it does alert the clinician that pain management is a significant issue in particular for female patients. In AS, females will develop peripheral arthritis more frequently, with fewer manifestations of inflammatory back pain. This may have diagnostic implications in the clinical setting.

Disclosure: C. C. M. Barnabe: None; **L. Bessette:** None; **C. Flanagan:** None; **S. LeClercq:** None; **V. P. Bykerk:** None.

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Sleep Disturbances in Adults with Arthritis: Prevalence, Mediators, and Subgroups at Greatest Risk. Grant H. Louie[2], Maria G. Tektonidou[1], Alberto J. Caban-Martinez[4] and Michael M. Ward[3]. [1]National University Health System, Singapore, Athens, Greece, [2]NIH, Bethesda, MD, [3]NIH, NIAMS, IRP, Bethesda, MD, [4]University of Miami Miller School of Medicine, Miami, FL

Background: Sleep disturbance is a common medical condition that may adversely affect daily functioning, vocational performance, and health-related quality of life. Few studies have examined the prevalence of sleep disturbances in adults with arthritis in a nationally-representative sample, mediators of sleep disturbances, and subgroups of individuals with arthritis at greatest risk.

Methods: Using data on U.S. adults aged ≥ 18 years participating in the 2007 National Health Interview Survey, we estimated the prevalence of three measures of sleep disturbance (insomnia, excessive daytime sleepiness, and sleep duration < 6 hours) among persons with physician-diagnosed arthritis. We used hierarchical logistic regression analysis to examine if the association of arthritis and sleep disturbances was independent of sociodemographic characteristics and comorbidities, and to identify potential mediators. We used classification trees to identify subgroups at highest risk.

Results: In the sample of 23,134 individuals, 19.9% (representing 44.3 million civilian, noninstitutionalized U.S. adults) reported having arthritis. Adults with arthritis had a mean (± standard error of the mean) age of 59.6 ± 0.3 years, and were more likely women (58.0%), non-Hispanic white (79.1%), and overweight or obese (71.8%). Age-, sex-, race-, and disease-adjusted prevalence of insomnia was 23.1%, excessive daytime sleepiness 11.0%, and sleep duration < 6 hours 7.3%. Adjusted prevalences were similar to those with other chronic diseases, such as diabetes and cardiac disease. Adults with arthritis were 2.9-fold more likely than those without arthritis to report insomnia, but adjustment for sociodemographic characteristics and comorbidities attenuated this association (Table). The association between arthritis and insomnia was further attenuated after adjusting for joint pain and limitation due to joint pain, suggesting pain mediated the relationship between arthritis and insomnia. Similarly, adults with arthritis were significantly more likely to report excessive daytime sleepiness and sleep duration < 6 hours in univariate and multivariate analyses. Adjusting for joint pain and limitation due to pain attenuated these associations. Among adults with arthritis, those with depression and anxiety were at highest risk for sleep disturbance.

Table. Association between sleep disturbances and presence of arthritis (compared to absence of arthritis) among adult participants in the 2007 National Health Interview Survey. Odds ratios (OR) with 95% confidence intervals (CI).

	Unadjusted		Adjusted for sociodemographic characteristics and comorbidities		Further adjusted for joint pain and limitation due to joint pain	
	OR	95% CI	OR	95% CI	OR	95% CI
Insomnia						
+ Arthritis (vs. − Arthritis)	2.92	2.68–3.17	1.53	1.36–1.71	1.06	0.93–1.21
Excessive daytime sleepiness						
+ Arthritis (vs. − Arthritis)	2.48	2.23–2.76	1.37	1.16–1.61	0.96	0.80–1.16
Sleep duration < 6 hrs						
+ Arthritis (vs. − Arthritis)	1.79	1.58–2.03	1.38	1.18–1.62	1.09	0.91–1.29

Conclusions: Up to 23% of the U.S. adult population with arthritis, representing 10.2 million persons, report having a sleep disturbance. The association appears to be mediated by joint pain and limitation due to pain. Among individuals with arthritis, those with depression and anxiety are at greatest risk.

Disclosure: G. H. Louie: None; **M. G. Tektonidou:** None; **A. J. Caban-Martinez:** None; **M. M. Ward:** None.

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The Comparative Responsiveness of the EQ-5D and SF-6D to Change in Patients with Early Arthritis: Results from the ESPOIR Cohort. Cécile Gaujoux-Viala[1], Anne-Christine Rat[2], Francis Guillemin[2], René-Marc Flipo[5], Patrice Fardellone[4], Pierre Bourgeois[3] and Bruno Fautrel[3]. [1]1INSERM, CIC-EC CIE6 2CHU Nancy, Epidemiologie et Evaluation Cliniques 3Nancy-University, Metz University, Paris Descartes University, EA 4360 Apemac 4Paris 6 – Pierre et Marie Curie University; Rheumatology, Pitie-Salpêtriere Hospital, [2]1INSERM, CIC-EC CIE6, Nancy, France 2CHU Nancy, Epidemiologie et Evaluation Cliniques, Nancy, France 3Nancy-University, Paul Verlaine Metz University, Paris Descartes University, EA 4360 Apemac, Nancy, France, [3]Paris 6 – Pierre et Marie Curie University; Rheumatology, Pitié-Salpêtrière Hospital, Paris, France, [4]Rheumatology, Amiens University, France, [5]Rheumatology, Lille University 2, France

Background: The revolution of early aggressive therapy have fueled the search for better approaches to establish the cost-utility ratio in early arthritis (EA). The EQ-5D and the SF-6D are indirect preference-based health related quality of life instruments increasingly used for economic evaluation of clinical interventions and health programs. Comparative evidence regarding the responsiveness of the EQ-5D and SF-6D in arthritis patients is conflicting and insufficient.

Objective: To compare the responsiveness of the EQ-5D and SF-6D in a large multicenter prospective cohort of patients with EA to guide the choice of instruments and their interpretation.

Methods: The ESPOIR cohort is a nationwide cohort that included 813 patients with EA with a high suspicion of rheumatoid arthritis, between 2002 and 2005. Data, including EQ-5D and SF-6D, were collected every 6 months during the first 2 years then every year. Responsiveness was tested using the standardised response mean (SRM) at 6 and 12 months for the entire sample and for subgroups categorized by their evolution (DAS28 improvement or deterioration>0).

Results: The EQ-5D provided larger absolute mean change estimates with greater variance than the SF-6D whatever the direction of change. The SF-6D and the EQ-5D SRM were higher for improvement than for deterioration of the DAS28 response at 12 months: SRM= 0.83 and 0.55 for the 2 instruments respectively. The SF-6D and the EQ-5D did not respond well to deterioration in patients with early arthritis: SRM= 0.08 and 0.2 in patients with deterioration of the DAS28 at 12 months, respectively (Table).

Das28 improvement at 12 months	Mean change at 12 months	STD of change at 12 months	SRM
DAS28	*−2.20*	*1.30*	*1.67*
HAQ	−0.508	0.652	0.78
SF6D	0.105	0.127	0.83
EQ5D	0.173	0.313	0.55
Das28 deterioration at 12 months			
DAS28	*0.68*	*0.55*	*1.25*
HAQ	0.129	0.518	0.25
SF6D	−0.008	0.097	0.08
EQ5D	−0.053	0.259	0.20

The SF-6D was more responsive to improvement and the EQ-5D more responsive to deterioration. The results were similar at 6 months.

Conclusion: The comparative responsiveness of the EQ-5D and SF-6D differs according to the direction of change. The SF-6D was more responsive than the EQ-5D in case of improvement. However both utility measures were less responsive to deterioration than improvement. The level of mean change of the EQ-5D relative to the SF-6D has implications for cost-effectiveness analysis. Use of the SF-6D in patients with early arthritis may be more appropriate.

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The Economic Burden of Uveitis. S. E. Kirbach, O. A. Hayes and M. A. Cifaldi. Abbott Laboratories

Background and Purpose: Uveitis is a common extra-articular manifestation of rheumatic conditions (including ankylosing spondylitis and juvenile idiopathic arthritis). It often recurs and is associated with potentially serious sequelae that greatly increase the risk of vision loss.[1] Uveitis is responsible for ≥10% of blindness in the United States and is associated with a total direct

cost of approximately $2.74 billion.[2,3] Despite this financial burden, there is a dearth of literature examining the economic burden specific to uveitis, especially with regard to the impact of uncontrolled disease and the presence of blindness and vision loss. We determined the average annual medical costs for individuals newly diagnosed with noninfectious uveitis based on location of inflammation, presence of blindness, and number of subsequent uveitis-related medical visits.

Methods: Patients (N=26,079) with noninfectious uveitis (based on ICD-9 codes) and ≥2 years of continuous enrollment (≥1 year before and after diagnosis of first episode) were identified in the MedStat MarketScan database (2000–2008) and categorized by uveitis type (anterior vs. intermediate/posterior/panuveitis [IPP]), incident and prevalent blindness, and number of uveitis-related medical visits (1, 2, 3, or >3 visits). Average annual medical costs were calculated for the year following the initial diagnosis of uveitis. Patients with health maintenance organization, point of service with capitation, or missing insurance plans were excluded from cost summations.

Results: The average annual cost for all individuals with noninfectious uveitis was $8,450 vs. $4,688 for nonuveitis controls. For all patients with uveitis, those with IPP uveitis incurred greater costs than those with anterior uveitis ($12,149 vs. $7,834, respectively). Patients who became blind during the observation period had greater costs than those who maintained their sight ($21,384 vs. $8,236, respectively) and those who were blind at the start of the follow-up period ($14,404). The largest driver of medical costs for patients with noninfectious uveitis was outpatient hospitalizations (29% of all costs) followed by drug costs (22% of all costs). In terms of uveitis-related medical visits, medical costs uniformly increased with number of visits (table).

Annual Medical Costs for Noninfectious Uveitis Patients by Type, Presence of Blindness, and Number of Uveitis-Related Medical Visits

	All ($)	1 Visit ($)	2 Visits ($)	3 Visits ($)	>3 Visits ($)
Noninfectious Uveitis					
All (N = 34,632)	8,450	7,908	8,723	10,016	12,513
Blind (N = 770)	17,846	16,567	15,152	18,972	25,882
Nonblind (N = 33,862)	8,236	7,742	8,554	9,729	11,859
IPP Uveitis					
All (N = 4,708)	12,149	10,900	11,523	15,117	23,976
Blind (N = 229)	23,619	16,758	19,880	30,686	50,207
Nonblind (N = 4,479)	11,607	10,684	10,994	13,907	21,185
Anterior Uveitis					
All (N = 29,924)	7,834	7,412	8,265	9,117	10,523
Blind (N = 541)	15,503	16,498	12,864	12,725	15,213

Conclusions: Uveitis results in a large degree of economic burden, especially for individuals with more severe disease or blindness and for those with repeated uveitis-related medical visits.

References:
[1]Durrani O, et al. *Ophthalmologica.* 2004;218:223–36.
[2]Rothova A, et al. *Br J Ophthalmol.* 1996;80:332–6.
[3]Prevent Blindness America 2007. Available at: www.preventblindness.org. Accessed October 30, 2009.

Disclosure: S. E. Kirbach: Abbott Laboratories, 1, 3; **O. A. Hayes:** Abbott Laboratories, 1, 3; **M. A. Cifaldi:** Abbott Laboratories, 1, 3.

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The Effect of Health Insurance and Physician Specialty on Quality of Care for SLE. Edward H. Yelin[6], Jinoos Yazdany[6], Laura Trupin[6], Chris Tonner[6], Gabriela Schmajuk[3], Patricia P. Katz[5], Lindsey A. Criswell[4], Laura J. Julian[6], Joann Z. Gillis[2] and Pantelis Panopalis[1]. [1]McGill University, Montreal, QC, Canada, [2]National Jewish Medical Center, Denver, CO, [3]Stanford University, Palo Alto, CA, [4]UCSF-Box 0500, San Francisco, CA, [5]Univ of CA San Francisco, San Francisco, CA, [6]University of California, San Francisco, San Francisco, CA

Background: Quality indicators (QIs) describe the extent to which health care meets minimal standards for quality of care. The authors have recently developed 20 QIs for SLE covering diagnosis, general preventive strategies, osteoporosis prevention and treatment, drug toxicity monitoring, renal disease, and reproductive health.[1] Of the 20 QIs, we deemed 14 amenable to self-report. The present study evaluates the extent to which health care in a community-based sample of persons with SLE (PWSLE), the Lupus Outcomes Study (LOS), adheres to these 14 QIs as a function of the kind of health insurance and specialty of physicians seen for SLE.

Methods: In 2009, 814 PWSLE were in the LOS. Principal data collection is an annual structured telephone interview regarding kind of health insurance, specialty of physicians seen, and health services received, including specific medications. Participants vary in their eligibility for the 14 QIs: all are eligible for the QIs related to counseling about sun avoidance and assessment of cardiovascular risk factors while only 1% are eligible for the QI related to treatment of new-onset proliferative lupus nephritis. We report here the overall pass rate, the % of all QIs for which PWSLE are eligible for which they report requisite health care services, as a function of the kind of health care coverage (HMO vs. non-HMO settings in public and private sectors) and combinations of care for SLE by generalists and rheumatologists. We use logistic regression to estimate the impact of type of health insurance and specialists, with and without adjustment for demographics (age, gender, race/ethnicity, education, and poverty status), disease duration and activity as measured by SLAQ, and number of physician visits on the pass rate. In these estimations, each QI for which PWSLE are eligible represents an observation; we account for the correlation among multiple observations of individuals via generalized estimating equations.

Results: The 814 PWSLE in the LOS were eligible for an average of 5.1 QIs (range 2–12) per person. The overall pass rate was.66 (95% CI.64-.67). The pass rate improved with increasing number of physician visits in the year prior to interview. It was also significantly higher among PWSLE in public sector HMOs than in private sector HMOs or in public and private sector non-HMO settings (Table 1). Those receiving care from generalists and rheumatologists singly or in combination had higher pass rates than those treated by neither. Adjustment had little effect on the results for kind of insurance or specialty of physician.

Conclusions: Pass rates for QIs vary significantly by kind of health insurance coverage and specialties seen by PWSLE and rise with increases in the number of physician visits, suggesting that aspects of health care amenable to policy changes may improve quality of care for PWSLE.

Table 1. Pass Rates (95% CI) for QIs among PWSLE, by Kind of Insurance and Specialties Seen

	Kind of Insurance			
	HMO		Non-HMO	
	Public	Private	Public	Private
Unadjusted	.76 (.70, .81)	.63 (.60, .67)	.66 (.63, .69)	.64 (.62, .67)
Adjusted*	.74 (.69, .80)	.64 (.60, .68)	.66 (.63, .69)	.65 (.62, .68)
	Types of Physicians Seen in Past Year			
	No generalist or rheumatologist	Rheumatologist only	Generalist only	Generalist and rheumatologist
Unadjusted	.53 (.42, .65)	.61 (.57, .66)	.63 (.59, .68)	.68 (.66, .70)
Adjusted*	.57 (.45, .68)	.64 (.59, .68)	.62 (.57, .66)	.67 (.65, .69)

*Adjusted for age, gender, race/ethnicity, education, poverty status, disease activity and duration, #MD visits.

[1]Yazdany J, et al., Arthritis Rheum 2009; 61: 370–377.

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The Georgia Lupus Registry: Health Care Utilization Rises during the Transition from Pediatric to Adult Systemic Lupus Erythematosus (SLE) Care. S. Sam Lim[3], Gaobin Bao[1], Larry B. Vogler[4] and Cristina M. Drenkard[2]. [1]Emory University, [2]Emory University, Atlanta, GA, [3]Emory University, Atlanta, GA, [4]Emory University School of Medicine, Atlanta, GA

Background: Some studies have reported childhood onset SLE as being more severe than in adults. Therefore, children with SLE may be at high risk for entering adulthood with disease related morbidity, damage, and disability. Furthermore, medical and psychosocial barriers can complicate the transition from pediatric to adult care. The aim of this study is to describe how health care utilization may change during this transition period.

Methods: The Georgia Lupus Registry is a population-based registry designed to estimate the incidence and prevalence of SLE in Atlanta, Georgia, from 2002 through 2004. Case-finding utilizes multiple sources. As a public health project, trained abstractors are able to document nearly 250 demographic and clinical elements from medical records of potential SLE patients without having to obtain consent. All facilities with potential pediatric SLE patients have been abstracted. All patients met the following case definition:

having either ≥4 ACR criteria or 3 ACR criteria with a diagnosis of SLE by a pediatric rheumatologist at age ≤18 years. The validated SLE patients were matched to the 1999–2004 Georgia Hospital Discharge Database, which captures all emergency room visits (ERV) and hospital admissions (HA) throughout the state and assigns a standardized direct cost to that care.

Results: 37 with childhood-onset SLE turned 19 years old between 1/1/1999 and 12/31/2004. 23 of these recorded at least one ERV or HA during this period (217 total visits) and had an average of 6.3 ACR criteria. The remaining 14 patients did not record an ERV or HA and averaged 5.1 ACR criteria.

	before turning 19 years old (person-years = 104)		after turning 19 years old (person-years = 108)		
	ERV	HA	ERV	HA	P-value*
Visits, total	38		117		<.0001
		21		41	0.01
Visits, Gender					
Male (n = 4)	1		13		0.001
		0		5	–
Female (n = 19)	37		104		<.0001
		21		36	0.047
Visits, Race					
Black (n = 20)	33		103		<.0001
		19		39	0.009
White (n = 3)	5		14		0.039
		2		2	1.00
Cost per Visit, $ Mean	11858		8978		0.37
		13570		13598	0.41
Male (mean)	2528	-	4732	22686	
Female (mean)	12110	13570	9509	12335	
Black (mean)	11709	13269	9884	13936	
White (mean)	12843	16432	2318	6995	
Duration, days					
Median	1		1		0.21
		7		3	0.002
Male (mean)	2.0	-	1.5	7.0	
Female (mean)	4.3	7.1	3.0	3.7	
Black (mean)	4.4	7.2	3.0	4.2	
White (mean)	3.4	7.0	1.5	1.5	

* Based on Wilcoxon Rank-Sum Test

Conclusions: The health care utilization burden of childhood-onset SLE is significant. With nearly equal amount of person-time follow-up before and after turning 19 years old, there is a striking increase in the number of ERV (tripling from 38 to 117) and HA (doubling from 21 to 41). This may signal the need to better coordinate the transfer of care for these patients. Access to care may be a factor as children without resources lose Medicaid coverage when turning 19. Further research is needed to elucidate the modifiable factors driving this change.

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The Impact of RA Diagnoses on Cost Related Medication Nonadherence in Older Patients: 2004–2007. Leslie R. Harrold[3], Becky A. Briesacher[4], Daniel Peterson[2], Jeanne Madden[1], Jerry H. Gurwitz[2] and Stephen B. Soumerai[1]. [1]Harvard Medical School, Boston, MA, [2]Meyers Primary Care Institute, Worcester, MA, [3]UMass Medical Schl, Worcester, MA, [4]UMass Medical School, Worcester, MA

Introduction: The treatment of rheumatoid arthritis (RA) can involve costly medications. We sought to examine whether cost-related medication nonadherence (CRN) was higher among patients with RA as compared to those without the condition from 2004 through 2007.

Methods: We identified a nationally-representative sample of elderly and disabled patients with rheumatoid arthritis (RA), based on two claims diagnoses (ICD-9 714.XX), and those without RA using the Medicare Current Beneficiary Survey. There were 219 to 241 RA patients and 14279 to14575 non-RA patients annually from 2004–2007 (unweighted n). We compared self-reported CRN (skipping or reducing medication doses or not obtaining prescriptions) among beneficiaries with and without RA. Using logistic regression, we examined whether there were trends over time in the occurrence of CRN among those with and without RA. Then we evaluated whether an RA diagnosis was associated with CRN after controlling for year, demographic characteristics, socioeconomic status, and comorbidities.

Results: The unadjusted annual prevalence of CRN in 2004, 2005, 2006, and 2007 among beneficiaries with RA was 20.7%, 17.5%, 16.7%, and 15.6%, respectively, compared with 15.1%, 14.0%, 11.4%, and 10.6% among beneficiaries without RA (statistically significant differences between RA vs non-RA in 2004 and 2006). In RA patients, the absolute decrease in CRN 2004 to 2007 was 5.1% and relative decrease was 24.6%, while among non-RA patients these were 4.5% and 29.8%, respectively.

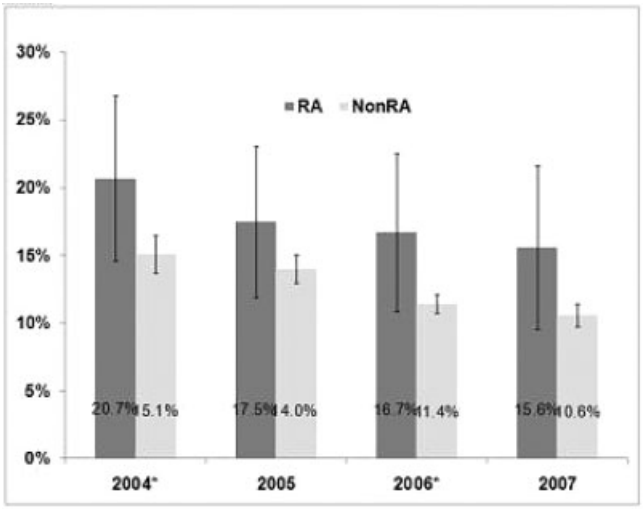

Figure 1. The prevalence of cost-related medication nonadherence among elderly Medicare beneficiaries with a diagnosis of rheumatoid arthritis (RA) versus those without (non-RA), 2004–2007.

The trend in CRN over time was not significant for those with RA ($p=0.23$) but was for those without the condition ($p < 0.0001$). The diagnosis of RA increased the likelihood of CRN (OR 1.27; 95% CI 1.01–1.60) in adjusted analyses.

Conclusions: CRN is a persistent problem for older adults, especially those with RA. While there have been decreases in CRN over time related to the Medicare Replacement Drug Demonstration program and Medicare Part D, substantial numbers of RA patients continue to report problems affording their medications.

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The Influence of Immunosuppressive Therapy and Underlying Diseases on Vaccine Responses to Influenza A H1N1/09 Vaccines in Inflammatory Rheumatic Diseases. Cem Gabay, Sara Meier, Danielle Gascon, Karin Posfay-Barbe, Christophe Combesure, M. Bel, Laurent Kaiser, Pierre-Andre Guerne and Claire-Anne Siegrist. Univ Hosp of Geneva, Geneva, Switzerland

Background: Influenza A H1N1 is a new virus that emerged in spring 2009 and rapidly spread around the world causing a pandemic. As patients with inflammatory rheumatic diseases (IRD) exhibit some form of immunodeficiency related to their diseases and the use of immunosuppressive drugs, the Swiss Society of Rheumatology recommended the vaccination of all IRD patients under immunosuppressive agents. However, two important questions remain unresolved: 1) are immunocompromised hosts able to raise successful vaccine responses, 2) is the use of adjuvanted vaccines safe in patients with autoimmune diseases.

Objectives: To determine the efficacy and safety of influenza A H1N1/09 vaccine formulated in a lipid adjuvant (squalene) in patients with IRD.

Patients and Methods: 173 patients with IRD and 138 healthy controls were included from November 2009 to January 2010 in this prospective, open-labeled, single center, parallel-cohorts study. Among IRD patients, there were 82 cases of rheumatoid arthritis (RA), 45 cases of spondylarthropathies (SpA), and 46 cases of connective tissue diseases (18 systemic lupus erythematosus (SLE)) or vasculitis. All received a first vaccine dose and 154 (89%), the second prescheduled vaccine dose. Safety after vaccination was assessed, respectively, in 173 and 149 patients using medical history and clinical indices of disease activity (DAS28, RADAI, and HAQ for RA, BASDAI for axial SpA, SLEDAI for SLE, and BVAS for vasculitis). The kinetic of the vaccine response and antibody titers (using a standardized

in-house hemagglutination inhibition assay) were assessed after the first and the second dose and compared to titers obtained in a control group of healthy individuals vaccinated once. Cellular immune responses to influenza H1N1/09 vaccine will be also determined in a subset of patients and controls.

Results: Disease modifying antirheumatic drugs were used in 85% of RA, 63% of SpA, 94% of SLE patients; oral corticosteroids in 31% of RA, 11% of SpA, and 70 of SLE patients; anti-TNF in 43% of RA and 71% of SpA; and rituximab in 21% of RA and 11% of SLE patients. The different indices of disease activity were not significantly different at baseline and after vaccination. Despite immunosuppression, injection-site tolerability and systemic inflammatory reactions were similar in patients with IRD than in healthy controls. Seroprotection rates (defined by IHA titer >= 1/40) after dose 1 were 129/146 (88.4%) in controls and 103/138 (74.6%) in patients ($P<0.001$). This rate increased to 128/148 (86.5%) after 2 doses. The analysis of the pattern of vaccine immune responses in the different IRD patient groups is in progress and will be presented.

Conclusions: The adjuvanted vaccine against influenza A H1N1/09 is well tolerated and does not induce short-term exacerbation in patients with IRD treated with immunosuppressive agents.

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The Risk of Myocardial Infarction among Patients with Psoriatic Arthritis. Thorvardur J. Love[1], Daniel Hal Solomon[3] and Elizabeth W. Karlson[2]. [1]Brigham and Women's Hospital, Boston, MA, [2]Brigham and Womens Hosp, Boston, MA, [3]Brigham and Womens Hospital, Boston, MA

Background: Severe psoriasis is associated with an increased risk of myocardial infarction (MI). A recent study found a standardized prevalence ratio of 2.51 for MI among psoriatic arthritis (PsA) patients compared to individuals from a telephone survey of the general population. We examined data from a hospital-based PsA repository, a population based survey, and medical records of patients without PsA to evaluate the risk of MI.

Methods: We performed two matched cohort analyses, using a single group of validated cases of PsA from a psoriatic arthritis patient repository seen at a tertiary care teaching hospital between 1995 and 2008, with each PsA case matched 2:1 on birth year, gender, and race to two separate comparison groups: non-PsA patients drawn from the same hospital population, and participants in the NHANES 2005–2008 population survey. The first documented diagnosis of PsA marked the beginning of follow up. The start of follow up for the hospital non-PsA group was the visit date closest in time to the diagnosis of the matched PsA case. Incident MI was determined by the presence of an ICD9 code in medical records, or self report in the NHANES cohort. Each individual was followed from either the onset of PsA or the matched index date, until they had an MI or follow-up ended. We excluded anyone with less than 12 months of follow up, and those with pre-existing cardiovascular conditions.

Results: We successfully matched 1404 BWH non-PsA patients to 702 PsA cases found in our repository. From NHANES we found two matched controls for each of 734 PsA cases. Cumulative follow up time in the three arms of the study was 21,509 person years. There were 33 incident cases of MI in the PsA-group, 67 in the BWH non-PsA group, and 18 in the NHANES group. The incidence rate (IR) for MI per 10,000 patient years was 72 [50–101], 80 [62–102], and 21 [12–33] per 10,000 patient years at risk in the three groups, respectively. The crude incidence rate ratio for MI in PsA was 0.93 [0.60–1.44] and 3.46 [1.89–6.52] compared to the hospital and NHANES groups. Table 1 shows the results of the multivariate Cox proportional hazards analysis adjusted for age, calendar year, diabetes, hypertension, and hyperlipidemia for the risk of MI.

Table 1. Cox proportional hazard analysis of the risk of MI associated with psoriatic arthritis, adjusted for age, calendar year, diabetes, hypertension, and hyperlipidemia.

	Hospital comparison			NHANES comparison		
	HR	[95% CI]		HR	[95% CI]	
Psoriatic arthritis	**0.99**	**0.94**	**1.04**	**1.18**	**1.08**	**1.28**
Age	1.04	1.02	1.05	1.05	1.03	1.08
Calendar year	1.02	0.95	1.10	1.06	0.94	1.19
Diabetes	1.94	1.28	2.94	2.34	1.29	4.24
Hypertension	4.92	2.51	9.63	3.25	1.49	7.06
Hyperlipidemia	2.82	1.66	4.80	2.14	1.13	4.06

Conclusion: We did not find any difference in the risk of MI in the PsA group when comparing to a non-PsA group drawn from the same hospital based source population. We replicated a previously demonstrated association between PsA and MI when comparing cases of PsA to individuals from the general population. Furthermore, we quantified the risk by estimating the IR, the IRR, and the adjusted HR. This suggests that the choice of control population affects the results of analyses of MI risk in PsA. Studies of PsA cases drawn from the general population are needed to support the hypothesis that PsA increases the risk of MI in the general population.

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Validation of a Self-Administered Inflammatory Arthritis Detection Tool for Rheumatology Triage. Mary J. Bell[6], George A. Wells[7], Vivian P. Bykerk[3], Peter Tugwell[1], Ruben Tavares[2], Francis Guillimen[4] and Joel Scarf[5]. [1]Institute of Population Hlth, Ottawa, ON, Canada, [2]MaMaster University, [3]Mt Sinai Hospital, Toronto, ON, Canada, [4]Nancy University, [5]Sunnybrook Health Sciences Ctr, [6]Sunnybrook Health Sciences Ctr, Toronto, ON, Canada, [7]Univ of Ottawa Faculty of Med, Ottawa, ON, Canada

Background: A self-administered tool for the early detection of inflammatory arthritis (IA) has been developed. A systematic review was used to identify stage-one case ascertainment dimensions and constructs amenable to self-assessment. Using a three-round Delphi consensus panel involving 169 arthritis stakeholders, the identified constructs were formulated into lay language items and refined into twelve questions with binary, 'yes'/'no' response options. Studies to validate the tool in various community and clinical settings are ongoing. The objective of the current study was to establish a scoring algorithm for, and validate, the tool for IA triage in the rheumatology wait-list population.

Methods: The tool was self-administered by 143 patients on the waiting lists of two Canadian, academic rheumatologists. At rheumatology presentation, the blinded rheumatologists assigned a clinical diagnosis and categorized each patient as IA or not. Multivariable logistic regression was conducted using IA as an outcome and age, sex, and the twelve tool items as independent variables. Multivariable-adjusted estimates of independent variable effect sizes were used as weights for the tool. Bootstrap AGGregatING (BAGGING) of 200 multivariable models was used to refine estimates of independent variable weights and the tool's performance properties. Receiver operating characteristic (ROC) curves for the models were derived. The predictive performance for the tool was determined from the area under the ROC curve (AUC), and sensitivity and specificity using the optimal model probability cutoff score. The optimal model probability cutoff score was determined from the maximum sum of sensitivity and specificity along the ROC curve. All analyses were performed using SAS/STAT® v. 9.2.

Results: The sample was comprised of a variety of rheumatologic conditions including 30 IA (ankylosing spondylitis, psoriatic arthritis, reactive arthritis, rheumatoid arthritis, and undifferentiated inflammatory arthritis) and 113 non-IA cases (osteoarthritis, pain syndromes, systemic lupus erythematus, and other miscellaneous rheumatologic disorders. Using an equally-weighted, unidirectional scoring scheme, where all 'yes' responses contributed positively towards the detection of IA, a cut-off score of 7 of 12 (0.58) produced an ROC AUC of 0.77, with a sensitivity of 0.87 and specificity of 0.52. Using multivariable logistic regression, a model probability cut-off score of 0.33 produced an ROC AUC of 0.91, with a sensitivity of 0.80 and specificity of 0.89. The model goodness-of-fit was supported by a non-significant Hosmer-Lemeshow test ($p=0.64$). The BAGGING-refined model with a probability cutoff of 0.28 (0.20–0.41) produced an ROC AUC of 0.95 ± 0.02 with a sensitivity of 0.90 (0.85–0.95) and specificity of 0.90 (0.85–0.96).

Conclusions: A scoring algorithm for a self-administered, twelve-item tool was developed and validated for IA detection in the rheumatology wait-list population. Together with its self-assessment mode of administration, the high sensitivity and specificity of the tool render a potential advance in rheumatology triage of IA.

Disclosure: M. J. Bell: None; **G. A. Wells:** None; **V. P. Bykerk:** None; **P. Tugwell:** None; **R. Tavares:** None; **F. Guillimen:** None; **J. Scarf:** None.

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Validation of the SF-6D Utility Measure in Patients with Systemic Lupus Erythematosus (SLE). Mark J. Harrison[5], Nicola Dale[1], Sahena Haque[2], Joanna Shelmerdine[6], Lee-Suan Teh[4], Yasmeen Ahmad[3] and Ian N. Bruce[1]. [1]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [2]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [3]Betsi Cadwaladr University Health Board-West, Rheumatology, Llandudno, United Kingdom, [4]Department of Rheumatology, Royal Blackburn Hospital, Blackburn, United Kingdom, [5]Health Sciences Research Group, The University of Manchester, Manchester, UK, [6]The Kellgren Centre for Rheumatology, Central Manchester Foundation Trust, Manchester, UK

Purpose: Collection of health-related quality of life (HRQoL) questionnaire with sets of utility values, such as the SF-6D, allow quality-adjusted life years used in cost-utility evaluations to be calculated. However these measures should be evaluated for validity in each setting they are applied. Few studies in systemic lupus erythematosus (SLE) have included a generic HRQoL measure; therefore the validity of these measures for this setting is unclear. This study aims to explore the construct validity and the minimum important difference (MID) of the SF-6D in SLE patients.

Methods: Female patients with SLE (≥4 ACR criteria) were recruited from routine outpatient clinics at 2 time points 5 years apart. At baseline and 5 years patients had a clinical assessment including the SLEDAI 2000 and SLICC damage index. Patients also completed the generic RAND Medical Outcome Study 36-Item Short-Form Survey version 1 (MOS SF-36), which allows the SF-6D to be calculated, at baseline and 5-years and the (disease specific) LupusQoL® was completed at the 5-year time point.

Construct validity was tested by (1) correlation (Pearson) of SF-6D with SLICC (damage), SLEDAI (activity), patient characteristics (age, disease duration, education, smoking, depression, fatigue), and LupusQoL® (at 5-years). The ability to discriminate between groups was tested using the t-test. The minimum important difference (MID) was estimated in two ways: (1) multiplying the SF-6D standard deviation by a small effect size (0.2), and (2) regressing the SF-6D onto SLICC to estimate the change associated with change equivalent to the MID of SLICC.

Results: 181 patients (mean age 48 years, mean disease duration 11 years) had SF-6D scores at baseline; the mean SF-6D score was 0.60 (0.12). The SF-6D correlated more strongly with age (−0.19) and SLICC (−0.24) than disease duration (−0.04), education (0.08) or SLEDAI (−0.06). In 113 patients with an SF-6D calculated score at 5-years, the correlation of the SF-6D with LupusQoL® domains was 0.6–0.8 for all domains apart from intimacy (0.44) and body image (0.36) The SF-6D could distinguish between those who smoked (−0.07, p=0.003), had carotid plaque (−0.05, p=0.027), had depression (−0.09, p<0.001), and reported fatigue (−0.06, p=0.006), from those who did not. The MID was estimated to be 0.024 to 0.028.

Conclusions: The SF-6D is valid for the measurement of HRQoL in patients with SLE; the measure reflects a number of key outcomes of the disease. Low correlation with aspects of intimate relationships and body image represents a concern and reinforces the need for collecting disease-specific measures of HRQoL alongside generic measures. The MID for the SF-6D is 0.024–0.028, smaller than estimates for other rheumatic disease such as rheumatoid arthritis.

Disclosure: M. J. Harrison: None; **N. Dale:** None; **S. Haque:** None; **J. Shelmerdine:** None; **L.-S. Teh:** None; **Y. Ahmad:** None; **I. N. Bruce:** None.

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Working Status in Patients with Early Inflammatory Polyarthritis: Results from the Norfolk Arthritis Register (NOAR). S. M. M. Verstappen[1], M. Lunt[1], T. Marshall[2], D. K. Bunn[2], J. Chipping[2] and D. P. M. Symmons[1]. [1]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [2]Norfolk Arthritis Register, Norfolk and Norwich University Hospital, Norwich, United Kingdom, United Kingdom

Background: Loss of paid work is one of the major consequences in patients with inflammatory polyarthritis (IP) and its subset rheumatoid arthritis. The objectives of this study were to (i) describe the change in working status over 10 yrs and (ii) to identify possible predictors for loss of work due to ill-health in working patients with early IP.

Methods: Consecutive patients with early IP (≥ 2 swollen joints for ≥ 4 weeks) from a primary-care based inception cohort (NOAR), recruited between 1990 and 1994, aged <63 yrs at symptom onset were included in this study. Data about working status since symptom onset until 10 yrs after registration in the NOAR cohort were available for this study population. Job titles were coded and used to differentiate between manual and non-manual jobs. At registration (baseline), clinical assessments included the DAS28 and the HAQ-score. Blood was collected to determine CRP, RF and ACPA. The association of baseline disease characteristics and loss of paid work 10 yrs after inclusion was assessed using logistic regression analysis, adjusting for age at registration and gender (OR, 95%CI). These analyses were restricted to patients for whom 10 year follow-up employment status was available and who were working, temporarily on sick leave or temporarily unemployed at registration. Loss of paid work was defined as being retired due to ill-health or receiving incapacity benefits at 10 yrs. In paid work was defined as working or temporarily on sick leave. Patients who retired (early) not due to ill-health or became a houseperson were excluded from the regression analysis.

Results: The preliminary results of this study show that, of the 329 patients working at symptom onset, 38 (11.6%) had already stopped working due to ill-health before registration in the register. Data from 225 patients could be used to assess the association between baseline characteristics and loss of paid work at 10 yrs. The mean age at registration of these 225 patients was 43 (SD 10) yrs and 63% were women. At registration, 183 were working, 37 were temporarily on sick leave, and 5 were temporarily unemployed. At 10 yrs, 56/225 (25%) had lost their job due to ill-health. Women were less likely to stop working due to ill-health (OR 0.53, 95%CI 0.29, 0.98). Older age at registration was also associated with an increased risk of stopping work due to ill-health (OR 1.09, 95%CI 1.05, 1.13). Although a trend for an association was found for RF, none of the clinical variables measured at baseline were significantly associated with the loss of work when adjusting for age and gender, i.e.: DAS28 (OR 0.93, 95%CI 0.71, 1.21), HAQ (OR 1.11, 95%CI 0.64, 1.94), RF positive (OR 1.99, 95%CI 0.98, 4.07), ACPA positive (OR 1.90, 95%CI 0.87, 4.16). Furthermore, having a manual job was also not associated with the loss of work due to ill-health (OR 1.43, 95%CI 0.74, 2.77).

Conclusion: In this study we found that many patients with early IP had already stopped working within the first couple of months after symptom onset and before starting DMARDs. In this small study population, we could not confirm any of the associations between clinical and job related variables, which have been found in previous RA studies, with loss of work due to ill-health.

Disclosure: S. M. M. Verstappen: None; **M. Lunt:** None; **T. Marshall:** None; **D. K. Bunn:** None; **J. Chipping:** None; **D. P. M. Symmons:** None.

ACR Poster Session B
Fibromyalgia and Soft Tissue Disorders Poster II
Tuesday, November 9, 2010, 9:00 AM–6:00 PM

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A Randomized Attention-Controlled Study of Motivational Interviewing To Encourage Exercise in Fibromyalgia: Week 12 Interim Analysis. Dennis C. Ang[3], Anthony S. Kaleth[1], Sylvia M. Bigatti[2], Steven A. Mazzuca[3], Chandan K. Saha[2] and Robert W. Bandy[2]. [1]Indiana Univ Purdue Univ Indianapolis, [2]Indiana University, [3]Indiana University, Indianapolis, IN

Background: Aerobic exercise is an important treatment option for the management of fibromyalgia (FM). Unfortunately, the early benefits of structured, supervised exercise programs are often compromised by declining adherence as the exercise regimen transitions to an unsupervised, often home-based, program. Individuals who are able to maintain adherence almost always prolong the symptomatic benefits of exercise. We sought to determine the efficacy of motivational interviewing (MI) to maintain long-term adherence and extend the health benefits of exercise for FM patients.

Methods: Subjects met ACR diagnostic criteria for FM and had moderate pain severity at baseline (Brief Pain Inventory (BPI) ≥ 4). Subjects were randomized to MI or attention control (AC) conditions. All were advised to adopt a standard regimen of aerobic exercise and received two supervised training sessions. Subjects assigned to MI (n=107) participated in six counseling by telephone over the next 12 weeks. Subjects assigned to AC (n=109) participated in an identical schedule of telephone discussions about topics relevant to FM self-management (e.g., pain, fatigue, sleep). Clinical outcomes (BPI and Fibromyalgia Impact Questionnaire (FIQ)) were assessed at baseline and weeks 12, 24 and 36.

Results: Most of the sample was female (96%), white (88%), married

(61%), and employed (54%). Mean body mass index (BMI) was 31.4 kg/m^2. Baseline distributions for FIQ Total and BPI (mean ± SD = 67.0 ± 12.7 and 6.0 ± 1.3, respectively) suggested moderate-to-severe FM severity. The average self-reported total of physical activity (PA) of moderate or greater intensity (CHAMPS) was only 1.7 hours/wk. Treatment groups were similar at baseline with respect to demographic and clinical characteristics and retention rates at week 12 (MI: 91% vs. AC: 94%). Mean change (±SD) over 12 weeks in exercise adherence and clinical outcome measures are tabled below.

Outcome	MI (N = 96)	AC (N = 101)	*P*-value¶
Hours/wk of ≥moderate intensity physical activity*	2.8 ± 5.1	1.0 ± 3.6	0.007
Pain severity†	−1.3 ± 1.5	−0.9 ± 1.8	0.069
Symptom severity‡	−14.2 ± 14.7	−10.4 ± 17.4	0.105

*Community Health Activities Model Program for Seniors (CHAMPS)
†BPI (range; 0–10); Negative change represents improved pain
‡FIQ Total (range: 0–100): negative change represents improved symptoms
¶From ANCOVA, adjusted for baseline score and disease duration

Conclusion: MI is a directive, client-centered counseling style that focuses on enhancing motivation to change by helping clients explore and resolve ambivalence about a target behavior (e.g., exercise). Compared to AC, participants in the MI group reported greater improvement in both physical activity and clinical measures. Pending long-term efficacy data, exercise-based MI appears to be a promising tool to encourage increased PA and improve clinical symptoms in patients with FM.

Disclosure: D. C. Ang: None; **A. S. Kaleth:** None; **S. M. Bigatti:** None; **S. A. Mazzuca:** None; **C. K. Saha:** None; **R. W. Bandy:** None.

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Correlation between Bone Mineral Density and Urine Carboxyl Terminal of Collagen Type (CTX) in Premenopausal Fibromyalgia Patients. Alaa Alsalawy[3], Mohammed M. Kamel[2] and Ibrahim Eweis[1]. [1]AlAzhar University, Cairo, Egypt, [2]ALAzhar University, Alkhobar, Saudi Arabia, [3]Tanta University, Tanta, Egypt

Objective: The aim of the study was to compare Bone mineral Density (BMD), Serum Osteocalcin (OC), and Urine Carboxyl terminal of collagen type I(CTX) of premenopausal patients suffering from fibromyalgia(FMS), to that of healthy premenopausal females. Then to determine the relationship between (BMD), urine(CTX), and the development of rapid bone loss and early osteoporosis among premenopausal fibromyalgic patients.

Subjects and Method: Thirty-one premenopausal patients with fibromyalgia and thirty age matched healthy females subjects as a control group were included in this study. Serum osteocalcin and urine CTX were measured using ELISA technique (Enzyme Linked Immune Sorbent assay) in all cases, BMD was measured in femoral neck and lumber spine by using X- ray absorptiometry. Statistical analysis were done using SPSS virgin 15. Student's unpaired (t)test and pearson's correlation analysis were performed to assess the correlation between BMD and urine CTX.

Results: BMD of lumber and femoral neck were significantly lower in fibromyalgic patients compared to the healthy females ($p<0.001$). Serum Osteocalcin were lower in fibromyalgic patients with no significant difference compared to healthy females. There were a significant negative correlation between urine CTX and BMD of lumber spine and femoral neck in fibromyalgic patients.

Conclusion: The results of this study indicate that the fibromyalgic premenopausal patients are highly susceptible to develop osteopenia and early osteoporosis comapred to normal healthy subjects. We recommend to measure BMD of all fibromyalgia patients especially those with high level of urine CTX.

Disclosure: A. Alsalawy: None; **M. M. Kamel:** None; **I. Eweis:** None.

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Cyclobenzaprine (CBP) Is a Potent Antagonist of Serotonin Receptor 2a (5-HT2a) and α-2 Adrenergic Receptors: Mechanistic Implications for Promoting Restorative Sleep in Fibromyalgia Syndrome (FMS). Herbert W. Harris[1] and Seth Lederman[2]. [1]Krele Pharmaceuticals, Saddle Brook, NJ, [2]Krele Pharmaceuticals, New York, NY

Background: Cyclobenzaprine (CBP) at very low dosages (VLD)(≤ 4 mg q.h.s.) is being investigated to improve sleep quality, reset circadian rhythm and treat daytime symptoms of fibromyalgia syndrome (FMS) (ref 1). The mechanism of action of cyclobenzaprine remains obscure. Indirect evidence from pharmacological studies implicates antagonism of either Serotonin Type 2a (5-HT2a) receptors (ref 2, 3) or α-2 adrenergic receptors (ref 4, 5). In these studies cyclobenzaprine was shown to block the biological effects of known 5-HT2a receptor agonists, or α-2 adrenoreceptor agonists in tissue slices or spinal cord sections. The objective of the present studies was to provide more direct evidence of the mechanism of action of CBP treatment by determining the binding affinities for relevant receptors.

Methods: Affinities (pK_i values) of CBP were determined for the 5-HT2(a, c) receptors, the histamine H1 receptor, and the α-2(a,b,c) adrenoreceptor family. Binding assays were are carried out in 50 mM Tris-HCl (pH 7.4) containing 1mM EDTA. Ligands used included: 5-HT2a, [^{3}H] Ketanserin (60–80 Ci/mmol); 5-HT2c, [^{3}H] Mesilulergine (60–80 Ci/mmol); α-2 adrenoreceptors, [^{3}H]MK-912 (60–80 Ci/mmol); H1, [^{3}H]-Pyrilamine (60–80 Ci/mmol). Receptor sources used included: 5-HT2a, rat cortical membranes; 5-HT2c, pig choroid plexus membranes; α-2 adrenoreceptors, human recombinant receptors expressed in SF9 cell lines; H1, bovine cerebellar membranes.

Results: CBP showed nanomolar affinity (9.0 nM) for the 5-HT2a receptor. In addition, CBP showed high affinity for members of the α-2 adrenoreceptor family (α-2a, 110 nM; α-2b, 9.9 nM; α-2c, 66 nM). CBP showed no measurable affinity (>5,000 nM) for histamine H1 or 5-HT2c receptors.

Conclusions: CBP binds with high affinity at the 5-HT2a receptor and members of the α-2 adrenoreceptor family, antagonizes the binding of known agonists and has been shown previously to block agonist activity *in vivo*. 5-HT2a binding is a property of trazodone, which is FDA approved as an antidepressant but which is prescribed off-label to promote sleep and as such, is the second most commonly prescribed treatment for insomnia in the US (ref 6). Published findings suggest a role for 5-HT2a receptors in the regulation of deep non-REM sleep reviewed in (ref 7). The combination of 5-HT2a and α-2 adrenoreceptor antagonism is associated with the antidepressants mianserin and mirtazepine (but mirtazepine also has significant H1 blockade.) CBP's absence of measurable affinity for the histamine H1 receptor may be associated with low potential for weight gain. Together, the functional antagonism of 5-HT2a and α-2 adrenoreceptors may underlie the ability of bedtime CBP to improve sleep quality in FMS.

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Disclosure: H. W. Harris: Krele Pharmaceuticals, 1, 3; **S. Lederman:** Krele Pharmaceuticals, 1, 5.

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Developing an Improved PROMIS Fatigue Short-Form for Use in Patients with Fibromyalgia. Stephen Schilling[5], Steven I. Blum[1], Stavros Tourkodimitris[2], Andy Stankus[3] and David A. Williams[4]. [1]Forest Research Institute, Jersey City, NJ, [2]Forest Research Institute, [3]KantarHealth, [4]Univ of MI Hlth System-Lobby M, Ann Arbor, MI, [5]University of Michigan

Purpose: The NIH roadmap project "Patient-Reported Outcomes Measurement Information System (PROMIS)" has developed calibrated item banks for a variety of domains relevant to chronic illnesses, including fatigue, which can be used to administer computer adaptive testing or to develop static questionnaires and short forms. PROMIS has developed a 7-item Short-Form for general use in fatigue, but it is unclear how well this short-form performs in measuring the fatigue of individuals with Fibromyalgia (FM). This study sought to develop and test an improved fatigue short-form for use in FM patients, constructed from the PROMIS fatigue item bank using calibrations derived from individuals with FM.

Methods: An Item Response Theory (IRT) analysis was conducted using data collected from an internet-based survey of 1207 self-identified individuals (88.9% Female; 90.5% Caucasian) currently suffering from FM. Participants had to be ≥ 18 years at the time of response and have been previously diagnosed with FM by a physician. In order to reduce response burden,

respondents were randomized into one of 3 cohorts, each of which completed one-third of the 95 items from the entire PROMIS v1.0 Fatigue Item Bank (www.nihpromis.org). Items were balanced between cohorts so that there was no overlap of questions. IRT analysis was conducted using Samejima's Graded Response Model (GRM) to fit the data using MULTILOG 7. The relative contribution of items measuring the latent trait was assessed by the item information function (IIF). Polyserial Correlations and the average of the IIF for all items from the full item bank were compared with those items included in the PROMIS Fatigue-Short Form to identify candidate items for an alternative scale. Cronbach's alpha was used to assess the reliability of the existing and proposed alternative scales.

Results: The current 7-item PROMIS Fatigue Short-Form contains 3 Fatigue Experience items and 4 Fatigue Impact Items. The Fatigue Experience items had a Cronbach's alpha reliability score of 0.77. The Fatigue Impact items had a reliability score of 0.81; including one item [IMP40: *How often did you have enough energy to exercise strenuously?*] which had the lowest information function (IIF=0.11) in the full item-bank. By contrast, the items with the highest IIF from both Fatigue Experience [EXP40: *How fatigued were you on average?* (IIF=6.22)] and Fatigue Impact [IMP51: *To what degree did you have trouble finishing things?* (IIF=2.94)] are not included in the current PROMIS Short-Form. A proposed short-form containing items with high average IIFs for Fatigue Experience and Fatigue Impact, each containing 5 items achieved reliability scores of 0.95 and 0.92 respectively. It is likely that the concept of fatigue for individuals with FM differs to some degree from other clinical populations; this is reflected in the identification of a new set of items showing greater discriminative ability for measuring fatigue in FM patients.

Conclusions: A new Short-Form can provide improved precision in measurement of the fatigue associated with fibromyalgia compared with the current 7-item PROMIS Fatigue Short-Form. Further testing and validation of the alternative short-form is needed.

Disclosure: S. Schilling: Forest Laboratories, 5; **S. I. Blum:** Forest Laboratories, 1, 3; **S. Tourkodimitris:** Forest Laboratories, 3; **A. Stankus:** None; **D. A. Williams:** Forest Laboratories, 5, 8.

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Evaluation of Drug-Drug Interactions of Sodium Oxybate: Results from Pharmacokinetic/Pharmacodynamic Studies with Duloxetine, Lorazepam, and Tramadol. Mark Eller, Whitney Halladay and Annette Madrid. Jazz Pharmaceuticals, Inc.

Background: Clinical trials have demonstrated the efficacy and tolerability of sodium oxybate (SXB) for fibromyalgia treatment. Since polypharmacy is common in fibromyalgia, we evaluated SXB for interactions with three drugs commonly used by fibromyalgia patients.

Methods: Three phase 1 studies characterized the pharmacokinetics (PK) and pharmacodynamics (PD) of SXB (2.25 g single dose) with duloxetine (60 mg/day for 4 days; N=24), lorazepam (2 mg single dose; N=18), and extended release tramadol (100 mg/day for 5 days; N=19) in healthy volunteers. Drugs were administered individually and in combination with SXB in a double-blind, placebo-controlled, crossover design. Blood sampling at pre-defined time points enabled estimation of PK parameters for drugs administered alone and combined with SXB. Assessment of PD interactions at pre-defined time points included subject self-assessment of sleepiness/alertness (100 mm visual analogue scale [VAS]; 0=very alert to 100=very sleepy) and the Digit Symbol Substitution Test (DSST) for cognition and attention. Tolerability was evaluated based on the occurrence of adverse events (AEs), physical examination including vital signs, laboratory, and clinical tests including 12-lead electrocardiograms.

Results: Subjects were Caucasian (≥95%), mean age was similar across studies (31–33 years); the proportion of females varied (duloxetine, 54%; tramadol, 47%; lorazepam, 39%). The PK of each drug was consistent with established profiles; no statistically or clinically significant PK effects were observed for any of the drugs when administered in combination with SXB. The PD paralleled the PK profile of individual drugs. SXB+duloxetine and SXB+tramadol resulted in increases in sleepiness VAS scores that were similar to SXB alone. Sleepiness VAS scores with SXB+lorazepam were higher than when each drug was administered individually ($p<0.05$) and had a later and more prolonged peak than SXB alone. SXB alone peaked earlier (1.5 hours) than lorazepam alone (4 hours), and declined more rapidly. Compared to administration of the single agents, decreases in DSST scores with co-administration were only consistently seen with SXB+duloxetine (generally significant across time points vs duloxetine alone, and significant vs SXB alone at 1.5 hours only; $p<0.05$). All AEs were mild to moderate. One discontinuation, due to ventricular extrasystole in a patient administered tramadol, was not related to study medication.

Conclusions: The PK, PD, and tolerability profiles suggest that the combination of SXB with duloxetine or tramadol are not likely to result in clinically relevant effects. Sleepiness ratings increased when SXB and lorazepam were combined.

Disclosure: M. Eller: Jazz Pharmaceuticals, Inc., 1, 3; **W. Halladay:** Jazz Pharmaceuticals, Inc., 3; **A. Madrid:** Jazz Pharmaceuticals, Inc., 1, 3.

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Fibromyalgia Patients with High Global Disease Severity, Depression, Anxiety or Cognitive Dysfunction Are Likely To Benefit from Cognitive Behavioral Therapy. Chad S. Boomershine[1], Cara L. Hammonds[1], Jennifer Y. Hong[2] and Kenneth A. Wallston[2]. [1]Vanderbilt University, Nashville, TN, [2]Vanderbilt University

Background: Cognitive behavioral therapy (CBT) is recommended for treating fibromyalgia (FM) patients. However, due to cost and limited availability, a system for identifying patients most likely to benefit from CBT is needed. Because CBT works by increasing two aspects of cognitive adaptability (CA), perceived competence (PC) and dispositional optimism (DO), FM patients with low CA are likely to benefit from CBT. We studied CA levels in FM patients to identify characteristics that could be used to guide patient selection for CBT.

Methods: Data from FM patients (n=99) referred to a rheumatology clinic were analyzed. FM diagnosis was made on clinical grounds by an experienced rheumatologist (CSB). CA was measured using the 8-item CA Index (CAI),[1] with higher CAI scores reflecting greater PC and DO. Severity of FM symptoms were assessed using the Fibromyalgia Impact Questionnaire (FIQ) for global disease severity, the fatigue severity scale (FSS) for fatigue, the Everyday Cognition Scale 20 (ECog20) for cognitive dysfunction, the Athens Insomnia Scale (AIS) for sleep quality, the Physician Health Questionnaire 9 (PHQ9) for depression, the Generalized Anxiety Disorder 7 (GAD7) for anxiety and a pain visual analogue scale (VAS pain) for pain. The Regional Pain Scale (RPS) and tender point count (TPC) were both used to quantify number of painful body areas. Spearman rank correlations and Mann-Whitney U testing compared questionnaire scores (PASW Statistics 17). Data is reported as median (interquartile range).

Results: CA level negatively correlated with global FM disease severity (CAI vs FIQ global $\rho=-0.53$, $p<0.001$) and the severity of mental symptoms including fatigue (CAI vs FSS score $\rho=-0.36$, $p<0.0001$), cognitive dysfunction (CAI vs ECog20 $\rho=-0.46$, $p<0.0001$), sleep quality (CAI vs AIS $\rho=-0.33$, $p=0.001$), depression (CAI vs PHQ9 score $\rho=-0.70$, $p<0.0001$), and anxiety (CAI vs GAD7 score $\rho=-0.59$, $p<0.0001$). CA level did not correlate with the severity of physical symptoms including pain severity (CAI vs VAS pain score $\rho=-0.08$, $p=0.458$) or number of painful body areas (CAI vs RPS $\rho=-0.20$, $p=0.053$; CAI vs TPC $\rho=0.03$, $p=0.842$). To determine characteristics that best identified patients with low CA, patients were divided into two groups: those with normal (CAI ≥36) versus below-normal (CAI <36) CA levels. Median scores on questionnaires that significantly correlated with CAI scores were compared between the CA level groups. FM patients with low CA were best identified as those with high levels of global disease severity [FIQ global 72.3 (63.9,79.8) vs 60.6 (45.8,63.7), $p<0.0001$], depression [PHQ9 16 (12,19.25) vs 7.86 (4.25,10.75), $p<0.0001$], anxiety [GAD7 13.5 (8,19) vs 3 (2,10), $p<0.0001$] or cognitive dysfunction [ECog20 41 (32,47) vs 28 (22,36), $p<0.0001$].

Conclusions: CA level negatively correlates with the severity of mental symptoms of fatigue, cognitive dysfunction, sleep quality, depression and anxiety but not physical symptoms of pain or number of painful body areas in FM patients. FM patients with high global disease severity, depression, anxiety or cognitive dysfunction are most likely to benefit from cognitive behavioral therapy.

[1]Wagner et al. AIDS Behav. 2008;14:410–20

Disclosure: C. S. Boomershine: Cypress Biosciences, Inc., 8, Eli Lilly and Company, 8, Forest Pharmaceuticals, Inc, 8, Pfizer Inc, 2, 8; **C. L. Hammonds:** None; **J. Y. Hong:** None; **K. A. Wallston:** None.

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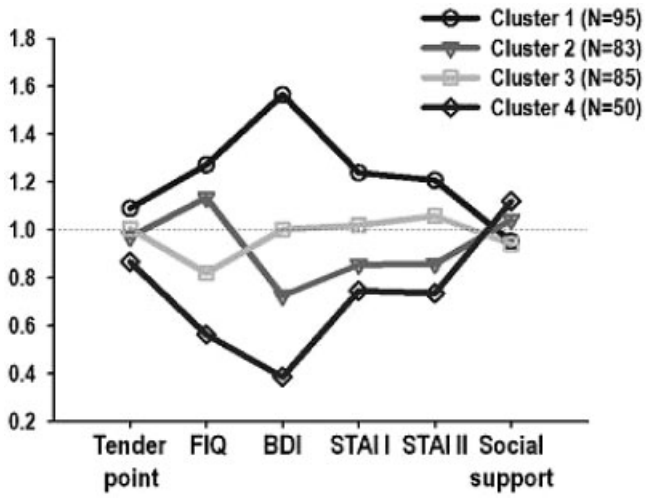
Identifying Fibromyalgia Subgroups Using Cluster Analysis: Relationships with Clinical Variables. Shin-Seok Lee[3], Seong-Ho Kim[6], Seong-Su Nah[11], Ji Hyun Lee[8], Seong-Kyu Kim[2], Yeon-Ah Lee[10], Seung-Jae Hong[10], Hyun-Sook Kim[4], Hye-Soon Lee[5], Hyoun Ah Kim[1], Chung-Il Joung[7] and Sang-Hyon Kim[9]. [1]Ajou University Hospital, Ajou University School of Medicine, [2]Catholic University of Daegu, School of Medicine, [3]Chonnam Natl Univ Med School, Gwangju, Korea, Republic of, [4]College of Medicine, Chosun University, [5]Hanyang University College of Medicine, [6]Inje University Haeundae Paik Hospital, [7]Konyang University Medical School, [8]Maryknoll Medical Center, [9]School of Medicine, Keimyung University, [10]School of Medicine, Kyung Hee University, [11]Soonchunhyang University, College of Medicine

Purpose: Patients with fibromyalgia (FM) do not form a homogenous group and have different clinical symptoms, physical, social, and psychological functions, and therapeutic responses. This study determined whether FM patients could be distinguished based on pain and physical, social, and psychological variables, and if so, whether the identified subgroups differ with respect to clinical features and treatment patterns.

Methods: 313 FM patients were interviewed using a structured questionnaire that included sociodemograhpic data, current or past FM symptoms, and current use of relevant medications. A k-means cluster analysis was conducted using variables reflecting tender points, the Fibromyalgia Impact Questionnaire, Beck Depression Inventory, State-Trait Anxiety Inventory, and Social Support Scale. Cluster subgroups were compared with chi-square tests for categorical variables and analysis of variance for continuous variables.

Results: Four distinct clusters were identified in these patients. Group 1 was characterized by high pain levels, severe physical and mental impairment, and low social support. Group 2 had moderate pain and physical impairment, mild mental impairment, and moderate social support. Group 3 had moderate pain, low physical and moderate mental impairment, and low social support. Group 4 had low pain levels, nearly normal physical and mental function, and high social support. Group 1 was more often a current or past smoker, more likely to have a variety of symptoms, including swelling, cognitive dysfunction, dizziness, syncope, esophageal dysmotility, dyspepsia, irritable bladder, vulvodynia, and restless leg syndrome, and less often a current non-steroidal anti-inflammatory drug user.



Conclusion: We identified four subgroups of FM patients based on pain and physical, social, and psychological function. These subgroups had different clinical symptoms and medication profiles, suggesting that the management of FM patients should be tailored to the individual patients' characteristics.

Disclosure: S.-S. Lee: None; **S.-H. Kim:** None; **S.-S. Nah:** None; **J. H. Lee:** None; **S.-K. Kim:** None; **Y.-A. Lee:** None; **S.-J. Hong:** None; **H.-S. Kim:** None; **H.-S. Lee:** None; **H. A. Kim:** None; **C.-I. Joung:** None; **S.-H. Kim:** None.

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Lack of Detection of Xenotropic Murine Leukemia Virus-Related Virus (XMRV) in Patients with Fibromyalgia. Jorge J. Gonzalez Martin[1], Gabriel Herrero-Beaumont[2] and Rafael Delgado[3]. [1]Reumatología, IIS-Fundación Jiménez Díaz, 28040, [2]Reumatología, IIS-Fundación Jimenez Díaz, 28040, [3]Servicio de Microbiología, Imas12, Hospital Universitario 12 de Octubre

Xenotropic murine leukemia virus-related virus (XMRV) is a recently described human retrovirus that has been associated with prostate cancer. Recently, XMRV sequences and specific immune responses have been detected in 67% of patients with the diagnosis of Chronic Fatigue Syndrome (CFS) in North America. Based in the common features between CFS and Fibromyalgia (FM), we decide to study the presence of XMRV in a group of 15 patients previously diagnosed with FM. DNA was extracted from whole blood and analyzed by nested PCR using 3 sets of primers corresponding to the *gag* and *env* regions of XMRV. Primers for human beta-globin (hBG) were used as positive control of human DNA amplification. The sensitivity of the nested PCR procedure, estimated by spiking the XMRV molecular clone VP62 into negative samples, was 1–10 copies per sample. We did not found any evidence of this new agent in any patient with FM studied and XMRV does not appear to be related with FM. With this relative small population we cannot absolutely exclude an association of XMRV with FM, however it would be highly unlikely a proportion of FM cases with XMRV greater than 22% (3 of 15 cases, 95% confidence interval), which is clearly insufficient to support a significant association between XMRV and FM.

Disclosure: J. J. Gonzalez Martin: None; **G. Herrero-Beaumont:** None; **R. Delgado:** None.

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Milnacipran Improves Pain and Global Status Independent of Changes in Depressive Symptoms in Patients with Fibromyalgia. Lesley M. Arnold[5], R. Michael Gendreau[1], Judy Gendreau[2], Allan Spera[3] and Wei Chen[4]. [1]Cypress Bioscience, Inc., San Diego, CA, [2]Cypress Bioscience, Inc., [3]Forest Research Institute, Jersey City, NJ, [4]Forest Research Institute, [5]University of Cincinnati, Cincinnati, OH

Purpose: Milnacipran is effective in improving multiple symptom domains in fibromyalgia (FM), including pain, physical function, and depressive symptomatology. This post hoc analysis was conducted to elucidate the relationship between changes in pain and patient global status and changes in depressive symptomatology.

Method: In this phase 3 trial, FM patients were randomized to milnacipran 100 mg/day (n=516) or placebo (n=509) for 12 weeks of stable-dose treatment. Patients with current major depressive episodes (assessed by MINI) or Beck Depression Inventory (BDI) scores >25 were excluded from the trial; however, 30% of patients had a history of depression at screening and in many cases had some evidence of depressive symptomatology. Outcome measures included a pain responder assessment (≥30% improvement from baseline in pain VAS scores), Patient Global Impression of Change (PGIC) responder analysis (rating of "very much improved" or "much improved"), and a 2-measure composite responder analysis (individual patients were required to meet both pain and PGIC responder criteria) at the end of the 12-week stable-dose treatment period. Changes in depressive symptoms were assessed with the BDI. Path analysis was used to describe the association between improvements in depressive symptoms and pain relief. The analysis was based on a regression model that partitioned the overall treatment effect into direct and indirect components.

Results: Patients treated with milnacipran had a small but statistically significant decrease in BDI scores relative to placebo (−2.12 vs −1.24; $P=.008$); these changes were significantly correlated with improvements in pain VAS ($r=0.210$) and PGIC ($r=0.309$) scores (both $P<.001$). Pain, PGIC, and 2-measure composite responder rates were the highest in patients with the largest improvements in BDI scores and the lowest in patients with no improvement or worsening of BDI scores. However, even in patients with no improvement or worsening in BDI scores, milnacipran treatment resulted in significantly higher responder rates than placebo on pain, PGIC, and 2-measure composite responder analyses ($P<.05$, all measures). Path analysis demonstrated that 12.8% (90% CI: 4.8%, 23.5%) of the milnacipran treatment effect on pain relief at endpoint can be explained by improvements in depressive symptoms, and the remaining 87.2% (90% CI: 76.3%, 95.2%) was unexplained by improvements in depressive symptomatology.

Conclusion: In patients with FM, treatment with milnacipran 100 mg/day significantly improves multiple domains, including pain, global status, and depressive symptoms. Much of the improvement in pain and global status with milnacipran is independent of improvements in depressive symptoms.

Disclosure: L. M. Arnold: Allergan, 2, 5, AstraZeneca, 5, Boehringer Ingelheim, 2, 5, Cypress Biosciences, Inc., 2, 5, Eli Lilly and Company, 2, 5, Forest Laboratories, 2, 5, 8, sanofi-aventis, 5, Takeda Pharmaceuticals North America, 5, Theravance, 2; **R. M. Gendreau:** Cypress Biosciences, Inc., 3; **J. Gendreau:** Cypress Biosciences, Inc., 3; **A. Spera:** Forest Laboratories, 3; **W. Chen:** Forest Laboratories, 3.

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Milnacipran Reduces the Overall Severity of Fibromyalgia Symptoms in Patients with Fibromyalgia. Robert H. Palmer[2], Robert M. Bennett[4], Yong Wang[3] and R. Michael Gendreau[1]. [1]Cypress Bioscience, Inc., San Diego, CA, [2]Forest Research Institute, Jersey City, NJ, [3]Forest Research Institute, [4]Oregon Health & Science Univ, Portland, OR

Purpose: Fibromyalgia (FM) is a disorder characterized by chronic widespread pain, fatigue, and impaired physical and global function. Patients with FM often have a multitude of other symptoms that include stiffness, poor sleep quality, and cognitive dysfunction. The Fibromyalgia Impact Questionnaire (FIQ) is a validated instrument that measures the spectrum of these FM-related symptoms and can identify patient responses to therapy. Milnacipran, approved in the US for the management of FM, has shown efficacy in treating multiple symptoms in FM patients. This post hoc analysis examines the effect of milnacipran on patients' FM severity.

Method: Data from a randomized, double-blind, placebo-controlled trial were analyzed. Patients with FM received milnacipran 100 mg/day (n=516) or placebo (n=509) for 4 to 6 weeks of flexible dose escalation followed by 12 weeks of stable-dose treatment. The FIQ was administered to patients at baseline and at each study visit. Patients were classified into 3 severity categories based on their FIQ total scores at baseline: <39 (mild impairment); ≥39 to <59 (moderate impairment); ≥59 (severe impairment). Improvements in FM severity were determined by the percentage of patients at endpoint shifting from the severe to the moderate or mild categories, or from the moderate to the mild category. Odds ratios (OR) for milnacipran were calculated for shifts in each severity category and are expressed relative to placebo treatment. Analysis was based on LOCF.

Results: FM severity based on the total FIQ score at baseline was mild (8.1%), moderate (48.5%), and severe (43.4%). At all study visits, patients treated with milnacipran had significantly larger decreases from baseline in FIQ total scores than placebo ($P<.001$ vs placebo). Of patients with severe FM at baseline, 61.1% of patients treated with milnacipran improved by at least one category of severity (32.2% to moderate and 28.9% to mild) compared with 46.1% of patients treated with placebo (26.5% to moderate and 19.6% to mild) (OR, 1.8; $P=.002$; number needed to treat, 7). Of patients with moderate or severe FM at baseline, 52.2% of milnacipran patients improved by at least one category, compared with 42.0% of placebo patients (OR, 1.5; $P=.002$; number needed to treat, 10).

Conclusion: These results represent an assessment of efficacy that indicate that milnacipran 100 mg/day is effective for treating the overall symptoms of FM, as measured by improvements in FIQ total scores. Patients with moderate or severe impairment at baseline were more likely to improve their FM severity with milnacipran than with placebo.

Disclosure: R. H. Palmer: Forest Laboratories, 3; **R. M. Bennett:** Eli Lilly and Company, 9, Jazz Pharmaceuticals, 2, 9, Pfizer Inc, 2, 9, Schwarz, 2, 9; **Y. Wang:** Forest Laboratories, 3; **R. M. Gendreau:** Cypress Biosciences, Inc., 3.

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National Fibromyalgia Association Survey on Children with Fibromyalgia: Preliminary Results. Sanjida Ali[1] and Rae Marie Gleason[2]. [1]Forest Research Institute, Jersey City, NJ, [2]National Fibromyalgia Association

Purpose: Juvenile fibromyalgia (FM) is a musculoskeletal pain condition that can impact the functional status and psychosocial development of children and adolescents. Currently, there is limited information on the prevalence of juvenile FM in the U.S. The National Fibromyalgia Association (NFA), in collaboration with Forest Research Institute, is conducting an internet survey to gather information on juvenile FM. One aim of the survey is to collect data that will help researchers and clinicians to better understand the nature and prevalence of FM in children. This report presents preliminary findings from the NFA survey.

Methods: The survey was completed by parents or guardians of children who have "fibromyalgia symptoms such as body-wide chronic pain, fatigue, stiffness, sleep problems, headache, irritable bowel and restless legs." For each child, respondents selected responses for the following items: age, gender, symptom severity, FM diagnosis, treatment information (ie, treating physician, medications, nonpharmacologic therapies), and lifestyle information. Responses from surveys submitted by parents or guardians of children (<18 years) from 12/05/2009 to 06/02/2010 were analyzed.

Results: Completed surveys were submitted for 284 children with symptoms of juvenile FM, >85% of whom were from the U.S. Results show that 76.4% of the children were female and 23.2% were male (0.4%, no response). Mean age was 13.6 years, with 17.6% ages ≤10 years, 33.5% ages 11–14 years, and 48.9% ages 15–17 years. 44.3% of the children were being treated by a healthcare professional, 26.4% by a rheumatologist and 10.6% by a primary care/family physician. 121 children (42.6%) had received a confirmed FM diagnosis; 60.3% were diagnosed by a rheumatologist and 23.1% by a primary care/family physician. Among children with a confirmed FM diagnosis, the most frequent symptoms (>90%) were widespread pain, pain influenced by stressors, fatigue, stiffness, sleep problems, headaches, foggy thinking, and anxiety. The frequency at which these symptoms were rated moderate or severe was 62.0% to 91.7%. Since developing FM symptoms, >50% of the diagnosed children had moderately or substantially decreased their involvement in strenuous physical activities or socializing with peers; 47.9% had changed schooling as a result of their FM symptoms. Current treatment with prescribed medications (i.e. serotonin-norepinephrine reuptake inhibitor, antiepileptic, tricyclic antidepressant, sedative-hypnotic, selective serotonin reuptake inhibitor, muscle relaxant, dopamine agonist) was reported in ≤12.4% of diagnosed children. Rates of previous use of these medications ranged from 0% to 21.5%. Nonpharmacologic therapies were more common, with >30% of diagnosed children currently using hot baths, exercise, and/or supplements to manage FM symptoms.

Conclusions: Results from the NFA's internet survey suggest children with FM present with higher rates of many of the classical symptoms of FM than observed in adults with FM. Also, less than half of the children with symptoms suggestive of FM had received a confirmed diagnosis, suggesting a possibility of underdiagnosis of FM in the pediatric population.

Disclosure: S. Ali: Forest Laboratories, 3; **R. M. Gleason:** National Fibromyalgia Association, 3.

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Nocturnal Heart Rate Variability Parameters. A Potential Fibromyalgia Biomarker. Claudia Lerma, Aline Martinez, Natllely Ruiz, Angelica Vargas, Oscar Infante and Manuel Martinez-Lavin. National Institute of Cardiology, Mexico

Background: Researchers strive to identify biomarkers for fibromyalgia (FM). Heart rate variability (HRV) analyses provide a quantitative marker of autonomic nervous system activity. Several HRV studies in FM have described changes consistent with relentless sympathetic hyperactivity. Sleep is modulated by autonomic activity. Sleeping problems are prominent in FM.

Objective: To explore different HRV parameters measured during sleeping hours as potential FM biomarkers.

Patients and Methods: We studied 21 women with FM according to the 1990 ACR criteria and 21 age-matched healthy women. None of the participants was on any medication that could affect autonomic activity. All participants used a Holter monitor while sleeping at home. Calculations were done from 00.00 to 06.00 hours. The following time-domain HRV parameters were studied: mean NN interval (mean NN), standard deviation of the NN intervals (SDNN), mean standard deviation of the average NN intervals calculated over 5 minutes (SDANN), and finally a HRV parameter developed by one of the authors (CL); transient heart rate acceleration episodes (THRAE).

Statistical analysis: Student T test compared parameters from both groups. The best cut-off point for each parameter was determined from ROC curves. Sensitivity, specificity, positive predictive value, negative predictive value and odds ratio were estimated for each parameter.

Results: Are shown in tables 1 and 2. Both groups have similar demographic characteristics. HRV values clearly differentiated patients from controls. Nocturnal SDNN had the greatest odds ratio (12, with confidence intervals 95% = 3.2–44.9) followed by SDANN (8.5, CI 95%, 2.2–31.8)

Table 1. Demographic data and HRV analyses from 00.00 to 06.00 hr.

	FM n = 21	Controls n = 21	p
Age (years) ± SD	32.7 ± 8.0	30.5 ± 7.6	0.37
Body mass index	24.5 ± 4.6	25.2 ± 3.2	0.56
NN mean (ms)	857 ± 92	937 ± 132	0.02
SDNN (ms)	91 ± 22	122 ± 33	< 0.01
SDANN (ms)	58 ± 22	78 ± 28	0.03
THRAE	23 ± 14	41 ± 31	0.01

Table 2. Predictive values of the potential HRV biomarkers.

	Cutoff point	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	OR (CI 95%)
NN mean at night (ms)	888.1	0.67	71	67	68	70	5 (1.3–18.7)
SDNN (ms)	113.1	0.79	86	67	72	82	12 3.2–44.9)
SDANN (ms)	68.8	0.71	81	67	71	78	8.5 (2.2–31.8)
THRAE	28.5	0.65	76	52	62	69	3.5 (0.9–13.1)

AUC = area under ROC curve, PPV = positive predictive value, NPV = negative predictive value, OR = odds ratio.

Conclusions: We identify 4 nocturnal HRV parameters that differentiate FM patients from healthy individuals. Multivariate analysis of these values could possibly yield more discriminative information. The specificity of these findings for FM when compared to other painful rheumatic syndromes remains to be established.

Disclosure: C. Lerma: None; **A. Martinez:** None; **N. Ruiz:** None; **A. Vargas:** None; **O. Infante:** None; **M. Martinez-Lavin:** None.

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Orthostatic Stress Reverses Sympathetic but Not Parasympathetic Abnormalities of Fibromyalgia Patients. Florence Luong[2], Donald D. Price[2], Michael E. Robinson[2] and Roland Staud[1]. [1]Univ of Florida JHMHC, Gainesville, FL, [2]University of Florida

Fibromyalgia syndrome (FM) is characterized by widespread chronic pain and tenderness. Previous studies have shown alterations of the central nervous system functions in FM including increased sensitivity to painful and non-painful stimuli and dysfunctional autonomic nervous system (ANS) responses. Dysfunctional ANS responses in FM patients include orthostatic hypotension, diminished microcirculatory vasoconstriction, and sympathetic hyporeactivity. The ANS can be assessed using heart rate variability (HRV) analysis which can provide important information on sympathetic and parasympathetic functions in FM.

Methods: We sought to determine the autonomic adaptability of FM patients using a mild orthostatic stressor. Whereas VLF and LF bands of HRV represent sympathetic ANS function, HF band variability correlates with parasympathetic function. We performed HRV spectral analysis of 55 FM and 44 normal control subjects (NC) during 15 min of rest followed by 5 min of standing. Heart and respiratory rate as well as blood pressure were monitored.

Results: Frequency analysis of FM subjects showed significantly lower variability in VLF, LF, and HF bands compared to NC during rest ($p < .05$) indicating sympathetic ANS dysfunction.

Table 1. Average (SD) of HRV during rest in NC and FM subjects

	VLF	LF	HF	VHF
NC	849.7 (998.4)	1412.2 (1778.4)	2096.1 (3593.6)	166.6 (335.5)
FM	442.4 (457.0)	597.7743 (777.9)	618.5089 (932.1)	56.8811 (71.0)
P value	.049	.01	.03	>.05

During 5 min of standing heart and respiratory rates as well as blood pressure of FM subjects were similar to NC (all $p > .05$). Whereas variability of VLF and LF normalized HF of FM subjects remained abnormal.

Table 2. Average (SD) of HRV during standing in NC and FM subjects

	VLF	LF	HF	VHF
NC	1368.3 (1622.5)	1306.7 (1301.1)	1357.5 (2504.3)	145.5 (195.1)
FM	1076.2 (2235.5)	1013.2 (1216.4)	388.8 (402.3)	60.0 (60.5)
P value	>.05	>.05	.03	.01

Conclusion: FM patients demonstrate sympathetic dysfunction that normalizes during standing. In contrast, parasympathetic function of FM patients is abnormal not only at rest but also during mild orthostatic stress.

Disclosure: F. Luong: None; **D. D. Price:** None; **M. E. Robinson:** None; **R. Staud:** None.

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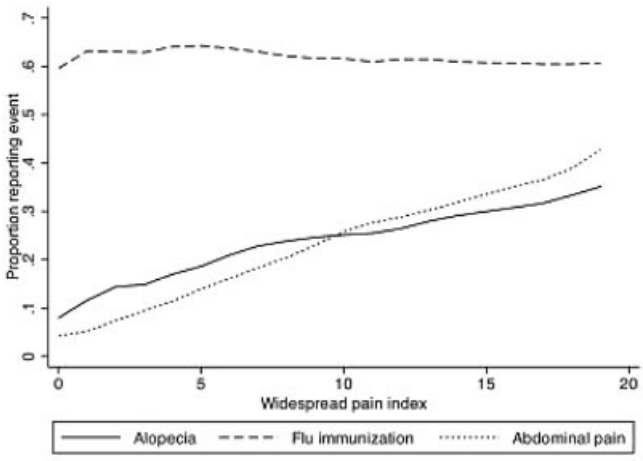
Over-Reporting Is a Central Determinant of Pain and Symptom Reporting in Fibromyalgia. Frederick Wolfe. National Data Bank for Rheumatic Diseases, Wichita, KS

Purpose: Central sensitization (CS) and global sensory augmentation (GSA) have been demonstrated in laboratory experiments, and have been proposed as major mechanisms to explain increased pain and sensory reporting in fibromyalgia (FM) and chronic widespread pain (CWP). However, there are other possible mechanisms in clinical FM, including over-reporting (OR), which might be considered to be related to increased concern about symptoms and non-symptom events. It is possible that the CS and GCA as well as OR could be operating at the same time. In this study we investigated the presence of GCA and OR as a function of widespread pain (WP), a measure related to pain threshold.

Methods: We studied 3 sets of variables to determine if their probability increased with increasing WP. We hypothesized that influenza immunization (FI) would not increase with increasing WP, as it was not a matter of personal concern to patients; that abdominal pain (AP) and other symptom variables would increase, observations that are consistent with the CS and GSA hypotheses. Finally we tested whether non-symptom events such as hair loss or alopecia (AL) and hearing loss (HL) would increase, According to the GSA hypothesis, these events would not increase; but they might increase if OR was present.

To be certain that the presence of patients diagnosed with FM would not distort the analyses, we excluded them from analysis, and studied 10,228 patients with rheumatoid arthritis or osteoarthritis. By self-report, we determined the presence of FI in the last 12 months, and symptom events (AP) and non-symptom events (AL, HL) present in the last 6 months. WP was determined using the Widespread Pain Index (WPI).

Results: Adjusted for age, sex and education level, FI was not significantly associated with WPI, $p=0.839$ ROC AUC = 0.618. AP was strongly associated with WPI, $p<0.001$, ROC AUC =0.732; and AL was also associated with WPI, $p<0.001$, ROC AUC = 0.659. The association are shown graphically in Figure 1.



To determine the associations of VAS pain (0–10) with these variables, we noted that there was 0.0 pain level difference for FI+ vs. FI- (3.6 vs. 3.6), but there was a 1.3 unit difference comparing AP+ with AP- patients (4.7, 3.4) and a 0.9 difference for AL+ vs. AL- patients (4.3, 3.4). A similar pattern was found in analyses of fatigue. Similar results were obtained with FM patients added, and for HL substituted for AL.

Conclusions: These data show that events that are not of personal concern are unrelated to WPI and pain. However, events such as AL that are not symptoms but may be of personal concern to patients are associated with increased WPI and pain, suggesting that OR influences WPI, pain, symptoms

and non-symptoms in the clinic. CS and GSA are not sufficient to explain observed pain and symptoms in FM. The degree to which CS/GSA and OR each contribute to WPI, FM and CWP in the clinic is a central question that should be the subject of future research.

Disclosure: F. Wolfe: None.

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Proteomic Mass Spectra Classification in Fibromyalgic Patients. Camillo Giacomelli[3], Laura Bazzichi[3], Federica Ciregia[2], Chiara Baldini[3], Francesca Sernissi[2], Pasquale Pepe[1], Laura Giusti[2], Antonio Lucacchini[2] and Stefano Bombardieri[3]. [1]Department of Clinical Pharmacology, University of Pisa, Pisa, Italy, [2]Department of Psychiatry, Neurobiology, Pharmacology and Biotechnology. University of Pisa, Pisa, Italy, [3]Rheumatology Unit. Department of Internal Medicine. University of Pisa, Pisa, Italy

Background: Fibromyalgia (FM) is a chronic non inflammatory musculoskeletal disorder characterised by widespread pain and by the presence of at least 11 out of 18 specific tender points on physical examination. Currently no validated laboratory biomarkers are available for FM and the diagnosis of the disease remains exclusively clinical. The aim of the present study was to perform a proteomic analysis of FM patients' saliva with surface-enhanced laser desorption/ionization time-of-flight/mass spectrometry (SELDI-TOF/MS).

Methods: For this study, we enrolled 66 patients, all female (mean age 43.60±11.30 yrs, Mean±SD), all fulfilling the ACR criteria and 50 healthy controls matched for age and sex.

Whole saliva samples are centrifuged to remove undissolved material. Aliquots of resulting supernatants are analysed by SELDI-TOF/MS. Saliva is applied to the spots of Protein Chip Arrays (CM10, Q10, H50). After an incubation period, unbound proteins and other contaminants are washed off the spots using buffers as required by the array chemistry; only proteins interacting with the chemistry of the array surface are retained for analysis. Finally matrix (sinapinic acid-SPA) is applied to each spot to facilitate laser desorption and ionization. The datasets are obtained from biological samples collected from different patients classified in different classes (e.g. disease versus control). Univariate and multivariate Logistic analysis was performed.

Summary of Results: Univariate analysis identified 22 peaks differently expressed in FM in comparison to healthy controls in a range of m/z between 2618 and 29533. One of these well overlap with molecular weight of Phosphoglycerate mutase-1 (MW 29 KDa) found alterated in our previous work (1). Multivariate analysis showed as best independent predictors for FM three peaks between m/z range from 2500 to 12000 which were able to classify FM patients with a percentage error of 24%.

Conclusion: These preliminary results showed the possibility to identify a salivary biomarker through salivary proteomic analysis with SELDI-TOF in FM patients. The next step will be the identification of the alterated proteins by purification by purification with chromatography and immunoprecipitation techniques.

Reference:

1) Bazzichi et al. Proteomics Clin. Appl. 2009, 3, 1296–1304.

Disclosure: C. Giacomelli: None; **L. Bazzichi:** None; **F. Ciregia:** None; **C. Baldini:** None; **F. Sernissi:** None; **P. Pepe:** None; **L. Giusti:** None; **A. Lucacchini:** None; **S. Bombardieri:** None.

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Sexual Dysfunction in Female Fibromyalgia Patients. Jacob N. Ablin[4], Inna Gurevitz[3], Hagit Cohen[1] and Dan Buskila[2]. [1]Ben-Gurion University of the Negev, Beer Sheva, Israel, [2]Soroka Medical Center, Beer Sheva, Israel, [3]Soroka Medical Center, Beer - Sheva, Israel, [4]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Background or Statement of Purpose: Fibromyalgia, the prototypical central pain syndrome, is characterized by widespread pain, tenderness and fatigue.

Fibromyalgia causes significant impairment in general well-being and quality of life, often inflicted on young, predominantly female, patients. Sexual functioning is considered an important parameter determining quality of life and is often negatively affected by rheumatological disorders. Impaired sexual function has negative effects on intimacy, on self – esteem and on the ability to maintain a long-term relationship.

In Fibromyalgia, various factors may impact on sexuality, including contact—avoidant behavior due to tenderness, depression, fatigue and the effect of medications.

The purpose of the current study was to evaluate sexual dysfunction among fibromyalgia patients.

Methods: Subjects: Fifty female subjects were recruited. Participants were asked to complete a questionnaire regarding sexual functioning.

Inclusion criteria included age over 18 and fulfillment of the ACR 1990 criteria for classification of fibromyalgia. Patients were consecutively recruited from the Rheumatology clinic. Exclusion criteria included conditions deemed to preclude informed consent.

The control group included fifty-five healthy volunteers, who were matched for age and gender.

The study was approved by the local Institutional Review Board of the hospital.

Demographic data regarding age, education, marital status and past medical history were collected. Participants underwent physical examination and tender point assessment was performed using manual palpation. All participants filled out the Arizona Sexual Experience Scale, which evaluates five areas of sexual functioning: sexual drive, sexual arousal, vaginal wetting, orgasm and sexual satisfaction.

Statistics: demographic parameters were compared using the Chi squared method. Sexual function parameters were compared using analysis of variance (ANOVA) for each parameter. Linear regression coefficients were calculated to describe the association between sexual function parameters and variables of age and pain intensity.

Summary of the Results: Table 1 presents the results of the Arizona sexual experience scale among fibromyalgia patients and controls.

Table. sexual function parameters among fibromyalgia patients and healthy controls.

	FM patients N = 50 Mean (Std.Dev)	Healthy Controls N = 55 Mean (Std. Dev)	ANOVA
Arizona Sexual Experience			
Sexual drive	4.8 (1.1)	3.2 (1.0)	F (1,13)=52.9, p<0.0001
Sexual arousal	4.6 (1.2)	2.8 (0.8)	F (1,13)=79.0, p<0.0001
vagina wetting	4.2 (1.0)	2.9 (0.7)	F (1,13)=59.3, p<0.0001
Orgasm	4.4 (1.3)	2.8 (1.0)	F (1,13)=47.1, p<0.0001
Sexual satisfaction	4.1 (1.5)	2.5 (1.0)	F (1,13)=41.0, p<0.0001
Total score	22.0 (5.4)	14.3 (4.0)	F (1,13)=68.9, p<0.0001

Conclusions: The results of the current study indicate a multi – factorial sexual dysfunction among female fibromyalgia patients. All stages of sexual functioning, evaluated were significantly disturbed in comparison with healthy controls. Physicians treating fibromyalgia patients should be aware of, and actively inquire about sexual dysfunction as part of a multi-disciplinary evaluation of female fibromyalgia patients.

Disclosure: J. N. Ablin: Eli Lilly and Company, 8, Pfizer Inc, 8; **I. Gurevitz:** None; **H. Cohen:** None; **D. Buskila:** Eli Lilly and Company, 8, Pfizer Inc, 8.

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Simplifying Fibromyalgia Assessment: The VASFIQ Brief Symptom Scale. Chad S. Boomershine, Gergana Zlateva, Yi Wang, Ed Whalen and Birol Emir. Vanderbilt University, Nashville, TN

Background: Fibromyalgia (FM) is a complex disorder of chronic widespread pain and tenderness associated with symptoms of fatigue, poor sleep, depression, and anxiety. Due to its complexity, identifying clinically significant symptoms and monitoring treatment response in FM is difficult. While the Fibromyalgia Impact Questionnaire (FIQ) can quantify global disease severity, scoring complexity, length and the inability to identify patients with significant symptoms limit its clinical utility. We hypothesized a more clinically useful FM scale could be formed from the 7 FIQ visual analogue scales (the VASFIQ), with the sum of VASFIQ scores providing a global disease severity measure and cut-off scores for individual VASs derived to identify clinically significant symptoms of fatigue, poor sleep, depression and anxiety.

Methods: Data from 2229 patients enrolled in 3 pregabalin FM treatment

trials (LIFT[1], RELIEF[2] and 1100[3]) were analyzed including scores from the FIQ, the Hospital Anxiety and Depression Scale (HADS), the Medical Outcomes Study (MOS) Sleep Problems Index 9 (SLP) and the Multidimensional Assessment of Fatigue Global Fatigue Index (MAF). Spearman rank correlations compared scores. Receiver operating characteristic (ROC) analysis identified cut-off scores on individual FIQ VASs with corresponding validated questionnaires used to define cases.

Results: VASFIQ global scores correlated with FIQ global scores at baseline (ρ=0.94, p<0.0001) and study endpoints (ρ=0.97, p<0.0001). Change in VASFIQ and FIQ global scores at study endpoints correlated (ρ=0.96, p<0.0001). Individual FIQ VAS scores correlated with all corresponding validated questionnaire scores at baseline (VASfatigue with MAF ρ=0.67; VASsleep with SLP ρ=0.50; VASdepressed with HADS-D ρ=0.57; VASanxiety with HADS-A ρ=0.64, all with p<0.0001) and study endpoints (VASfatigue with MAF ρ=0.76; VASsleep with SLP ρ=0.67; VASdepressed with HADS-D ρ=0.62; VASanxiety with HADS-A ρ=0.67, all with p<0.0001). Change in individual FIQ VAS scores correlated with change in corresponding validated questionnaire scores at study endpoints (VASfatigue with MAF ρ=0.64; VASsleep with SLP ρ=0.57; VASdepressed with HADS-D ρ=0.43; VASanxiety with HADS-A ρ=0.47, all with p<0.0001). ROC analyses showed a VASfatigue score of ≥7.5 was 76.0% sensitive and 82.2% specific for fatigue defined as a ≥30 score on the MAF [ROC area 0.87, 95% confidence interval (CI) 0.85–0.89], a VASsleep score of ≥7.9 was 68.7% sensitive and 71.2% specific for poor sleep defined as a ≥50 score on the SLP (ROC area 0.76, 95% CI 0.74–0.79), a VASdepression score of ≥5.8 was 71.3% sensitive and 72.6% specific for depression defined as a ≥11 score on the HADS-D (ROC area 0.80, 95% CI 0.77, 0.82) and a VASanxiety score of ≥6 was 71.2% sensitive and 77.7% specific for anxiety defined as a ≥11 score on the HADS-A (ROC area 0.83, 95% CI 0.81, 0.84).

Conclusions: The VASFIQ is a brief FM scale to assess global disease severity and identify patients with clinically significant symptoms of fatigue, poor sleep, depression and anxiety.

1) Mease et al. J Rheumatol. 2008;35:502–14
2) Arnold et al. J Pain. 2008;9:792–805
3) Pauer et al. Ann Rheum Dis. 2008;67(Suppl2):256

Disclosure: C. S. Boomershine: Cypress Biosciences, Inc., 8, Eli Lilly and Company, 8, Forest Pharmaceuticals, Inc, 8, Pfizer Inc, 2, 5, 8; **G. Zlateva:** Pfizer Inc, 3; **Y. Wang:** Pfizer Inc, 3; **E. Whalen:** Pfizer Inc, 3; **B. Emir:** Pfizer Inc, 3.

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Sodium Oxybate Improves Pain, Function, and PGIC in Patients with Fibromyalgia: A Pooled Analysis of 2 Pivotal Clinical Trials. I. Jon Russell[5], Robert M. Bennett[3], Cayetano Alegre[1], John B. Winfield[4], Chinglin Lai[2], Y. Grace Wang[2] and Beverly Benson[2]. [1]Hospital de la Vall d'Hebron, Alella, Spain, [2]Jazz Pharmaceuticals, Inc., [3]Oregon Health and Science University, Portland, OR, [4]University of North Carolina, Chapel Hill, NC, [5]University of Texas Health Science Center, San Antonio, TX

Background: In addition to chronic pain, fibromyalgia (FM) patients exhibit fatigue, sleep disturbances, and functional impairment. Sodium oxybate (SXB) demonstrated efficacy and tolerability for the treatment of FM in two pivotal phase 3 clinical trials. The current analysis further evaluates the effects of SXB on pain, function, and global status using pooled data from the two trials.

Methods: The trials were of similar design (randomized, double-blind, placebo-controlled), length (14 weeks), and dosing regimens (placebo, SXB 4.5 g and 6 g dosing equally divided between bedtime and 2.5 to 4 hours later). The primary outcome variable for both studies was the proportion of patients who achieved a 30% reduction in pain on a 0–100 mm visual analog scale (PVAS). Other measured variables included quantitative changes in PVAS, changes in daily function assessed as the proportion of subjects with ≥30% reduction in Fibromyalgia Impact Questionnaire (FIQ) score, changes in patient-reported health status (Patient Global Impression of Change [PGIC]), and two composite endpoints: a "Pain Composite" with two measures (PGIC of "very much better" or "much better" + ≥30% reduction in PVAS) and an "FM Composite" with three measures (PGIC of "very much better" or "much better" + ≥30% reduction in PVAS + ≥30% reduction in FIQ). Last observation carried forward was used for missing data.

Results: A total of 1121 subjects were randomized (placebo n=371; SXB 4.5 g n=377; SXB 6 g n=373). The demographic characteristics of the patients in the pooled trials were comparable (overall, 90.4% female; 91.2% white; median age 48.0 years). The proportion of patients with ≥30% pain reduction was significantly greater with SXB; 47.8% and 54.8% for 4.5 g and 6 g, respectively, relative to placebo (30.9%; p<0.001). Pain reduction ≥50% was reported by 36.0% of SXB 4.5 g patients and 40.4% of SXB 6 g patients compared with 18.9% on placebo (both p<0.001). Least squares mean changes from baseline showed greater PVAS reductions with both SXB doses relative to placebo, beginning at Week 1 and maintained through Week 14 (p<0.001). Greater proportions of patients treated with SXB 4.5 g (52.6%) and 6 g (55.6%) achieved ≥30% reduction in FIQ total score relative to placebo (34.3%; p<0.001). Improvements in pain and function were paralleled by greater proportions of SXB patients reporting PGIC scores of "much better" or "very much better" (p<0.001 for both doses). The proportion of patients at Week 14 meeting the Pain Composite criteria and those achieving the FM Composite criteria were significantly greater with both SXB doses compared with placebo (p<0.001). The most common adverse events with an incidence greater than 5% in either SXB treatment group and twice the placebo rate were nausea, dizziness, vomiting, anxiety, and fatigue.

Conclusions: This pooled analysis supports the results of the individual trials in demonstrating that SXB provides statistically and clinically significant improvements in FM pain, function, and global health status relative to placebo.

Disclosure: I. J. Russell: Autoimmune Technologies, 2, 5, 8, 9, Daiichi Sankyo, 9, Eli Lilly and Company, 2, 5, 8, 9, International MYOPAIN Society, 2, 5, 8, 9, Jazz Pharmaceuticals, Inc., 2, 5, 8, 9, NicOx, 9, Ortho-McNeil Pharmaceuticals, 9, Pfizer In; **R. M. Bennett:** Eli Lilly and Company, 5, Jazz Pharmaceuticals, Inc., 2, 5, Pfizer Inc, 2, 5; **C. Alegre:** Esteve, 2, 5, Grünenthal, 2, 5, Jazz Pharmaceuticals, Inc., 2, 5, Pfizer Inc, 5; **J. B. Winfield:** Eli Lilly and Company, 2, 8, Forest Laboratories, 5, 8, Jazz Pharmaceuticals, Inc., 2, Novartis Pharmaceuticals Corporation, 5, Pfizer Inc, 5, 8; **C. Lai:** Jazz Pharmaceuticals, Inc., 1, 3; **Y. G. Wang:** Jazz Pharmaceuticals, Inc., 1, 3; **B. Benson:** Jazz Pharmaceuticals, Inc., 1, 3.

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Sodium Oxybate Improves Sleep and Fatigue in Patients with Fibromyalgia: Pooled Analysis from 2 Pivotal Clinical Trials. Stuart L. Silverman[3], Andrew J. Holman[4], Beverly Benson[1], Sarah Alvarez-Horine[1], Y. Grace Wang[1] and Piercarlo Sarzi-Puttini[2]. [1]Jazz Pharmaceuticals, Inc., [2]L. Sacco University Hospital, Milano, Italy, [3]Osteoporosis Medical Center, Beverly Hills, CA, [4]Pacific Rheumatology Associates, Inc., Renton, WA

Background: Fibromyalgia (FM) is characterized by chronic widespread pain as well as sleep disturbance and fatigue. Two pivotal clinical trials of sodium oxybate (SXB) demonstrated that SXB significantly reduced pain and fatigue, and improved sleep relative to placebo. This analysis further evaluates the effects of SXB on sleep and fatigue using pooled data from the two trials.

Methods: Both trials were of similar design (randomized, double-blind, placebo-controlled), length (14 weeks), and dosing regimens (placebo, SXB 4.5 g and 6 g equally divided between a dose at bedtime and another one 2.5 to 4 hours later). Baseline assessments were made after a washout period (up to 30 days) and prior to treatment initiation. Data from each treatment group were pooled (n=371 placebo; n=377 SXB 4.5 g; n=373 SXB 6 g) to evaluate the efficacy of SXB for pain (0–100 visual analogue scale [VAS]), fatigue (0–100 VAS), sleep disturbances (Jenkins Sleep Scale [JSS]; a validated, 4-item, self-report questionnaire for sleep disturbances), and effects of excessive daytime sleepiness on daily functioning (Functional Outcomes of Sleep Questionnaire [FOSQ]; a patient-report questionnaire); last observation carried forward was used for missing data.

Results: Demographics of the pooled patients are consistent with the FM population (90.4% female, and 91.2% white, median age 48.0 years). Mean baseline pain, fatigue, sleep disturbance, and FOSQ scores were also similar to the individual studies and consistent with significant impairment. The proportions of patients who achieved 30% and 50% reductions in pain were significantly greater with SXB than placebo (p<0.001). Least squares mean changes from baseline in fatigue VAS showed significant reductions with both SXB doses beginning at Week 1 that were maintained over the duration of treatment and were significantly greater than placebo at each weekly assessment (p<0.001). At 14 weeks, changes from baseline in fatigue VAS were −25.3 and −28.0 for SXB 4.5 g and 6 g, respectively, compared with −15.5 for placebo. SXB resulted in reduction in sleep disturbances at Week 14 as indicated by a significant overall treatment effect (p<0.001) and pairwise comparisons with placebo (p<0.001 for both SXB groups) on the JSS total score; least squares mean changes at Week 14 were −5.4 and −6.0 for the SXB 4.5 g and 6 g groups, respectively, compared with −2.9 for placebo. Similarly, treatment effects on functioning related to daytime sleepiness and tiredness at Week 14 were observed for the FOSQ, with least squares mean changes (improvement) from baseline of 2.2 for both SXB groups compared with 1.3 for placebo (both p≤0.001). The most common adverse event was headache, 22.9%, 18.4%, and 15.1% in the pooled SXB

6 g, SXB 4.5 g, and placebo groups, respectively. Adverse events with an incidence >5% in all SXB treated patients and twice the rate in placebo were nausea, dizziness, vomiting, and anxiety.

Conclusions: This pooled analysis of two pivotal clinical trials supports the efficacy of SXB. SXB significantly reduced pain and fatigue, improved sleep, and lessened the impact of daytime sleepiness on daily functioning.

Disclosure: S. L. Silverman: Eli Lilly and Company, 5, Jazz Pharmaceuticals, Inc., 2, Pfizer Inc, 5; **A. J. Holman:** Eli Lilly and Company, 8, Forest Laboratories, 8, Jazz Pharmaceuticals, Inc., 2, National Fibromyalgia Association, 2, National Fibromyalgia Research Association, 2; **B. Benson:** Jazz Pharmaceuticals, Inc., 1, 3; **S. Alvarez-Horine:** Jazz Pharmaceuticals, Inc., 1, 3; **Y. G. Wang:** Jazz Pharmaceuticals, Inc., 1, 3; **P. Sarzi-Puttini:** Jazz Pharmaceuticals, Inc., 2.

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SPECT Imaging of the Brain: Regional Cerebral Blood Flow before and after Treatment of Patients with Primary Fibromyalgia. Manal Osman[3], Osama Hajji[3], Ola Abdul Nasser[3], Ahmad Khodair[2] and Nashwa Al Sarraf[1]. [1]Internal Medicine Department, Faculty of Medicine, Cairo University, Cairo, Egypt, [2]Radiology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt, [3]Rheumatology and Rehabilitation Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Objective: Whether regional cerebral blood flow (rCBF) is affected by Duloxitine Hcl in Egyptian women with primary fibromyalgia (FM) and if it correlates with clinical findings.

Methodology: Thirty untreated women with FM were subjected to full history taking and thorough clinical examination(headache, anxiety, fatigue, sleep disturbances, wide spread pain, tender points). The patients (group I) and ten apparently healthy controls (group II) were studied with single photon emission computed tomography of the brain (brain SPECT) after IVI of Tc-99^{m} HMP[lrm]AO as a cerebral perfusion agent. The resting state (rCBF) was measured for the deep structures (thalamus and caudate nucleus) and cerebral cortices (anterior, lateral, posterior) of both sides. Fifteen patients(group Ia) received the conventional therapy of fibromyalgia and the other fifteen (group Ib) received Duloxitine Hcl (a potent serotonin and norepinephrine reuptake inhibitor which is approved by FDA) 60 mg daily for 3 months followed by measuring rCBF.

Results: There was a statistically highly significant lower (rCBF) in the thalamus and caudate nucleus in patients as compared to controls but no such difference in the anterior, lateral and posterior cerebral cortices. No significant difference clinically or radiologically was found comparing group Ia results before and after 12 weeks. There was a highly significant difference with fatigue and a significant difference as regard neck pain, headache, generalized body ache and morning stiffness when comparing group Ib results before and after 12 weeks. The rCBF to thalamus and caudate nucleus showed a high significant increase in group Ib after 3 months. There was a significant difference in number of tender points, the duration of morning stiffness as well as thalamic and caudate nucleus blood flow comparing the change in Ia and Ib groups.

Conclusions: The decrease of regional cerebral blood flow to thalamus and caudate nucleus in patients with primary FM may be the cause of their symptoms. Improvement of the symptoms by administration of duloxitine Hcl may be due to increase of blood flow to the thalamus and caudate nucleus.

Disclosure: M. Osman: None; **O. Hajji:** None; **O. Abdul Nasser:** None; **A. Khodair:** None; **N. Al Sarraf:** None.

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The Prevalence of Fibromyalgia in Patients with Chronic Hepatitis C Infection. Ausaf Mohammad[1], John J. Carey[4], Eoin R. Storan[2], Margaret Scarry[2], Mary B. Keane[2], Angela Moore[2], Ann Lyons[2], Maureen O' Grady[2], Catriona Minihan[2] and John M. Lee[3]. [1]Department of Hepatology and Rheumatology, Galway University Hospital, Ireland, [2]Galway University Hospital, [3]Hepatology Galway University Hospital, [4]Rheumatology Merlin Park University Hospital

Purpose: Chronic HCV infection is associated with rheumatologic conditions including arthritis and vasculitis. Previous studies have not specifically addressed the presence of fibromyalgia syndrome (FMS) in this population. In this study we assessed the prevalence of fibromyalgia in a cohort of subjects with chronic HCV and its relationship to subject demographics, viral characteristics and quality of life.

Methods: Cross-sectional study of a cohort of HCV infected individuals at our university hospital. Study was approved by local I.R.B. and all subjects gave written informed consent prior to participation. Patients with decompensated liver disease, concomitant autoimmune liver disease, arthritis, vasculitis, co-infection with hepatitis B or D, or HIV, end-stage renal failure, organ transplantation, cancer and those patients who were currently receiving anti-viral treatment were excluded. All subjects underwent a single interview including a fibromyalgia impact questionnaire, pain assessment measured on a 100-mm visual analogue scale (VAS) and the Stanford Health Assessment Questionnaire 20-Item Disability Scale (HAQ-DI). All patients underwent clinical examination including a standard assessment for fibromyalgia tender points. Additional details were recorded from the medical record including information about their HCV infection and its treatment, laboratory data including antibody profiles, other illnesses and medications.

Results: 185 patients attending the hepatology unit consented to participate. 110 (59%) were females with a mean age of 46.7 years. 106 (57%) subjects met criteria for the presence of FMS. Widespread pain and ≥11 tender points were present in all of the subjects with fibromyalgia, fatigue in 98 (92%), depression in 60 (57%), and arthralgia/ joint stiffness in 16 (15%). Among those with FMS mean pain score was 70 ± 11.78 and 36% reported some functional impairment on HAQ-DI (>0), with 17% reporting moderate-severe functional impairment (HAQ-DI ≥1.5). Compared to subjects who did not meet criteria for fibromyalgia, patients with fibromyalgia were more likely to be older, females, living alone, smokers, have a history of depression, had acquired HCV via a blood transfusion, and had HCV genotype-1(table 1, $p < 0.005$ for all categories).

Table 1. Comparing HCV infected subjects with and without FMS

	Chronic HCV patients with FMS (n = 106)	Chronic HCV patients without FMS (n = 79)	*t, p* value
Female	82 (77%)	28 (35%)	17.6; 0.001
age ≥ 45 years	80 (73%)	26 (33%)	17.9; 0.001
Wide spread pain	106 (100%)	20 (25%)	25.7; 0.001
Depression	60 (57%)	20 (25%)	15.3; 0.001
HCV acquisition via blood transfusion	65 (61%)	26 (33%)	15.0; 0.001
Genotype 1	82 (77%)	20 (25%)	20.4; 0.001

Conclusions: The prevalence of FMS was very high (57%) among subjects with HCV infection, one third of whom reported some degree of functional impairment. Further research is needed to better understand FMS in patients with HCV.

Disclosure: A. Mohammad: None; **J. J. Carey:** None; **E. R. Storan:** None; **M. Scarry:** None; **M. B. Keane:** None; **A. Moore:** None; **A. Lyons:** None; **M. O' Grady:** None; **C. Minihan:** None; **J. M. Lee:** None.

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The Prevalence of Fibromyalgia in Patients with Hereditary Hemochromatosis. Ausaf Mohammad[1], John J. Carey[4], Eoin R. Storan[2], Margaret Scarry[2], Mary B. Keane[2], Angela Moore[2], Ann Lyons[2], Maureen O' Grady[2], Catriona Minihan[2] and John M. Lee[3]. [1]Department of Hepatology and Rheumatology Galway University Hospital, Ireland, [2]Galway University Hospital, [3]Hepatology Galway University Hospital, [4]Rheumatology Merlin Park University Hospital

Introduction: Hereditary hemochromatosis (HH) is a well-defined syndrome characterized by the toxic accumulation of iron in parenchymal cells of liver, heart, and endocrine glands and is associated with inflammatory arthritis. Although studies have reported arthralgia and fatigue as common symptoms of this disorder little data exist of the presence of fibromyalgia syndrome (FMS) in this population.

Purpose: In this study we assessed the prevalence of fibromyalgia in a cohort of subjects with HH and it's relationship to subject demographics, HH status, and quality of life.

Methods: Cross-sectional study of a cohort of individuals with HH at our university hospital. Study was approved by local I.R.B. and all subjects gave informed consent. Patients with decompensated or concomitant autoimmune liver disease, arthritis, and vasculitis were excluded. All subjects underwent a single interview which included a fibromyalgia impact questionnaire, pain assessment measured on a 100-mm visual analogue scale (VAS) and disability assessment measured on the Stanford Health Assessment Questionnaire 20-Item Disability Scale (HAQ-DI) [10]. All patients underwent clinical examination by a trained physician which included assessment for arthritis and fibromyalgia tender points. Demographic data, details of HH and

laboratory data including autoantibody profiles and iron studies were recorded from the patients' medical record.

Results: 350 patients with HH attending the hepatology unit consented to participate, 230 (66%) of whom were males with a mean age of 43 years (range 27–70). 170 (41%) subjects met criteria for the presence of FMS. In subjects with fibromyalgia, fatigue and ≥11 tender points were present in all of the subjects, wide spread pain in 150 (88%), depression and arthralgia/joint stiffness in 70 (41%). Among those with FMS mean pain score was 69 ± 10.25 and 33% reported some functional impairment on HAQ-DI (>0), with 10% reporting moderate-severe functional impairment (HAQ-DI ≥1.5). Patients with fibromyalgia were more likely to be older, males with wide spread pain and history of depression, and had C282Y homozygosity in the HFE gene (table 1, $p < 0.005$ for all categories).

Table 1. Comparing HH subjects with and without FMS

	Patients with FMS (n = 170)	Patients without FMS (n = 180)	*p* value
Male	140 (82%)	90 (50%)	0.001
age ≥ 45 years	90 (53%)	50 (28%)	0.001
Wide spread pain	150 (88%)	40 (22%)	0.001
Depression	70 (41%)	30 (16%)	0.001
C282Y Homozygous Genotype	160 (94%)	110 (61%)	0.001

Conclusions: There is a high prevalence of FMS (41%) among subjects with HH, one third of whom showed some degree of functional impairment.

Disclosure: A. Mohammad: None; **J. J. Carey:** None; **E. R. Storan:** None; **M. Scarry:** None; **M. B. Keane:** None; **A. Moore:** None; **A. Lyons:** None; **M. O' Grady:** None; **C. Minihan:** None; **J. M. Lee:** None.

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Use of Path Analysis To Evaluate the Effects of Sodium Oxybate on Pain Reduction in Patients with Fibromyalgia. Fowzia Ibrahim[2], Chinglin Lai[1] and Ernest Choy[3]. [1]Jazz Pharmaceuticals, Inc., [2]King's College London, [3]Kings College Hospital, London, United Kingdom

Background: Although chronic widespread pain is the hallmark symptom of fibromyalgia (FM), sleep disturbances are also a characteristic of patients with FM. In clinical trials, sodium oxybate (SXB) has been shown to reduce pain and improve sleep. This study explores the relationship of the effects of SXB on these two outcomes.

Methods: All randomized patients in two placebo-controlled phase 3 clinical trials of SXB for the treatment of FM were included in the analyses. Ordinal linear regression models were used initially to explore the association between reduction in pain and other covariates. In addition, we perform path analysis to examine the direct and indirect treatment effect of SXB on reduction of pain and sleep disturbances. Pain reduction was based on changes from baseline in pain visual analogue scale (VAS) scores, and sleep improvement was based on changes from baseline in the Jenkins Sleep Scale (JSS) total score, with question 4 of the JSS, and the sleep question of the Fibromyalgia Impact Questionnaire (FIQ) used in sensitivity analyses.

Results: The analysis included 1,121 subjects with mean age of 46.8 (SD: 11.0) years. Ninety percent were female and 91% were White. Mean change in JSS score: [−2.76 (SD: 5.32); −5.44 (5.75); −6.05 (5.88)] and change in pain reduction: [−9.02 (21.75); −14.53(21.33); −18.37 (23.16)] for placebo, SXB 4.5 g and SXB 6 g, respectively. Multivariate linear regression shows that change in JSS score was associated with reduction in pain [Coefficient 95% CI: 1.50 (1.27, 1.72); p<0.001]. However, when the effects of other factors (tired upon awakening, stiffness, and fatigue) were adjusted for, the change in JSS score was not statically significant (0.01(−0.14, 0.17); p=0.86).

The path analysis showed the standardized direct (unmediated) effect of JSS score on pain reduction was 0.40, 95% CI (0.38, 0.48), indicating when JSS score changes by 1 standard deviation, pain intensity changes by 0.4 standard deviations in the same direction. In addition, change in fatigue is strongly associated with change in pain. The standardized direct effect of fatigue on pain was 0.84 (0.77, 0.85) and the indirect effect of JSS score mediated by fatigue is 0.35 ((0.31, 0.39); p=0.001). Since fatigue is highly correlated with stiffness (0.59) and tiredness upon awakening (0.67), adding these effects to the model showed the mediation effect of fatigue was reduced to 0.023 ((0.01, 0.04) p=0.002).

Conclusions: The results show that SXB reduces pain and improves sleep. However, the reduction in pain cannot solely be explained by improvement in sleep as measured by JSS, suggesting there is direct effect of SXB on pain reduction. For the component of reduction in pain mediated through improvement in sleep, it is mediated by reducing fatigue, tiredness upon awakening, and stiffness. This suggests that for SXB improvement in quality of sleep is associated with improvement in fatigue, tiredness upon awakening, and stiffness.

Disclosure: F. Ibrahim: Jazz Pharmaceuticals, Inc., 2; **C. Lai:** Jazz Pharmaceuticals, Inc., 1, 3; **E. Choy:** Abbott Laboratories, 2, 5, 8, Allergan, 2, 5, 8, Boehringer Ingelheim, 2, 5, 8, Celltech, 2, 5, 8, Chelsea Therapeutics, 2, 5, 8, Chugai, 2, 5, 8, Eli Lilly and Company, 2, 5, 8, GSK, 2, 5, 8, Jazz Pharmaceuticals, Inc., 2, 5, 8, Mer.

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Very Low Dosage (VLD) Bedtime Cyclobenzaprine (CBP) Reduces Cyclic Alternating Pattern (CAP) Rate Indices of EEG Sleep Instability and Improves Pre-Sleep Fatigue in Fibromyalgia Syndrome (FMS). Harvey Moldofsky[1], Herbert W. Harris[2], Tad Archambault[4], Terence Kwong[1] and Seth Lederman[3]. [1]Centre for Sleep & Chronobiology, Toronto, ON, Canada, [2]Krele Pharmaceuticals, Saddle Brook, NJ, [3]Krele Pharmaceuticals, New York, NY, [4]VirtuStat Ltd, North Wales, PA

Background: The importance of nonrestorative sleep in the pathophysiology of FMS suggests new treatments that improve sleep quality may improve daytime symptoms of fibromyalgia (FMS). We previously reported a randomized double-blind placebo-controlled 8 week study of very low dose (VLD) (≤4 mg) cyclobenzaprine (CBP) h.s. in 36 patients with FMS, which showed that bedtime CBP treatment (Tx) was associated with significant improvements in pre-sleep/p.m. fatigue, pain, and pain sensitivity (dolorimetry) with increased Stage 2 non-REM sleep (ref 1). Previous EEG sleep studies in FMS identified increased Cyclic Alternating Patterns (CAP) A2 & A3 in non-REM sleep, measures of sleep instability related to the symptoms of FMS (ref 2 & 3). We now report the effect of CBP Tx on nocturnal sleep EEG CAP and daytime fatigue in FMS.

Methods: CAP A2 & A3 rates are objective EEG sleep measures of sleep instability whereas CAP A1 rate is associated with sleep stability. To investigate whether the CAP A2 & A3 rates are decreased by Tx that target unrefreshing sleep in FMS patients, we retrospectively analyzed the polysomnography (PSG) data from a study in which bedtime CBP improved fatigue, pain and subjective sleep in a 8 week dose-escalating, double-blind, placebo-controlled randomized trial involving 36 FMS subjects. Each subject had screening and baseline PSGs (combined 2 pre-Tx PSGs) and 3 single nights of PSG during Tx after 2, 4 and 8 weeks. We analyzed whether subjects had an increased number of nights with decreased CAP(A2+A3) after the initiation of Tx by classifying the subjects nightly into responders and non-responders based on a CAP(A2+A3) rates normalized for the total CAP rate (A1+A2 +A3). Three placebo-Tx subjects, but no CBP-Tx subjects, withdrew from the study after initiation of Tx and without any nights of PSG. Consequently, the LOCF analysis imputed no improvement for these subjects.

Results: Initially we analyzed the study data for CAP(A2+A3)/(A1+A2+A3) over a range (10–50%) to identify cut-offs for responders by LOCF and OC (for ≥ 1 night improvement) and found that defining responders as ≤30% or ≤33% had the greatest difference between CBP and placebo-Tx and the smallest p-value (p<0.05). CAP response of ≥1 night of sleep EEG analyses that compared 2 pre-Tx drug free nights to 3 post-Tx PSG nights (defined by CAP(A2+A3)/(A1+A2+A3) ≤33% was analyzed for correlations with clinical improvement measures of patient-reported fatigue (pre-sleep/p.m. and post-sleep/a.m.); pain (p.m. and a.m.) and dolorimetry. Reduction in p.m. fatigue in CBP-Tx subjects is significantly correlated with CAP response (p = 0.0064), whereas p.m. fatigue was neither decreased nor correlated with responder status in placebo-Tx subjects.

Conclusions: 1. Normalized CAP A2 & A3 rates are novel physiological sleep EEG indices of nonrestorative sleep in FMS.

2. Very low dose CBP at bedtime decreases CAP A2 & A3 sleep EEG measures of nonrestorative sleep which correlates strongly with improvement in p.m. fatigue in FMS patients.

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Disclosure: H. Moldofsky: Krele Pharmaceuticals, 2; **H. W. Harris:** Krele Pharmaceuticals, 1, 3; **T. Archambault:** Krele Pharmaceuticals, 4, 5, VirtuStat Ltd., 4, 5; **T. Kwong:** Krele Pharmaceuticals, 2; **S. Lederman:** Krele Pharmaceuticals, 1, 9.

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Vibrotactile Analgesia Is Not Abnormal in Fibromyalgia Patients. Casey T. Goldman[2], Donald D. Price[2], Michael E. Robinson[2] and Roland Staud[1]. [1]Univ of Florida JHMHC, Gainesville, FL, [2]University of Florida

Vibrotactile analgesia formerly known as Gate-Control analgesia is dependent on input from myelinated A-beta nerve fibers during noxious stimuli. This type of analgesia can be elicited by vibrotactile stimulation either homotopically or heterotopically to a pain stimulus. Because multiple analgesic mechanisms including diffuse noxious inhibitory controls (DNIC) and spatial summation have been found to be abnormal in fibromyalgia (FM) patients and may contribute to the clinical pain of this chronic pain population, we hypothesized that another analgesic mechanism i.e. vibrotactile analgesia would also be deficient in FM patients.

Methods: 28 normal control (NC) and 29 FM subjects were enrolled into this protocol. Mean age was 30 (10.7) and 39 (11.1) years for NC and FM subjects, respectively. The overall clinical pain of FM subjects was 4.2 (2.1) VAS units. The NC were pain-free. A bio-thesiometer was used for application of 25 mA vibratory stimuli to the forearms. Sensitivity adjusted 10 sec heat stimuli (MEDOC) between 42 and 50 deg C were used to elicit heat pain ratings of 3.5 ± 0.5 VAS units (0–10) at the forearms of all subjects.

Results: When vibrotactile and noxious stimuli were simultaneously applied to the forearms NC and FM subjects experienced a 46% and 35% reduction in experimental pain intensity, respectively. These pain reductions were similar for homotopic and heterotopic stimulation. Vibrotactile analgesia was not statistically different between NC and FM subjects.

Conclusion: Vibrotactile stimulation of the skin resulted in substantial experimental pain reductions of FM patients. Thus not all types of endogenous analgesic mechanisms seem to be dysfunctional in FM patients. Furthermore, vibrotactile analgesia may represent a clinically relevant method of pain reduction for FM patients.

Disclosure: C. T. Goldman: None; **D. D. Price:** None; **M. E. Robinson:** None; **R. Staud:** None.

ACR Poster Session B

Genetics, Genomics and Proteomics in the Rheumatic Diseases

Tuesday, November 9, 2010, 9:00 AM–6:00 PM

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A Putative Functional Variant within the Ubiquitin-Associated Domain-Containing Protein 2 Gene (UBAC2) Is Associated with Increased Risk of Behcet's Disease. Amr H. Sawalha[7], Travis Hughes[6], Ajay Nadig[6], Vuslat Yilmaz[2], Kenan Aksu[1], Gokhan Keser[1], Ayse Cefle[3], Ayten Yazici[3], Andac Ergen[5], Haner Direskeneli[4] and Güher Saruhan-Direskeneli[2]. [1]Ege University, [2]Istanbul University, [3]Kocaeli University, [4]Marmara University, Istanbul, Turkey, [5]Okmeydani Research and Education Hospital, [6]OMRF, [7]University of Oklahoma, OMRF, VAMC, Oklahoma City, OK

Purpose: Using a genome-wide association scan and DNA pooling, we previously identified 5 novel genetic susceptibility loci for Behcet's disease. Herein, we fine-map the genetic effect within the UBAC2 gene, replicate this genetic association in an independent cohort of Behcet's disease patients and controls, and identify a functional polymorphism in this locus.

Methods: Two independent cohorts of Behcet's disease patients and controls from Turkey were studied. The discovery and replication cohorts included 152 patients and 172 controls, and 376 patients and 369 controls, respectively. Genotyping of 14 SNPs within and around UBAC2 was performed using TaqMan SNP genotyping assays.

Results: The genetic association between Behcet's disease and UBAC2 was established and confirmed in two independent cohorts of patients and controls (Meta-analysis OR= 2.05, meta-analysis P= $1.75\times10-7$). Haplotype analysis identified both a disease risk and a protective haplotype (P= 0.00014 and 0.0075, respectively). Using conditional haplotype analysis we identified that the SNP rs7999348 (A/G) within UBAC2 is the most likely SNP to explain the genetic effect in this locus. Indeed, we demonstrate that rs7999348 is a putative functional SNP that results in increased mRNA expression of a UBAC2 transcript variant in PBMCs of individuals homozygous for the Behcet's disease-associated "G" allele.

Conclusion: We establish and confirm the genetic association between UBAC2 and Behcet's disease in two independent cohorts of patients and controls. Fine mapping of this genetic effect and conditional analysis followed by functional studies identified the minor allele in rs7999348 as a disease-risk allele that alters UBAC2 expression.

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A Role for PACE4 in Pain in Mice and Humans: Pain Phenotype of a PACE4 Null Mutant and Genetic Association with Knee Osteoarthritis Pain. Anne-Marie M. Malfait[6], Albert B. Seymour[5], Ana M. Valdes[4], Linda S. Wood[5], Kathryn Durham[5], Micky Tortorella[3], Nigel K. Arden[8], Frances L. Vaughn[7], Paul E. Leaverton[7], Deborah J. Hart[4], Robert E. Sorge[1], Susana G. Sotocinal[2], Ara Schorscher-Petcu[1] and Jeffrey S. Mogil[1]. [1]Dept of Psychology and Alan Edwards Centre for Research on Pain, McGill University, Montreal, QC, Canada, [2]Dept of Psychology and Alan Edwards Centre for Research on Pain, McGill University, [3]Guangzhou Institute of Biomedical Health, Guangzhou, China, [4]King's College London, London, United Kingdom, [5]Pfizer Global Research and Development, Cambridge, MA, [6]Rush University Medical Center, Chicago, IL, [7]The Arthritis Research Institute of America, Clearwater, FL, [8]University of Oxford, Oxford, United Kingdom

Background: PACE4 is a member of the proprotein convertase family of serine proteases essential for the proteolytic maturation of a wide variety of proteins, including growth factors, hormones, and zymogens. We recently reported that PACE4 activates the aggrecanases, ADAMTS-4 and ADAMTS-5, in human osteoarthritic (OA) cartilage. The aim of the current study was to assess if genetic variants in the PACE4 gene are implicated in the risk for knee OA.

Methods and Subjects: The rs900414 single nucleotide polymorphism (SNP) in the PACE4 gene (*PCSK6*) was genotyped in three independent cohorts ("Discovery": 508 symptomatic knee OA cases, 159 asymptomatic knee OA, and 276 controls; "Clearwater": 85 symptomatic and 92 asymptomatic knee OA cases; and "Chingford" 62 symptomatic, 157 asymptomatic knee OA cases, and 527 controls). In follow-up to the human findings, PACE4 KO mice and wildtype littermates (C57BL/6) were tested on a battery of algesiometric assays, including mechanical and thermal hypersensitivity in response to intraplantar administration of substance P (SP) (2.5–20 μg), and for pain behavior in response to intrathecal SP (5–45 ng) or in response to intraperitoneal injection of 0.6% acetic acid.

Results: The minor allele at rs900414 (allele frequency 32%) was found to be significantly associated with symptomatic OA in the discovery samples and to be consistently increased among asymptomatic OA cases compared to symptomatic knee OA in all three cohorts. A fixed-effects meta-analysis yielded OR=1.34 (95% CI 1.09 –1.64) p=0.005 (Figure 1) and no between-study hetereogeneity was observed (I^2=0%). PACE4 KO mice displayed normal baseline sensitivity to thermal and mechanical stimuli as assessed by paw withdrawal, von Frey, tail-clip, hot-plate and tail-withdrawal tests. However, PACE4 KO mice developed significantly less thermal and mechanical hypersensitivity in response to intraplantar injection of SP. In addition, intrathecal injection of substance P resulted in a dose-dependent induction of pain behaviors (scratching, biting and licking) in wildtype but not in PACE4 KO mice. Moreover, compared to wildtypes, PACE4 KO mice showed >50% less pain behavior in the acetic acid writhing test.

Conclusions: These results suggest that the rs900414 SNP in the human PACE4 gene is strongly associated with protection against pain in knee OA. Studies in PACE4 KO mice further implicate PACE4 in pain.

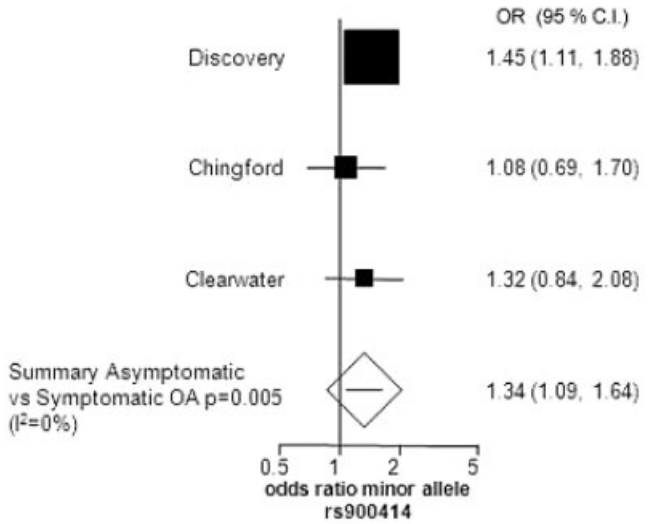

Figure 1. Forest plot showing study specific effect size estimates and summary odds ratio for the association between the PACE4 SNP rs900414 and risk of asymptomatic OA vs symptomatic OA.

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Analysis of the Influence of PTPN22 Gene Polymorphisms in Systemic Sclerosis. Lina Marcela Diaz-Gallo[7], Pravitt Gourh[27], Jasper Broen[4], Carmen Simeón[16], Vicent Fonollosa[16], Norberto Ortego-Centeno[13], M. C. Vonk[4], Marieke Coenen[5], Gabriela Riemekasten[2], Nicolas Hunzelmann[1], Roger Hesselstrand[3], Filemon K. Tan[26], Sandeep K. Agarwal[26], John D. Reveille[26], Shervin Assassi[26], Francisco J. García-Hernandez[17], Patricia Carreira[18], Maria Teresa Camps[12], Antonio Fernandez-Nebro[19], Paloma Garcia de la Peña[23], R. Rios[13], T. Nearney[30], D. Hilda[28], Miguel Angel González-Gay[22], Paolo Airo[25], Lorenzo Beretta[8], Raffaella Scorza[8], Ariane Herrick[10], Jane Worthington[9], Ana Pros[21], Inmaculada Gómez-Gracia[24], Luis Trapiella[15], Gerard Espinosa[14], Ivan Castellvi[20], Torsten Witte[6], Filip De Keyser[29], Marie Vanthuyne[11], Maureen D. Mayes[26], Timothy R. D.J. Radstake[4], Frank C. Arnett[26], Javier Martin[7] and Blanca Rueda[7]. [1]Department of Dermatology, University of Cologne, Germany, [2]Department of Rheumatology and Clinical Immunology, Charité University Hospital, Berlin, [3]Department of Rheumatology, Lund University Hospital, Lund, Sweden, [4]Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, [5]Departmentof Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, [6]Hannover Medical School, Hannover, Germany, [7]Instituto de Parasitología y Biomedicina Lopez-Neyra CSIC, Granada, Spain, [8]Referral Center for Systemic Autoimmune Diseases, University of Milan, Milan, Italy, [9]Rheumatic Diseases Centre, University of Manchester, Salford Royal NHS Foundatin Trust, UK, [10]Rheumatic Diseases Centre, University of Manchester, Salford Royal NHS Foundation Trust, UK, [11]Rheumatology Department, Universite Catholique de Louvain, [12]Servicio de Medicina Interna, Hospital Carlos Haya, Málaga, Spain, [13]Servicio de Medicina Interna, Hospital Clinico Universitario, Granada, Spain, [14]Servicio de Medicina Interna, Hospital Clinico, Barcelona, Spain, [15]Servicio de Medicina Interna, Hospital Universitario Central de Asturias, Oviedo, Spain, [16]Servicio de Medicina Interna, Hospital Valle de Hebron, Barcelona, Spain, [17]Servicio de Medicina Interna. Hospital Virgen del Rocio, Sevilla, Spain, [18]Servicio de Reumatología, Hospital 12 de Octubre, Madrid, Spain, [19]Servicio de Reumatología, Hospital Carlos Haya, Málaga, Spain, [20]Servicio de Reumatología, Hospital de Sant Pau, Barcelona, Spain, [21]Servicio de Reumatología, Hospital del Mar, Barcelona, Spain, [22]Servicio de Reumatología, Hospital Marques de Valdecillas, Santander, Spain, [23]Servicio de Reumatología, Hospital Ramon y Cajal, Madrid, Spain, [24]Servicio de Reumatología. Hospital Reina Sofía, Córdoba, Spain, [25]Servizio di Reumatologia ed Immunologia Clinica Spedali Civili, Brescia, Italy, [26]The University of Texas Health Science Center at Houston Medical School, Department of Internal Medicine, Division of Rheumatology and Clinical Immunogenetics, [27]The University of Texas Health Science Center at Houston Medical School, Department of Internal Medicine, Division of Rheumatology and Clinical Immunogenetics., [28]The University of Texas Health Science Center at San Antonio, San Antonio, TX, [29]University of Ghent, Belgium, [30]University of Texas Medical Branch at Galveston, Galveston, TX

Objective: Two functional single nucleotide polymorphisms (SNPs) in the PTPN22 gene (R620W, C1858T, rs24746601; and R263Q, G788A, rs33996649) have been previously associated with autoimmune diseases. The aim of the present study was to investigate the role of the R263Q SNP for the first time and to re-evaluate the role of the R620W PTPN22 polymorphism in the genetic predisposition to systemic sclerosis (SSc) susceptibility and clinical phenotypes.

Methods: A total of 3422 SSc patients (2020 with limited cutaneous SSc (lcSSc) and 1208 with diffuse cutaneous SSc (dcSSc)) and 3638 healthy controls from an initial case-control set of Spanish Caucasian ancestry, as well as seven independent replication cohorts of Caucasian ancestry (from Belgium, England, Germany, Italy, the Netherlands, USA and Sweden), were included in our study. Genotyping was performed using the TaqMan allelic discrimination assay for both the rs33996649 and the rs2476601 PTPN22 polymorphisms. A meta-analysis was then performed to test the overall effect of these PTPN22 gene polymorphisms in SSc.

Results: We observed evidence of association of the rs2476601 T allele with SSc susceptibility in the meta-analysis results (P=0.01 pooled, OR=1.15, 95% CI 1.03–1.28). Moreover, the rs2476601 T allele is significantly associated with anti-centromere (ACA) positive status (P=0.01 pooled, OR=1.22, 95% CI 1.05–1.42). Although we found that the rs33996649 A allele was significantly associated with SSc in the Spanish population (P=0.02, OR=0.58, 95% CI 0.36–0.92), this association was not confirmed in the meta-analysis (P=0.36 pooled, OR=0.89, 95% CI 0.72–1.1).

Conclusion: Our study suggests that the PTPN22 R620W polymorphism influences SSc genetic susceptibility but that the novel R263Q genetic variant does not. Moreover, our data strengthen the evidence that the R620W mutation is a common risk factor in autoimmune diseases.

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BLK Is Expressed in Human Peripheral T Cells and Thymocytes and Regulates CD4+ T Cell Numbers in Cord Blood. Kim R. Simpfendorfer[1], Lina Olsson[2], Nataly Manjarraz-Orduno[2], Houman Khalili[2], Annette T. Lee[2] and Peter K. Gregersen[1]. [1]Feinstein Institute for Medical Research, Manhasset, NY, [2]Feinstein Institute for Medical Research

Background: B-lymphocyte kinase (BLK) is an intracellular tyrosine kinase previously presumed to exert its major funtion in B cells. SNP variants in the 5′UTR/ promoter region of *Blk* lie on a common haplotype that is associated with both rheumatoid arthritis and lupus. In humans the functional affect of *Blk* risk alleles to disease susceptibility is yet to be elucidated. The risk haplotype has been associated with lowered mRNA expression of *Blk* in human B cell lines. In mice, *Blk* expression is reportedly restricted to B cells, yet *Blk* knockout animals fail to exhibit a phenotype. Interestingly, both naïve and memory B cells fail to show allelic imbalance for *Blk* in humans, and while B cell activation lowers the expression of *Blk*, the risk allele shows no difference in rates of downregulation. Therefore, it is possible that in humans the influence of BLK on autoimmunity may be mediated at a particular stage of B cell differentiation, or by a non-B cell compartment. Recently, our laboratory demonstrated allelic imbalance of *Blk* in peripheral blood $CD4^+$ T cells.

Analytical procedures and results: We examined the influence of *Blk* genotypes on BLK expression and the distribution of T and B cell populations in human umbilical cord blood, peripheral blood and thymus. Western blot and quantitative RT-PCR was used to examine BLK expression and flow cytometry was performed to compare immune cell populations.

Results: We found that BLK is expressed in thymocytes and purified CD4+ T cells in humans at both the mRNA and protein level, with higher expression in the thymus than in mature peripheral blood T cells. Furthermore, similar to human B cell lines, the *Blk* risk haplotype exhibits evidence of lower expression in both T cells and human thymus. In healthy individuals homozygous for the *Blk* risk allele (A/A) there is a significantly greater

proportion of CD4+ T cells than in individuals homzygous for the protective allele (T/T).

Conclusions: These data suggest that the causative *Blk* allele may play a role in disease pathogenesis by its action in CD4+ T cells as opposed to, or in addition to, B cells. Future studies will examine mRNA expression of Blk, FoxP3 and cytokine expression in CD4+ T cells and phosphorylation of signalling molecules in UCB and thymus samples to further dissect the role of BLK in CD4+ T cell numbers and function.

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Epigenetic Studies Characteristic of Muscle Biopsies (MBx) from Untreated Children with Juvenile Myositis (JM). Lauren M. Pachman, Min Wang, Hehuang Xie, Peter Hendrickson, Sheela Shrestha and Gabrielle Morgan. Children's Memorial Research Center, Chicago, IL

Background: Previous Affymetrix array-based gene expression studies of muscle biopsies (MBx) from children with definite/probable juvenile dermatomyositis (JDM) showed that, despite a florid display of IFN-α induced genes, patients with a longer duration of untreated disease (DUD) >2 months had a marked upregulation of genes related to vascular remodeling compared with muscle from JDM with a DUD of 2 months or less (Chen Y-W, Duration of chronic inflammation alters gene expression in muscle from untreated girls with juvenile dermatomyositis, BMC Immunol. 2008 Jul 31;9:43).

Objective: To profile the methylation patterns in a cohort of children with JDM in order to determine: 1) the impact of methylation alterations in JDM, and 2) the association of methylation profiles with the chronicity of the inflammatory response as determined by DUD.

Materials and Methods: DNA from diagnostic MBx from 20 white girls and boys (mean age = 6.4 ± 3.5 yrs) with definite/probable JDM were used for this study: five with DUD ≤2 mos; 15 with DUD >2 mos at MBx were compared with four age-, gender- and race-matched controls. The DNA was tested using the Illumina Methylation27 BeadChip for genome-wide methylation profiling and further analyzed with GenomeStudio Data Analysis Software. Bisulfite pyrosequencing confirmed DNA methylation from 10 matched controls and 71 children with a spectrum of juvenile myositis (56 JDM, 7 overlap, 5 juvenile polymyositis [JPM], and 3 other). The patient population (50/71 girls, mean age 7.6 ± 4.1 yrs) included 41 white, 14 Hispanic and 16 others. Among the 71 patients, 54 of them had DUD ≥2 mos untreated symptoms.

Results: In the first part of this study, 20 untreated JDMs displayed distinct methylation profiles from the four age-, gender-, and race-matched controls. Twenty-two genes showed significant differential methylation, including WT1 and the transcriptional regulation genes HOXC11, HOXD4, and EMX2. Specific pyrosequencing studies confirmed the Illumina methylation profiles for both hypo and hypermethylation responses respectively. Further investigation of WT1 methylation status in 71 JDM muscle samples showed no significant difference in methylation within JDM samples with respect to the specific JDM diagnosis vs other forms of JM, DUD, race, age at MBx, TNF-α-308 A allele, or treatment status at MBx.

Conclusions: Epigenetic studies of untreated JDM muscle showed specific patterns of methylation alteration, including WT1, which targets Bcl2, a critical factor in apoptosis. Unlike the gene expression and microRNA expression studies of JDM diagnostic muscle biopsies, disease chronicity, as measured by DUD, does not appear to alter the DNA methylation profiles.

Speculation: We speculate that further epigenetic studies will be highly informative, suggesting new concepts concerning the pathophysiology of JDM.

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Functional Change of 5-Aminoimidazole-4-Carboxamide Ribonucleotide Formyltransferase in Dermal Fibroblasts from Methotrexate-Sensitive and Resistant Mice. Xin You[2], Bruce N. Cronstein[2], Adrienne Williams[2] and Thierry Dervieux[1]. [1]Cypress Pharmaceuticals, [2]NYU

Background: Methotrexate (MTX) has been widely used in the treatment of RA but it is effective in only 60% of patients and its mechanism is complex. To date, the adenosine-mediated anti-inflammatory effect of MTX is best supported by the in vitro, in vivo, and clinical data. Pharmacogenetic studies indicate that genetic polymorphisms in adenosine pathway enzymes are associated with good response to MTX therapy in RA and animal experiments showed that MTX suppressed inflammation in air pouches of C57Bl/6 and BALBc, but not DBA/1J mice. To investigate the mechanism for genetically based resistance to the anti-inflammatory effects of MTX, functional change of a critical enzyme in MTX metabolism and the adenosine pathway, 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase (AICAR TF) was measured.

Methods: Dermal Fibroblasts (DF) from BALBc and DBA/1J mice were cultured from skin. Following MTX incubation with DFs, AICAR TF activity before and after MTX treatment was analyzed after preparation of (6*R*,6*S*)-10-formyltetrahydrofolate from 5,10-Methenyltetrahydrofolate. Protein concentration was determined by the Bradford protein assay. AICARFT activity was monitored by the formation of FHat *A* for 4 min using a Perkin-Elmer Lambda2 spectrophotometer. In addition, MTX polyglumate (pg) concentration was measured and AICAR TF mRNA was quantited by real time (RT) PCR.

Results: *In silico* analysis of the sequence of folyl polyglutamate synthase and AICAR TF indicate differing haplotypes of the enzymes in BALB/c and DBA1J mice. MTX treatment inhibited AICAR TF activity in DF from BALBc mouse in a dose-dependent manner (2.61 nmole/μg.min, 1.00 nmole/μg.min, and 0.9 nmole/μg.min at the dose of MTX 0, 10-7M, and 10-6M, respectively). Seventy percent decrease was observed at MTX 10-6M. AICAR TF activity was not reduced in DF from DBA1J mouse by MTX, and even increased after hydrogen peroxide stimulation with MTX (1.98 nmol/μg.min, 2.78 nmol/μg.min, and 3.83 nmol/μg.min at the dose of MTX 0, 10-7M, and 10-6M, respectively). The cellular concentration of MTXPG in BALBc fibroblasts is more than 2-fold greater than that observed in DBA1J fibroblasts at MTX 10-6M. There is no significant difference in AICAR TF mRNA in DFs between BALBc and DBA1J mice.

Conclusions: Genetic polymorphisms of the critical enzymes involved in MTX metabolism and the adenosine pathway contribute to the different responses to MTX in the treatment of Rheumatoid Arthritis.

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Functional Polymorphisms in the Inhibitory FCGR2B Associate with Efficacy of IVIG Treatment Response among Patients with Kawasaki Disease. Sadeep Shrestha[2], Howard W. Wiener[1], Aditi Shendre[1], Richard A. Kaslow[1], Aaron K. Olson[3], Mary Beth Lee[3], Jeffrey C. Edberg[4] and Michael Portman[3]. [1]Department of Epidemiology, University of Alabama at Birmingham, [2]Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, [3]Department of Pediatrics, University of Washington, Seattle Children's Hospital, [4]Division of Clinical Immunology and Rheumatology, Department of Medicine, University of Alabama at Birmingham

Background: Intravenous immunoglobulin (IVIG) is the principal treatment for Kawasaki disease (KD). Approximately 20% of KD patients in US are refractory to IVIG, and display higher coronary artery disease and aneurysm rates than those non-refractory. Studies in animal model systems have demonstrated a requirement for expression of the inhibitory Fcγ receptor FCGR2B in IVIG therapeutic responses. We hypothesized that naturally occurring functional SNP variants in the human FCGR2B gene would influence efficacy of IVIG treatment in patients with KD.

Methods: We examined three well-characterized and functionally relevant SNPs in the inhibitory FCGR2B gene among 197 patients (104 European-American (EA), 47 Asians, 46 Other) with KD (based on criteria recommended by the American Heart Association) that had been treated with IVIG as standard of care. Among these patients, 56 were defined as non-responders (persistent fever (temperature >38°C) at >36 hours from the initiation of IVIG infusion or recurrent fever at >36 hours after completion of the initial IVIG infusion) and 141 as responders. SNPs chosen for study are 2 promoter variants at −120 and −386 that alter transcription factor binding and quantitative gene expression and a non-synonymous SNP in the transmembrane region of the protein that alters lipid domain association and quantitative inhibitory potential. Genotyping was performed by Pyrosequenc-

ing. Race and ethnicity were genetically determined using Principle component analysis with 162 ancestry informative markers.

Results: Significant association between all of the functional FCGR2B variants and IVIG response were observed in EA patients. Both the more active promoter variants (−120A/−386C, OR = 4.46 [1.30–15.3], p=0.01/ OR=4.38 [1.28–15.1], p=0.01 respectively) and the more functionally active non-synonymous variant in the transmembrane domain (+775T, OR = 2.38 [1.00–5.88], p=0.05) were positively associated with IVIG response. The 2 promoter variants are in complete linkage disequilibrium and are not independent effects. Because of lower allele frequency and smaller sample size in the other populations, we did not have sufficient power to demonstrate associations between FCGR2B variants and IVIG responses.

Conclusions: Our data are the first to demonstrate a genetic basis in humans for IVIG responses in KD. The known functional consequences of the variants in FCGR2B that associate with IVIG response result in high receptor expression and function and thus are biological plausible and consistent with murine model studies demonstrating a requirement for FCGR2B in IVIG efficacy. Replication of these findings could suggest a role for screening of patients for FCGR2B genotypes prior to treatment.

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Functional Variants in the *Pre-B Cell Colony Enhancing Factor* Gene Are Associated with Systemic Sclerosis Susceptibility and the Clinical Hallmark Pulmonary Arterial Hypertension. Jasper Broen[9], Pravitt Gourh[7], Madelon Vonk[9], Lorenzo Beretta[10], Blanca Rueda[8], Lenny Geurts-van Bon[9], Christel Brouwer[9], Roger Hesselstrand[5], Ariane Herrick[11], Jane Worthington[11], Nico Hunzelmann[2], Chris Denton[1], Carmen Fonseca[1], Gabriela Riemekasten[6], Hans Kiener[4], Raffaella Scorza[10], C. Simeon[14], N. Ortego-Centeno[13], M. Gonzalez-Gay[12], Paolo Airo'[15], Marieke Coenen[3], Maureen Mayes[7], Diego Kyburz[16], Frank Arnett[7], Javier Martin[8] and Timothy Radstake[9]. [1]Centre for Rheumatology, Royal Free and University College Medical School, London, United Kingdom, [2]Department of Dermatology, University of Cologne, Germany, [3]Department of Human Genetics, Radboud University Nijmegen Medical Center, The Netherlands, [4]Department of Internal Medicine, Division of Rheumatology, University of Vienna, Austria, [5]Department of Rheumatology, Lund University Hospital, S-221 85 Lund, Sweden, [6]Dept of Rheumatology and Clinical Immunology, Charité University Hospital and German Rheumatism Research Centre, a Leibniz Institute, [7]Division of Rheumatology and Clinical Immunogenetics, Department of Internal Medicine, University of Texas Health Science Center at Houston (UTHSC-H), Houston, TX, [8]Instituto de Parasitología y Biomedicina, CSIC, Granada, Spain, [9]Radboud University Medical Center, Department of Rheumatology, Nijmegen, The Netherlands, [10]Referral Center for Systemic Autoimmune Diseases, University of Milan, Italy, [11]Rheumatic Diseases Centre, University of Manchester, Salford Royal NHS Foundation Trust, UK, [12]Servicio de Medicina Interna, Hospital Clinico Universitario, Granada, Spain., [13]Servicio de Medicina Interna, Hospital Universitario Central de Asturias, Oviedo, Spain., [14]Servicio de Medinina Interna, Hospital Valle de Hebron, Barcelona, Spain, [15]Servizio di Reumatologia ed Immunologia Clinica, Spedali Civili, Brescia, Italia., [16]University Hospital Zurich Div. of Rheumatology Zurich, Switzerland.

Systemic sclerosis (SSc) is a rare autoimmune disorder, characterized by severe vasculopathy and fibrosis of the skin and internal organs. The most severe complication is pulmonary artery hypertension (PAH). Several variants in immune regulatory genes have already been implicated in SSc. The *PBEF* gene plays an important role in immune modulation, and two polymorphisms in the promoterregion, namely *PBEF −1001T>G* (rs9770242) and *PBEF −1543C>T* influence the predisposition to pulmonary disease. For this reason we investigated the role of these two polymorphisms in the genetic predisposition to systemic sclerosis (SSc) and clinical phenotype susceptibility in 2737 SSc patients and 1913 healthy controls. In two separate populations and in a meta-analysis, the combined *PBEF −1543CC −1001TT genotype*, was found associated with SSc susceptibility (P=0.009 OR 1.20 (95%CI: 1.05–1.37). In addition, these subjects showed an increased decline in forced vital capacity (FVC) over 15 years (P=0.02) (RR 1.64, 95% CI: 1.02–2.64) and a higher PBEF serum concentration (P<0.01), compared to carriers of the minor alleles. On the other hand, patients with genotype *PBEF -1001TT* were at lower risk for PAH development compared to the carriers with genotypes *PBEF −1001GG* and *PBEF −1001TG* (P<0.001) (RR 3.29, 95% CI: 1.52–7.12). These results reveal an important role for PBEF in the genetic predisposition to SSc and its clinical hallmark PAH.

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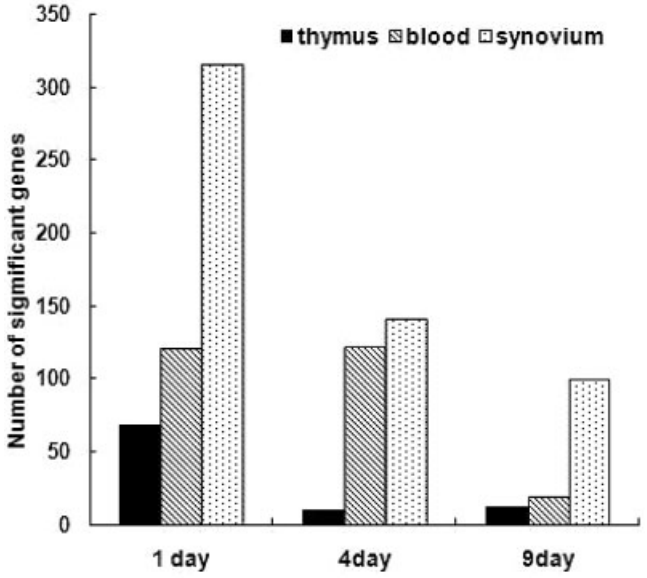
Gene Expression Profile at the Initial Phase of Collagen-Induced Arthritis in the Synovium, Peripheral Blood and Thymus. Seung-Cheol Shim[2], Mi-Kyung Lim[1] and Dong-Hyuk Sheen[1]. [1]Eulji University, Daejeon, Korea, Republic of, [2]Eulji University, Daeejon, Korea, Republic of

Background: Current management strategies aim to detect rheumatoid arthritis (RA) at an early stage. Transcription profiling is applied in the search for biomarkers for detecting early stage disease. Peripheral blood T cells in RA show incomplete activation which is unclear whether this process occurs in the peripheral or central lymphoid organs. Eventhough gene profilings in several RA animal models have been reported previously, most of these studies were performed after active arthritis developed and only in the peripheral organs.

Objective: To explore gene expressions at the initial phase of collagen induced arthritis (CIA) before the arthritic features develop in the synovium, peripheral blood and thymus.

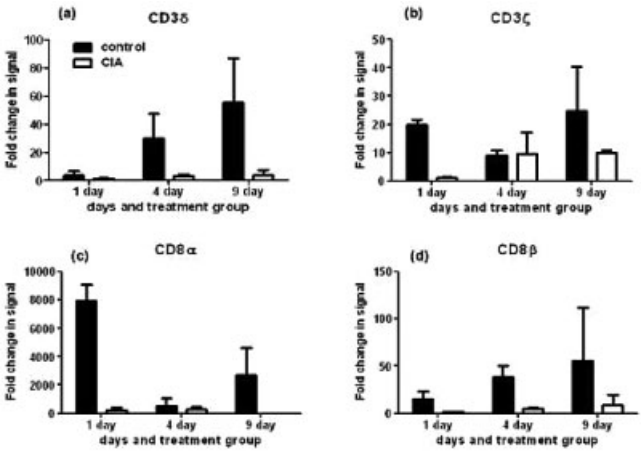
Methods: For gene expression analysis using cDNA microarray technology, samples of thymus, blood, and synovium were collected from CIA and control rats on days 0, 1, 4 and 9 after the first immunization. Labeled cRNA samples were hybridized to each Rat-12 expression bead array for 16–18 h at 58°C, according to the manufacturer's instructions (Illumina, Inc., San Diego, USA). Detection of array signal was carried out using Amersham fluorolink streptavidin-Cy3 (GE Healthcare Bio-Sciences, Little Chalfont, UK) following the bead array manual. Arrays were scanned with an Illumina bead array Reader confocal scanner according to the manufacturer's instructions. Array data export processing and analysis was performed using Illumina BeadStudio. We also performed real-time RT-PCR to validate our microarray findings.

Results: Of the 22,517 genes on the array, 1,243 genes were differentially expressed at least 2 fold in various organs of CIA compared to controls. Even on day 1, over 300 genes were differentially expressed in the synovium of CIA.



10% of the genes expressed differentially were immune-related genes in synovium and thymus, and 25% in blood. Among 20 genes related with T-cell mediated immunity, 9 genes were significantly down-regulated in the synovium of CIA compared to controls, which include cd3ζ, cd3δ, cd8α, cd8β. However, the expression levels of those genes showed no difference in the thymus and blood between CIA and controls.

The differential expressions of cd3ζ, cd3δ, cd8α, cd8β in CIA, as revealed by real-time RT-PCR, agreed well with the microarray data.



Conclusions: This study provides evidence that the most genes start to express differentially on day 1 after the first immunization in CIA. And the downregulation of cd3ζ, cd3δ, cd8α, cd8β occurs just in the synovium at the initial phase of CIA, which might play a role in the pathogenesis of CIA.

Disclosure: S.-C. Shim: None; **M.-K. Lim:** None; **D.-H. Sheen:** None.

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Genetic Variants Associated with Susceptibility to Knee Osteoarthritis: The Johnston County Osteoarthritis Project. Xiaodong Wu[3], Venkateswarlu Kondragunta[4], Jordan B. Renner[2], Gordon W. Duff[5], Kenneth S. Kornman[4] and Joanne M. Jordan[1]. [1]Chapel Hill, NC, [2]Department of Radiology and Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, [3]Interleukin Genetics, Inc., Waltham, MA, [4]Interleukin Genetics, Inc., [5]School of Medicine, University of Sheffield

Purpose: Factors that differentiate individuals who develop osteoarthritis (OA) from those who do not may be valuable in developing prevention strategies. Although several genetic variants have been associated with susceptibility to OA, most have not been replicated in adequately sized cohorts. We therefore sought to validate genetic variants predictive of OA susceptibility in a Caucasian patient sample in the United States, in a population-based study.

Method: Caucasian participants (N=1,173; 38% men; mean age=60 years) in the Johnston County OA Project were examined for susceptibility to radiographic knee OA in a cross-sectional analysis. Anterior-posterior standing knee radiographs were obtained with footmat positioning and read by a single musculoskeletal radiologist for Kellgren-Lawrence grade (K-L, 0–4). OA cases were defined as having KL>=2 in at least one knee. Non-OA controls were defined as having KL=0 in both knees. Genotypes of 37 single nucleotide polymorphisms (SNPs) in 16 genes, including gene variants previously shown to be associated with OA and variants in genes that are functionally implicated in OA, such as the proinflammatory IL-1 gene family, were determined using the single-nucleotide primer extension method. Logistic regression with adjustment for age, gender and body mass index was used to determine associations between gene polymorphisms and susceptibility to radiographic knee OA. Since this was not an exploratory analysis, we analyzed the data without correction for multiple comparisons, but also report the results of a permutation test for multiple comparisons. An association was considered a positive validation if the p-value after adjustment for age, gender and BMI <0.05 for the risk allele, genotype or haplotype previously reported to be associated with OA.

Results: Out of 16 genes tested, 6 were significantly associated with susceptibility to radiographic knee OA. These included ABCG2, GDF5, IL1R1, IL1RN, IL6 and VDR genes (table 1). VDR rs731236 also showed significance after correction for multiple comparisons.

Table 1. Genetic variants associated with susceptibility to radiographic knee OA.

Gene	SNP	Allele/ genotype	OR	95% CI (L)	95% CI (U)	P
GDF5	rs143383	C/C	0.57	0.36	0.91	0.018
VDR	rs1544410	T/*	1.51	1.07	2.13	0.020
IL6	rs1800797	A	1.38	1.09	1.74	0.008
ABCG2	rs2231142	A/*	0.64	0.42	0.97	0.036
IL1R1	rs2287047	T	0.74	0.56	0.97	0.029
IL1RN	rs380092	T/T	0.56	0.33	0.96	0.034
VDR	rs731236	C/*	1.69	1.19	2.39	0.003

Conclusion: This study validated several genetic markers for association with susceptibility to radiographic knee OA in a population-based study of Caucasians.

Disclosure: X. Wu: Interleukin Genetics, Inc., 1, 3; **V. Kondragunta:** Interleukin Genetics, Inc., 1, 3; **J. B. Renner:** None; **G. W. Duff:** Interleukin Genetics, Inc., 9; **K. S. Kornman:** Interleukin Genetics, Inc., 1, 3; **J. M. Jordan:** Interleukin Genetics, Inc., 5.

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HLA-DRB1*04 Is a Novel Fetal Susceptibility Allele in Congenital Heart Block. Therese Östberg[2], Stina Salomonsson[2], Bo Ding[4], Håkan Eliasson[4], Lars Alfredsson[4], Lars Klareskog[5], Anders Hamsten[2], Tomas Olsson[4], Leonid Padyukov[2], Tomas Axelsson[6], Swedish Congenital Heart Block Study Group[7], Fredrik Gadler[2], Anders Jonzon[6], Sven-Erik Sonesson[3], Ingrid Kockum[4] and Marie Wahren-Herlenius[1]. [1]Department of Medicine, Karolinska Institutet, Stockholm, [2]Department of Medicine, Karolinska Institutet, [3]Department of Women and Child Health, Karolinska Instituet, [4]Karolinska Institutet, [5]Karolinska University Hospital, Stockholm, Sweden, [6]Uppsala University, [7]www.combinesweden.se

Objective: Congenital heart block may develop in the fetus of Ro52 autoantibody positive women. The reported recurrence rate for autoantibody associated congenital heart block is however only 10–25%, indicating that other factors than maternal autoantibodies influence the disease development and fetal outcome. The most potent genetic influence on susceptibility to autoimmune diseases is the HLA locus, and as there is a strong and well-known HLA-DR*03 allele association with SLE, Sjögren's syndrome and production of Ro/SSA autoantibodies, we hypothesized that specific alleles of the HLA locus may render the fetus susceptible to congenital heart block induced by maternal autoantibodies.

Methods: Genotyping was performed for 561,490 SNPs in DNA from 348 individuals of 88 Swedish Caucasian families with a Ro/SSA autoantibody positive mother and with at least one case of congenital heart block (83 mothers and 72 fathers, 92 index cases and 101 unaffected siblings). Full HLA-A, -C and HLA-DRB1 allele typing was performed by SSP-PCR in 60 families with complete trios. Swedish Caucasian population-based healthy controls from the EIRA (n=1056) and PROCARDIS (n=654) studies were used in case-control association analysis. Genetic linkage was analyzed by transmission disequilibrium test (TDT).

Results: A case-control analysis between the index cases and population-based controls revealed an association of congenital heart block with 6 SNPs in the 6p21 MHC locus at a genome-wide significance of $p<5\times10-8$ (OR 2.57–3.12). In family-based TDT analysis of distinct MHC class I and II alleles we observed an association of the HLA-DR*04 allele with congenital heart block, and that this variant was significantly more often transmitted to children that developed congenital heart block (p=0.01). No difference in the transmission frequency of the DRB1*04 allele from mothers (maternal DRB1*04 allele frequency 7.6%) compared with fathers (paternal DRB1*04 allele frequency 20.8%) was observed. No other HLA-DRB1, -A or -C association with congenital heart block was found. The previously described HLA-DRB1*03 association in the mothers compared with controls was observed also in our cohort, and 79.7% of the mothers carried DRB1*03.

Conclusions: Our study identifies HLA-DRB1*04 as a novel fetal genetic variant that confers susceptibility to develop congenital heart block in response to exposure to Ro/SSA autoantibodies, and indicates equal maternal and paternal genetic influence on fetal susceptibility to maternal autoantibody exposure.

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IL13 Is a Risk Locus for Psoriatic Arthritis but Not Psoriasis Vulgaris. John Bowes[1], Pauline Ho[2], Salma Salah[1], Richard B. Warren[5], Eleanor Korendowych[7], Neil McHugh[7], Oliver FitzGerald[4], Jonathon Packham[3], Ann W. Morgan[6], Christopher E. M. Griffiths[5], Ian N. Bruce[2], Jane Worthington[1] and Anne Barton[2]. [1]Arthritis Research UK Epidemiology Unit, The University of Manchester, UK, [2]Arthritis Research UK Epidemiology Unit, The University of Manchester, UK; The Kellgren Centre for Rheumatology, Manchester, UK, [3]Arthritis Research UK, National Primary Care Centre, Keele University UK, [4]Department of Rheumatology, University College Dublin, Ireland, [5]Dermatological Sciences, The University of Manchester, UK., [6]NIHR-Leeds Musculoskeletal Biomedical Research Unit, University of Leeds, UK, [7]Royal National Hospital for Rheumatic Diseases

Background: Psoriasis vulgaris (PsV) is a chronic inflammatory skin disease in which up to 30% of subjects have additional joint involvement. This has led to psoriatic arthritis (PsA) being recognised clinically as a distinct entity. Both conditions are complex diseases influenced by environmental and genetic factors. All the currently known genetic risk factors are shared between the two conditions. The identification of genetic risk factors that could differentiate the two diseases would allow a better understanding of why some patients with PsV develop arthritis. Two recent PsV genome-wide association studies, both containing a significant proportion of PsA cases, identified an association to the Interleukin 13 (*IL13*) gene as a susceptibility risk factor. However further investigation of this effect in one study found it to be primarily restricted to those individuals with PsA, thus suggesting the discovery of a potential specific genetic risk factor for PsA. Given this intriguing evidence we have investigated association to this gene in large sample collections of PsA and PsV patient samples compared to a common set of healthy controls.

Methods: Two SNPs (rs20541 and rs1800925) mapping to the *IL13* gene were genotyped in 1057 PsA patients and 1136 PsV patients using the Sequenom genotyping platform. Control data for 5575 healthy individuals was available from the WTCCC2 genotyped on the Illumina Human 1M-Duo platform. Association tests, Hardy-Weinberg equilibrium (HWE), and linkage disequilibrium (LD) were performed using the PLINK software package. Additional analyses were performed in phenotypic subgroups of PsA (Type I or II psoriasis and seronegative for rheumatoid factor).

Results: Both SNPs were in HWE and found to be highly associated with susceptibility to PsA (rs1800925 ptrend = 6.1×10^{-5} OR = 1.33 CI 1.16:1.53, rs20541 ptrend = 8.0×10^{-4} OR = 1.27 CI 1.10:1.45), but neither was associated with PsV. LD between the SNPs, calculated in the control samples, was found to be low ($r^2 = 0.23$). Sub-phenotype analysis revealed that the two SNPs remained associated with PsA in patients with both type I and type II psoriasis.

Conclusions: This study confirms that the effect of *IL13* risk locus is specific for PsA, thus highlighting the first key biological pathway that differentiates PsA from PsV. The identification of markers that differentiate the two diseases raises the possibility in the future of allowing screening of PsV patients to identify those at risk of developing PsA.

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Major Differences among Proteomes of Macro-Vascular and Micro-Vascular Endothelial Cells: 2D-DIGE Approach. Hanadi Dib[1], Philippe Chafey[3], Guilhem Clary[3], Morgane Le Gall[3], Cedric Broussard[4], Luc Camoin[4], Christian Federici[3], Veronique Witko-Sarsat[3], Mathieu C. Tamby[3] and Luc Mouthon[2]. [1]INSERM 1016, Cochin Institute, Paris Descartes University, Paris, France, [2]INSERM 1016, Cochin Institute, Paris Descartes University, Paris, France, [3]INSERM 1016, Cochin Institute, Paris, France, [4]Proteomics Platform of Paris Descartes, Paris, France

Rationale: Progress on the isolation and culture of various endothelial cells (EC) has allowed comparison of their biochemical and physiologic properties. However, very few studies compared the proteomes of EC from different sources.

Objective: To compare proteomes of macro-vascular and micro-vascular EC.

Methods: Proteomes of human umbilical vein EC (HUVEC) and 2 sources of micro-vascular EC, human pulmonary (HMVEC-P) and dermal micro-vascular EC (HMVEC-D) from healthy Caucasian donors (4 in each group) were compared using two-dimension differential in gel electrophoresis (2D-DIGE) at pH ranges of 3–11 and 4–7 and mass spectrometry.

Results: Among the 2167+/−50 protein spots detected in pH 4–7 gels, 100 were differentially expressed between HUVEC and micro-vascular EC with a ratio ≥ 2 and a T-test ≤ 0.01. Sixty-three proteins were identified including fatty acid binding protein 4 and retinal dehydrogenase 1 that were over-expressed in micro-vascular EC at 235.7 and 5.8 average ratio, respectively. Ingenuity software analysis interestingly showed that numerous proteins over-expressed in micro-vascular EC are implicated in the retinoic acid pathway. Sixteen protein spots were differentially expressed between HMVEC-D and HMVEC-P with a ratio ≥ 2 and a T-test ≤ 0.01 in pH 4–7 gels and 9 were identified. In pH 3–11 gels, 41 protein spots were differentially expressed between HUVEC and HMVEC-D and HMVEC-P with a ratio ≥ 2 and for a T-test ≤ 0.01. Among these protein spots, 33 were identified. Four protein spots were differentially expressed between HMVEC-D and HMVEC-P with an average ratio ≥ 2 and for a T-test ≤ 0.01 and were identified, corresponding to cytoskeleton proteins or enzymes implicated in glycolysis.

Conclusion: Major differences were observed between proteomes of macro-vascular and micro-vascular EC. Some of the differentially expressed proteins might be of great importance in the homeostasis and pathophysiology of EC.

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mtDNA Haplogroups Define Two Phenotypes of Osteoarthritis (OA). Ignacio Rego-Pérez[4], Mercedes Fernández-Moreno[5], M. Deberg[1], Sonia Pértega[3], Carlos Fernández-López[5], Natividad Oreiro[5], Manuel Acasuso[2], Victoria Bonome-González[2], Y. Henrotin[1] and Francisco J. Blanco[5]. [1]Bone and Cartilage Res. Unit. Univ. of Liege, Liege, Belgium, [2]Centro de Salud Matogrande - SERGAS, A Coruña, Spain, [3]Epidemiology Unit. INIBIC-Complejo Hosp. Univ. A Coruna, A Coruna, Spain, [4]Osteoarticular and Aging Res. Lab. Rheumatology Div, INIBIC-Complejo Hosp, Univ. A Coruña, Coruña, Spain, [5]Osteoarticular and Aging Res. Lab. Rheumatology Div, INIBIC-Complejo Hosp, Univ. A Coruña, A Coruña, Spain

Background: Recent findings evidence that mitochondria mediate in the pathogenesis of the osteoarthritis (OA). Biomarkers are a promising tool to detect patients with OA preferably in an early stage of the disease. In this work we aim to assess a mitochondria-related phenotype in patients with OA.

Methods: We analyzed the determinations of serum levels of 12 OA-related biomarkers: MMP-1, MMP-3, MMP-13, MPO, Coll2-1 Coll2-1NO_2, C2C, CPII, hyaluronic acid, YKL-40, COMP and cathepsin K, in 48 OA patients and 52 healthy controls carrying the haplogroups H and J, to perform logistic regression models and receiver operating characteristic (ROC) curves that permit us to predict diagnosis of OA. This models also included clinical variables such as gender, age and smoking status.

Results: The MMP-13 was the only biomarker significantly increased in OA patients, when compared with healthy controls, in both mtDNA haplogroups H and J ($p<0.001$). Type II collagen biomarkers Coll2-1, Coll2-1NO_2, Coll2 ratio, C2C, CPII and C2C:CPII ratio were significantly increased in OA patients that carry the mtDNA haplogroup H when compared with OA carriers of the mtDNA haplogroup J ($p<0.01$ in all cases). The logistic regression model for diagnosis for carriers of the mtDNA haplogroup H showed that those biomarkers significantly associated with OA were hyaluronic acid and C2C:CPII; the area under the curve (AUC) of the ROC curve for this model was 0.926 (95% CI=0.857–0.995) and the optimal probability cutoff for discriminate between OA and healthy controls was 0.269, with a sensitivity of 96%, a specificity of 78%, and a positive likelihood ratio of 4.3. For carriers of the mtDNA haplogroup J, the logistic regresion model for diagnosis showed that those biomarkers significantly associated with OA were MMP-13, MMP-3 and C2C; the AUC for this model was 0.880 (95% CI=0.782–0.978), and the optimal probability cutoff for discriminate between OA patients and healthy controls was 0.271, with a sensitivity of 96%, a specificity of 68%, and a positive likelihood ratio of 3.

Conclusions: MMP-13 appears to be a good candidate biomarker for diagnosing OA. Some of the OA-related biomarkers clearly show a different profile depending on the mtDNA haplogroup. This permitted us to perform two models of haplogroup-based diagnoses of OA.

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Neurotransmitter Receptor Gene Polymorphisms Are Associated with Widespread Pain: Findings from the First Genome-Wide Association Study of Musculoskeletal Pain. Kate L. Holliday[3], Tuhina Neogi[2], David Felson[2], Ke Wang[1], Wendy Thomson[4] and John McBeth[4]. [1]Boston University School of Public Health, [2]Boston University School of Medicine, [3]University of Manchester, Manchester, United Kingdom, [4]University of Manchester

Background: Musculoskeletal pain disorders are prevalent with 10% of the general population reporting widespread pain. Heritability estimates for widespread pain are around 50% although the susceptibility loci have yet to be identified. The purpose of this study was to identify susceptibility loci by conducting the first genome-wide association study (GWAS) of widespread pain.

Methods: As part of the Framingham SHARe project, subjects from 3 generations were genotyped using Affymetrix 500k and 50k gene-focused SNP chips. Genotypes were called using the BRLMM algorithm. Samples were excluded for low call rate (<95%), excess heterozygosity and mendelian errors. SNPs were excluded for deviation from HWE ($p<10^{-6}$), low call rate (<97%), MAF<0.01 and mendelian errors (>100). Whole genome imputation was carried out using HapMap CEU data and MACH v1.0.15. Data on musculoskeletal pain was available for a subset of these subjects (n=3850) from 2 generations. The reporting of painful regions on a homunculus was used to classify cases with widespread pain (reporting pain in contra-lateral body quadrants above and below the waist and in the axial skeleton) and controls (reporting no pain). Generalised estimating equation regression analysis was used to perform a case-control GWAS analysis under an additive genetic model on autosomal SNPs with a MAF>0.03, while accounting for relatedness between subjects and using genomic control to adjust for population stratification in R.

Results: Imputation was conducted on 378,163 SNPs meeting quality control criteria providing 2,321,937 SNPs for analysis in 572 cases and 1587 controls. The genomic inflation factor was 1.02. Using a p-value cut off of 1×10^{-5}, we identified 52 SNPs in association with widespread pain which comprise 8 individual loci, many of which are strong candidate loci for susceptibility to widespread pain. In particular, an intronic SNP in the neurotransmitter receptor gene GABA B receptor 2 (*GABBR2*) was associated with an increased risk of having widespread pain (OR=1.37 (1.24, 1.51) $p=6.7 \times 10^{-6}$). A SNP 100 Kb downstream of another neurotransmitter receptor, glutamate receptor 2 (*GRIA2*), was also associated with an increased risk of having widespread pain (OR=1.54 (1.35, 1.73) $p=8.96 \times 10^{-6}$).

Conclusion: This study, the first GWAS of widespread pain, implicates a number of biologically relevant loci in neurotransmitter genes that are directly linked to pain pathways. Validation of these findings is now required in independent cohorts to ascertain the true impact of these loci on widespread pain susceptibility and is currently underway.

Disclosure: K. L. Holliday: None; **T. Neogi:** None; **D. Felson:** None; **K. Wang:** None; **W. Thomson:** None; **J. McBeth:** None.

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Pathogenesis of Idiopathic Recurrent Pericarditis and Role of the *TNFRSF1A* Gene Mutations. Luca Cantarini, Orso Maria Lucherini, Maria Giuseppina Brizi and Mauro Galeazzi. Unit of Rheumatology, University of Siena, Siena, Italy

Background: Recurrences develop in up to 20–50% of patients with acute pericarditis. Although many causes of pericarditis are well known, the etiology remains obscure in about 85% patients and it is therefore labelled as idiopathic. Recurrent pericarditis is common in familial Mediterranean fever (FMF), due to mutations in the *MEFV* gene, and tumor necrosis factor receptor-associated periodic syndrome (TRAPS), due to mutations in the *TNFRSF1A* gene, but it rarely occurs alone. Colchicine is the standard treatment for FMF, while patients with TRAPS do not respond to colchicine therapy. Basing on its efficacy in preventing polyserositis in FMF, colchicine has been also proposed for the treatment of recurrent pericarditis and demonstrated to decrease the recurrence rate.

Objective: Our aim was to investigate the possible involvement of *TNFRSF1A* mutations in a group of patients with idiopathic recurrent pericarditis who were refractory to colchicine treatment.

Methods: 102 patients characterized by a poor response to colchicine were enrolled. Mutations of *TNFRSF1A* were searched for by amplifying, using polymerase chain reaction (PCR), genomic DNA, and direct sequencing.

Results: *TNFRSF1A* mutations were found in 7 of 92 patients. Two of the 7 patients had a family history of recurrent pericarditis (they were siblings). One of the 7 patients carried a novel heterozygous deletion (ΔY103-R104), 5 patients carried a heterozygous low-penetrance R92Q mutation and 1 patient carried a rare V95M mutation.

Conclusions: Our data suggest that TRAPS should be kept in mind in the differential diagnosis of recurrent pericarditis and mutation analysis of the *TNFRSF1A* gene should be considered in patients of Mediterranean origin. A poor response to colchicine treatment, and a positive family history, recently reported in up to 10% of recurrent pericarditis patients, may indicate the need to investigate mutations in the TNFRSF1A gene in recurrent pericarditis patients. However, to date, further studies are needed in order to better determine additional criteria for identifying the few subjects who might carry such mutations.

Disclosure: L. Cantarini: None; **O. M. Lucherini:** None; **M. G. Brizi:** None; **M. Galeazzi:** None.

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Radiographic Kellgren-Lawrence (KL) Grade 1 Is Genetically Distinct from KL 0: Implications for Genetic Studies of Knee Osteoarthritis (OA). Venkateswarlu Kondragunta[3], Xiaodong Wu[3], Jordan B. Renner[2], Gordon W. Duff[4], Kenneth S. Kornman[3] and Joanne M. Jordan[1]. [1]Chapel Hill, NC, [2]Department of Radiology and Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, [3]Interleukin Genetics, Inc., [4]School of Medicine, University of Sheffield

Purpose: The Kellgren-Lawrence (KL) radiographic grading system is widely used in studies of osteoarthritis (OA). Although KL grades 1 and 0 together often form the control group in epidemiologic studies, Hart and Spector (2003) showed different knee OA progression rates for KL1 and KL0, suggesting distinct phenotypes. We explored whether KL grades 1 and 0 are genetically distinct by comparing frequencies of genetic markers between subjects with the two KL grades.

Method: Caucasian participants (N=1,173; 38% men; mean age=60 years) in the Johnston County OA Project with 4–11 year follow-up data were examined. Anterior-posterior standing knee radiographs were obtained with footmat positioning at both time points and read by a single musculoskeletal radiologist for K-L grades (0–4). Genotypes of 37 single nucleotide polymorphisms (SNPs) in 16 genes reported to be associated with OA were determined using the single-nucleotide primer extension method. Incidence of OA was defined by an increase in KL grade at follow up, in those with KL 0 bilaterally at baseline. Differences in genotype or allele frequencies between KL1 and KL0 and between subjects with incident OA and those without incident OA were determined by Chi-Square test or logistic regression with adjustment for age, gender and body mass index (BMI). Since all SNPs had been previously associated with OA, we present the data both with (permutation test) and without correction for multiple comparisons. An association was considered positive if the adjusted p-value was <0.05 for the risk allele, genotype or haplotype.

Results: Compared to subjects with KL0 (n=407), those with KL1 (n=383) were older (65.4 yrs vs. 63.0 yrs) and heavier (BMI 29.2 kg/m^2 vs. 28.4). Frequencies of alleles or genotypes in 4 genes, including IL1RN, IL6, ABCG2, and DVWA, were significantly different between KL0 and KL1 subjects (table 1). After adjusting for multiple comparisons, genotype T/T of IL1RN rs579543 was still significantly associated with KL1. Among these genetic markers, four variants in 2 genes, IL1RN (rs419598, p=0.039; rs579543, p=0.008; and rs9005, p=0.03) and IL6 (rs1800797, p=0.014), were also associated with incidence of radiographic knee OA. In addition, compared to KL0 subjects, KL1 subjects were more likely to progress to KL>=2 (33.5% vs 8.5%) as previously reported. No population genetic substructure was detected in this Caucasian population.

Table 1. Distribution of genetic markers between KL0 and KL1.

Gene	SNP	Allele/ genotype	KL-1	KL-0	P
ABCG2	rs2231142	A/*	0.17	0.23	0.043
DVWA	rs11718863	T	0.15	0.19	0.026
IL 1 RN	rs419598	C/C	0.08	0.04	0.022
IL 1 RN	rs579543	T/T	0.09	0.04	0.008
IL 1 RN	rs9005	A/A	0.10	0.06	0.042
IL6	rs1800797	A	0.47	0.40	0.017

Conclusion: This study provides genetic evidence to support differentiating KL1 and KL0 subjects in radiographic knee OA studies.

Disclosure: V. Kondragunta: Interleukin Genetics, Inc., 1, 3; **X. Wu:** Interleukin Genetics, Inc., 1, 3; **J. B. Renner:** None; **G. W. Duff:** Interleukin Genetics, Inc., 9; **K. S. Kornman:** Interleukin Genetics, Inc., 1, 3; **J. M. Jordan:** Interleukin Genetics, Inc., 5.

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Salivary Proteomic Profile in Behçet's Disease. Rosaria Talarico, Chiara Baldini, Laura Giusti, Ylenia Da Valle, Camillo Giacomelli, Elena Donadio, Francesca Sernissi, Anna d'Ascanio, Laura Bazzichi, Antonio Lucacchini and Stefano Bombardieri. Rheumatology Unit, Department of Internal Medicine, University of Pisa, Pisa, Italy

Background: Behcet's disease (BD) is a chronic, systemic vasculitis characterized by recurrent oral and genital ulcers, skin lesions and ocular involvement. In the recent years proteomics has provided new insights for biomarker research in many autoimmune diseases. We have previously described some qualitative and quantitative differences in the composition of saliva in a limited number of BD patients with respect to healthy controls. No data are available on differences in the salivary proteomic profile between active and inactive subsets of disease.

Aim: Following our preliminary results, the primary aim of this study was to analyse the expression of proteomic biomarkers in a larger group of BD patients. The secondary aim was to search for biomarkers of disease activity in BD, by comparing the proteomic profile of active and inactive BD patients.

Methods: Twenty-seven BD consecutive patients (Mean age at disease onset 25±4 years; male/female:19/8; mean disease duration: 11±5 yrs) all fulfilling the ISG criteria for BD and the same number of healthy controls with similar demographic characteristics were enrolled in this study. Clinical manifestations of BD patients at the time of sample collection were recorded. Saliva samples were collected under standard conditions. Aliquots from the individual salivary samples were pooled into various groups for analyses by 2-dimensional-electrophoresis (2DE). The first set of 2DE gels compared a group of pooled healthy volunteers with a group containing all BD samples. The second analysis was performed comparing the group of active BD patients with inactive disease.

Results: Out of 27 BD patients, 11 were active (ocular involvement: 5; CNS involvement: 2; mucocutaneous: 4) and 16 were under remission. The analysis of the obtained protein profiles allowed us to observe significant differences in the expression of 37 spots; eight out of 37 collapsed into 5 separate proteins, and specifically: lipocalin, calgranulin B, prolactin inhibitor precursor (PIP), carbonate anhydrase VI, Cystatine SN precursor. In addition 29 differently expressed spots were cut out for digestion with trypsin and addressed to the MALDI-TOF-MS in order to be identify. When BD active patients were compared to those inactive, 30 spots significantly different were observed; in particular, a >2 fold decrease of PIP, PLUNC 2 and Cystatine SN precursor and a >2 fold increase of calgranulin B differentiated the profile of active from inactive BD patients. Again 10 non identified spots were addressed to the MALDI-TOF-MS to complete the identification.

Conclusions: The results of this study allow us to identify a number of proteins differently expressed in BD with respect to healthy subjects. Some of them, particularly Calgranulin B, appeared to be able not only to distinguish BD patients from controls, but also to differentiate active from inactive BD patients. This seems to be of particular interest since Calgranulin B is a S100 calcium-binding protein known to promote phagocyte migration and infiltration of granulocytes and might be implicated in the pathogenetic background of BD.

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Study of the Chondrogenic Differentiation Process by Metabolic Labeling of Mesenchymal Stem Cells. Beatriz Rocha[1], Valentina Calamia[2], Patricia Fernández-Puente[2], Jesús Mateos[2], Cristina Ruiz-Romero[2] and Francisco J. Blanco[2]. [1]Osteoarticular and Aging Research Lab, Proteomics Unit, Nodo Asociado de ProteoRed. INIBIC-Complejo Hospitalario Universitario A Coruña, A Coruña, Coruña, Spain, [2]Osteoarticular and Aging Research Lab, Proteomics Unit, Nodo Asociado de ProteoRed. INIBIC-Complejo Hospitalario Universitario A Coruña, A Coruña, Spain

Background: Osteoarthritis (OA) is the most common degenerative joint disease, mainly characterized by articular cartilage degradation. Today, there is a growing interest in treating this articular failure with mesenchymal stem cells (MSCs), which are thought to be capable of differentiating into chondrocytes and repair injured joints.

The aim of this study is to standardize the stable isotope labeling by amino acids in cell culture technique (SILAC) with human bone marrow MSCs, and to apply this quantitative proteomic approach for the identification of those molecular mechanisms that participate in chondrogenesis.

Methods: Bone marrow cells were plated in DMEM medium for SILAC, lacking lysine and arginine. Light media was supplemented with standard amino acids, while isotope-labelled L-lys and L-arg were employed in the heavy media. Then, chondrogenic differentiation was induced by micromass culture under control conditions (DMEM), or with two different chondrogenic media: a home-made (HMCM) medium containing 10 ng/mL TGF-β3 and other factors, and a commercial medium from Pierce Biotechnology (CCM). Evaluation of a proper chondrogenesis was performed by histological and genetic means on the micromasses at 7 and 14 days of culture, in order to analyze the expression of chondrocyte phenotype such as SOX9, type II collagen and proteoglycans. For the proteomic analyses, heavy (H) and light (L) samples were mixed 1:1, and separation and analysis of the resulting mixtures was performed by nanoscale LC-MALDI-MS/MS. The identification and quantification of proteins was carried out with Protein Pilot 2.0 software.

Results: To determine the feasibility of this approach and the optimal time points of study during the differentiation process, we first performed a pilot study with metabolic labelling of undifferentiated cells and on various days of differentiation. We assessed the chondrogenic capacity of these cells when cultured in SILAC media, and evaluated their differentiation to chondrocytes under the two diverse chondrogenic media and the control medium.

Finally, we were able to identify 190 MSCs intracellular proteins. Most of these proteins could be quantified, and we found 20 that were altered during the differentiation process with statistical significance ($p<0.05$). Among them, a relevant increase in several histones was detected using both media, pointing out their role in the chromatin remodelling processes that are driven by the chondrogenic factors. Moreover, glycolytic enzymes decreased at 14 days of chondrogenesis only with the commercial medium, suggesting a decrease in the activity of this pathway. We also found that fibronectin levels decline during the induction of chondrogenesis with the commercial medium, confirming previously published results.

Conclusions: We have standardized the SILAC technique with human bone marrow MSCs in culture for the study of their differentiation to chondrocytes (chondrogenesis). Most of the differences that we have found are specific of the chondrogenic media employed. The analysis of those proteins secreted from the micromasses (secretomes) will also be essential for the evaluation of changes in ECM synthesis.

Disclosure: B. Rocha: None; **V. Calamia:** None; **P. Fernández-Puente:** None; **J. Mateos:** None; **C. Ruiz-Romero:** None; **F. J. Blanco:** None.

841

The *FAAH* Gene Is Involved in Risk of Symptomatic Osteoarthritis of the Knee and in Pain in Osteoarthritis. Ana M. Valdes[1], Anne-Marie Malfait[3], Sally Doherty[5], Rosalina Das[4], Margaret Wheeler[5], Deborah Hart[2], Tim D. Spector[2], Cyrus Cooper[6], Michael Doherty[5] and Nigel K. Arden[6]. [1]King's College London, London, United Kingdom, [2]King's College London, [3]Rush University Medical Center, Chicago, IL, [4]Rush University Medical Center, [5]University of Nottingham, United Kingdom, [6]University of Southampton - University of Oxford, United Kingdom

Objective: Osteoarthritis (OA) is the most common large joint (hip or knee) pathology in older people and the main cause for large joint pain and disability in this age-group. FAAH (fatty acid amide hydrolase) is an enzyme that degrades the endocannabinoid anandamide. In animal models genetic or pharmacological inactivation of FAAH produces analgesic, anti-inflammatory, anxiolytic, and antidepressant phenotypes and human genetic variants have been associated with increased cold perception. Our aim was to assess if a genetic variant in the *FAAH* gene previously implicated in peripheral pain sensitivity is involved in risk for large joint OA.

Methods and Subjects: The rs4141964 SNP in the *FAAH* gene was typed in 1847 knee OA cases, 1199 hip OA cases and 2036 controls from three independent UK cohorts (Nottingham, Chingford and Hertfordshire). Expression of the *faah* gene was tested in the dorsal root ganglia (DRG) of naive and medial meniscus destabilized (DMM) C57BL/6 mice. DMM

operated mice were tested for mechanical allodynia at 4, 8, and 16 weeks after surgery, using von Frey fibers. At each of these time points, the DRG L2-L5 were harvested and mRNA was extracted for RT-PCR analysis.

Results: The minor allele (A) at rs4141964 –previously implicated in higher pain sensitivity - was found to be consistently increased among OA cases compared to controls in all three cohorts. A fixed effects meta-analysis for knee OA yielded OR= 1.17 95% CI 1.05 –1.29; p=0.003 (Figure 1) and OR= 1.15 95% CI 1.01 –1.30; p=0.034 for hip OA. No significant between-study heterogeneity was observed (I^2=0%).

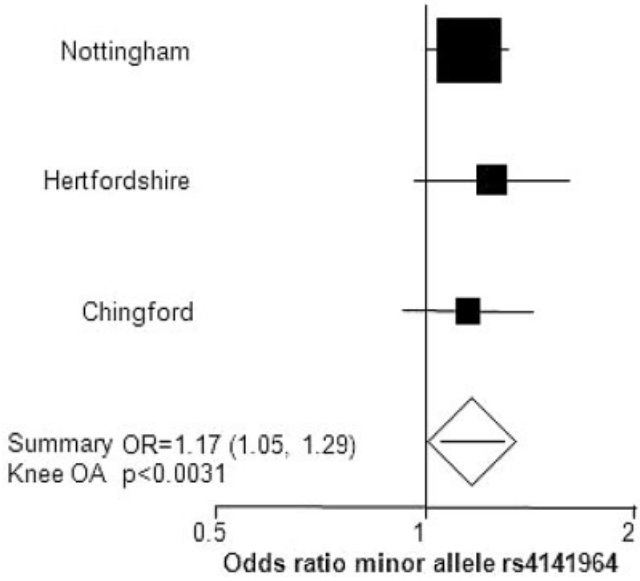

Figure 1. Genetic association between the *FAAH* polymorphism rs4141964 and knee OA in three UK cohorts. Forest plot showing the study specific estimates and the fixed effects meta-analysis estimate.

In the Hertfordshire cohort study the AA genotype was increased among OA patients with knee pain compared with those with asymptomatic OA (p<0.06). In the murine DMM model, progressive mechanical allodynia was apparent in the operated hind limb, 4–8 weeks post surgery, and then resolved 8–16 weeks after surgery. FAAH mRNA levels in the innervating DRG correlated with the mechanical allodynia, and FAAH mRNA was over-expressed relative to naive mice at 8 weeks, but not at 4 or 16 weeks post-surgery.

Conclusions: The *FAAH* gene appears to be implicated in large joint OA and OA pain.

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The Profile of miRNA Expression during the Differentiation of Murine Osteoclast. Inhye E. Ahn[1], Ji Hyeon Ju[2] and Jin Sil Park[3]. [1]Department of Internal Medicine, The Methodist Hospital, Houston, TX, [2]Division of Rheumatology, Department of Internal Medicine, Catholic University of Korea, Seoul, Korea, Republic of, [3]Rheumatology Research Center, Catholic University of Korea, Seoul, Korea, Republic of

Objectives: By identifying chronological patterns of miRNA expression during the differentiation of murine osteoclast, this study aimed to reveal clusters of non-coding genes involved in the regulation of bone metabolism.

Methods: Murine bone marrow-derived monocytes were stimulated with M-CSF only or with the combination of RANKL. Cultured cells were harvested at the designated time points critical for osteoclastogenesis, which ranged from the 24-hour after the monocyte culture, at the point of precursor cells (day 3), when cell-to-cell fusion occurred (day 5), and when mature osteoclasts were formed (day 7). Isolated miRNA underwent microarray analysis. Types and patterns of miRNA expression were compared between two stimulation groups and also between chronological points within each stimulation group.

Results: At the point of cell fusion, six miRNAs were identified to be expressed significantly higher in monocytes stimulated with both M-CSF and RANKL than in those with M-CSF only (p<0.05). This number of differentially expressed genes between two stimulation groups increased to 35 as osteoclast matured. Patterns of miRNA expression in M-CSF plus RANKL-stimulated monocytes were categorized into nine clusters by K-mean clustering analysis.

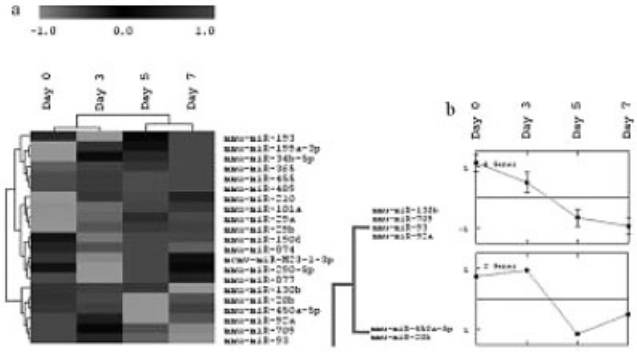

Figure 1. Patterns of gene expression patterns during the differentiation of osteoclast stimulated with M-CSF plus RANKL. Critical time points for osteoclastogenesis were designated for analysis, which ranged from the 24-hour after the monocyte culture (day 0), at the point of precursor cells (day 3), when cell-to-cell fusion occurred (day 5), and when mature osteoclasts were formed (day 7).

In all clusters, the most distinctive change of differential gene expression was observed during cell fusion. Two clusters showed declining patterns throughout the differentiation which included miR-20b, 92a, 93, 130b, 450a and 709.

Conclusion: The number of differentially expressed genes in murine osteoclastogenesis increased as cell maturation progressed. The most critical time point with marked changes in miRNA expression was when cell fusion occurred.

Disclosure: I. E. Ahn: None; **J. H. Ju:** None; **J. S. Park:** None.

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Towards Allele-Specific Dynamic Proteomics: Measuring Protein Synthesis and Turnover Using Heavy Water Labelling and Peptide Mass Spectrometry. Michael J. Deery[1], Alessandra De Riva[2], Claudia Prevosto[2], Sarah McDonald[2] and Robert Busch[2]. [1]Centre for Proteomics, University of Cambridge, [2]Dept of Medicine, University of Cambridge

Background: Genome-wide association studies have uncovered structural and promoter polymorphisms associated with autoimmune disease and confirmed long-established associations with major histocompatibility complex (MHC) alleles. The underlying mechanisms often remain unclear; allelic differences in protein synthesis, folding, maturation, and turnover are of interest. Numerous techniques exist for measuring protein synthesis and turnover, but they suffer drawbacks when studying allelic effects in biologically relevant systems. Here, we have combined stable isotope labelling using heavy water (^2H_2O) with peptide mass spectrometry to devise a biosynthetic labelling approach suitable for allele-specific dynamic proteomics.

Methods: MHC proteins were studied as a model system with disease-relevant isotypic and allelic variation. Antigen-presenting cells (APCs), such as B-lymphoblastoid cell lines, murine splenocytes, or short-term cultures derived from peripheral blood, were subjected to continuous labelling with ^2H_2O. MHC proteins were isolated by immunoprecipitation and SDS-PAGE, fragmented with trypsin, and peptides identified using LC/MS/MS. Selected peptides were analysed for ^2H incorporation by LC/MS. Labelling patterns were interpreted using mass isotopomer distribution analysis and used to calculate fractional protein synthesis as a function of labelling time.

Results: Analysis of tryptic peptides from murine or human MHC class I or class II proteins enabled protein identification and measurement of biosynthetic label incorporation, using small samples of a variety of APC types. Measured peptide mass isotopomer distributions were consistent with ^2H label incorporation from ^2H_2O at a fixed number of effective labelling sites and allowed calculation of fractional synthesis rates. Protein turnover was

quantifiable after accounting for cell growth or turnover and changes in protein levels. Estimates of fractional protein synthesis from analysis of different peptide mass isotopomers, and from different peptides derived from the same protein, were internally consistent and congruent with literature estimates based on other methods. Well-labelled peptides were identified that distinguished selected MHC class I and class II isotypes or alleles, enabling allele-specific measurements of protein synthesis and turnover. Analysis of multiple peptides indicated that multiple amino acids contributed to label incorporation from ^2H_2O; algorithms for predicting labelling patterns from sequence are being refined.

Conclusions: The safety, simplicity, and versatility of ^2H_2O labelling combine with the sensitivity, precision, and specificity of LC/MS to enable allele-specific measurements of MHC protein synthesis and turnover. The approach is readily extended to other proteins and can be applied to primary cells and *in vivo*. These capabilities will aid studies of protein dynamics as a link between genetic polymorphisms and mechanisms of pathogenesis. The ability of the technique to accommodate complex samples suggests potential for proteome-wide studies of protein dynamics.

Disclosure: M. J. Deery: None; **A. De Riva:** None; **C. Prevosto:** None; **S. McDonald:** None; **R. Busch:** KineMed, Inc., 1, 5.

ACR Poster Session B
Innate Immunity and Rheumatic Disease (Poster)
Tuesday, November 9, 2010, 9:00 AM–6:00 PM

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β2 Integrins Control the Pro-Inflammatory Phenotype of Type 1 Macrophages and Dendritic Cells. Kim C. M. Santegoets[2], Mark H. Wenink[2], Richard Huijbens[2], Lenny van Bon[2], Alessandra Cambi[2], Piet L. Van Riel[3], Wim B. Van Den Berg[1] and Timothy R. D. J. Radstake[2]. [1]Radboud Univ Nijmegen Med Cntr, Nijmegen, The Netherlands, [2]Radboud University Nijmegen Medical Center, [3]University Hosp Nijmegen, Nijmegen, The Netherlands

Background: Initially in inflammation pro-inflammatory macrophages are necessary to initiate a full inflammatory response thereby facilitating the control of a possible threat (e.g. tissue damage or pathogens). However, at a certain point this pro-inflammatory program should switch off to prevent chronic inflammation. We hypothesized that the accumulation of monocytes at a site of inflammation induces a shift from an initially pro-inflammatory macrophage phenotype to a phenotype aimed at suppressing the initiated immune response.

Methods: To investigate this we cultured monocytes with GM-CSF or M-CSF into pro-inflammatory type 1 or anti-inflammatory type 2 macrophages, respectively, in different cell densities. After differentiation the macrophages were harvested and replated in a fixed concentration before stimulation with single TLR ligands or heat-killed M. tuberculosis. Dendritic cells (DCs) were also cultured in increasing cell densities to determine the effect on T cell proliferation and differentiation. FACS analysis was performed on the expression of a wide range of markers including TLRs. Quantitative-PCR was used to determine the expression of TLR signaling inhibitors. Furthermore, various integrins were selectively blocked during culture with blocking antibodies.

Results: Differentiation of type 1 macrophages in increasing cell densities dramatically lowered their TNFa, IL-1β and IL-6 release and increased the production of IL-10 and VEGF upon TLR stimulation with single ligands or M. tuberculosis. Increasing cell density had no effect on the cytokine production by type 2 macrophages. The shift towards a more anti-inflammatory type 1 macrophage depended on cell-cell contact via β2 integrins and was due to a soluble factor. TGFβ, IFNβ and IL-6 were excluded as playing roles in this phenotypical shift. However, TGFβ was capable of reversing the anti-inflammatory phenotype induced by cell-cell contact through β2 integrins, resulting in highly inflammatory type 1 macrophages. The pro-inflammatory phenotype of DCs was also restricted by cell-cell contact leading to a high production of IL-10 while the release of IL-12p70 was potently reduced. Correspondingly, DCs cultured in low density were strong inducers of T cell differentiation into IFNγ producing cells upon TLR7/8 stimulation while this capability was potently suppressed when DCs were cultured in high cellular density.

Conclusions: These data show for the first time that cell-cell communication via β2 integrins on type 1 macrophages and DCs alters their differentiation, suppressing their pro-inflammatory phenotype. In many chronic inflammatory diseases high levels of TGFβ are present. This appears to prevent the shift towards more anti-inflammatory macrophages. Concluding, β2 integrin activation during macrophage differentiation is likely to be crucial in the suppression of ongoing immune responses thereby preventing chronic inflammation and possibly tolerance breakthrough, which might be impaired by the excessive presence of TGFβ.

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"Alarmins" S100A8 and A9 Are Expressed in Synovium of Early OA Patients and Regulate Synovial Activation and Joint Destruction during Experimental Osteoarthritis. Peter van Lent[1], Arjen Blom[1], Rik Schelbergen[1], Annet Sloetjes[1], Thomas Vogl[2], Johannes Roth[2] and Wim van den Berg[1]. [1]Dep of Rheumatology University Hospital Nijmegen Medical Centre, Nijmegen, Gelderland, The Netherlands, [2]Institute of Immunology Muenster, Muenster, Germany

Purpose: Prominent proteins released by activated macrophages are the "alarmins" S100 A8 and A9. There is increasing belief that synovial tissue activation contributes to OA cartilage pathology The aim is to evaluate the presence of S100A8/S100A9 in synovia of patients with early OA and to explore active involvement of S100A8/A9 in cartilage destruction in experimental osteoarthritis models that differ in degree of synovial activation.

Methods: Arthroscopic biopsies were taken from 30 early OA patients. mRNA levels (RT-PCR) and immunolocalisation was determined and related to joint destruction (Kellgren Lawrence score). Experimental OA was either induced by transection of the medial anterior meniscotibial ligament which leads to destabilisation of the medial meniscus (DMM) or by injection of collagenase into murine knee joints, which causes overall ligament damage and broad instability. Collagenase-induced-osteoarthritis involves chronic synovial activation in contrast to DMM. Synovial expression of S100A8 and S100A9 was measured using immunolocalisation. Both models were induced in $S100A9^{-/-}$ deficient mice (myeloid cells also lack S100A8 at the protein level). Primary chondrocytes were stimulated with S100A8 and A9 and MMP levels were measured using RT-PCR

Results: mRNA and protein levels of S100A8 and A9 were significantly higher in synovial biopsies of early OA patients when compared to control joints. S100A8 and A9 was predominantly found in synovial macrophages. Of great interest, high levels correlated to increased joint destruction (KL score). The function of S100A8 and S100A9 was further studied in experimental OA models. Kinetic studies show that in surgically induced DMM model, S100A8 and A9 was marginally expressed within the synovium, only evident at day 7 after induction and consistent with limited synovial thickening. The degree of OA cartilage pathology in the knee joint was similar in $S100A9^{-/-}$ and WT mice at day 42 after induction of DMM.

In contrast, during the course of collagenase-induced osteoarthritis, S100A8 and S100A9 was strongly upregulated in synovium at day 7 and remained high at days 14, 28 and 42. Expression of these proteins nicely correlated with thickening of the synovial lining layer comprising activated macrophages. When collagenase-induced-osteoarthritis was elicited in $S100A9^{-/-}$ mice, significantly lower synovial activation was observed when compared to WT mice. Synovial activation was 62% lower at day 42. Cartilage destruction was significantly lower in all surfaces and ranged from a 45% reduction in the lateral tibia to 73% reduction in the medial femur. When primary mouse chondrocytes were stimulated with S100A8 or S100A9, a strong upregulation of particularly MMP-3 mRNA level was found indicating a direct role of S100A8/A9 in cartilage destruction.

Conclusions: Alarmins S100A8/S100A9 are expressed by macrophages in biopsies of early OA patients. S100A8/A9 play a crucial role in synovial activation and cartilage destruction in an osteoarthritis model that shows clear synovial involvement. S100A8/A9 expression in the synovium causes pathology probably by stimulating MMP-mediated damage in the cartilage matrix.

Disclosure: P. van Lent: None; **A. Blom:** None; **R. Schelbergen:** None; **A. Sloetjes:** None; **T. Vogl:** None; **J. Roth:** None; **W. van den Berg:** None.

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Altered T Cell Signaling in Systemic Lupus Erythematosus (SLE): A Role for FcγRIII and Immune Complexes (ICs). Anil Chauhan[1], John P. Atkinson[3] and Terry L. Moore[2]. [1]Saint Louis University, Saint Louis, MO, [2]St Louis University, St Louis, MO, [3]Washington University School of Medicine, St Louis, MO

Purpose: The presence of immune complexes (ICs) in systemic lupus erythematosus (SLE) has been documented. In addition, a role for altered T cell responses has been suggested. Previously, we have shown the activation of T cell receptor (TCR) in response ICs and sublytic dose of memebrnae attack complex (MAC). In this study, we wanted to explore the presence of low affinity FcγRIII that are responsible for ICs binding to human peripheral naive $CD4^+$ T cells and explore their downstream signaling partners.

Methods: We used Alexa Floour 488 labeled model ICs to develop a flow based assay to evaluate the presence of the Fc receptor (FcR) on $CD4^+$ human naïve T cells. Thereafter, we used antibodies specific to FcγRIIIA/B or FcγRIIIB to achieve a 50% inhibition of the labeled IC binding. Subsequently, using immunoprecipitates generated from T cells treated with ICs purified from SLE patients plasama and Western blotting we explored the presence of FcγRIII. Furthermore, we co-localized the FcγRIIIA/B, FcRγ-chain and phosphorylated Syk in human naïve $CD4^+$T cells using confocal microscopy. In the immunoprecipitates generated with anti-FcγRIII, we analyzed the phosphorylation of Syk in response to ICs. The phopshorylated Syk was co-localizated with FcγRIII with confocal microscopy. The presence of the IC binding FcγRIII was carried out from peripheral $CD4^+$ T cells from SLE patients by flow cytometry.

Results: Human peripheral naive $CD4^+$ T cells show binding to labeled ICs. We show a 27 to 29 kD protein that correspond to previously reported mass for FcγRIIIA/B in the $CD4^+$ T cells. A total of 5 to 10% peripheral $CD4^+$ T cells from SLE patients show binding to labeled model ICs. The antibodies against FcγRIIIB and FcγRIIIA/B inhibited binding of labeled ICs by 50%. Upon treatment with ICs, the cells show recruitment of FcRγ chain with FcγRIIIA/B. Treatment of cells with ICs and sublytic MAC resulted in phosphorylation and association of Syk with FcγRIIIA.

Conclusions: For the first time, we show the presence of low affinity FcγRIIIA/B on human $CD4^+$T cells. FcR play critical role in B cell responses and are critical in IC clearance. However, the presence of FcR on human T cell is controversial (Nature reviews,(8) 34,2008). Although, the presence of FcγRIIIA has been shown in NKT and γδ T cells, the FcγRIIIB is only known to be expressed by neutrophils and macrophages and is shown on basophils recently. Using an antibody specific for FcγRIIIB, we demonstrate inhibition of model IC binding in flow based assay. We further show upon treatment of these cells with ICs, the FcRγ is recruited to the FcγRIIIA receptor. This also resulted in phosphorylation and recruitment of Syk with FcγR. Altered Syk mediated T cell signaling in SLE T cells has been reported earlier. We show that ICs and sublytic MAC activates Syk in peripheral T cells. The naïve $CD4^+$ T cells also proliferate in response to IC and sublytic MAC. We have previously shown TCR activation and T cell differentiation in response to ICs and sublytic MAC. It is for the first time, we demonstrate a possible role for FcR in activation of T cells in response to ICs and MAC, a complex of late complement cascade. This study provides a link between ICs, complement, and adaptive immunity.

Disclosure: A. Chauhan: None; **J. P. Atkinson:** None; **T. L. Moore:** None.

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C5aR Is Expressed by Macrophages and Dendritic Cells in Close Proximity to T-Cells in Synovial Tissue from Patients with Rheumatoid Arthritis. Ditte Tornehave[1] and Lars Hornum[2]. [1]Histology, Biopharmaceuticals Research Unit, Novo Nordisk A/S, Måløv, Denmark, [2]Immunopharmacology, Biopharmaceuticals Research Unit, Novo Nordisk A/S, Måløv, Måløv, Denmark

Objective: The aims of the present study were to investigate the expression of the C5a receptor (C5aR) and to characterize the C5aR-positive cells in the synovium of rheumatoid arthritis (RA) patients.

Method: Immunohistochemical studies investigating the C5aR protein expression were performed on synovial biopsies from patients with RA (n=35), osteoarthritis (OA) (n=15) and normal synovial biopsies (n=5). Characterization of C5aR-positive cells was performed by double immunofluorescence staining on another set of synovial biopsies: RA (n=19), OA (n=27) and normal (n=5) with markers for neutrophils (myeloperoxidase, MPO), T cells (CD3), dendritic cells (DCs) (CD1a), and macrophages (CD68).

Results: Infiltrating C5aR-positive ($C5aR^+$) cells were demonstrated in synovial tissue from 28 out of 35 patients with RA, and from 11 out of 15 patients with OA whereas no $C5aR^+$ cells were present in normal synovium. The $C5aR^+$ infiltrating cells in the sublining layer of OA synovial tissue were observed only when lymphoid aggregates were present, and with less positive cells present compared to RA. In the synovial lining $C5aR^+$ cells were observed in 18 out of 35 and 10 out of 15 patients with RA and OA, respectively. Double immunostainings for C5aR and neutrophils, T-cells, DCs and macrophages showed profound infiltration of neutrophils into the synovium (in 60% of patients with RA and 25% with OA), and most of these were C5aR-negative (> 95%), whereas 90% of neutrophils located in the lumen of synovial blood vessels were $C5aR^+$. $CD3^+$ T cells did not express C5aR in synovial tissue from patients with RA or OA. C5aR and CD1a double-positive DCs were observed in 8 out of 19 RA and 8 out of 27 OA patients. More than 95% of the $CD1a^+$ DCs in these patients co-expressed C5aR. All $C5aR^+CD1a^+$ DCs were found intermingled in lymphoid aggregates in close proximity to $CD3^+$ T cells. In the synovial sublining tissue 11 out of 16 patients with RA and 10 out of 21 patients with OA contained up to 50% $C5aR^+$ and $CD68^+$ macrophages. The $C5aR^+CD68^+$ macrophages were interspersed in the synovial tissue and the majority intermingled in lymphoid aggregates. In addition, in 10 out of 16 patients with RA, 12 out of 20 OA and 3 out of 4 normal synovial biopsies all $C5aR^+$ cells in the synovial lining were $CD68^+$ macrophage-like synoviocytes.

Conclusion: An association between C5aR expression and rheumatoid arthritis was demonstrated based on the finding that $C5aR^+$ cells were present in 80% of patients with RA, whereas no $C5aR^+$ cells were present in normal synovium. $C5aR^+$ cells were also found in patients with OA, but less $C5aR^+$ cells were observed in the lymphoid aggregates compared to patients with RA. The majority of infiltrating $C5aR^+$ cells are $CD68^+$ macrophages and a minor part are $CD1a^+$ DCs, whereas very few of the extravascular neutrophils are $C5aR^+$. The majority of the $C5aR^+$ macrophages and DCs were intermingled in lymphoid aggregates in close proximity to $CD3^+$ T cells, and it can be speculated that C5a-activated macrophages and DCs are interacting with T cells in the sublining synovial tissue.

Disclosure: D. Tornehave: Novo Nordisk A/S, 1, 3; **L. Hornum:** Novo Nordisk A/S, 1, 3.

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Cellular Immunity in Rheumatoid Arthritis Patients Not Responding to Synthetic DMARDs. Andra Balanescu[3], Ionela Victoria Neagoe[5], Florian Berghea[3], Carolina Negrei[2], Magda Parvu[1], Ruxandra Ionescu[4], Denisa Predeteanu[4], Violeta Bojinca[4], Vasile Preoteasa[6] and Gina Manda[6]. [1]Colentina Clinical Hospital, Bucharest, Romaia, [2]Department of Toxicology, University of Medicine and Pharmacy Carol Davila, Bucharest, Romania, [3]Research Center of Rheumatic Diseases, Sf. Maria Hospital, University of Medicine and Pharmacy Carol Davila, Bucharest, Romania, [4]Research Center of Rheumatic Diseases, Sf. Maria Hospital, University of Medicine and Pharmacy Carol Davila, Bucharest, Romania, [5]Victor Babes National Institute of Pathology, Bucharest, Romania, [6]Victor Babes National Institute of Pathology, Bucharest, Romania

Background: Rheumatoid arthritis (RA) is considered a T cell-driven disease, but there are consistent evidences that the final bone and cartilage destruction is confined to the monocytic lineage.

Purpose: The aim of our study was to explore cellular immune markers in RA patients (pts) not responding to therapy with synthetic DMARDs, focusing on cellular immune response.

Methods: The study included 35 RA pts diagnosed according to the 1987 revised ACR criteria (age: 46.4±24.3 years; disease duration: 48.7±38.6 months; 86.6% were women). All RA pts had an erosive, seropositive (rheumatoid factor and/or anti-citrullinated peptide antibodies) and active disease (DAS28: 5.9±2.0), despite treatment with a synthetic DMARDs (Methotrexate or Leflunomide) for at least 6 months at standard doses. Clinical response was evaluated according to EULAR response criteria. None of them received corticosteroids or biological agents in the last 6 months. Peripheral blood samples were collected for assessing the cellular immune status: the phenotype of lymphocytes, their early activation capacity (CD69) when stimulated *ex vivo* with CD2, phytohemagglutinin (PHA), pokeweed mitogen (PWM) or IL-2, and the oxidative activity developed *ex vivo* by monocytes and granulocytes when challenged with *E. coli* or phorbol myristate acetate (PMA).

Results: RA pts exhibited high peripheral monocyte counts. Monocytes proved to be activated as a high percentage of cells developed constitutive oxidative burst and had an increased capacity to respond *ex vivo* to *E. coli* or PMA. Such abnormal monocytes released constitutively proinflammatory cytokines (IL-6, IL-8, TNFα, GM-CSF). Granulocytes had a less obvious abnormal oxidative activity. Peripheral lymphocytes were in the normal range (as counts and percentage of CD4+ or CD8+ lymphocytes). T lymphocytes proved to be activated as they expressed the early activation marker CD69. When challenged *ex vivo*, CD4+ lymphocytes, but not CD8+ ones, were less

able than normal cells to get activated. Similarly, NK cells were activated *in vivo*, but had a lower response to IL-2 *ex vivo*.

Conclusions: Our study emphasized that RA pts not responding to therapy with synthetic DMARDs presented functional disturbances at the level of peripheral CD4+ lymphocytes, monocytes and NK cells. These immune parameters could represent markers for monitoring the impact of therapy and the disease course.

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Comprehensive Flow Cytometric Profiling of Peripheral Blood Dendritic Cells in Rheumatoid and Psoriatic Arthritis Patients. James Kobie[6], Ben Panepento[6], Jyh-Chiang E. Wang[6], Grace Chiu[6], Darren Tabechian[8], Allen P. Anandarajah[2], Richard J. Looney[3], Ralf G. Thiele[5], Jennifer H. Anolik[1], Ignacio Sanz[4], Sally Quataert[6], Alex Rosenberg[6] and Christopher T. Ritchlin[7]. [1]University of Rochester, Rochester, NY, [2]Univ of Rochester Med Ctr, Rochester, NY, [3]University of Rochester, Rochester, NY, [4]University of Rochester, Rochester, NY, [5]University of Rochester, Rochester, NY, [6]University of Rochester, [7]University of Rochester Medical Center, Rochester, NY, [8]University of Rochester School of Medicine, Rochester, NY

Purpose: Dendritic cells (DC) are pivotal cells in the initiation of adequate immune responses. Peripheral blood dendritic cells (PBDC) have pleiotropic effects on T and B lymphocytes, however, their phenotypic and functional properties in rheumatoid (RA) and psoriatic arthritis (PsA) and vaccine responses are not well understood. Therefore, we performed a comprehensive examination of the PBDC profile of RA and PsA patients.

Methods: Peripheral blood was collected longitudinally from a cohort of approximately 150 arthritis patients including, recently diagnosed RA (n=33), RA treated with methotrexate (MTX) (n=70), RA treated with TNF inhibitors (TNFi) (n=61), and PsA patients treated with anti-TNF (n=25). Samples from healthy control (HC) subjects (n=97) were also obtained. Peripheral blood was examined by an 11-color flow cytometry assay to identify, phenotype and assess endocytic ability of PBDC subsets. Subset analysis included resolution of previously characterized myeloid dendritic cell 1 (MDC1: CD11c+CD1c+), myeloid dendritic cell 2 (MDC2: CD11c+CD141+), and plasmacytoid (PDC: CD303+CD141-) populations in addition to several putative, poorly characterized PBDC subsets. A systems biology approach was utilized to assess differences in individual PBDC subsets and also differences in the overall composite PBDC profile.

Results: Examination of myeloid DC subsets did not reveal any significant differences in the frequency or endocytic ability of MDC1 among study groupsRecently diagnosed RA patients exhibited a consistent decrease in the frequency of MDC2 as compared to HC that reached significance at one time point. No consistent differences in the frequency of PDC was observed among study groups, although a trend toward decreased PDC in RA patients treated with MTX as compared to HC was observed. Principal components analysis of composite PBDC profiles revealed consistent significant differences in the PBDC profile of RA patients treated with MTX at multiple time points as compared to HC, that were largely influenced by relative changes in the frequency of PDC and a putative PDC-like subset. A significant decrease in MDC1, independent of study group was observed shortly after seasonal influenza vaccination.

Conclusions: Although variations were observed in the frequency of PBDC subsets in arthritis patients, no substantial dysregulation was observed that was specific to RA or PsA patients or treatment with methotrexate or anti-TNF. Subtle changes in the overall PBDC profile were observed in RA patients treated with MTX that warrant further examination and may reflect alteration in PBDC development. Decreases in MDC1 after influenza vaccination, likely reflecting altered trafficking, highlight the dynamic nature of the PBDC profile and may represent a surrogate marker of vaccine response. These data also demonstrate that anti-TNF therapy does not significantly impact the circulating frequency or ratios of PBDC.

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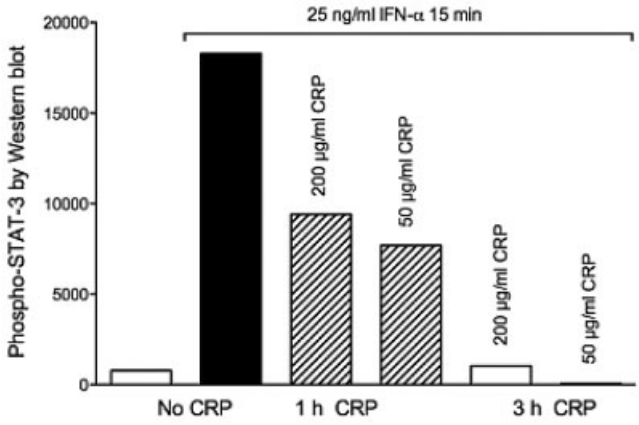
C-Reactive Protein Inhibition of the Response to Type I Interferon (IFN). Carolyn Mold[2], Daniel Goldberg[1], Carol Morris[1] and Terry Du Clos[1]. [1]University of New Mexico, [2]University of New Mexico, Albuquerque, NM

Background: A pivotal role for the type I IFN pathway in SLE is supported by expression analysis, genetic associations, in vitro experiments and animal models. In peripheral blood, plasmacytoid dendritic cells (pDC) are the primary producers of IFN, which acts on monocytes, myeloid DC and lymphocytes to promote antigen presentation and activation. This study investigated the regulation of this pathway by the pentraxins, C-reactive protein (CRP) and serum amyloid P (SAP). Both pentraxins recognize apoptotic cells and nuclear antigens and both bind to FcgR and activate complement. CRP promoter polymorphisms associated with decreased basal expression of CRP show increased risk of SLE. We hypothesized that pentraxins would regulate the IFN response to SLE autoantigens.

Methods: To determine whether pentraxins induce IFN, PBMC were incubated with CRP, SAP or serum containing anti-RNP and apoptotic cells or purified autoantigen (snRNP). Cytokine responses (TNF-a, IL-10, IFN- a) were measured at 24 h by ELISA. Purified monocytes or macrophages were incubated with CRP or CRP with apoptotic blebs and cytokines were measured by multiplex. To determine whether CRP treatment would affect the response to IFN, macrophages were preincubated with CRP for 1–3 h before 15 min treatment with IFN. Phosphorylation of STAT-1 and STAT-3 was determined by Western blot.

Results: PBMC produced IFN-a in response to immune complexes containing apoptotic cells or snRNP. In contrast, CRP or SAP complexed to these same autoantigens induced IL-10 and TNF-a but no IFN-a. Depletion of monocytes eliminated the cytokine responses to CRP complexes, but did not affect the IFN-a response to immune complexes, which is mediated by pDC. The IFN-a response to anti-RNP-snRNP complexes was sensitive to RNase treatment. Purified monocytes incubated with pentraxins complexed with apoptotic blebs released cytokines, IL-10, IL-6 and TNF-a, associated with a regulatory phenotype. The IL-10 response to CRP alone or CRP complexes was greatly increased by differentiation into macrophages with M-CSF. Pretreatment of macrophages with CRP for 3 h or longer completely blocked IFN-a-induced signaling.



Conclusions: These findings support the hypothesis that pentraxins regulate the IFN-a pathway. Although both CRP and SAP bind to apoptotic cells and nuclear autoantigens, in contrast to immune complexes, pentraxin complexes containing these autoantigens do not induce IFN-a. Instead monocytes dominate the response, producing TNF-a and IL-10, which both inhibit the pDC IFN response. Macrophages responded to CRP complexes with high amounts of IL-10 and after CRP incubation became unresponsive to IFN-a. Thus, pentraxins may provide both a non-inflammatory means to remove autoantigens exposed during cell death and a mechanism to decrease the stimulatory effects of IFN-a.

Disclosure: C. Mold: None; **D. Goldberg:** None; **C. Morris:** None; **T. Du Clos:** None.

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Endosomal Trafficking of Antigen in Antigen Cross-Presentation and the Cause of Lupus Tissue Injuries. Mai Takimoto[1], Ken Tsumiyama[1] and Shunichi Shiozawa[2]. [1]Department of Biophysics, Kobe University Graduate School of Health Sciences, Kobe, Japan, [2]Department of Biophysics, Kobe University Graduate School of Health Sciences/Department of Medicine, Kobe University Graduate School of Medicine/The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan

Objective: We previously showed that repeated immunization with a conventional antigen caused systemic autoimmunity in the mice otherwise

not prone to spontaneous autoimmune diseases; systemic autoimmunity necessarily takes place when host's immune 'system' is overstimulated by repeated exposure to antigen, to the levels that surpass system's self-organized criticality. This novel thesis 'self-organized criticality theory' explaining the cause of autoimmunity of ours (Tsumiyama K, *et al*. PLoS ONE 4(12):e8382, 2009) shows that overstimulating $CD8^+$ T cell into a full-matured MHC class I-restricted, antigen-specific effector cytotoxic T lymphocyte (CTL) *via* antigen cross-presentation in dendritic cell (DC) causes lupus tissue injuries. Here we examine molecular details of antigen cross-presentation to clarify how effector CTL is generated. The results indicate that the endosomal pathway, rather than the pathway through endoplasmic reticulum (ER), is essentially important for antigen cross-presentation and subsequent generation of lupus tissue injuries.

Methods: The bone marrow cells of BALB/c mice were stimulated with granulocyte-macrophage colony-stimulating factor (GM-CSF) to generate bone marrow-derived DC. The bone marrow-derived DC was cultured with fluorescent-labeled ovalbumin (OVA). Early endosome antigen-1 (EEA-1) and calnexin were detected to identify endosome and ER respectively, by using immunofluorescent staining. To examine whether or not engulfed antigen is exported from endosome to cytoplasm, Sec61, which is known as a translocon, was also detected by using immunofluorescent staining. Localization of OVA, endosome, ER and Sec61 was examined under confocal laser scanning microscopy.

Results: In the bone marrow-derived DC, upon engulfment, OVA was co-localized with EEA-1, an endosomal marker. However, by 15 min after engulfment, OVA was gradually separated from EEA-1. In contrast, OVA did not co-localize with calnexin, a marker of ER, until 30min after engulfment clearly indicating that OVA was not transferred into ER. Instead, Sec61 was found to be co-localized with OVA after 15 min to 30min, which indicated that OVA was transported from endosome to cytoplasm *via* Sec61.

Conclusion: The result shows that endosomal pathway, bypassing ER, is important in the case of antigen cross-presentation. Further, the export of antigen from endosome to cytoplasm *via* Sec61 could be the first step in antigen cross-presentation, hence the generation of lupus tissue injuries.

Disclosure: M. Takimoto: None; **K. Tsumiyama:** None; **S. Shiozawa:** None.

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Exposure to U1-RNP Components Induces Bone Marrow-Derived Dendritic Cell Trafficking to the Lung. Luis Sorell[4], YunJuan Zang[4], Irina Fernandez[4], Laisel Martinez[1], Maria Carpintero[3] and Eric L. Greidinger[2]. [1]Miami VA Medical Center, [2]Miami VA Medical Center and University of Miami Miller School of Medicine, Miami, FL, [3]University of Miami Miller School of Medicine, Pembroke Pines, FL, [4]University of Miami Miller School of Medicine

Background: We have previously found that upon adoptive transfer into naive syngeneic mice, splenic dendritic cells (DCs) from anti-RNP immunized mice with clinical lung disease preferentially home to the lung and transfer interstitial pneumonitis, but that splenic DCs from naive mice or even from immunized mice without lung disease do not home to the lung or induce lung disease. We hypothesize that DC tissue targeting is determined by interactions between RNP targets and DCs directly, without the intervention of adaptive immune cells.

Methods: Bone marrow was harvested from B6 substrain study mice, and differentiated in vitro for a week with GM-CSF and IL-4 following published protocols. In the last 24 hours in culture, cells were transferred into fresh medium containing the same factors in the presence or absence of 50 mcg/ml each of 70k fusion protein and U1-RNA. Cells were harvested, loaded with CFSE or QTracker 655, subjected to FACS analysis and/or adoptively transferred into naive syngeneic hosts via the tail vein, 1 million cells per recipient. Recipients were subsequently sacrificed and analyzed by FACS for the presence of labeled cells in single cell suspensions from organ homogenates, and for the development of clinical manifestations of inflammatory disease.

Results: Bone marrow-derived DCs differentiated with GM-CSF/IL-4 showed evidence of preferential homing to the lung after incubation with 70k/U1-RNA, with mean of over 5% of pulmonary CD11c+ cells showing specific QTracker 655 labeling one week after cell adoptive transfer, compared to less than 1% of cells without 70k/U1-RNA. Persistence of lung-targeting DCs by vital dye staining was observed up to 2 months after cell transfer. In 6/6 mice receiving lung-targeting BM-derived DCs followed for at least 2 months, histologic evidence of interstitial pneumonitis was observed. Lung-targeting DCs were characterized by the development of CD11c+/CD11b+ surface expression, TLR3 expression, and preferential expression of a long form of the IRF5 mRNA 3' UTR similar to that observed in anti-RNP patients with lung disease.

Conclusions: Spliceosomal targets of anti-RNP autoimmunity can influence tissue targeting of autoimmune responses by direct effects on dendritic cells. A subset of myeloid dendritic cells targeting the lung mediates anti-RNP lung disease, and may represent a target for future therapeutic strategies.

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Fas Expression in Myeloid Cells Is Required To Prevent Systemic Autoimmunity. Carla M. Cuda[1], Hemant Agrawal[1], Evan Weber[2], G. Kenneth Haines[3] and Harris R. Perlman[1]. [1]Northwestern University, Chicago, IL, [2]Northwestern University, [3]Yale University

Significance: Rheumatoid arthritis (RA) manifests in persistent synovial inflammation, cellular infiltration, and pro-inflammatory cytokine production, and results in progressive cartilage and bone destruction. While the mechanisms underlying these phenotypes are not fully elucidated, insufficient apoptosis is a key player in RA pathogenesis. A critical mediator of the extrinsic apoptotic pathway includes the death receptor (DR) Fas. Lymphocyte-specific deletion of Fas reveals non-apoptotic roles for this DR in proliferation, and although lymphocytes are necessary for the initiation of RA, macrophages are crucial for its persistence. These highly activated and non-proliferating cells contribute to synovial inflammation and cartilage and bone destruction through the production of degradative enzymes, cytokines, and chemokines. However, the impact of myeloid cell-specific loss of Fas and its relationship to RA development and/or progression has yet to be examined.

Methods: Mice with Fas flanked by loxP sites (Fasflox/flox) were crossed with mice expressing Cre under control of the murine lysozyme M gene promoter (CreLysM), which functions in mature lysozyme-expressing cells of the myelomonocytic lineage. CreLysMFasflox/flox mice were verified by Real-time PCR and examined to determine non-apoptotic roles of Fas in myeloid cells. Flow cytometric analysis was employed to characterize both myeloid and lymphoid cell distribution and activation in bone marrow, blood and spleen. Luminex-based assays and ELISAs were used to detect serum cytokine and Ig levels as well as in vitro cytokine production by macrophages in response to LPS. Immunofluorescent and immunohistochemical staining revealed kidney pathology.

Results: Myeloid cell-specific loss of Fas significantly increased both total numbers of peripheral circulating blood cells and splenocytes. Increased percentages of bone marrow resident macrophages were seen. Selective deletion also disrupted myeloid cell homeostasis in the periphery by increasing levels of peripheral blood resident and inflammatory monocytes, as well as increasing both the number and activation level of total and inflammatory splenic macrophages. Additionally, in vitro LPS stimulation of both peritoneal macrophages and bone marrow-derived macrophages lacking Fas resulted in increased production of IL-6, TNFα and IL-1β. Loss of Fas in myeloid cells also affected dendritic cells and T cells, with these populations presenting a more activated phenotype. CreLysMFasflox/flox mice displayed significantly increased serum IL-1α, IgG, total IgM and anti-dsDNA IgM levels and presented with more severe kidney pathology based on positive IgG staining, increased cellular infiltration and higher disease scores.

Conclusion: These results demonstrate that loss of Fas in myeloid cells is sufficient to induce inflammatory phenotypes in mice. Thus, we are the first group to show via myeloid cell-specific deletion of Fas that this DR typically associated with apoptosis also acts to prevent systemic autoimmunity. These data will have implications for RA by elucidating previously unknown functions of a potentially useful target for therapy.

Disclosure: C. M. Cuda: None; **H. Agrawal:** None; **E. Weber:** None; **G. K. Haines:** None; **H. R. Perlman:** None.

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FLIP: The Novel Regulator of Macrophage Differentiation and Granulocyte Homeostasis. Qi Quan Huang[2], Harris R. Perlman[2], Zan Huang[3], Robert Birkett[3], John D. Crispino[3] and Richard M. Pope[1]. [1]Northwestern Univ Med School, Chicago, IL, [2]Northwestern University, Chicago, IL, [3]Northwestern University

Background and Purpose: Macrophages are important mediators of innate immunity and chronic inflammation, and play an important pathogenic role in rheumatoid arthritis. In order to further understand the cellular

mechanisms contributing to the persistence of macrophages in RA, a myeloid lineage Flip knock out mouse line has been generated. Characterization of these mice demonstrated that FLIP was necessary for macrophage differentiation and survival, that macrophages are essential for maintaining granulocyte homeostasis.

Methods: Mice bearing floxed Flip alleles crossed with LysM-cre mice resulted in FLIP deletion in the myeloid cell lineage. The cell types in circulation and tissues were examined by morphology and by flow cytometry. Mixed chimera bone marrow reconstitution experiments were performed employing by CD45.1+ and CD45.2+ congenic C57BL/6 mice. Serum cytokines were quantified by LUMINEX 200. In vitro macrophage differentiation was performed from CD117+ bone marrow hematopoietic stem cells. Flip In vitro deletion was induced by recombinant Cre retro-virus.

Results: In addition to postnatal growth retardation and premature death, myeloid specific FLIP deficient mice exhibited a dramatic increase of circulating neutrophils and multi-organ neutrophil infiltration, which was mediated by increased cytokines and growth factors. Mature macrophages in the spleen, lymph nodes and the peritoneal cavity were significantly reduced. Further analysis of cells in peritoneal cavity discovered a significant inverse non-linear correlation of peritoneal macrophages and granulocytes. That is if macrophages were present, neutrophils were kept in a homeostatic level. In vitro, CD117+ bone marrow progenitor cells failed to differentiate into macrophages when Flip was deleted. This defect was observed not only in the mature macrophages, and there are also decreased numbers of the less mature myeloid progenitors. The bone marrow reconstitution experiments demonstrated that the primary defect was a cell autonomous defect of the bone marrow derived cells, since these cells were capable to transferring the disease, in the absence of competitor wild type cells. Further, the mixed chimera experiments demonstrated that knockout bone marrow cells were not able to compete with the wild type cells, due to increased cytokines and growth factors induced stem cell exhaustion, prior to cell transfer from the knockout mice.

Conclusions: These observations demonstrate that FLIP is necessary for macrophage differentiation and survival. The myeloid specific deletion of FLIP resulted in the loss of macrophages and consequently an increase of neutrophils. Neutrophilia and inflammation is secondary to the loss of macrophages and contributed by increased cytokines and growth factors. Since both macrophages and granulocytes are major inflammatory cell types involved in the pathogenesis of rheumatoid arthritis, further understanding of their homeostatic regulation will provide new insights into the mechanisms that control of inflammation.

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IκB Kinase (IKK)ε: Bridging Innate and Adaptive Immunity in Collagen-Induced Arthritis (CIA). Deepa Hammaker[2], Katharyn Topolewski[3], David L. Boyle[1] and Gary S. Firestein[1]. [1]UCSD School of Medicine, La Jolla, CA, [2]Univ of California San Diego, La Jolla, CA, [3]University of California, San Diego

Purpose: The IKK related kinase IKKε regulates innate immune responses through the production of interferon-beta (IFNβ), pro-inflammatory cytokines and chemokines. Recent studies show that IKKε-deficiency can synergize with IFNβ therapy to reduce inflammation in passive K/BxN serum-induced arthritis, where the innate immune system is indispensable for disease initiation. However, there is no information on whether IKKε regulates inflammation in a model of arthritis that depends on adaptive immunity. Therefore, we evaluated whether IKKε plays a role in murine collagen-induced arthritis.

Method: Wild type (WT), and IKKε−/− mice were immunized on days 0 with type II bovine type II collagen in complete Freund's adjuvant and on day 21 in PBS. Joint histology on day 42 was evaluated for synovitis, bone erosion, extra-articular inflammation and proteoglycan damage (max score=16). Serum anti-type II collagen antibody levels were measured by ELISA. Levels of cytokines and chemokines in serum were measured by multiplex analysis. Gene expression in joint extracts was determined by quantitative real time PCR.

Results: Arthritis severity was significantly reduced in IKKε−/− mice compared with WT ($p=0.02$, n=13/group). Scores at peak arthritis severity on day 35 were 13.1±2.2 in WT compared with 8.3±2.2 in IKKε−/− mice. Histological analysis showed that bone erosion and proteoglycan loss in IKKε−/− mice was significantly reduced by 70% and 60%, respectively compared with WT ($p<0.04$). Surprisingly, levels of the pathogenic anti-collagen IgG2a antibody were reduced by 32±10% ($p=0.04$) in IKKε−/− serum while total IgG levels were similar to WT mice. Serum IL-6 and G-CSF levels were similar in WT and IKKε−/− mice with arthritis on day 35 and were significantly higher than in naive mice. Synovial MMP3 gene expression was significantly lower in IKKε−/− mice compared with WT mice (63±8% inhibition, $p=0.02$). Induction of MMP9 and IFNβ genes was also decreased in IKKε−/− mice by 45±13% and 84±4%, respectively ($p=0.058$). Despite improved clinical scores, IL-1Ra, IL-6 and MMP-13 gene expression was not significantly reduced in IKKε−/− mice compared with WT mice.

Conclusions: IKKε unexpectedly regulates adaptive immune responses as shown by decreased production of pathogenic anti-type II collagen antibodies. Diminished disease severity in the model is probably due to a combination of decreased anti-collagen antibody production and suppression of synovial innate immune responses. This kinase represents a novel therapeutic target to suppress synovitis by regulating complex components of the immune system implicated in RA.

Disclosure: D. Hammaker: None; **K. Topolewski:** None; **D. L. Boyle:** None; **G. S. Firestein:** None.

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IMO-3100, a Toll-Like Receptor (TLR) Antagonist, Suppresses TLR7- and TLR9-Mediated Immune Responses in Non-Human Primates. Lakshmi Bhagat[2], Jimmy X. Tang[2], Tim Sullivan[2], Ekambar R. Kandimalla[1] and Sudhir Agrawal[2]. [1]Idera Pharmaceuticals, Inc, Cambridge, MA, [2]Idera Pharmaceuticals, Inc

Background: Immune complexes containing host-derived nucleic acids have been shown to induce inflammatory responses mediated through TLR7 and TLR9 and manifest autoimmune diseases, such as lupus and psoriasis. Blocking TLR7- and TLR9-mediated immune responses through use of an antagonist represents a novel approach for the treatment of selected autoimmune diseases. IMO-3100 is a dual antagonist of TLR7 and TLR9, which has shown potent activity in preclinical disease models of lupus, collagen-induced arthritis, psoriasis, and hyperlipidemia. In the current study, we have evaluated IMO-3100 for its pharmacodynamic mechanism of action in non-human primates.

Methods: IMO-3100 was administered to cynomolgus monkeys (N=4) as a weekly dose of 1.5 mg/kg for 4 weeks. Blood samples were collected prior to and 72 hours after each IMO-3100 injection (i.e. Days 0, 3, 7, 10, 14, 17, 21, and 24) and also at days 28 and 35. PBMCs were isolated by Ficoll density gradient centrifugation method. PBMCs (1×10^6 cells/0.2 ml/well in 96 well plates) were incubated with agonists of TLR7 (50 μg/ml), TLR9 (3 μg/ml) or TLR4 (LPS, 100 ng/ml) for 24 hrs. Supernatants were harvested and IL-1β, IL-1Ra, IL-6, IL-8, IL-12, TNF-α, MIP-1α, MIP-1β, RANTES and MCP-1 levels in culture supernatants were determined using human cytokine antibody bead kits. IFN-α and IP-10 levels were measured by ELISA.

Results: Weekly administration of IMO-3100 for 4 weeks resulted in 25 to 95% reduction in various cytokines and chemokines induced by TLR7 and TLR9 agonists, including IL-1β, IL-6, IL-12, IP-10, IFN-α, MIP-1α and MIP-1β, compared with pre-dose cytokine levels. The magnitude and duration of inhibition varied for different cytokines. Weekly administration of IMO-3100 led to continued suppression of cytokines at all time points up to day 28. By day 35, two weeks after the last dose of IMO-3100 administration, secretion of cytokines/chemokines rebounded or started to rebound to pre-dose levels. IMO-3100 showed insignificant suppression of TLR4 agonist (LPS)-induced cytokines in isolated PBMCs, suggesting specific inhibition of TLR7- and TLR9-mediated immune responses.

Conclusion: These results demonstrate that weekly administration of IMO-3100 to non-human primates suppresses ex-vivo immune responses mediated through TLR7 and TLR9, but not TLR4. IMO-3100 is in phase 1 clinical evaluation for potential applications in autoimmune and inflammatory diseases.

Disclosure: L. Bhagat: Idera Pharmaceuticals, Inc, 1, 3; **J. X. Tang:** Idera Pharmaceuticals, Inc, 1, 3; **T. Sullivan:** Idera Pharmaceuticals, Inc, 1, 3; **E. R. Kandimalla:** Idera Pharmaceuticals, Inc, 1, 3; **S. Agrawal:** Idera Pharmaceuticals, Inc, 1, 3.

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Involvement of Toll-Like Receptor 2 in Pristane-Induced Lupus. Vilma Urbonaviciute[3], Silke Frey[2], Carsten Kirschning[1], Georg Schett[2] and Reinhard E. Voll[2]. [1]Essen, Germany, [2]Erlangen, Germany, [3]Department Internal Medicine 3, University Hospital Erlangen, University of Erlangen-Nuremberg, Erlangen, Germany

Background: Autoantibodies against nuclear autoantigens such as double-stranded DNA (dsDNA) and nucleosomes represent a serological hallmark of systemic lupus erythematosus (SLE) and may directly contribute to the pathogenesis of the disease (1). However, it is still unclear, how such poorly immunogenic ubiquitous nuclear components become targets of an immune response in patients with SLE. Recent data indicate that Toll–like receptors (TLRs) recognizing endogenous ligands may be critically involved in breaking peripheral tolerance against nuclear autoantigens (2). Results of our recent studies in non-autoimmune mice provide evidence of a critical role of TLR2 in the anti-dsDNA and anti-histone IgG autoantibody induction by High Mobility Group Box protein 1 (HMGB1)-nucleosome complexes purified from apoptotic cells, whereas TLR4 was dispensable (3).

Objective: Using the pristane-induced mouse model of SLE, we further investigated the requirement of TLR2 signaling for induction of lupus-specific autoantibody production and SLE like disease.

Methods: Female C57BL/6 wild type (wt), TLR2- and TLR2/4-deficient mice were injected intraperitoneally with a single dose of 500 μl of the hydrocarbon oil pristane (2,6,10,14 tetramethylpentadecane). The concentrations of autoantibodies in sera were measured by ELISA. Renal disease was assessed by semiquantitative measurement of proteinuria in spot urine and quantified over 24 hours after collection in metabolic cages as well as by histological analyses.

Results: TLR2-deficient mice displayed delayed and significantly reduced anti-dsDNA, anti-histone, and some anti-nuclear (ANA) antibody IgG responses compared to pristane treated wt controls. Interestingly, pristane treated TLR2/4-deficient mice developed even somewhat higher amounts of the autoantibodies than wt control mice, suggesting a so far unexplained protective function of TLR4. However, both, pristane-treated TLR2- and TLR2/4-deficient mice developed significantly milder renal disease compared to the wt control group, indicating a role of TLR2 and TLR4 in the inflammatory process in the kidneys.

Conclusion: TLR2 is specifically required for anti-dsDNA, anti-histone, and antinuclear autoantibody production as well as for development of renal disease in pristane-induced murine lupus model. Specific blocking of TLR2 signaling may therefore be a promising novel strategy for treatment of SLE.

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Mir-19b Regulates TLR2 Expression in Rheumatoid Arthritis Fibroblast-Like Synoviocytes. Lucas Philippe[3], Guillaume Suffert[1], Ghada Alsaleh[3], Arnaud Theulin[3], Jacques Eric Gottenberg[3], Jean Sibilia[3], Sebastien Pfeffer[2] and Dominique Wachsmann[3]. [1]Architecture et Réactivité de l'ARN, Université de Strasbourg, Institut de Biologie Moléculaire et Cellulaire du CNRS, Strasbourg, France, Metropolitan, [2]Architecture et Reactivite de l'ARN, Universite de Strasbourg, Institut de Biologie Moleculaire et Cellulaire du CNRS, Strasbourg, France, Metropolitan, [3]Laboratoire de Physiopathologie des Arthrites, EA4438, Faculté de Pharmacie, 74 Route du Rhin, Illkirch-Graffenstaden, France, Metropolitan

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease of which the main characteristic is irreversible joint destruction. An excessive stimulation of resident cells such as fibroblast-like synoviocytes (FLS) seems to be a fundamental event. This activation is in part due to microbial components such as PAMPs (Pathogen Associated Molecular Patterns) or DAMPs (damage associated molecular patterns) that activate cells by interacting with Pattern Recognition Receptors (PRRs) such as Toll like receptors (TLRs). Their activation triggers the transcription of numerous genes coding for pro-inflammatory cytokines and metalloproteases implicated in cartilage and bone destruction. MicroRNAs (miRNA) are small non-coding RNA that have emerged as key players in the regulation of translation and degradation of target mRNAs. The aim of this work was to evaluate their potential involvement in the control of TLR expression by RA FLS.We focused on TLR2 expression which is up-regulated in RA synovium.

Materials and Methods: FLS were obtained from RA patients at the time of joint surgery.TLR2 mRNA and protein expression was assessed by RT-qPCR and western blot after stimulation of RA FLS with BLP, a ligand of TLR2. MiRNAs expression was analyzed using a microarray-based approach and confirmed by RT-qPCR. Transfection of FLS was performed using the AMAXA nucleofactor kit II (c) system. Identification of 19b targets was assessed by the luciferase assay using the psiCHECK™-2 Vectors. IL-6 secretion was evaluated using the ELISA sandwich method.

Results: We first showed that RA FLS expressed constitutively TLR2 and that TLR2 expression was up-regulated in response to BLP. Using a miRNA microarray analysis, we identified the downregulation of miR-19b which was predicted to target TLR2 mRNA. Down regulation of miR-19b was confirmed by qRT-PCR. Transfection of RA FLS with miR-19b mimic decreased TLR2 expression. Using a luciferase assay, we also showed that miR-19b targets directly TLR2 mRNA 3'UTR. In addition, direct targeting of TLR2 mRNA by 19b mimic inhibited IL-6 secretion by BLP activated RA FLS.

Conclusion: Together, these data demonstrated a critical functional link between miR-19b, TLR2 expression and IL6 secretion by RA FLS, which could play an important role in RA inflammation.

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Myeloid but Not Lymphoid Bim Expression Is Required Suppress SLE-Like Disease. Hemant Agrawal[1], Evan Weber[1], Alexander Misharin[1], Carla M. Cuda[1], G. Kenneth Haines[2], Rosalind Ramsey-Goldman[1] and Harris Perlman[1]. [1]Dept Med/Div Rheumatology, Northwestern University, [2]Yale University

Purpose: Systemic lupus erythematosus (SLE) is a multifactorial autoimmune disease of unknown etiology characterized by production of autoantibodies and extensive end organ damage. While it is clear that T and B cells are critical to SLE pathogenesis, intrinsic differences in myeloid cells, such as macrophages (Mφ) and dendritic cells (DC), may influence the T and B cell phenotypes observed in patients with SLE. To date, few studies have focused on the loss of Bim, a pro-apoptotic member of the Bcl-2 family, specifically in monocytes/Mφ and its non-apoptotic roles such as activation, cytokine production, and presentation and their relationship to the pathogenesis of lupus.

Method: Peripheral blood from aged and sex matched healthy controls and patients with inactive (SLAM <2) or active SLE (SLAM >10) were analyzed for monocyte expression of Bim and markers of activation. Additionally, mice lacking Bim specifically in T cells (CreCD4Bimflox/flox), B cells (CreCD19Bimflox/flox) and monocytes/Mφ (CreLysMBimflox/flox) using the Cre-loxP system were generated and the deletion of Bim was verified by real time PCR. Bimflox/flox (Bim intact) mice were used as controls. Young (<2 mon) and aged mice (>6 mon) were phenotyped using histological and flow cytometric analyses. Luminex based assays and ELISAs were performed to detect antibody isotypes, autoantibodies, cytokines/chemokines, and activation of kinases. A pathologist blinded to the study scored all tissues for SLE-like disease.

Summary: SLE patients with active disease displayed reduced expression of Bim in monocytes but not in lymphocytes or granulocytes, which was associated with increased expression of HLA-DR, CCR2, CD62L, and CCR5 but not CD163. To further understand the importance of the reduction of Bim in monocytes, we studied mice lacking Bim in monocytes/Mφ. Young and aged CreLysMBimflox/flox mice showed severe splenomegaly compared to Bimflox/flox, CreCD4Bimflox/flox and CreCD19Bimflox/flox mice. While both young and aged CreLysMBimflox/flox mice had increased numbers of activated splenic Mφ and DC, only the aged CreLysMBimflox/flox mice had increased numbers of splenic Mφ. Furthermore, young and aged CreLysMBimflox/flox mice showed increased accumulation of activated splenic B and T cells. Mφ from young CreLysMBimflox/flox mice induced increased OT-II T-cell responses as compared to Bimflox/flox mice and displayed reduced phospho-AKT but increased phospho-cJun, and p38. Additionally, Mφ from aged mice showed reduced caspase 3/7 activation. There were elevated levels of circulating autoantibodies (total IgM and isotypes of IgG) and cytokines (IL-12p70 and IL-17) in CreLysMBimflox/flox mice serum. Moreover, CreLysMBimflox/flox mice displayed severe renal damage as evident by increased glomerular size, cellular infiltration, retention of immune complexes, and high kidney disease scores.

Conclusion: These data demonstrate that reduction of Bim leads to a novel and non-apoptotic phenotype in monocytes/Mφ and the loss or reduction of Bim in monocytes/Mφ is sufficient to activate lymphocytes and SLE-like disease. Thus, the level of Bim in monocytes/Mφ may be a biomarker of SLE-disease activity.

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Natural Killer (NK) Cells Resident in Normal Human Skin Are Distinct from Blood and Lung NK Cells. Ahmed Gehad[1], Sandra King[1] and Robert Fuhlbrigge[2]. [1]Brigham and Women's Hospital, [2]Children's Hospital- Boston, Boston, MA

Normal human skin contains a broad collection of leukocytes, including T cells, dendritic cells and NK cells, that form an intricate network important for immunosurveillance and active in inflammatory skin disease. Although skin homing T cells and skin resident dendritic cell populations have been described in detail, little is known regarding the characteristics of NK cells resident in skin. Published studies of NK cell subsets in humans have focused primarily on surface receptor expression of NK cell populations circulating in peripheral blood, rather than cells recovered from tissue. We hypothesized that skin resident NK cells may represent a distinct subset of NK cells with phenotypic, homing and functional properties distinct from NK cells in peripheral blood and resident in other tissues. For this study, we used a short term non-enzymatic explant culture method for leukocyte isolation. Samples of non-inflamed human skin obtained from cosmetic surgery procedures in accordance with IRB guidelines were cultured on tantalum-coated carbon matrices in the absence and presence of various cytokines including IL-2, IL-15, IL-18, IL-21, and FLT-3 ligand. Leukocytes were recovered after 2–3 wk in culture and analyzed by flow cytometry. CD3- CD56+ NK cells present in normal skin represented a small but reproducible fraction (2–12%) of total skin leukocytes recovered. A combination of IL-15 and IL-18 yielded maximal recovery of NK cells, though analyses were performed on both cytokine stimulated and non-stimulated cultures. The majority of skin NK cells (as well as skin T cells recovered in parallel) expressed skin homing receptors (CLA, and E- and P-selectin ligands), as well as both α4 and αL integrins, but did not express L-selectin or CCR7, consistent with a peripheral tissue homing phenotype. However, in contrast to skin T cells, only a small fraction of NK cells expressed CCR4 and CCR6 and were negative for CCR10 and CXCR4, indicating skin homing NK cells utilize a different chemokine signal pathway than skin homing T cells. NK cells recovered from peripheral blood or cultures of normal lung tissue expressed much higher levels of CD16 and much lower levels of skin homing receptors (E- and P-selectin ligand) compared to skin resident NK cells, providing evidence for subset selection among the cells resident in skin. The majority of skin NK cells expressed both the surface receptor NKG2D and intracellular perforin and granzyme B, molecules required for NK cell cytotoxic function, and also produced IFN-γ and TNF, but not IL-10 or IL-6. These data show that NK cells in the skin represent a unique population with a distinct profile of homing receptors, cytokine production, and cytotoxic functions as compared to NK cells from blood or lung tissue and compared to T cells from skin. These data suggest that skin resident NK cells may play a role in innate and adaptive immune responses in the skin that is independent from cells recruited from blood, and suggests similar subsets with unique characteristics may be present as resident cells in other tissue sites.

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p21 Suppression of Inflammatory Arthritis Requires the PCNA Domain and Inhibition of p38. Angelica K. Gierut[1], Melissa Mavers[3], Carla M. Cuda[2], Alexander Misharin[2], Evan Weber[2] and Harris R. Perlman[1]. [1]Northwestern University, Chicago, IL, [2]Northwestern University, [3]St. Louis University

Purpose: The etiology of rheumatoid arthritis (RA) is unknown. We have previously shown that RA patient synovium has a reduction of p21, a cell cycle inhibitor. We are also the first to demonstrate a novel role for p21 as suppressor of inflammation. Knock down of p21 in healthy human peripheral blood monocyte-derived macrophages leads to increased production of inflammatory cytokines IL-1β, TNF-α, and IL-6. In addition, mice deficient in p21 have increased in vivo production of inflammatory cytokines and mortality with lipopolysaccharide (LPS)-induced endotoxic shock. Here, we sought to determine the role and mechanism of p21-mediated suppression of experimental inflammatory arthritis.

Methods: WT or p21−/− (C57BL/6) mice were injected intraperitoneally (IP) with 300 μL of K/BxN serum and ankle circumference was measured over 7–25 days. Ankles were then harvested, sectioned, stained for histochemical or immunohistochemical analysis and scored by a pathologist blinded to the study. For phosphoprotein assays, WT or p21−/− mice were injected IP with thioglycollate, and peritoneal macrophages were harvested and cultured in vitro overnight. Cells were stimulated with 10 ng/mL of LPS and cell lysates were collected and analyzed for the phosphorylation status (activation) of various proteins using a multiplex bead array. Similarly, thioglycollate-elicited peritoneal macrophages from WT mice were incubated with several Tat-conjugated peptides corresponding to different domains of the p21 protein (10uM) for 2 hours prior to the addition of LPS (in the presence of peptide). Lysates were analyzed by multiplex bead array. For in vivo studies, WT mice were injected IP with 10 mg/kg peptide 30 minutes prior to K/BxN serum and daily throughout.

Results: Mice deficient for p21 developed increased ankle swelling, joint destruction, and inflammatory infiltrate, as compared to WT mice. There was increased numbers of macrophages in the pannus of p21−/− mice that correlated with bone destruction. Furthermore, the disease failed to fully resolve in p21−/− mice even after 25 days post injection of serum. Treatment with a peptide corresponding to the proliferating cell nuclear antigen (PCNA) binding domain of p21 was superior in suppressing inflammatory arthritis and reduced the numbers of synovial macrophages compared to control peptide. Peritoneal macrophages from mice deficient in p21 demonstrated a consistent increase in the phosphorylation status of the mitogen-activated protein kinase (MAPK), p38, following LPS stimulation compared to those from WT controls. In comparison, a peptide corresponding to the PCNA binding domain of p21 added before LPS significantly decreased the level of phosphorylated p38 compared to those treated with a control peptide.

Conclusion: These data indicate that deficiency of p21 augments experimental arthritis in mice, and that a peptide corresponding to the PCNA binding domain of p21 acts to decrease experimental arthritis via decreased activation of p38. These efforts suggest that p21 is a potential biomarker and/or therapeutic target for RA.

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Peripheral Blood Mononuclear Cells and Plasmacytoid Dendritic Cells from Healthy Human Females Exhibit Altered TLR7-Mediated Immune Responses Compared to Males. Melissa Precopio[1], Dong Yu[2], Ekambar R. Kandimalla[2] and Sudhir Agrawal[2]. [1]Idera Pharmaceuticals, Cambridge, MA, [2]Idera Pharmaceuticals

Background: Toll-like receptors (TLR) are a family of pathogen-associated molecular pattern recognition receptors expressed by cells of the immune system. TLR7 and TLR9 are expressed in endosomal compartments of human B cells and plasmacytoid dendritic cells (pDCs) and recognize molecular patterns of nucleic acids. There is growing evidence that immune complexes containing nucleic acids induce proinflammatory cytokines through TLR7 and TLR9 and exacerbate certain autoimmune diseases. Women are more prone to manifestation of autoimmune diseases than men. This study was carried out to evaluate the differences in immune responses induced through TLR7 and TLR9 in peripheral blood mononuclear cells (PBMCs) and plasmacytoid dendritic cells (pDCs) of healthy female and male subjects.

Methods: We measured cytokine induction and costimulatory marker upregulation in response to specific TLR agonists in PBMCs and pDCs obtained from healthy male (n=15, age: 23–60 years) and female (n=15, age: 18–58 years) subjects. The agonists used in these studies include an RNA-based TLR7 agonist and a DNA-based TLR9 agonist. To further discern differences in TLR7- and TLR9-mediated immune responses in systemic lupus erythematosis (SLE) patients (n=9, age: 29–78 years) on treatment with plaquenil/hydroxychloroquine and healthy female subjects (n=10, age: 22–56 years), we measured cytokine induction in PBMCs in response to TLR7 and TLR9 agonists.

Results: In PBMCs from healthy females, TLR7 agonist induced higher levels of IFN-α, and IP-10 and lower levels of IL-1Ra, IL-1β, IL-6, IL-8 and IL-10 compared with PBMCs from healthy males. The levels of IL-12, MIP-1β, and MCP-1 induced by TLR7 agonist were not different in PBMCs from females and males. pDCs from females showed higher levels of TLR7

agonist-induced IL-12, IP-10, IFN-α, and TNF-α than pDCs from males. TLR9 agonist induced similar levels of immune responses in PBMCs and pDCs from females and males, except IL-1Ra levels were higher in PBMCs from males than females. In studies comparing SLE patients with healthy female controls, TLR7 agonist induced lower levels of IFN-α, TNF-α, IP-10, and IL-6 in PBMCs from SLE patients than healthy females. TLR9 agonist induced lower levels of TNF-α, IL-6, MIP-1α, and MIP-1β in PBMCs from SLE patients than PBMCs from healthy females. The lower levels of TLR7- and TLR9-mediated immune responses in PBMCs from SLE patients could be a result of treatment with plaquenil, an inhibitor of endosomal TLR-mediated immune responses through neutralization of endosomal acidification.

Conclusions: Notable differences in TLR7-mediated immune responses were observed in PBMCs and pDCs from healthy females compared with males that may play a role in autoimmune diseases afflicting females disproportionately.

Disclosure: M. Precopio: Idera Pharmaceuticals, 1, 3; **D. Yu:** Idera Pharmaceuticals, 1, 3; **E. R. Kandimalla:** Idera Pharmaceuticals, 1, 3; **S. Agrawal:** Idera Pharmaceuticals, 1, 3.

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Post-Translational Control Mechanisms Regulate Dendritic Cell Activation of T Cell Responses. Dana Orange[1], Jak Fak[2], Nathalie Blachere[2] and Robert Darnell[2]. [1]The Hospital for Special Surgery, [2]The Rockefeller University

Purpose: In addition to being some of the most potent of antigen presenting cells, dendritic cells (DCs) have the unique capability of cross presenting. When DCs phagocytose an apoptotic cell, antigen acquired from that cell can be presented on the cell surface in the context of MHCI in addition to MHCII to activate cytotoxic CD8 T cells. It has been demonstrated that in order for this cross presentation pathway to lead to CD8 T cell activation, the DC needs to be licensed by an activated CD4 T cell via CD40L stimulation. The steps downstream of CD40 signaling that allow for cross presentation remain unclear. Work from our group previously showed that although they are both calcineurin inhibitors, FK506 but not cyclosporine blocks DCs from being able to stimulate T cells via the cross presentation pathway. Microarray from cyclosporine and FK506 treated DCs failed to show any differences on the level of mRNA expression. The goal of this project was to evaluate whether new gene transcription or translation is required for DCs to cross present to CD8 T cells.

Methods: Healthy donors PBMCs were cultured with IL 4 and GMCSF for 6 days. Immature DCs were allowed to phagocytose flu infected apoptotic 3T3 cells and then matured with TNF and PGE2. Antigen presenting DCs were then treated with either actinomycin D or cycloheximide, inhibitors of transcription and translation respectively, and cocultured with MACS purified CD8 T cells + CD40L to substitute for CD4 help and assayed for IFNγ induction via RT-PCR.

Results: DCs treated with actinomycin D were blocked in their ability to accomplish any new gene transcription via PCR for IL12p35, IL12p40, TNF, IL6 and IP10 in response to LPS stimulation when compared to untreated control. Despite the transcriptional blockade, they were competent in their ability to cross present and activate antigen specific T cell responses as measured via RT-PCR for T cell induction of IFNγ mRNA. Similarly, cycloheximide treated DCs were also competent to activate T cell responses via the cross presentation pathway.

Conclusion: This work demonstrates that DC licensing for the cross presentation pathway is under a mechanism of post-translational control. In the absence of CD40L signaling, DC cross presentation results in cross tolerance. The finding that transcriptionally and translationally blocked dendritic cells can still activate CD8 T cell responses indicates that key signaling events downstream from CD40L stimulation do not require transcription or translation. As immune responses require some of the fastest reaction times in the body, it stands to reason that a critical switch between activation and tolerance would not require the time for new gene transcription or translation. Instead, we propose that the essential control of DC licensing is likely to be a protein that has been translated but held in a conformationally inactive state.

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Reduced T-Cell-Dependent Humoral Immune Response in Microsomal Prostaglandin E Synthase-1 Null Mice. Rahul G. Matnani[2], Fumiaki Kojima[2], Jerold G. Woodward[2] and Leslie J. Crofford[1]. [1]Univ of KY, Lexington, KY, [2]Univ of KY

Microsomal prostaglandin E synthase-1 (mPGES-1) is an inducible enzyme that specifically catalyzes the conversion of prostaglandin (PG)H_2 to PGE_2, most prominently in inflammatory conditions. We previously showed that mPGES-1 null mice had a significantly reduced incidence and severity of collagen-induced arthritis (CIA) compared to wild-type mice. Reduced CIA was associated with a marked reduction of antibodies to type II collagen, known to be required for developing autoimmune inflammatory arthritis in this model. In the present study, we further elucidated the role of mPGES-1 in the humoral immune response. Basal levels of serum IgM and IgG were significantly reduced in mPGES-1 null compared with wild-type mice ($P<0.05$), but IgM and IgG production in splenocytes treated *ex vivo* with LPS were not different. Immunization with either the T-cell independent type-1 antigen TNP-LPS or the T-cell independent type-2 antigen DNP-Ficoll revealed minimal differences in hapten-specific antibody levels when comparing mPGES-1 null and WT mice. However, mPGES-1 null mice exhibited significant reduction of hapten-specific serum antibodies compared with wild-type mice in response to immunization with the T-cell dependent antigen DNP-KLH in CFA including IgM (days 7–21 post-immunization, $P<0.05$) and IgG (days 7–28 post-immunization, $P<0.05$). Germinal center formation in the spleen of mPGES-1 null mice was phenotypically similar to WT mice in response to immunization with DNP-KLH when evaluating the %PNA positive germinal centers to IgD positive regions (43.5 ± 1.8 vs 40.8 ± 2.1, P=NS). To determine if the effect of mPGES-1 and PGE_2 was related to hematopoietic or non-hematopoietic cells, we generated bone marrow chimeras. The results indicate that mPGES-1 deficiency in non-hematopoietic cells was the critical factor for reduced antibody production after immunization with DNP-KLH since transfer of mPGES-1 null bone marrow (BM) to non-lethally irradiated WT recipients expressed hapten-specific antibodies equal to the WT BM→WT, but WT BM→mPGES1 null expressed reduced antibodies similar to mPGES1 null BM→null. We conclude that PGE_2-dependent inflammation during immunization plays a key role in T-cell dependent humoral immune responses, likely as a result of altered T-cell phenotype. These findings may have relevance to the pathogenesis of autoimmune inflammatory arthritis associated with autoantibodies such as rheumatoid arthritis.

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Regulation of VLA-4 in SLE Monocytes. Homaira Rahimi[1] and Kathleen E. Sullivan[2]. [1]Children's Hosp Philadelphia, Philadelphia, PA, [2]Childrens Hosp of Philadelphia, Philadelphia, PA

Objectives: The development of atherosclerosis and subsequent increased risk of cardiovascular disease (CVD) is known to be associated with inflammation. Studies have shown an increased risk of CVD in systemic lupus erythematosus (SLE). Inflammation seen in atherosclerosis involves various immune mediators, including interactions between adhesion molecules on endothelial cells and on monocytes. Very late antigen-4 (VLA-4) is an adhesion molecule in the integrin family found on monocytes and has been implicated in monocyte recruitment during development of atherosclerosis. A recent study noted an increased expression of VLA-4 in SLE monocytes, but the regulation is poorly understood. We aimed to further define variables governing the expression of VLA-4 on monocytes in patients with SLE compared to healthy controls.

Methods: CD14+ human monocytes were obtained from whole blood of healthy adult patients and SLE patients. Flow cytometry was used to measure expression of VLA-4 at rest and upon exposure to various agents, including interferon gamma, interferon alpha, interleukin-4, and vitamin D. VLA-4 mRNA expression in SLE and healthy monocytes was measured using qRT-PCR. Healthy monocytes were incubated in control and SLE sera, and VLA-4 was expression evaluated using flow cytometry and immunofluorescence (IF).

Results: VLA-4 (CD49d) expression was significantly higher on control monocytes compared to SLE monocytes as measured by mean fluorescence intensity ($p<0.05$). However, levels of VLA-4 mRNA were significantly lower in control monocytes compared to SLE monocytes ($p<0.05$). Exposure

of healthy monocytes to healthy human sera compared to SLE sera did not result in differences in cell surface expression of VLA-4; however, VLA-4 was redistributed to the interior of the cell. IF staining of VLA-4 of healthy monocytes incubated in SLE sera demonstrated VLA-4 in a vesicular compartment whereas healthy monocytes incubated in healthy sera or RPMI media alone exhibited VLA-4 staining on the surface or diffusely in the cytoplasm.

Conclusion: There was a significant down-regulation of cell surface expression of VLA-4 in SLE monocytes as compared to the healthy population, although mRNA levels were increased. We demonstrated that exposure to SLE sera causes increased internal IF staining of VLA-4, suggesting that decreased surface expression, in spite of increased RNA levels, in SLE is due to altered distribution. VLA-4 has increased expression in atherosclerosis and understanding its up-regulation in SLE patients could have implications for the prevention and treatment of advanced atherosclerosis in SLE. In addition, VLA-4 is capable of intracellular signaling. If there is an altered distribution of VLA-4 in SLE monocytes, this might affect the inflammatory pathway in SLE. These data provide a context for considering novel therapeutics to treat atherosclerosis in SLE.

Disclosure: H. Rahimi: None; **K. E. Sullivan:** None.

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The Cholinergic Anti-Inflammatory Pathway as a Modulator of Immune Complex-Induced Acute Inflammation. Milena Vukelic[2], Gloria Koo[2] and Jane E. Salmon[1]. [1]Hospital for Special Surgery, New York, NY, [2]Hospital for Special Surgery, New York, NY

Purpose: The "cholinergic antiinflammatory pathway" is a neural mechanism by which the efferent vagus nerve leads to stimulation of nicotinic acetylcholine receptors (nAchR) on immune cells and thereby inhibits their synthesis of proinflammatory mediators in response to innate immune stimuli. Its role in antibody-mediated injury, such as that present in SLE, has not been explored. We hypothesized that ligation of nAChRs would downmodulate C5aR- and FcγR-triggered activation of neutrophils and monocytes and limit immune complex-triggered inflammation. We examined effects of nAChR ligation on in vitro markers of activation related to tissue damage generation of reactive oxygen species (ROS), production of TNFα, IL-6 and expression of adhesion molecule, as well as in vivo effects with the peritoneal Arthus reaction.

Methods: Human or mouse (C57/Bl6) neutrophils (PMNs) and human monocytes were incubated with C5a (100nM) or model IC (heat-aggregated IgG) in a presence of cholinergic agonists, acetylcholine (Ach) (10mM), nicotine (1mM) or GTS21 (specific α7nAChR agonist) (1mM), nAchR agonist with a competitive nAchR antagonist meccamylamine, or control medium. ROS was measured by dihydrorhodamine$_{123}$ by FACS. TNF$^{\alpha}$, IL-6 levels were analyzed by ELISA. Peritoneal reverse passive Arthus reaction was initiated by injecting OVA i.v. and anti-OVA IgG i.p. After 3hrs PMN recruitment in peritoneal lavage fluid was assessed by FACS.

Results: In human PMN ligation of nAchR with $^{\alpha}$7nAChR agonist GTS21, Ach (naturally occurring nAchR ligand) or nicotine markedly inhibited C5a-induced ROS generation (vs control, 69±8%,p=0.014; 48±9%, p=0.035; 30±5%, p<0.05, respectively). This effect was partially reversed by nAchR antagonist meccamylamine. Similarly, FcγR-mediated ROS was decreased by nicotine (38±11%; p=0.029) and ROS generation by immune complexes (IC) in a presence of normal human serum, reflecting the synergism between C5aR and FcγR in PMN, was also attenuated (63±14%; p=0.029). Experiments with mouse PMN showed similar results. PMN recruitment to the sites of inflammation in response to C5aR requires upregulation CD11b, another effect inhibited by nicotine (251±46 vs. 139±20; p<0.05). At sites of IC deposition, proinflammatory cytokine release is blunted by nAchR. C5aR-triggered TNFα release by human monocytes was abrogated (9045±4402 vs. 49±10pg/mg). There was a similar, albeit less dramatic, decrease in FcγR-mediated cytokines production (TNFα 45±44%; IL-6 46±2%). In vivo effects of nAChR ligation confirmed our in vitro studies. In the peritoneal Arthus reaction, a single i.p. dose of the nAChR agonist GST21 or nicotine decreased PMN recruitment by 65% (342±50×10^6 vs. 122±29x 10^{6}cell/ml;p<0.05) and by 54% (318±27×10^6 vs. 144±7×10^{6}cell/ml;p<0.05), respectively. In addition, GTS21 decreased TNFα levels in the peritoneal fluid (35±2.4 vs. 23±3.2pg/ml).

Conclusions: Our data show that cholinergic anti-inflammatory pathway modulates responses to elements of the adaptive immune system, FcγR and C5aR. We identified nAchR as a novel target to attenuate release of oxidants, influx of inflammatory cells and generation of injurious cytokines at sites of IC deposition.

Disclosure: M. Vukelic: None; **G. Koo:** None; **J. E. Salmon:** None.

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The Help of Autoantibody-Inducing CD4$^+$ T Cell and Antigen Cross-Presentation Are Required for the Full-Maturation of Cytotoxic T Lymphocyte and Subsequent Lupus Kidney Disease. Yumi Miyazaki[1], Ken Tsumiyama[1] and Shunichi Shiozawa[2]. [1]Department of Biophysics, Kobe University Graduate School of Health Science, Kobe, Japan, [2]Department of Biophysics, Kobe University Graduate School of Health Science/ Department of Medicine, Kobe University Graduate School of Medicine/The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan

Objective: A novel 'self-organized criticality theory' explaining the cause of systemic lupus erythematosus (SLE) of ours (Tsumiyama K. *et al.* PLoS ONE 4(12):e8382, 2009) shows that overstimulation of CD4$^+$ T cell beyond its self-organized criticality results in *de novo* generation of autoantibody-inducing CD4$^+$ T (*ai*CD4$^+$ T) cell with T cell receptor (TCR) revision. The *ai*CD4$^+$ T cells induced not only autoantibodies including rheumatoid factor (RF), anti-Sm and anti-dsDNA antibody but also full-matured cytotoxic T lymphocyte (CTL) *via* antigen cross-presentation, after which the CTL caused lupus kidney disease. Here we investigated the contribution of *ai*CD4$^+$ T cell-help to the pathogenesis of immune tissue injury, and show that *ai*CD4$^+$ T cell-help and antigen cross-presentation are both essentially required for generating full-matured effector CTL and subsequent lupus tissue injuries.

Methods: BALB/c mice were immunized 12x with ovalbumin (OVA). The mice were depleted CD4$^+$ T cells by treating anti-CD4 antibody 24 hours prior to 6x, 9x, and 12x immunization with OVA, and IFNγ$^+$CD8$^+$ T cell in spleen and proteinuria were examined. The *ai*CD4$^+$ T cell of the mice immunized 12x with keyhole limpet hemocyanin (KLH) was transferred into the CD4$^+$ T cell-depleted mice immunized 8x with OVA, and IFNγ$^+$CD8$^+$ T cell and proteinuria were examined. We also transferred pre-mature CD8$^+$ T cell of the mice immunized 8x with OVA into the mice immunized 12x with KLH to induce *ai*CD4$^+$ T cell. These recipient mice were immunized 1x with OVA and KLH, followed by treating with chloroquine to inhibit antigen cross-presentation.

Results: In the mice immunized 12x with OVA, depletion of CD4$^+$ T cells by treating anti-CD4 antibody abrogated the induction of IFNγ-producing effector CD8$^+$ T cell and lupus kidney disease. To test whether this CD4$^+$ T cell-mediated help is mediated by *ai*T cells or antigen-specific T cells, we have transferred CD4$^+$ T cells from mice immunized 12x with KLH into the CD4$^+$ T cell-depleted BALB/c mice immunized 8x with OVA. The result showed that both immune tissue injury and OVA-specific IFNγ$^+$CD8$^+$ T cells arose in these mice after transfer, indicating that *ai*CD4$^+$ T cells with *de novo* TCR revision are required for the full-maturation of CD8$^+$ T cell and lupus kidney disease. We next studied if *ai*CD4$^+$ T cell could induce effector CTL and/or tissue injury in the absence of antigen cross-presentation or not, we transferred the pre-matured CD8$^+$ T cells obtained from the mice immunized 8x with OVA, in which CTL was not full-matured, into the mice immunized 12x with KLH containing *ai*CD4$^+$ T cells. Upon booster immunization 1x with KLH and OVA, *ai*CD4$^+$ T cell, IFNγ-producing effector CD8$^+$ T cell (CTL) and proteinuria were all increased. However, when chloroquine which inhibits antigen cross-presentation was added, IFNγ-producing effector CTL and proteinuria were both abolished, indicating that *ai*CD4$^+$ T cell-help and antigen cross-presentation are required for the development of lupus kidney disease.

Conclusion: The help of *ai*CD4$^+$ T cell and antigen cross-presentation are *sine qua non* for the full-maturation of effector CTL and subsequent lupus kidney disease.

Disclosure: Y. Miyazaki: None; **K. Tsumiyama:** None; **S. Shiozawa:** None.

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Unique Role of the FcγRI (CD64) Cytoplasmic Domain in Mediating Phosphorylation Dependent Lipid Raft Localization. Andrew G. Gibson[3], Xinrui Li[3], Jeffrey C. Edberg[2] and Robert P. Kimberly[1]. [1]Univ Alabama at Birmingham, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL, [3]University of Alabama at Birmingham

The overproduction of type I Interferon and systemic inflammation in lupus patients correlates with increased monocyte surface expression of FcγRI (CD64), a receptor for both IgG and C reactive protein (CRP). Despite signaling through the common ITAM motifs shared by other activating FcγRs, FcγRI mediates distinct cellular programs such as the cell surface cleavage and release of functional soluble BLyS/BAFF upon FcγRI cross-linking by CRP or IgG. To explore the mechanism(s) of additional unique

FcγRI properties, we probed the critical contributions of the distinct cytoplasmic tail (CY) of FcγRI α-chain in inducing receptor functions. Unlike other FcR, the FcγRI CY domain contains serine residues that are phosphorylated by CK2 in vitro, and the cytoplasmic domain of FcγRI is constitutively phosphorylated in resting cells. As a consequence, the binding of protein 4.1G, a novel partner associated with FcγRI α-chain CY but not with other FcR CY, is greatly promoted when FcγRI CY is phosphorylated. Since other members of the protein 4.1G family (the Four.1 protein, Ezrin, Radixin, Moesin (FERM) family) have been shown to facilitate lipid raft association of TCR and BCR to promote formation of immunological synapses, we hypothesized that serine phosphorylation of FcγRI CY with increased association with protein 4.1G would further promote the ability of FcγRI to associate with lipid rafts. Consistent with earlier reports, we observed that FcγRI constitutively resides in lipid rafts in macrophages transfected with human FcγRI. However, in cells transfected with a mutated form of human FcγRI lacking the ser-based CK2 phosphorylation site(s), FcγRI was distributed predominately outside of lipid microdomains, indicating that phosphorylation of FcγRI CY is required for lipid raft colocalization. These results are consistent with a role for protein 4.1G in tethering FcγRI within lipid rafts. The phosphotyrosine-based γ-chain signaling plus the phosphoserine-based α-chain signaling form a unique FcγRI signaling pathway. These results provide additional insights into the unique signaling potential of FcγRI that can explain the previously documented unique functional potential of FcγRI. Further mechanistic studies into the regulation of FcγRI function will allow a determination of the importance of increased expression of this receptor in patients with lupus.

Disclosure: A. G. Gibson: None; **X. Li:** None; **J. C. Edberg:** None; **R. P. Kimberly:** None.

ACR Poster Session B
Metabolic and Crystal Arthropathies - Pathogenesis, Epidemiology, and Clinical Manifestations II
Tuesday, November 9, 2010, 9:00 AM–6:00 PM

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A Prospective Study of Correlates of Axial Gout. Rukmini M. Konatalapalli[4], Elena Lumezanu[3], James Jelinek[3], Mark Murphey[1], Elizabeth Carter[2] and Arthur Weinstein[3]. [1]Armed Force Institute, [2]Medstar Health Research Institute, [3]Washington Hospital Center, [4]Washington Hospital Center, DC

Objective: Axial gout is considered to be a rare manifestation of gouty arthritis. In our earlier retrospective study we found prevalence of axial gout to be 14%. This prospective study was done to determine the prevalence of axial gout in a population of patients with established gouty arthritis and to analyze potential clinical, laboratory and radiological correlates.

Methods: Forty eight subjects with a history of gouty arthritis (ACR criteria) for 3 or more years and who had an attack of acute gouty arthritis or had hyperuricemia in the previous year, were included. Subjects were questioned about back pain, examined clinically for arthritis, joint deformities and subcutaneous tophi, and had radiographs of the hands and feet, as well as computerized tomographic (CT) scan without contrast (the preferred imaging modality to detect gouty erosive disease in the spine) of the cervical spine, lumbar spine and sacroiliac joints (SIJs), serum uric acid level and serum creatinine. CT scans were read by one of three radiologists who were blinded to results of the radiographs and the radiographs were read by an experienced rheumatologist (AW) who had no knowledge of CT scan results. Patients with characteristic erosions and/or tophi in the spine or SIJs were considered to have axial or spinal gout. For statistical analysis Fisher's exact test and Wilcoxon Two-Sample tests were used.

Results: Seventeen patients (35%) had CT scan evidence of spinal gout-erosions and/or tophi. Tophi in the axial skeleton were identified in 7 of the 48 subjects (14.6%). In the entire studied population the mean age was 61years, mean duration of gout was over 10years in 26 (54%) and less than 10years in 22 (46%), mean serum uric acid level was 7.7mg/dl and 22 (46%) had clinical tophi. Thirty five (73%) were men and 42 (87%) were African American. No correlations were found with these variables and spinal gout nor was there any correlation with the presence of back pain which occurred in 24 (50%) patients. The location of the characteristic CT changes of axial gout was 7 (42%) cervical, 16 (94%) lumbar and 1 (6%) SIJs. Fourteen patients (82%) had axial gout in more than one location. Abnormal hands and feet radiographs were found in 21 (44%) patients and strongly correlated with CT scan evidence of axial gout ($p < 0.0005$). All patients with tophi in the spine had abnormal hand and/or feet radiographs ($p<0.005$).

Conclusion: Axial gout may be a common feature of gouty arthritis, at least in our predominantly African American population with poorly controlled gouty arthritis. The lack of correlation with clinical back pain, the use of magnetic resonance imaging rather than CT imaging in patients with back pain and the lack of recognition of the problem of spinal gout by physicians, suggest that this diagnosis is often missed.

Disclosure: R. M. Konatalapalli: None; **E. Lumezanu:** None; **J. Jelinek:** None; **M. Murphey:** None; **E. Carter:** None; **A. Weinstein:** None.

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Acute Gout Results in Increased Plasma Myeloperoxidase: A Potential Mechanism for Increase Cardiovascular Risk? Lisa K. Stamp[1], Irada Khalilova[2] and Tony Kettle[2]. [1]University of Otago, Christchurch, New Zealand, [2]University of Otago

Background: Gout is the most common form of inflammatory arthritis in men >40 years age. While the joint manifestations of gout dominate, patients with gout have a substantially increased risk of cardiovascular disease (CVD). However, not all of the increase is explained by traditional cardiovascular risk factors. Myeloperoxidase (MPO), which is released from neutrophils as part of the inflammatory process, has been implicated in the pathogenesis of CVD and is associated with coronary artery disease. The aim of this study was to determine whether MPO concentrations were increased in patients with acute and/or controlled gout.

Methods: 40 patients with gout (20 with acute gout, 20 with inter-critical gout) and 12 healthy controls were recruited. Plasma was assayed for urate, MPO protein and MPO activity. Urate was measured by HPLC and MPO protein and activity by ELISA.

Results: 4/12 healthy controls (HC), 17/20 acute gout and 19/20 inter-critical gout patients were male. The age (mean (range)) was 40.5 years (20–52) HC, 55.5 years (34–91) acute gout, and 63.2 years (42–82) inter-critical gout. As expected plasma urate was significantly higher in the subjects with acute gout ($465 \pm 101 \mu M$) as compared to those with inter-critical gout ($357 \pm 87.8 \mu M$) ($p<0.05$). Plasma MPO protein was significantly higher in patients with acute gout compared to healthy controls, but not significantly different from those with inter-critical gout. MPO activity was significantly increased in patients with acute gout as compared to those with inter-critical gout and HC (Figure 1).

Conclusions: MPO is released during the acute inflammatory response associated with gout flare. This increase in MPO provides another mechanism for the increase in cardiovascular disease seen in gout patients. More active MPO in patients with acute gout may contribute to oxidative stress in the vasculature and the increased CVD risk. Further studies are required to determine the association between MPO and CVD in patients with gout.

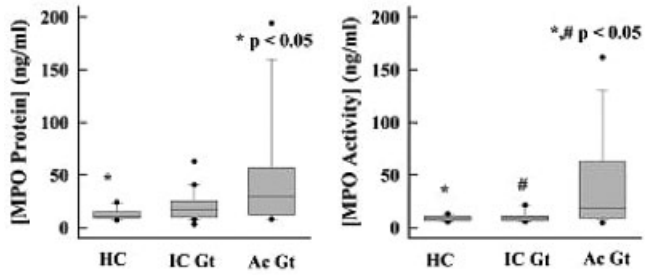

Figure 1. Plasma MPO protein and activity in 12 healthy controls (HC), 20 patients with inter-critical gout (IC Gt), and 20 patients with acute gout (Ac Gt). Comparisons were made using ANOVA on ranks and Dunn's method for post-hoc analysis.

Disclosure: L. K. Stamp: None; **I. Khalilova:** None; **T. Kettle:** None.

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A-SAA Induces Cytokine Production and Matrix Metalloproteinase Activity in Adipose and RA Synovial Tissue. Jennifer McCormick, Ronan M. Mullan, Mary Connolly, Chin Teck Ng, Ursula Fearon and Douglas J. Veale. Dublin Academic Medical Centre, Dublin, Ireland

Background: Rheumatoid Arthritis (RA) is associated with a significant increase in cardiovascular (CV) mortality. Serum Amyloid A (A-SAA), an acute phase protein with cytokine-like properties is increased 1000 fold

during inflammation. Previously we showed A-SAA correlates with RA disease activity and is produced at high levels in the synovial joint. Elevated A-SAA production has been observed in metabolic syndrome in adipose tissues (AT) of type II diabetics but to date the role and regulation of A-SAA in human AT remains to be fully elucidated.

Aim: To examine the relationship of A-SAA to CV risk in RA and whether a common pro-inflammatory pathway exists for A-SAA in RA and obesity.

Methods: Forty RA patients were recruited and assessed at baseline, 0.5, 1 and 4 years. RA disease activity measures and paired serum were collected. Baseline CV risk criteria were obtained and CV events were recorded in follow up. A-SAA serum levels were quantified by specific ELISA. Adipose tissue was obtained under direct visualisation from patients undergoing bariatric surgery or colonoscopy and primary adipocytes and whole tissue adipose explants were cultured. RA synovial biopsies were obtained at arthroscopy and whole tissue synovial explants established. Cell cultures were incubated in the presence of A-SAA (10–50 g/ml) and interleukin-6 (IL-6) and interleukin-8 (IL-8) production were quantified by specific ELISA. Matrix metalloproteinase-2 and −9 activation were assessed by gelatin zymography.

Results: RA patients who developed CV events up to 4 years later had significantly higher baseline A-SAA levels ($p<0.05$) which remained elevated in the follow-up period. No significant difference was found in traditional CV risk factors. A-SAA (10 and 50 g/ml) increased baseline production of IL-8 from 1528588 to 5194462 and 10963497 pg/ml and IL-6 from 549564 to 3392226 and 6629568 pg/ml in adipose tissue explant cultures in vitro. In adipocyte cultures, A-SAA (10 g/ml) markedly increased levels of IL-8 from 21495 to 33333 pg/ml and IL-6 from 4483 to 7566 pg/ml. Furthermore, a dramatical increase in MMP-9 activation was observed in adipose tissue explants, an effect greater than that on MMP-2 activity. Similar to adipose tissue cultures a dramatical upregulation of IL-8 from 1948 to 4739 and 5075 pg/ml production and activation of MMP-2 and 9 was demonstrated in RA synovial explant cultures in response to A-SAA (10 and 50 g/ml).

Conclusion: High serum A-SAA levels are associated with increased cardiovascular events over a 4 year period. Ex-vivo/in vitro A-SAA induced similar pro-inflammatory pathways in synovial and adipose tissue, which may represent common pathogenic pathways in RA and metabolic syndrome.

Disclosure: J. McCormick: None; **R. M. Mullan:** None; **M. Connolly:** None; **C. T. Ng:** None; **U. Fearon:** None; **D. J. Veale:** Abbott Laboratories, 2, 5, 8, Centocor Ortho Biotech Inc., 5, 8, GlaxoSmithKline, 2, 5, 8, Mundipharma, 2, 8, Opsona Therapeutics Ltd, 2, 8, Pfizer Inc, 5, 8, Schering-Plough, 5, 8, Wyeth Pharmaceuticals, 2, 5, 8.

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Association of Vitamin K and Chondrocalcinosis of the Knee: The MOST and Framingham Osteoarthritis Studies. Devyani Misra[3], Sarah L. Booth[8], Micheal LaValley[3], Irina Toltsykh[6], Micheal Nevitt[6], C. Elizabeth Lewis[5], James Torner[7], Piran Aliabadi[4], David T. Felson[2] and Tuhina Neogi[1]. [1]Boston Univ Schl of Med, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]BUSM, Boston, MA, [4]BWH, Harvard University, Boston, MA, [5]UAB, Birmingham, AL, [6]UCSF, San Francisco, CA, [7]U-Iowa, Iowa City, IA, [8]USDA HNRCA, Tufts University, Boston, MA

Purpose: Vitamin K (VK) plays a key role in regulation of calcification in soft tissue. A knockout mice model demonstrated that in absence of a VK–dependent protein (MGP), there was excessive calcification of cartilage. Because chondrocalcinosis (CC) has a low prevalence in the general population, we studied the association of VK with CC in two cohorts: The Multicenter Osteoarthritis (MOST) Study and the Framingham Osteoarthritis Study, to obtain sufficient numbers for this study.

Method: Participants were from the MOST Study (cohort of persons with or at high risk for knee osteoarthritis (OA) and the Framingham Osteoarthritis Study (community-based cohort unselected for OA) who had knee x-rays obtained and serum VK (phylloquinone) measured. X-rays for both studies were read for presence of CC at baseline and follow up visits by the same academically based MSK radiologist. A person was classified as having CC if it was present in either knee at either of two time points. We examined the association of VK with prevalent CC in both cohorts combined, with VK assessed as 1) dichotomous variable, deficient (serum phylloquinone <0.5 nM) vs not deficient and 2) quartiles, using Poisson regression to calculate prevalence ratios (PR), adjusting for age, sex, BMI, BMD, 25(OH)-D, warfarin use, race, cohort and history of knee injury. We also performed local regression (LOESS), which avoids assuming a parametric form, plotting phylloquinone concentrations (log-transformed) against prevalence of CC. Effect measure modification by cohort was tested separately.

Result: Among 1795 participants (1180 from MOST, 615 from Framingham; mean age 59±9.2 yrs, 59% women, mean BMI 29±5.6 kg/m^2, mean serum phylloquinone concetration 1.7±1.8 nM, range 0–22nM), there were 126 subjects with prevalent CC. Those who were VK deficient had 40% higher prevalence of CC compared with those who were not VK deficient, although this was not statistically significant (PR 1.4, 95% CI 0.8–2.4, $p=0.3$), and did not change with exclusion of warfarin users. Although all VK deficient individuals (n=173) were in the lowest quartile of VK, the analysis using serum VK quartiles did not demonstrate a dose-response relation, but rather suggested a potential U-shaped relation (adjusted PR: 1.0 (ref), 0.8, 0.9, 0.9 for quartiles 1 through 4, respectively). However, the local regression plot did not suggest any linear or other association (Fig. 1). There was no effect measure modification by cohort.

Conclusion: Although there seems to be a plausible biologic rationale for an association of deficient VK with CC, we were unable to find such an association in our study using serum phylloquinone. Because this association remains unclear, further studies are warranted to explore potential effects of VK on extra-skeletal mineralization, using different measures of VK.

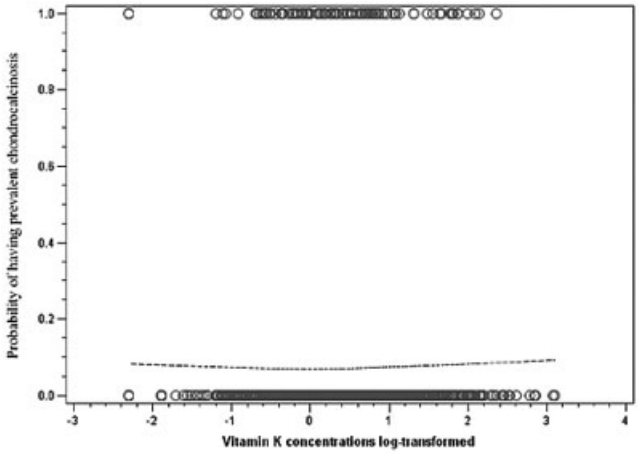

Fig. 1. Local regression (LOESS) plot of association of vitamin K with prevalent chondrocalcinosis.

Disclosure: D. Misra: None; **S. L. Booth:** None; **M. LaValley:** None; **I. Toltsykh:** None; **M. Nevitt:** None; **C E. Lewis:** None; **J. Torner:** None; **P. Aliabadi:** None; **D. T. Felson:** None; **T. Neogi:** None.

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Calcium Pyrophosphate Crystal Arthritis (CPPA) Is a Frequent Cause of "Refractory Gout". Fernando Perez-Ruiz[1], Ana M. Herrero-Beites[3], Alberto Alonso-Ruiz[2] and Marcelo Calabozo[2]. [1]Hospital de Cruces, Jopelana, Spain, [2]Hospital de Cruces, [3]Hospital de Górliz

Background: Proper treatment of hyperuricemia of gout is associated with a reduction in the number of flares to less than 10% of patients after 12-month therapy suffer from gout flares (Schumacher HR, Rheumatology 2009, Becker MA, J Rheumatol 2009).

Objective: to evaluate the impact of coexistent CPPA in joint flares in patients with gout.

Methods: analysis of data from a cohort of 610 patients with a diagnosis of gout based on monosodium urate (MSU) crystal observation and who showed proper control (serum urate <6 mg/dl) of uric acid at 12-month follow-up, and colchicine prophylaxis stopped. CPPA was defined as presence of CPP crystals in the cytoplasm of white cells in synovial fluid (SF) samples and radiographic chondrocalcinosis. Microscopy procedures for observation and identification of MS and CPP crystals included normal light and polarized light with first order red compensator 400x. Contrast-phase 400x and 1000x microscopy was used was used in addition to further investigate SF samples negative for crystals with normal and polarized microscopy.

Results: 23/610 (3.8%) patients with crystal-proven gout also had a diagnosis of CPPA. Of them, 6 showed both MSU and CPP crystals in the same synovial fluid sample, prior or during the first year of urate-lowering treatment, so they were maintained on colchicine prophylaxis and not included in further analysis. The remaining 17 patients showed CPP crystals during further follow-up, CPPA appearing at mean follow-up of 40±16 months (range 18 to 94). Overall, 49/610 (8.03%) patients had at least an episode of acute arthritis that was attributed to "refractory" gout, 17/49 (34.7%) showing CPP crystals in the cytoplasm of leukocytes and Xray chondrocalcinosis. There was no difference in any feature in patients with gout vs. patients with gout+CPPA, except for mean age (59±12 vs.

71±12 years), BMI (28.1±3.6 vs.26.5±3.3 kg/m^2), and clearance of creatinine (87±33 vs. 62±30 ml/min).

Conclusions: definite CPPA in patients with crystal proven gout is found in up to 4% of patients with gout. CPP arthritis comprised for one third of the flares that appeared after 1-yr control of hyperuricemia. Synovial fluid samples should be obtained and carefully studied before considering "refractory gout" diagnosis.

Disclosure: F. Perez-Ruiz: None; **A. M. Herrero-Beites:** None; **A. Alonso-Ruiz:** None; **M. Calabozo:** None.

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Clinical and Genetic Subtypes of Hyperuricemia in a Renal Transplant Cohort. Gabriela Hernandez-Molina, Julio Granados, Adriana Torres, Antonio Cachafeiro-Vilar and Marina Rull-Gabayet. Instituto Nacional de Ciencias Medicas y Nutricion, Mexico City, Mexico

Background: Hyperuricemia, a highly frequent condition (84%) in renal transplant (RT) patients, has been mainly associated with the use of calcineurin inhibitors. We reported a higher incidence of gout in patients with hyperuricemia pre-transplant than patients who developed this condition after the allograft (19.7 vs. 2.6 ×1000 patient-years). The use of cyclosporine and tacrolimus were not the major variables linked to this finding.

Objective: We hypothesized that a specific HLA background may influence the development or not of hyperuricemia in RT patients.

Methods: We included 162 RT patients with at least one year of follow-up post-transplant. Hyperuricemia was defined as at least one elevated serum uric acid determination of >6 mg/dl in women and >7 mg/dl in men. Patients were divided in groups: 1) without hyperuricemia pre-transplant but with it after the allograft (n=40), 2) without hyperuricemia pre and post-transplant (n=28) and 3) with established pre-transplant hyperuricemia (n=94). HLA class I (HLA-A, HLA-B) and HLA class II (HLA-DRB1, HLA-DQB1) were assessed by a PCR-SSP procedure. Gene frequencies were compared using the Mantel-Haenszel chi-square or Fisher's exact test. HLA allele and haplotype frequencies were obtained by gene counting. Hardy–Weinberg (HW) equilibrium and LD (Arlequin ver. 2.0) as well as admixture estimations using the HLA-B typing in a trihybrid model with the *maximum likelihood* method (Leadmix software) were calculated. Ethnic-specific HLA-A/-B/-DRB1/-DQB1 haplotypes in a Mexican-mestizo parental population (n=381) were used as controls.

Results: The mean follow-up of the cohort was 4.7±2.9 years. Group 1 had a tendency to be increased of HLA-B*35 and B*39 as compared to Group 2 (p=0.07). HLA-B*35 and B*39 were significantly increased in Group 2 as compared to Group 3 (p=0.04, RR=1.6, CI 95%=1.0–2.7); likewise these alleles were also significantly increased in Group 2 as compared to ethnically matched healthy controls (p=0.008, OR=2.3, CI 95%=1.2–4.4 for B*35; and p=0.03 OR=2.3, CI 95%=1.0–4.8 for B*39). The HLA-B*07 allele was significantly increased in Group 3 as compared to healthy controls (p=0.03, OR=2.1, CI 95%=1.0–4.5). None patient belonging to Group 2 was positive for HLA-B*07. Group 2 also had an increased frequency of HLA-DR*08 as compared to healthy controls (p=0.04, OR=2.1, CI 95%=1.0–4.4) that was independent for that observed in alleles at the HLA-B locus. The frequency of the rest of the HLA-B and HLA-DR alleles as well as the haplotype analysis was similar among groups.

Conclusion: The hyperuricemia observed in RT patients is clinical and genetically heterogeneous, suggesting subgroupsof patients with different physiopathogenic mechanisms. Typing for the MHC alleles might select patients highly sensitive or refractory for its development and may help in the selection of immunosuppressive and hypouricemic treatments.

Disclosure: G. Hernandez-Molina: None; **J. Granados:** None; **A. Torres:** None; **A. Cachafeiro-Vilar:** None; **M. Rull-Gabayet:** None.

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Diffuse Calcium-Containing Crystal Deposits in Human Osteoarthritic Articular Cartilage: Not Limited to the Medial Compartment. Christelle Nguyen[4], Hang-Korng Ea[4], Didier Hannouche[2], Michel Daudon[3], Dominique Bazin[1] and Frédéric Lioté[4]. [1]Laboratoire de Physique des Solides; Paris Sud University; Orsay; France, [2]Orthopaedic Surgery Department; Lariboisière Hospital; Paris Diderot University; Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, [3]Service de Biochimie A; Necker Hospital; Paris Sud University; AP-HP; Paris, [4]UMR-S 606, INSERM & Paris Diderot University; PRES Sorbonne Paris-Cite; Lariboisiere Hospital; Paris; France

Purpose: Calcium-containing crystals (CC), including basic calcium phosphate crystals (BCP) and calcium pyrophosphate crystals (CPP) are associated with destructive forms of osteoarthritis (OA). Recent reports showed that mineralization of articular cartilage of the medial compartment is an indissociable process of end-stage OA. However, accurate characterisation of CC by conventional techniques remains challenging.

Objectives: To assess biochemical composition and spatial distribution of mineral phases in human OA cartilage, and to determine their morphological aspects.

Methods: Fourteen patients (12 women and 2 men), who underwent total knee joint replacement for primary OA, were prospectively included. A 24-year-old woman who underwent total knee joint replacement for chondrosarcoma served as control. Specimen included femoral condyle and tibial plateau cartilages, from both medial and lateral compartments. Clinical data and preoperative knee X-rays were obtained. For each femoro-tibial compartment, 4 samples (2 from femoral condyles and 2 from tibial plateau) were collected, consisting in 1-mm-thick slices. Slices were cut tangentially to the articular surface, within the superficial and deep layers of the articular cartilage, respectively. Biochemical composition was assessed using Fourier-transform infra-red (FTIR), and morphological aspects were determined using scanning electron microscopy (SEM). All results are expressed as mean (SD).

Results: Age and body mass index at the time of intervention were 74.4 (8.3) years, and 28.8 (6.2) kg/m^2, respectively. Preoperative X-rays found uni-, bi- or tricompartmental knee OA in 2, 8 and 4 cases, respectively. In all cases, the compartment mainly affected was medial femoro-tibial, and Kellgren and Lawrence score was 3.8 (0.4). Joint calcifications were detected in only 2 cases on preoperative X-rays, but in 11 cases under macroscopic examination. FTIR analysis showed CC in all 14 specimens. CC were absent from the control sample. The overall mineral content represented 9.1 (12.6)%. CC were identified as BCP only in 6 patients, and as both BCP and CCP in 8. Remarkably, CC were widespread in all knee joint compartments and involved at least 3 areas out of 8 in all specimens. In addition, CC distribution was similar between superficial and deep layers, and between medial and femoral compartments (11.1 [14.7]% vs 7.3 [10.2]%, and 8.1 [11.2]% vs 9.5 [13.1]%, p=NS, respectively). Finally, SEM identified 2 different morphological aspects: 1/spherical structures, typical of biological apatite, resulting from an agglomeration of nm-scale cristallites surrounded by proteins, and localized in structures suggestive of chondrons, in the BCP-containing samples; 2/ acicular or cubic structures of different sizes, in the CPP-containing samples.

Conclusions: CC are constantly found in human OA articular cartilage at the time of knee joint replacement. Cartilage calcifications occur in all knee joint compartments, even in less weight-bearing ones, suggesting that cartilage mineralization process may reflect a generalized chondrocyte disease. In addition, their morphological aspects are specific to the crystal type.

Disclosure: C. Nguyen: None; **H.-K. Ea:** None; **D. Hannouche:** None; **M. Daudon:** None; **D. Bazin:** None; **F. Lioté:** None.

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Factors Associated with an Acute Attack of Chronic Gout without Hyperuricemia. MinWook So[1], SeungGeun Lee[3], YongGil Kim[3], ChangKeun Lee[3], HeeBom Moon[3], Jiseon Oh[4] and Bin Yoo[2]. [1]ASAN Medical Ctr, Seoul, Korea, Republic of, [2]ASAN Medical Ctr, Seoul, Korea, Republic of, [3]ASAN Medical Ctr, [4]Ulsan University

Background: Gout is a disease caused by deposition of monosodium urate crystals in articular and periarticular tissues. Hyperuricemia has been reported to be closely linked to the development and recurrence of gouty arthritis. Although, theoretically, gout cannot develop without hyperuricemia, there have been reports of development of gout without hyperuricemia. And in the clinical setting, some patients receiving a urate-lowering agent for chronic gout have experienced recurrent attacks of gout without hyperuricemia.

Purpose: To identify the factors associated with an acute attack of chronic gout without hyperuricemia.

Method: We reviewed the medical records of 860 patients with chronic gout and who regularly received allopurinol at one tertiary hospital from 2003 to 2009. Among these 860 patients, 135 maintained a serum urate level less than 6.0mg/dl. To minimize the effect of serum urate level change, we excluded all patients whose serum urate level exceeded 6.0mg/dl at least once. We divided the study patients into an Attack group (n=51) and a No-attack group (n=84). The patients who experienced an acute attack, even though with normouricemia (≤6.0mg/dl) at least once during follow-up period, were classified as the Attack group. The others were classified as the No-attack group. We prescribed colchicine to prevent gout attacks during the first six months of the study, and attacks which occurred during this period were not included.

Results: Fifty-one (37.8%) patients experienced at least one recurrence of an acute attack without hyperuricemia during the follow-up period (Attack group).

The remaining 84 (62.2%) patients never experienced an acute gout attack (No-attack group). During the follow-up period, the sampling frequency was similar in the two groups. The baseline characteristics of the patients in each group, including age, alcohol drinking, hypertension, chronic kidney disease, heart disease, type II diabetes mellitus, diuretics, and aspirin therapy showed no significant difference in the two groups. The presence of tophi and the number of involved joints were strongly associated with acute attacks of chronic gout without hyperuricemia, respectively (OR 5.9, P=0.001 and OR 1.7, P=0.001). On multivariate analysis, the presence of tophi and the number of involved joints were also independently associated with acute attacks of chronic gout, respectively (OR 4.2, P=0.010 and OR 1.5, P=0.028).

Conclusion: Our study revealed that the presence of tophi and multiple joint involvement were associated with acute attacks of chronic gout without hyperuicemia. We, therefore, recommend that patients with these risks should maintain a lower target level of serum urate.

Disclosure: M. So: None; **S. Lee:** None; **Y. Kim:** None; **C. Lee:** None; **H. Moon:** None; **J. Oh:** None; **B. Yoo:** None.

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Hyperuricemia and Gout: Nature Versus Nurture. Eswar Krishnan[3], Christina N. Lessov-Schlaggar[4], James F. Fries[2], Ruth Krasnow[1] and Gary E. Swan[1]. [1]SRI International, [2]Stanford Univ Medical Ctr, Palo Alto, CA, [3]Stanford University, Palo Alto, CA, [4]WUSTL

Background: Hyperuricemia and gout are known to have both genetic and environmental components in their etiology. However the relative significance of each has not been well studied.

Methods: We performed heritability analyses of hyperuricemia (SUA>7.0 mg/dL) and gout (self-reported physician diagnosis and/or use of gout medications) among the participants of a twin study. This study prospectively observed 508 twin pairs (253 monozygotic, MZ, and 261 dizygotic, DZ) over a period of 34 years. Pairwise-correlation was measured using Spearman's correlation coefficient. The relative contribution of genetic and environmental influences on phenotypic variance was estimated using standard twin methodology implemented in Mx software (PMID: 8024529).

Results: The mean (±SD) age of the cohort was 48 (± 3) years at baseline. The baseline prevalence of gout and hyperuricemia were 3.1% and 24%, respectively. The cumulative incidence of gout did not differ between MZ and DZ twins (11.1% and 10.9%). The concordance of hyperuricemia was 56% in MZ and 31% in DZ twin pairs (p<0.001). Twin modeling showed little to no genetic influences on individual variability in gout, but substantial influence of environmental factors shared between co-twins. In contrast, individual differences in hyperuricemia were influenced by significant genetic factors with little to no evidence for an effect of shared environmental factors.

Relative contribution of genetic (A), shared environmental (C) and non-shared environment (E) influences on dichotomous measures of gout and hyperuricemia

Model	A (95% CI)	C (95% CI)	E (95% CI)	χ^2	df	p	AIC	χ^2 diff	df diff	p diff
Gout										
ACE	0 (0, 55.0)	45.0 (0, 61.7)	54.6 (35.5, 73.6)	0.710	3	0.871	−5.290			
CE	—	45.5 (26.5, 61.7)	54.6 (38.3, 73.6)	0.710	4	0.950	−7.290	0.000	1	1.000
AE	50.5 (27.4, 69.3)	—	49.6 (30.7, 72.7)	4.383	4	0.357	−3.617	3.674	1	0.055
E	—	—	100	21.050	5	0.001	11.050	20.340	2	0.000
Hyperuricemia										
ACE	51.2 (0, 65.9)	0 (0, 42.8)	48.8 (34.1, 67.3)	4.525	3	0.210	−1.475			
CE	—	39.1 (24.8, 52.0)	60.9 (48.0, 75.2)	8.108	4	0.088	0.108	3.583	1	0.058
AE	51.2 (34.1, 65.9)	—	48.8 (34.1, 65.9)	4.525	4	0.340	−3.475	0.000	1	1.000
E-	—	100	34.985	50.000			24.985	30.460	2	0.000

χ^2-chi-square goodness of fit test; df=degrees of freedom; p-p value; AIC=Akaike information Criterion; χ^2 diff-chi-square difference between the fulACE model and the genetic (AE) or environmental (CE, E) submodels; df diff-degrees of freedom difference; p diff-p value associated with the chi-square goodness of fit difference

Conclusions: Hyperuricemia, but not gout had a significant heritability component in this twin cohort. Gout variability appears to be due to environmental factors shared between cotwins. These observations need to be further studied in larger cohorts.

Disclosure: E. Krishnan: Ardea, 2, Savient Pharmaceuticals, 1, Takeda Pharmaceuticals North America, 5; **C. N. Lessov-Schlaggar:** None; **J. F. Fries:** None; **R. Krasnow:** None; **G. E. Swan:** None.

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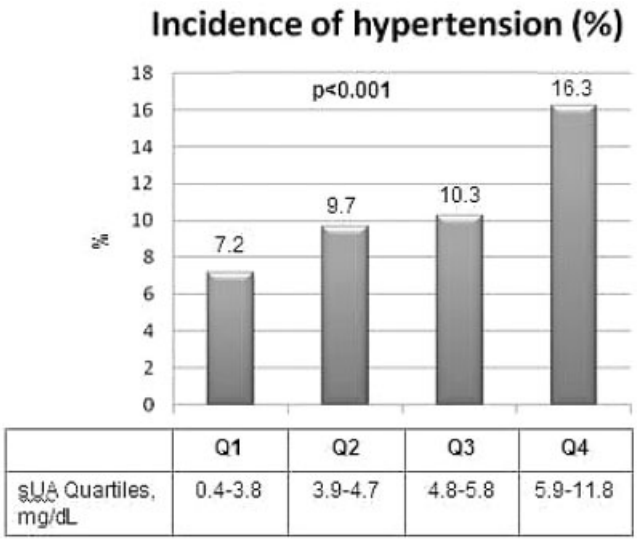
Hyperuricemia as a Risk Factor for Hypertension among Young Adults without Metabolic Syndrome. Eswar Krishnan[1], Bhavik Pandya[2], Ali Hariri[3] and Omar Dabbous[2]. [1]Stanford University School of Medicine, Stanford, CA, [2]Takeda Pharmaceuticals International, Inc, Deerfield, IL, [3]Takeda Pharmaceuticals North America, Inc, Deerfield, IL

Objective: Hyperuricemia has been shown to cluster with components of metabolic syndrome. A previous study[1] documented that hyperuricemia is a risk factor for hypertension independent of metabolic syndrome among middle-aged adults (aged 35–57). The objective of this analysis is to assess whether hyperuricemia is a predictor of hypertension independent of metabolic syndrome in young adults.

Methods: We analyzed data from the CARDIA (Coronary Artery Risk Development in Young Adults) cohort, a prospective observational study of 5,115 individuals in the community who were aged 18–30 years at baseline and followed for 15 years (1986–2001) with visits 2–5 years apart. We excluded individuals with hypertension (per The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [JNC 7] criteria) or any other components of metabolic syndrome (Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [ATP III] criteria) at baseline. The serum urate (sUA) cutoffs for quartiles were <3.9; 3.9–4.7; 4.8–5.8; and >5.8 mg/dL. Multivariate Cox regression analyses were utilized to adjust for the effects of potential confounders such as age, gender, race, serum creatinine concentration, and waist circumference.

Results: Data from 4,918 participants were included in this analysis; 45% were men, and 51% were African American. Baseline mean (standard deviation) for age, body mass index, sUA concentration, and systolic and diastolic blood pressure were: 25 (4) years; 24 (5) kg/m^2; 5 (1) mg/dL; and 110 (10) mmHg and 68 (9) mmHg, respectively. The incidence of hypertension increased with succeeding sUA quartiles (Figure).



In multivariable regressions, the hazard ratio (95% confidence interval) for the second, third, and top quartiles of sUA concentration compared with the bottom quartile were: 1.2 (0.9–1.7); 1.5 (1.1–2.1); and 1.8 (1.2–2.6), respectively.

Conclusions: The incidence of hypertension was higher with increase in sUA. Hyperuricemia is an independent predictor of hypertension among young adults and is independent of metabolic syndrome.

Reference:

1. Krishnan E, Kwoh CK, Schumacher HR, et al. Hyperuricemia and incidence of hypertension among men without metabolic syndrome. *Hypertension* 2007;49(2): 298–303.

Disclosure: E. Krishnan: ARDEA Biosciences, 2, Savient Pharmaceuticals, 1, Takeda Global Research and Development Center, Inc., 2; **B. Pandya:** Takeda Pharmaceuticals International, Inc., 3; **A. Hariri:** Takeda Pharmaceuticals North America, 3; **O. Dabbous:** Takeda Pharmaceuticals International, Inc., 3.

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Individuals in the US General Population with Gout and Hyperuricemia Have Significantly Higher Comorbidities: The National Health and Nutrition Examination Survey (NHANES) 2007–2008. Bhavik Pandya[2], Yanyan Zhu[1] and Hyon Choi[1]. [1]Boston University of School of Medicine, Boston, MA, [2]Takeda Pharmaceuticals International, Inc, Deerfield, IL

Objective: While the comorbidity burden of gout and hyperuricemia in the US has been considered substantial and has increased over the past decade, no contemporary data are available. The objective of the study was to estimate current prevalence of major comorbidities according to both gout status and hyperuricemia status based on NHANES 2007–2008 data.

Methods: Using data from 5,707 participants (2,797 men and 2,910 women) aged 20 years and older from NHANES 2007–2008, we determined the prevalence of major comorbidities according to both gout and hyperuricemia status, including hypertension, renal impairment, nephrolithiasis, diabetes, myocardial infarction, heart failure, stroke, and obesity. Obesity was defined as body mass index $\geq$30 kg/m^2. Other comorbidities and gout were defined based on an affirmative answer to a question asking if a physician or a health professional had diagnosed the corresponding condition. The primary NHANES definition of hyperuricemia was serum urate level >7.0 mg/dL in men and >5.7 mg/dL in women.

Results: Among the US adults with both gout and hyperuricemia, 78% had hypertension, 9% renal impairment, 20% nephrolithiasis, 27% diabetes, 12% myocardial infarction, 12% heart failure, 12% stroke, and 56% obesity (Table). These prevalences were substantially higher than those among individuals without gout or hyperuricemia. Having hyperuricemia was associated with a higher prevalence of comorbidities among individuals without gout. A similar trend was observed among individuals with gout, although the patterns are more difficult to characterize accurately due to smaller sample sizes (Table).

Table. Prevalence of Comorbidities According to Hyperuricemia and Gout in NHANES 2007-2008

	Gout		No Gout	
Comorbidities	Hyperuricemia	No Hyperuricemia	Hyperuricemia	No Hyperuricemia
Hypertension	77.7 (66.6-88.8)	70.8 (60.8-80.8)	47.2 (43.0-51.4)	24.3 (21.8-26.7)
Renal Impairment	8.8 (4.4-13.3)	4.1 (2.0-6.1)	3.1 (2.1-4.2)	1.8 (1.4-2.3)
Nephrolithiasis	20.2 (10.3-30.2)	26.2 (15.6-36.9)	11.6 (8.9-14.3)	7.8 (6.7-8.8)
Diabetes	26.9 (9.7-44.1)	21.4 (14.9-28.0)	12.2 (8.7-15.6)	6.7 (5.4-8.1)
Myocardial Infarction	11.6 (4.5-18.7)	14.1 (10.9-17.3)	4.5 (3.3-5.6)	2.6 (1.8-3.1)
Heart Failure	11.7 (5.1-17.4)	8.2 (4.4-12.0)	4.5 (3.4-5.5)	1.4 (0.8-2.0)
Stroke	11.8 (0.4-23.1)	8.0 (3.3-12.7)	5.1 (3.6-6.7)	2.3 (1.4-3.1)
Obesity	55.6 (45.5-65.7)	50.2 (35.7-64.7)	54.2 (49.0-59.4)	27.0 (23.9-30.1)

Conclusions: These findings from the latest nationally representative sample of US adults highlight that having gout and/or hyperuricemia substantially increases the prevalence of comorbidities. These prevalences are highest among individuals with both gout and hyperuricemia. These comorbidities add to the overall illness burden of gout and hyperuricemia to society, and provide support for consideration of these issues in optimizing gout and hyperuricemia care in the US.

Disclosure: B. Pandya: Takeda Pharmaceuticals International, Inc., 3; **Y. Zhu:** None; **H. Choi:** Takeda Pharmaceuticals International, Inc., 5.

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Low Prevalence of Coexistent Gout and Rheumatoid Arthritis in a Population of Veterans. Armine Tumyan[1], Kara H. Prescott[2] and Andreas M. Reimold[1]. [1]Dallas VA Medical Center and Univ of TX Southwestern Med Ctr, Dallas, TX, [2]Dallas VA Medical Center and Univ of TX Southwestern Med Ctr, Cross Roads, TX

Background: Clinical observations indicate that the coexistence of gout and rheumatoid arthritis in the same patient is rare, occurring at a lower frequency than the incidence of the two conditions would predict. Gout is a male-predominant disease with an estimated prevalence of 1 to over 7%, while the incidence of both gout and RA increases with older age. A population of veterans was studied to describe the overlap of gout and RA.

Methods: Medical records for all patients with ICD-9 codes for RA (714.0, 714.2 and 714.81) and gout (274.xx) from 01/01/1999-12/31/2007 were identified and reviewed in the north Texas Veteran's Integrated Service Network. In addition, a random sample of 50 gout and 50 RA patient records were reviewed for accuracy of ICD-9 codes. ACR criteria for RA and ACR 1977 Preliminary Criteria for diagnosis of gout were used, and lab data (joint fluid crystal analysis, hyperuricemia, RF, CCP), imaging, and medication use (allopurinol, DMARDs, TNF inhibitors) were documented. Patients were classified as having definite gout (joint fluid or tophi showing MSU crystals), presumed gout (met 6/13 ACR 1977 Preliminary Criteria for gout) or unlikely gout (failed to meet 6/13 gout criteria or gout was ruled out by a rheumatologist).

Results: A search of ICD-9 codes identified 2572 patients with RA codes and 8508 with gout codes, resulting in 277 patients with both RA and gout codes (overlap). By such codes, 10.8% of RA patients have a gout diagnosis, and 3.3% of gout patients have an RA diagnosis. In contrast, our longitudinal study of 545 well-characterized RA patients contained 10 with a comorbidity diagnosis of gout (1.8%) and 5 were confirmed by chart review (0.9%). Overlap patients were a mean of 71 years old, were 94.6% male, and 66.4% Caucasian. Patients with gout alone rarely saw a rheumatologist (8%, compared to 56% for patients with RA ICD-9, $p<0.001$). Definite or presumed gout was found in 40.4% of the overlap group, RA was confirmed in 19.2%, while not enough information was documented in the charts to confirm gout in 43.3% and RA in 62.4%. There were 16 cases (5.8% of 277 overlap patients) of definite or presumed gout with RA. Therefore, in this population 0.62% of RA patients had confirmed or presumed gout, and 0.19% of confirmed/presumed gout patients had RA.

	RA Registry	Veteran Population
RA ICD-9 (n)	545	2572
Gout ICD-9 (n)	10	8508
RA/Gout Overlap by ICD-9 (n)	10	277
RA confirmed in Overlap	10 (100%)	53 (19.2%)
Gout confirmed in Overlap	5 (50%)	112 (40.4%)
RA/Gout confirmed in Overlap	5 (50%)	16 (5.8%)
RA/Gout Overlap in Those With RA ICD-9	0.9%	0.62%

Conclusions: Diagnoses of either RA or gout are often assigned to patients by non-rheumatologists and frequently do not meet ACR criteria. Documentation of ACR criteria for both RA and gout in the same patient occurred in only 5.8% of patients carrying both diagnoses. Both in a general population of veterans carrying an RA ICD-9 code and a well-characterized registry of RA patients, the overlap of RA and gout was found in less than 1% of patients, a rate of gout far below the 6.5% incidence published previously for males in this age group.

Disclosure: A. Tumyan: None; **K. H. Prescott:** None; **A. M. Reimold:** None.

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Monosodium Urate Monohydrate Crystals Inhibit Osteoblast Viability and Differentiation; Implications for Development of Bone Erosion in Chronic Gout. Ashika Chhana[2], Karen Callon[2], Bregina Pool[2], Dorit Naot[2], Fiona M. McQueen[2], Jillian Cornish[2] and Nicola Dalbeth[1]. [1]Univ Auckland, Auckland, New Zealand, [2]University of Auckland, Auckland, New Zealand

Background: Bone erosion is a frequent manifestation of chronic gout, and may lead to joint damage and disability. Recent research has implicated an imbalance of bone remodeling in the development of bone erosion in gout, with enhanced formation of bone-resorbing osteoclasts in patients with erosive gout. We hypothesized that changes in the bone-forming osteoblasts also contribute to bone erosion in chronic gout. In this study we investigated the effects of monosodium urate monohydrate (MSU) crystals on osteoblasts.

Method: MSU crystals were prepared by recrystallisation of uric acid. Flow cytometry and the MTT assay were used to assess cell viability following culture with MSU crystals in the murine MC3T3-E1 and ST2 osteoblast-like cell lines, and in primary rat and human osteoblasts. Quantitative real-time PCR and von Kossa stained mineralised bone nodule formation assays were used to assess the effects of MSU crystals on the differentiation of MCT3-E1 osteoblast-like cells.

Results: MSU crystals rapidly reduced viability in all osteoblast assays in a dose-dependent manner (Figure). The inhibitory effect was maximal at the higher concentrations of 0.3 and 0.5mg/mL MSU crystals and was independent of crystal phagocytosis. The reduction of osteoblast viability was specific to urate crystals, as soluble uric acid did not alter cell viability. Furthermore, the effects on cell viability did not alter with different crystal lengths or addition of serum. Long term culture of MC3T3-E1 cells with MSU crystals showed decreased mineralisation (bone nodule formation) in a dose-dependent manner, and reduced expression of genes related to osteoblast differentiation such as *Ibsp* (bone sialoprotein), *Runx2*, *Sp7* (osterix) and *Dmp1*.

Conclusion: MSU crystals have profound inhibitory effects on osteoblast viability and differentiation. These data indicate that MSU crystals may contribute to bone erosion in gout not only through promotion of osteoclast formation, but also through reduction of osteoblast survival and function.

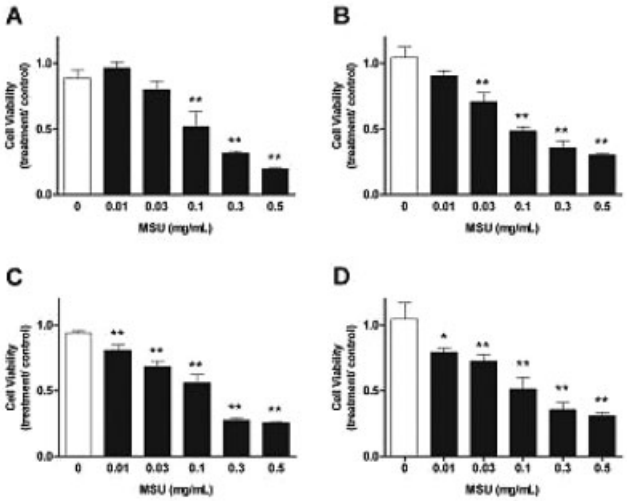

Figure. Effects of MSU crystals on cell viability in A. MC3T3-E1 cells; B. ST2 cells; C. primary rat osteoblasts; and D. primary human osteoblasts. Cell viability was assessed in the MTT assay following 26 hours of culture with MSU crystals. Data shown are mean (SEM); *p<0.001, **p<0.0001 versus control (no MSU crystals), one-way ANOVA with *post hoc* Dunnett's test.

Disclosure: A. Chhana: None; **K. Callon:** None; **B. Pool:** None; **D. Naot:** None; **F. M. McQueen:** None; **J. Cornish:** None; **N. Dalbeth:** None.

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Number of Flares Are Associated with Both Gastrointestinal and Vascular Complications in Patients with Gout. Another Issue for Early Intervention. Fernando Perez-Ruiz[1], Ana M. Herrero-Beites[2] and Miguel A. Gonzalez-Gay[3]. [1]Hospital de Cruces, Spain, [2]Hospital de Górliz, Spain, [3]Hospital Universitario Marqués de Valdecilla, Spain

Background: Before long-term serum urate control, patients with gout experience multiple flares that may expose them to the risk of complications, while EULAR recommendations suggest treating patients with recurrent flares or severe gout.

Objective: to evaluate risk factors associated with de development of severe vascular or gastrointestinal complications in patients with gout.

Methods: data from a prospective cohort of 787 patients with gout. Variables included age, gender, body mass index, number of flares-yr, number of joints involved, tophus present, diuretics, renal function, hypertension, diabetes, hyperlipidemia, and ethanol intake. Vascular events and BPO (Bleeding, Perforation, Obstruction) events were considered when there was a association recorded in the file of the patient with treatment of a flare or gout complaints and the event. Time from the onset of gout to the event was considered as time variable for exposure. Mantel-Hazel analysis with log-rank tests were used to select variables associated ($p<0.20$) with each group of events, and they were afterwards included in multivariant Cox proportional hazard regression analysis.

Results: mean age 58.8±12.6, 93% male, 5,352 patient-yr exposure, 31.3% tophaceous, 35.6% over 4 joint involved, 3.4±2.8 (0–24) flares-yr, 34.6% over 20 g-day ethanol intake, 42.7% hypertension, 19.6% diabetes, 41.9% hyperlipidemia, 24.2% obese. Prior urate-lowering treatment (ULT) in 38.5%. Overall, there were 65 events (1.21 per 100 patient-year exposure) in 62 patients (7.88%). There were 41 vascular events: 2 congestive heart failure, 30 acute renal failure, 2 pulmonary embolisms, and 7 ictus associated to flares or gout treatment, and 24 gastrointestinal events: 22 bleedings, 1 obstruction, and 1 perforation. The number of flares in the year previous to the event was associated with an increased risk of both vascular and BPO events. Polyarticular gout was also associated with and increased risk of BPO events, while diuretics were associated with vascular events. Higher rates of clearance of creatinine and previous urate-lowering treatment were associated with decreased risk of vascular events (Table).

Variables	Hazard ratio	95% CI limits	P
BPO			
Number of flares	1.089	1.002–1.183	0.044
Over 4 joints	9.591	3.124–29.441	0.000
Vascular			
Number of flares	1.084	1.014–1.159	0.017
Creat Clearance	0.987	0.975–0.998	0.023
Previous ULT	0.322	0.159–0.653	0.002
Diuretics	3.259	1.165–6.436	0.001

Conclusions: the number of recurrent flares in the year previous to the event was associated with an increased risk of both vascular and gastrointestinal events, which appeared in 8% of the patients. Also, polyarticular gout was associated with gastrointestinal events, while previous ULT seemed to be protective for vascular events. Early treatment of gout should be considered in recommendations.

Disclosure: F. Perez-Ruiz: ARDEA Biosciences, 5, 8, Menarini, 5, 8, Novartis Pharmaceuticals Corporation, 8; **A. M. Herrero-Beites:** ARDEA Biosciences, 5, 8, M enarini, 5, 8, Menarini, 5, 8, Novartis Pharmaceuticals Corporation, 8; **M. A. Gonzalez-Gay:** None.

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Patients with Gout May Have a Decreased Risk of Colonic Polyps Relative to Patients with Osteoarthritis (OA): Insights from the NY VA Gout Database. Aaron Lehmann[3], Laura Schneck[4], Robert T. Keenan[1], William O'Brien[2], Daria Crittenden[2], Kristen Lee[2], Rekha Tadoori, Fritz Francois[2] and Michael H. Pillinger[4]. [1]Duke University, Durham, NC, [2]NYU Langone Medical Center, [3]NYU Langone Medical Center, Flushing, NY, [4]NYU Langone Medical Center, New York, NY

Introduction: The role of uric acid (UA) in modulating immunity is an evolving area of investigation. UA can act as a "danger signal," alerting the immune system to damaged cells (tumor and/or virally-infected cells) and triggering removal of potentially dangerous altered host. In a murine model, UA supplementation promoted, and UA lowering inhibited tumor rejection (Hu et al, Canc Res 2004). UA also scavenges singlet oxygen, which can induce tumorigenic mutations. UA also activates the inflammasome, driving IL-1β production. One of us (Francois et al, unpublished) has shown in patients with obesity (associated with elevated serum UA), IL-1β levels correlate significantly with serum levels of IFNγ, TNFα, IL-2, IL-17, and that individuals with the IL-1βT allele are less likely to have colonic polyps. Based on possible relationships between uric acid and tumor immunity in general, and uric acid, IL-1β and colonic polyps in particular, we tested whether patients with gout (a hyperuricemic state) have lower rates of colonic polyposis vs patients with OA.

Methods: Using the EMR of the New York Harbor Healthcare System (N=40,107), we identified all patients receiving an ICD-9 gout code at the Manhattan, Brooklyn and Queens VA Hospitals in New York City between 2007 and 2008. Age, sex, BMI, UA level, smoking history and colonic polyp diagnosis were collected by chart review (problem list and note review as appropriate). Patients with OA (ICD-9 diagnosis) but no gout were identified to serve as controls.

Results: 1,287 gout patients were identified, and 1,287 patients with OA/no gout were randomly selected from 3,300 potential control enrollees. Gout and OA patients were identical in mean age (71), sex (99% male), BMI (29) and smoking history (11% vs 14%, ns). Average serum UA was 7.64 (gout, n=1124) vs. 6.026 (OA, n=730) mg/dL. Gout patients had a 12-fold decrease in colonic polyp diagnosis vs OA patients. Prevalence of colonic polyp diagnosis was 0.62% (n=8) in the gout vs. 8% (n=103) in the OA group (p=0.0001, 2 tailed Fisher's exact test). Pathology reports for the two groups were: for gout, hyperplastic (4), tubular (3), tubulovillous (2), no report available (4); for OA, tubular adenoma (55), hyperplastic (16), tubulovillous adenoma (11), villous adenoma (3), tubular adenoma with focal adenocarcinoma (2), serrated adenoma (2), well-differentiated adenocarcinoma (1), colonic mucosa with lymphoid aggregate (1), leiomyoma (1), no report available (29). Patients with gout had no decrease in lung or prostate cancer diagnosis vs OA controls (0.9% vs 1% for lung cancer and 11.8% vs 12.8% for prostate cancer, respectively, both ns).

Conclusion: In this retrospective study, presence of gout was associated with a significant decrease in colonic polyp diagnosis relative to

OA/no gout patients. The effect of gout presence on polyp risk may be unique, since similar effects were not seen in two other malignancies. The role of UA in this effect remains to be determined. We are currently re-analyzing our population to account for NSAID use, and to evaluate polyposis and colon cancer rates in a subpopulation undergoing screening colonscopy.

Disclosure: A. Lehmann: None; **L. Schneck:** None; **R. T. Keenan:** None; **W. O'Brien:** None; **D. Crittenden:** None; **K. Lee:** None; **R. Tadoori:** None; **F. Francois:** None; **M. H. Pillinger:** None.

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P-Homocysteine Levels Are Independently Correlated to S-Urate but Not to Urate Lowering Treatment. Results of an Observational Study of 112 Patients with Gout. Ole Slot. Dept. of Rheumatology, Copenhagen University Hospital, Glostrup, Denmark

Background: Gout is associated with an increased incidence of cardiovascular disease (CVD). In a previous report elevated levels in plasma homocysteine (p-HCT), a marker of CVD risk, was found in a group of gouty patients [1]. P-HCT was independently correlated to s-urate. The effect of urate lowering treatment (ULT) on p-HCT is not clear. Thus, the objective of this study was to examine the levels and correlations of p-HCT and metabolic factors that might effect the levels of p-HCT in gouty patients with or without ULT.

Methods: Data including results of routine laboratory tests from patients diagnosed with crystal proven gout during 18 months in an out-patient clinic were collected and analyzed for differences in unpaired samples (+ULT *vs* -ULT) and non-parametric correlations to p-HCT. The correlations were analyzed for co-variance in a backward multivariate regression analysis.

Results: 112 gouty patients of whom 50 received ULT (allopurinol: 47, probenecid: 1, benzbromarone: 2) were included. Data are shown in Table I.

Table 1. Medians (range) [Laboratory's reference values]

	Gout, all n = 112	Gout, −ULT, n = 62	Gout, + ULT, n = 50
N, Females/Males	24/88	15/47	9/41
Age, Females/Males	76 (49–90)/60 (33–86)	75 (49–90)/58 (33–85)	77 (49–86)/63 (40–86)
P-Homocysteine μmol/l [<15.0]	18.5 (7.3–94.5)	19.0 (8.2–94.5)	17.0 (7.3–34.4)
S-Urate mg/dl [2.7–8.0]	8.2 (3.2–13.5)	8.7 (5.7–13.5)*	7.0 (3.2–13.3)*
S-Urate mmol/l [0.16–0.48]	0.49 (0.19–0.81)	0.52 (0.34–0.81)*	0.42 (0.19–0.80)*
P-Folate nmol/l [1>6.0]	15.7 (3.0–45.0)	15.5 (3.0–45.0)	16.9 (4.3–44.1)
S-Cobalamine pmol/l [> 200]	243 (89–1480)	248 (89–756)	238 (107–1480)
S-CRP mg/l [<10]	6 (4–159)	6 (4–159)	6 (4–45)
S-Creatinine μmol/l [50–90]	91 (56–263)	92 (64–263)	85 (56–193)

*: P <0.001. Mann-Whitney test.

S-urate was significantly lower in the +ULT group. No differences in p-HCT or other parameters were found between the –ULT and +ULT groups. Overall 89 patients (80%) had p-HCT over the laboratory's upper limit of the normal range. Four patients (4%) had p-folate under the lower limit of the normal range of 6 nmol/l while 75 patients (68%) had p-folate below 20 nmol/l. 35 patients (32%) had S-cobalamine below the lower limit of the normal range. 55 patients (50%) had s-creatinine above the upper limit of the normal range.

P-HCT was correlated to s-urate, p-folate, s-creatinine, age (Spearmen's rho 0.34, −0.39, 0.46, and 0.44 respectively, $p<0.001$ for all), and s-cobalamine (rho –0.2, $p<0.05$). P-HCT was not correlated to CRP and ULT. In regression analysis age, p-folate, s-creatinine, s-cobalamine, and s-urate were independent predictors for p-HCT.

Conclusion: In patients with gout p-HCT, a marker of increased risk of cardio-vascular disease, is independently correlated to high levels of s-urate and s-creatinine and low levels of p-folate and s-cobalamine. P-HCT was not correlated to ULT in this observational study although s-urate levels were lower in the group of patients on ULT. The relations between p-HCT, s-urate and ULT should be examined in future prospective controlled studies.

1) Slot O et al: P-Homocysteine is elevated in gout and correlated to s-urate. ARD 2010;69(S3):611

Disclosure: O. Slot: None.

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Rates of Meniscal Tearing Seen on Arthroscopy of Patients with Chondrocalcinosis. William Chun[1], Humaira Hussain[3], Vincent J. Zarro[1], Carolyn R. O'Connor[1] and Angel E. Checa[2]. [1]Drexel University College of Medicine, Philadelphia, PA, [2]Drexel University College of Medicine, Cherry Hill, NJ, [3]Drexel University College of Medicine

Background: Internal derangement of the knee secondary to chondrocalcinosis (CC) is well established. Although several publications have shown cases of CC with meniscal tears, there is no data about the prevalence of meniscal tears in CC and vice versa.

Methods: The study population was a cohort of 1031 consecutive outpatients who underwent arthroscopy of the knee from 1991–2006. The specific subgroup of interest was 58 knees from 58 patients (25 males and 33 females) with CC. Mechanical symptoms or failure of conservative treatment were the main indications for arthroscopy. Although the study was cross sectional in design, surgical response was prospectively evaluated. The rates of meniscal tears in patients with and without CC as well as their response to surgery were analyzed by Chi square test.

Results: The mean age of patients with CC was 67 (range 47–83) years. Most patients with CC who underwent arthroscopy had mechanical complaints or failed conservative treatment (69% and 45% respectively). Pseudogout flare was documented in 7% of cases with meniscal tear and 40% with intact meniscus. Thirty-seven knees with meniscal tear and 13 knees with intact meniscus were classified as pseudo-osteoarthritis. Trauma was present in only 7 knees with meniscal tear and in 3 knees without meniscal involvement. Patients with CC had significantly higher rates of meniscal tear compared to those without CC (74.1% vs. 28.7%, $p<0.001$). An absolute and attributable risk of tear was 74% and 8% respectively in knees with CC. Relative risk of tear in knees with CC versus knees without CC was 2.58 (95% confidence interval 2.16–3.10). Arthroscopic surgery achieved good or excellent results in 22 (55%) knees with meniscal tearing. Knees with mild changes in the hyaline cartilage and involvement of only one compartment in the knee showed better response to surgery than knees with advanced degenerative changes and involvement of more than one compartment ($p=0.004$).

Conclusion: Although the prevalence of CC in this study population was 5.6% and therefore accounted for only 8% of the tears, CC was a strong predictor for meniscal tear. These patients represent an underestimated clinical-pathological subgroup and can often be successfully managed by arthroscopy. The low frequency of trauma in this study group suggests that CC is a factor in fibrocartilage fragility leading to meniscal tearing. Future controlled studies are needed to further characterize the impact of CC in meniscal vulnerability as well as its role in the hyaline cartilage.

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Screening for Hereditary Hemochromatosis in the Rheumatology Practice. Gunther Neeck[1], Helge Wernitzsch[2], Andreas Klüter[2], Martin Schulz[2] and Helmut Dotzlaw[2]. [1]Center for Rheumatology at Hospital Bad Doberan, Hohenfelde, Germany, [2]Center for Rheumatology at Hospital Bad Doberan, Germany

Objective: The most prominent features of hereditary hemochromatosis (HH) are joint pain and / or swelling, and this disease is often diagnosed by chance. We therefore systematically investigated iron metabolism in patients entering our rheumatology center for the first time over a time period of 2 ½ years in order to evaluate the incidence of HH in our rheumatology practice.

Methods: The serum concentrations of iron, ferritin, and transferrin were measured in 4244 patients and the iron-transferrin saturation was calculated. Patients with an iron-saturation > 45% and elevated ferritin levels were tested for HH by determination of mutations of the HFE-gene C282Y and H63D. If no mutations were detected and iron overload persisted we analyzed the non-HFE-genes hemojuvelin, herceptin, transferrin, transferrin receptor and ferroportin for possible mutations.

Results: Thirty seven patients showed iron overload (iron transferrin saturation > 45% and elevated ferritin). Of these, 21 patients were diagnosed as having HH by genetic analyses: 15 C282Y homozygotes, 2 H63D homozygotes, 2 compound heterozygotes C282Y/H63D, 1 homozygote for the non-HFE-gene ferroportin and 1 homozygote for the transferrin receptor 2. All patients suffered from arthralgias and 12 had typical HH-arthopathy of

the metacarpalia-phalangeal joints II and III of the hands. Most patients could be treated successfully by phlebotomy or iron chelation therapy.

Conclusions: In undifferentiated joint pain HH is an important differential diagnosis, and as such parameters of iron metabolism should be routinely determined in those patients.

Disclosure: G. Neeck: None; **H. Wernitzsch:** None; **A. Klüter:** None; **M. Schulz:** None; **H. Dotzlaw:** None.

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Synovial Extracellular Matrix Remodeling in Experimental Model of Diabetes. Sandra Aparecida Atayde[1], Priscila Cristina Andrade[2], Sérgio Catanozi[2], Edna Regina Nakandakare[2], Marisa Passarelli[2], Ana Paula Pereira Velosa[2], Vera Luiza Capelozzi[2], Edwin Roger Parra[2], Natalino Hajime Yoshinari[2] and Walcy Rosolia Teodoro[2]. [1]University of São Paulo, São Paulo, Brazil, [2]University of São Paulo

Purpose: Diabetes mellitus has been linked to disorders of bones and joints whose etiologic mechanisms could be linked to micro vascular disease. The synovia is the most vascularized tissue in the joint, therefore, can be made more resilient to endothelial injury in diabetic process. Our purpose was to evaluate the extracellular matrix components and specially the vascular lesion in this tissue after diabetes induction in rats.

Methods: Wistar young rats, were divided into diabetic group (DG; n=15) and control group (CG; n=15). Diabetes was induced by tail injection of streptozotocin (35mg/kg), while control group received saline solution. Weight, blood glucose and plasmatic anti-carboxymethyl lysine analysis had been done after 70 days. After euthanasia, knee joints were isolated, and included in paraffin. Histological sections stained with Hematoxilin-Eosin and Picrosirius were obtained for histomorphometric analysis. Total collagen quantification of this tissue was done in Picrosirius under polarized light. The distribution of collagens I, III and V and also carboxymethyl lysine receptor were assessed by immunofluorescence and immunochemistry was used for endothelin −1 detection in synovial tissue.

Results: Higher levels of blood glucose and plasmatic anti-carboxymethyl lysine was viewed in DG when compared to CG ($p<0,05$). Moreover the final weight was lower in DG than CG($p<0,05$). Histomorphometric analysis showed increased of thick collagen content and decrease of thin collagen fibers in synovial tissue. Immunofluorescence test demonstrated increase of collagen I expressions in synovial tissue of DG. The endothelin −1 and carboxymethyl lysine receptor were highly expressed in DG synovial tissue.

Conclusion: There were intense remodeling and collagen deposition in the synovia of animals with diabetes induced by streptozotocin, which may explain the pathophysiology of musculoskeletal dysfunctions observed in diabetic patients.

Disclosure: S. A. Atayde: None; **P. C. Andrade:** None; **S. Catanozi:** None; **E. R. Nakandakare:** None; **M. Passarelli:** None; **A. P. P. Velosa:** None; **V. L. Capelozzi:** None; **E. R. Parra:** None; **N. H. Yoshinari:** None; **W. R. Teodoro:** None.

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The GOSPEL 1000 Study. Features of the Metabolic Syndrome in 1003 French Patients with Gout. Frédéric P. Lioté[7], Hang-Korng Ea[2], Pascal Guggenbuhl[1], Alain Saraux[6], Charles Lambert, Sabine Lanz[4], Pierre Chiarelli[3] and Sylvie Lancrenon[5]. [1]Rennes, France, [2]Paris, France, [3]Courbevoie, France, [4]Chatou, France, [5]Bourg-la-Reine, France, [6]CHU de la Cavale Blanche, Brest Cedex, France, [7]Hopital Lariboisiere, Paris, France

Background: Gout is often poorly managed in primary care settings. 2006 EULAR gout recommendations (EULARrecs) have been developed on aspects related to the management of gout, but poorly evaluated in clinical practice. A key feature present in these EULARrecs was to determine and to treat specifically the metabolic syndrome (MS). In the GOSPEL study, we aimed to assess and compare the prevalence, features and management of MS associated with gout in primary care and in rheumatology, in concordance with the EULARrecs.

Methods: A prospective national survey of 1003 patients (pts) with gout or suspicion of gout was done between September 2008 & July 2009. A panel of 398 general physicians (GP) and 109 rheumatologists (RH) was randomly selected in France, each including 2 consecutive gouty pts. A structured questionnaire, including history with predefined items, allowed to monitor ACR classification criteria, as well as EULAR management recs (proposals 2 & 3); co-morbidities (CM), mainly cardiovascular (CV); clinical evaluation (BMI, MS (FID definition)); medications at visit. MS features and management were compared with the EULAR recs.

Results: 1003 pts were included as gout. 879 pts were male (M, 88%; age: 61.6(11), mean(±SD)) and 124 female (F, 12%; age:70.2(11.9)). 810 pts (81%) were seen by GP and 193 (19%) by RH. Mean disease duration was 7.9(8.1) yrs (GP) and 8.6(9.2) yrs (RH). Gout classification ACR criteria were present in 85.2% of pts (87.3% (GP); 76.7% (RH)). 48.6% of pts had acute gout, 24.4% chronic gout. Tophi were present in 19.4%. Mean BMI was 28.4(3.8) in M (BMI≥30: 28.1%) and 28.2(5.7) in F (BMI≥30: 33.1%). Overweight was present in 51.5%. MS was present in 440 pts (47.2%; M: 46.0%, F: 55.8%); with respect to MS features (hypertension (HT) 54.5%; high glycemia 43.6%; low HDL (43.7%); high TG (40.7%)); MS prevalence was more frequent in GP pts (51.9%) vs RH (27.0%). MS severity was also higher (# criteria) in GP pts. CKD was present in 43% (CrCl <60 ml/min). Coronary heart disease was present in 8.9% and 8.4%, GP and RH pts, respectively, whereas CVA was present in 3.5% and 1.6%, respectively.

EULAR proposal (P) #2: increased calories intake was identified in 27.2% pts. Diet modifications were proposed to 149/286 obese pts (56%), and to 22.6% of the total population. High beer (n=56 pts) and alcohol intake (M: 52.4%; F: 22.8%**)** were reported by GP<RH (7% and 49%, respectively). Advices for alcohol consumption reduction were only offered to 12.6 pts. Physical activity was recommended in 54 pts (6.0%) (39: GP; 15:RH). **P#3:** CV CM were present in 71% pts. Treatment was already appropriate or given at time of clinics in 87.2% of pts, with differences between GP (89.0%) and RH (78.7%). Overall 10%, 20%, 5% of pts with dyslipidemia, diabetes, and HT, respectively, were not treated.

Conclusion: MS is more frequent and severe in French gouty pts followed in general practice. Non pharmacological recs are not appropriate. However pharmacological of key features of the MS are largely implemented. Implementation of EULARrecs for management of gout should be regularly recalled since MS and identification of risk factors are underscored by both GP and RH, with differences related to clinical practice and education.

Disclosure: F. P. Lioté: Ipsen, 5, 9, LGV, 5, 9, Menarini, 5, 9; **H.-K. Ea:** None; **P. Guggenbuhl:** Ipsen, 9, Menarini, 9; **A. Saraux:** None; **C. Lambert:** Ipsen France, 3; **S. Lanz:** Mayoly-Spindler, 3; **P. Chiarelli:** LGV, 5; **S. Lancrenon:** Vivactis, 5.

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Ultrasound Detects More Erosions in Gout Than Conventional Radiography. Ralf G. Thiele[2] and Naomi Schlesinger[1]. [1]UMDNJ/RWJMS, [2]University of Rochester, Rochester, NY

Background: Ultrasound (US) can be helpful in the assessment of gout. Typical tophaceous deposits, erosions and synovial hyperemia can be detected [1, 2]. Conventional radiography (CR) is widely used to image characteristic erosions with sharp margins and overhanging edges. However, in the detection of erosions, CR has inherent disadvantages when compared with cross-sectional imaging. In CR, a three-dimensional bony structure is summarized on a two-dimensional film. Bony erosions can therefore only be confirmed if they are seen in profile, and a break in the cortical margin is demonstrated. Cross-sectional imaging including US detects more erosions in rheumatoid arthritis (RA).

Previous studies compared 2 radiographic views with US findings. In this study, 3 radiographic views are compared with findings on standardized US examination.

Objectives: To compare detection of erosions with US and CR in chronic gout.

Methods: Retrospectively, US studies performed during a 12 months period were reviewed. 42 patients with a history of crystal proven gout, US images and CR of corresponding joints were identified. The study was limited to assessment of first MTP joints. Complete data for 62 joints were available. All US studies were performed according to published guidelines, by a rheumatologist certified in musculoskeletal ultrasound, with >15 years US experience. Linear transducers with frequencies between 14–18 MHz were used. Erosions were defined as breaks in the cortical contour of metatarsal head or proximal phalanx, seen in two perpendicular planes. Tophaceous material was defined as hyperechoic crystalline concrements with a "wet clumps of sugar" appearance. Calcified tophi were defined as hyperechoic concrements with a pronounced posterior accoustic shadow.

In contrast to previous studies, 3 different radiographic views of the feet were obtained to facilitate detection of erosions. The radiologist's final impression was counted. At the time of the study, the sonographer was unaware of the CR results.

Results: Using US, erosions were seen in 41/62 joints (66%). Using multiview CR, erosions were seen in 21/62 of the same joints (34%). Intra-articular calcification was seen in 3/62 joints (5%) using US and 3/62 joints (5%) using CR. Intra-articular tophaceous material was seen in 59/62 joints (95%) using US and 0/62 joints (0%) using CR. Tophaceous material was seen within the erosion in 36/62 joints (58%).

Conclusion: US identified almost twice as many erosions as CR in gouty joints. The addition of a third radiographic view improved the yield only marginally over previous studies that used two CR views to assess erosions in gout. If tophi calcify, they are seen both with CR and US, but uncalcified tophaceous material escapes CR visualization. Similar to findings in RA, CR remains an imperfect tool for the assessment of erosions in gout when compared with US.

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[1] Thiele, R.G. and N. Schlesinger, Diagnosis of gout by ultrasound. Rheumatology (Oxford), 2007.

[2] Thiele, R.G. and N. Schlesinger, Ultrasonography shows disappearance of monosodium urate crystal deposition on hyaline cartilage after sustained normouricemia is achieved. Rheumatol Int., 2010

Disclosure: R. G. Thiele: GE Healthcare, 9, Novartis Pharmaceuticals Corporation, 5, SonoSite, 9; **N. Schlesinger:** Novartis Pharmaceuticals Corporation, 2.

ACR Poster Session B
Miscellaneous Rheumatic and Inflammatory Diseases I
Tuesday, November 9, 2010, 9:00 AM–6:00 PM

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A Comprehensive Tuberculosis Screening Program in Patients with Inflammatory Arthritis Treated with Golimumab, a Human Anti-TNF Antibody, in Phase 3 Clinical Trials. Elizabeth C. Hsia[4], John J. Cush[1], Eric L. Matteson[5], Anna Beutler[2], Mittie K. Doyle[4], Benjamin L. Hsu[3] and Mahboob U. Rahman[4]. [1]Baylor Research Institute, Dallas, TX, [2]Centocor Research and Development, Inc., Collegeville, PA, [3]Centocor Research and Development, Inc./Univ. of Pennsylvania School of Medicine, Wynnewood, PA, [4]Centocor Research and Development, Inc./Univ. of Pennsylvania School of Medicine, Malvern, PA, [5]Mayo Clinic, Rochester, MN

Background: Reactivation of *Mycobacterium tuberculosis* infection is a major complication in patients (pts) with inflammatory diseases treated with anti-tumor necrosis factor (TNF) agents. Screening and appropriate treatment (tx) for latent TB infection (LTBI) before initiation of TNF blockers, as well as prompt diagnosis (dx) of active TB cases, can decrease morbidity and mortality.

Objectives: To summarize active TB case reports by wk52 across 5 SC GLM studies (3 RA, 1 PsA, and 1 AS).

Methods: Pts enrolled from North & South America, Europe (Western + Eastern), Australia/New Zealand, and Asia. TB eligibility criteria included: no history of latent/active TB; no signs/symptoms of active TB; negative (-) tuberculin skin test (TST) and QuantiFERON®-TB Gold test In-Tube (QFT) *or* if newly identified +TST *or* +QFT with active TB ruled out, had tx for LTBI initiated before or at 1st dose. TST done using Mantoux method and + per local guidelines for immunosuppressed or if ≥5mm if no guidelines. All pts had chest x-ray (CXR) ≤ 3 months before 1st dose. Targeted questions for early dx of active TB were asked q4wks.

Results: Among 2294 randomized pts, 316 (13.8%) had either TST+ or QFT+ screening test and required tx for LTBI. Through wk52, none of those tx for LTBI developed active TB while on GLM. Active TB occurred in 5 pts by wk52 (Table). Cases were in countries with high background rates of TB. 2 cases occurred by wk24 and were more consistent with reactivation. There were no deaths due to TB.

Conclusion: Despite 2 screening tests and CXR, to detect LTBI, there were still cases of TB reactivation. However, given that many enrolled pts resided in TB endemic areas, the number of active TB cases may have been higher with a less conservative TB screening strategy. Even if TB screening tests are -, clinicians should remain vigilant for development of active TB after initiation of TNF blockers, as prompt dx and tx can lead to improved outcomes.

Case of TB Across Golimumab Phase 3 Studies

Study	Dx	Screening TB test results/ BCG status	TB test results at time of Dx	# Doses of GLM	Demographics/ GLM Dose	Outcome
RA, MTX naïve	Bone TB of spine	QFT-TST-(0 mm) CXR wnl BCG+(at birth)	QFT+ TST-CXR wnl	3	64-y/o WF Ukraine DD = 7.4 yrs GLM 50 mg	Residual disability due to paresis
	TB pleurisy	QFT- TST-(0mm) CXR wnl BCG-	QFT-TST-(0mm) CXR abnl	11	65-y/o AF Philippines DD = 1.4 yrs GLM 100mg	Rec
	Pulm TB	QFT-TST-(5mm) CXR ILD BCG-	QFT indeterminate TST+(10mm) CXR same as screening	7	67-y/o AF Philippines DD = 0.9 yrs GLM 50 mg	Rec
RA despite MTX	TB pleurisy	QFT-TST-(15m) CXR wnl BCG+(age 12)	QFT+TST+(20mm) CXR large pleural effusion	6	38-y/o AF Taiwan DD = 13.7yrs GLM 50mg	Rec
AS despite conventional tx	Pulm TB	QFT-TST-(3mm) CXR wnl BCG+ (age 4)	QFT+ TST+ (17 mm) CXR LUL infiltrate	10	25-y/o AM South Korea DD = 2 yrs GLM 100 mg	Rec

Pulm = pulmonary; BCC = Bacillus Calmette-Guérin; DD = disease duration; wnl = within normal limits; abnl=abnormal, y/o = year-old; yr(s) = year(s); LUL = left upper lobe; F = female; M = male; A = Asian; W = white; ILD = interstitial lung disease; Rec = recovered

Disclosure: E. C. Hsia: Centocor Research and Development, Inc., 3; **J. J. Cush:** Centocor Research and Development, Inc., 2, 9; **E. L. Matteson:** Centocor Research and Development, Inc., 2, 9; **A. Beutler:** Centocor Research and Development, Inc., 3; **M. K. Doyle:** Centocor Research and Development, Inc., 3; **B. L. Hsu:** Centocor Research and Development, Inc, 3; **M. U. Rahman:** Centocor Research and Development, Inc., 3.

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Anakinra in Adult Onset Stills Disease (AOSD). Clinically Beneficial Results in an Open, Randomized, Multicenter Study. Dan C. Nordström[3], Ann Knight[11], Reijo Luukkainen[8], Ronald V. Vollenhoven[5], Vappu Rantalaiho[9], Anna Karjalainen[7], Johan Brun[2], Anne Proven[6], Lotta Ljung[10], Hannu Kautiainen[1] and Tom Pettersson[4]. [1]Central Finland Central Hospital, Finland, [2]Haukeland University Hospital, Norway, [3]Helsinki Univerity Central Hospital, Finland, [4]Helsinki University Central Hospital, Finland, [5]Karolinska Hospital, Sweden, [6]Martina Hansens Hospital, Norway, [7]Oulu University Hospital, Finland, [8]Rauma Hospital, Finland, [9]Tampere University Hospital, Finland, [10]Umeå University Hospital, Sweden, [11]Uppsala University Hospital, Sweden

Background: AOSD is a rare systemic inflammatory disease of unknown cause characterized by spiking fevers, polyarthritis, evanescent rash, and other multiorgan involvement. The outcome is unpredictable and varies from monophasic, remitting/relapsing to chronically progressing. No etiology has emerged but high levels of pro-inflammatory cytokines (IL-1, IL-6, IL-18) involving possible polymorphisms, and acute phase reactants have been proposed as being pathogenetically relevant. Frequently, systemic immunosuppressive therapy is required for treatment, but for patients irresponsive to systemic steroids and immunosuppression, especially IL-1 suppression (anakinra) has given even striking responses. This is the first randomized study comparing IL-1 suppression therapy with traditional DMARDs.

Objectives: To follow the changes in clinical status and disease activity in patients receiving anakinra, compared to those of a traditional DMARD (methotrexate, azathioprine, leflunomide, or cyclosporin A) in addition to corticosteroids in patients with corticosteroid dependent, refractory AOSD.

Methods: Open 24 week, randomized, comparative, multicenter study. 22 patients on corticosteroids were randomized to receive anakinra (n=12) or DMARD (n=10). Patients entered the study only if considered refractory to corticosteroids (prednisolone equivalent ≥10 mg/day for at least two months after disease onset). Primary end point identified the proportion of patients reaching remission of disease after two months of study treatment (stated as afebrile [≤37°C of body temperature], acute phase reactants [C-reactive protein, ferritin] within normal limits, and joint scores being normal). Secondary end points included identification of patients reaching remission at two consecutive visits during 24 weeks, follow-up of acute phase reactants and corticosteroid dosage and identifying changes in disease related parameters such as general health, HAQ and SF-36.

Results: Patient groups (anakinra vs. DMARD) were comparable except regarding baseline ferritin levels (354, range 18–1740 vs. 186, range 17–680) and baseline prednisolone dose (22.5 mg, range 10–60 vs. 18.5, range 10–25), respectively. At week 4, 6/12 and 3/10 were in remission; at week 8, 7/12 and 5/10 were in remission; and at 24 weeks 6/12 and 2/10 were still in remission, respectively. In the Physical Health Summary of the SF-36 anakinra produced significantly more rapid and sustained responses compared to DMARD (p=0.011). Only patients on DMARDs (N=5) withdrew prematurely.

Conclusion: In refractory AOSD both DMARD therapy and especially anakinra showed good therapy responses during the 24 week intervention period. Responses were more robust with anakinra at 24 weeks with 50% of patients in strict remission according to criteria above. Withdrawals due to lack of efficacy occurred only in DMARD patients.

References:

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2. Nordström D. Anakinra in the treatment of rheumatoid arthritis and other IL-1 driven conditions. A Review. Future Rheumatology 2007;2:353–8

Disclosure: D. C. Nordström: None; **A. Knight:** None; **R. Luukkainen:** None; **R. V. Vollenhoven:** None; **V. Rantalaiho:** None; **A. Karjalainen:** None; **J. Brun:** None; **A. Proven:** None; **L. Ljung:** None; **H. Kautiainen:** None; **T. Pettersson:** None.

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Anti-Double Stranded DNA and Other Autoantibodies Are Common in Alaska Native Autoimmune Hepatitis Patients. Elizabeth D. Ferucci[1], Kathy J. Hurlburt[1], Stephen Livingston[1], Julia Plotnik[1], James Gove[1], Brian J. McMahon[1] and Judith A. James[2]. [1]Alaska Native Tribal Health Consortium, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK

Purpose: Autoimmune hepatitis has been associated with rheumatoid arthritis and other autoimmune diseases. The purpose of this study was to determine the prevalence of autoantibodies related to rheumatoid arthritis (RA) and connective tissue diseases in autoimmune hepatitis (AIH).

Methods: Alaska Native study participants were recruited at hepatitis clinics provided by the Alaska Native Tribal Health Consortium Liver Disease and Hepatitis Program. Patients with definite or probable AIH defined by the International Autoimmune Hepatitis Group (IAHG) criteria provided informed consent for participation in an observational study of AIH. Sera from a study visit were tested for the following autoantibodies: IgG rheumatoid factor (RF) by ELISA, CCP antibody by ELISA, anti-double stranded DNA (dsDNA) by immunofluorescence with Crithidia luciliea and ELISA testing, and anti-nRNP, Sm, Ro, La, and ribosomal P. Rheumatologic diagnoses were determined by medical record review. Diagnoses were documented by a clinical rheumatologist using established criteria, including American College of Rheumatology (ACR) criteria for RA and systemic lupus erythematosus (SLE).

Results: Sera were available from 70 patients with AIH. Of the 70 AIH patients, 66 (94.3%) were female, and the mean age at consent was 52.1 years (SD 18.2, median 56.7). Fourteen AIH patients (20%) had an established rheumatologic diagnosis (9 (12.9%) with RA, and 1 each with SLE, Sjogren's syndrome, mixed connective tissue disease, adult Still's disease, and psoriatic arthritis). In the 9 AIH patients with RA, 5 (55.6%) had RF present, 6 (66.7%) CCP, 5 (55.6%) both RF and CCP, 3 (33.3%) dsDNA, 3 (33.3%) nRNP, 5 (55.6%) Ro, and 2 (22.2%) La. In AIH patients without any known rheumatologic diagnosis (n=56), the most common autoantibody found was dsDNA (26/56, or 46.4%); followed by RF (6/56, or 10.7%), and Ro (6/56, or 10.7%). Other autoantibodies found were CCP in 2 patients, La in 2 patients, and anti-nRNP in 1 patient. No patient with or without a rheumatologic diagnosis had Sm or ribosomal P antibodies.

Conclusion: Antibodies to double stranded DNA are commonly found in Alaska Native patients with AIH, in the absence of diagnosed SLE. This information provides rheumatologists with additional information when considering the differential diagnosis of a positive dsDNA antibody, suggesting that anti-dsDNA is not universally associated with only SLE.

Disclosure: E. D. Ferucci: None; **K. J. Hurlburt:** None; **S. Livingston:** None; **J. Plotnik:** None; **J. Gove:** None; **B. J. McMahon:** None; **J. A. James:** None.

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Anti-U1C Autoantibody Specifically Interferes with the U1RNP-Mediated Splicing of Angiopoietin-1 (*Ang1*) Gene and Induces Functionally Defective *Ang-1*/ins Variant in the Patients with MCTD. Yuka Kosugi[1], Koichiro Komai[1], Shogo Funaki[1], Aya Mashida[1], Kazuko Shiozawa[3], Akira Hashiramoto[2] and Shunichi Shiozawa[2]. [1]Dep. of Biophysics, Graduate School of Health Sciences, Kobe Univ., Kobe, Japan, [2]Dep. of Biophysics, Graduate School of Health Sciences, Kobe Univ./Dep. of Medicine, Graduate School of Medicine, Kobe Univ./The Center for Rheumatic Diseases, Kobe Univ., Hosp., Kobe, Japan, [3]Rheumatic Diseases Center, Konan Kakogawa Hosp., Kakogawa, Japan

Purpose: Angiopoietin-1 (*Ang1*) is the ligand of endothelial tyrosine kinase receptor Tie2 and induces cell proliferation *via* ERK phosphorylation. *Ang1* is strongly up-regulated in the lung of patients with mixed connective tissue disease (MCTD) accompanied by pulmonary hypertension (PH) indicating that *Ang1* can play a key role in the pathogenesis of PH associated with MCTD. We previously showed that the frequency of the splicing variant of *Ang1* mRNA with nt805GGT insertion (*Ang1*/ins) encoding ^{269}Gly was significantly increased in the Japanese patients with MCTD and those with PH as compared with *Ang1*/del with nt805GGT deletion (Arth. & Rheum. 52 (9): S283, '05). We also found that *Ang1*/ins dose proliferate pulmonary endothelial cells and potentially induce hyperplasia of smooth muscle cell in relation to the pathogenesis of PH as compared with *Ang1*/del (Arth. & Rheum. 58 (9): S659, '08 and 60 (10): S8, '09). On the other hand, anti-U1RNP antibodies (Abs), elevated in MCTD significantly induced *Ang1*/ins mRNA in Jurkat cells (Arth. & Rheum. 58 (9): S224, '08). We have now studied the contribution of subclass of Abs against U1A, U1C or U1–70K to the induction of *Ang1*/ins variant. We also evaluated the reactivity of anti-U1RNP auto-Abs against each components of U1RNP in sera of patients with MCTD.

Methods: Anti-U1A, U1C and U1–70K Abs (LifeSpan Biosc. and Bio Acad.) were introduced into human pulmonary artery smooth muscle cells (HPASMC) using PULS-in reagent (Polyplus transfection), followed by treatment with IL6 and TNFα (20ng/ml each) for 24 h. *Ang1* mRNA was obtained by using RT-PCR and subjected to length analysis by using ABI3130xl sequencer. Expression levels of *Ang1* variants were evaluated with calculated peak areas. Anti-U1RNP Ab titer in sera of Japanese patients with MCTD was determined by using Autoimmune EIA Test (BIO-RAD) and the *Ang1* mRNA phenotype was determined. We also constructed ELISA by using recombinant U1A, U1C and U1–70K proteins (DIARECT), as coated antigen and Ab titers in sera of patients were determined.

Results: Anti-U1C and U1–70K Abs significantly induced *Ang1*/ins mRNA with IL6 and TNFα ($P<0.05$). Otherwise, neither anti-U1A, U1C nor U1–70K Abs did alter the *Ang1* splicing without cytokine. We also confirmed that *Ang1*/ins wasn't induced with cytokine. Frequency of the patients with MCTD having anti-U1RNP Ab titer exceeding 200 was 81.3% (39/48) and 50.0% (6/12) ($P<0.05$) among those with *Ang1*/ins dominant and *Ang1*/del dominant phenotypes, respectively. While comparison between *Ang1*/del and *Ang1*/ins dominant phenotypes wasn't possible because of 2 sera specimens of those *Ang1*/del dominant phenotype, the titer of each subclass of anti-U1RNP Ab in the sera of patients with MCTD among those with *Ang1*/hetero (n=13) and *Ang1*/ins dominant phenotypes (n=18) was: 11.8 ± 23.6 and 47 ± 58.9 ($P<0.05$) for anti-U1A Ab, 13.6 ± 25.7 and 122.1 ± 124.5 ($P<0.005$); for anti-U1C Ab, 406.2 ± 599.5 and 5512.9 ± 12484.7 (not significant); for anti-U1–70K Ab.

Conclusions: It is suggested that anti-U1RNP Ab, especially those reactive with U1C affect the splicing of *Ang1* with cytokines and induce functionally defective *Ang1*/ins in the patients with MCTD.

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Autoimmune Phenomena in Muckle-Wells Syndrome (MWS). Katharina Gramlich[1], Reinhild Klein[4], Sandra Hansmann[3], Susanne M. Benseler[5] and Jasmin B. Kuemmerle-Deschner[2]. [1]Division of Pediatric Rheumatology, Department of Pediatrics, University Hospital Tübingen, Tuebingen, Germany, [2]Division of Pediatric Rheumatology, Department of Pediatrics, University Hospital Tübingen, Tuebingen, Germany, [3]Division of Pediatric Rheumatology, Department of Pediatrics, University Hospital Tübingen, Germany, [4]Division of Rheumatology, Department of Internal Medicine, University Hospital Tübingen, [5]The Hospital for Sick Children, Toronto, ON, Canada

Background: Muckle-Wells Syndrome (MWS) is a rare inherited autoinflammatory disease which is driven by excessive interleukin-1β (IL-1β) production. IL-1 blocking therapies including anakinra and canakinumab have been shown to be safe and effective. Absence of autoantibodies is the hallmark of autoinflammatory diseases, discriminating them from autoimmune diseases. The aim of this study was to determine the frequency of autoantibodies in MWS-patients prior to therapy and during anakinra and canakinumab therapy.

Methods: A single center observational study was performed. Patients with confirmed MWS were tested for autoantibodies at baseline prior to IL-1 blockade, within 6 months of treatment with anakinra or canakinumab respectively, and at 6–12 months of treatment. Monitoring included antinu-

clear antibodies (ANA), smooth muscle antibodies (SMA), anti-endothelial antibodies (AEA), anti-sarcolemmal antibodies (ASA) by immunofluorescence test, and antibodies against serotonin, gangliosides and CNS-tissue of the IgG and IgM type by ELISA.

Results: We included 20 patients, 8 males, 12 females, median age at diagnosis, 34 years (3,5–72). All patients were screened for the presence of autoantibodies before starting anti-IL-1 therapy. Positive ANA were detected in 3 patients (15%); SMA, AEA or ASA were found in 6 patients (30%). 2/4 tested were positive for anti-serotonin antibodies and 2/15 for anti-ganglioside antibodies. Antibodies against CNS-tissue were detected in 5/15 tested.

During anakinra therapy no formation of ANA in initially ANA-negative patients was observed, ANA newly emerged in 4/14 during canakinumab therapy. New antibody formation against gangliosides occurred in 2 patients during anakinra and in 1 patient during canakinumab therapy. Antibodies against serotonin and CNS-tissue were frequently detected during both anakinra and canakinumab therapy; however there was no evidence of new formation of these antibodies. SMA, AEA and ASA were unchanged over the whole study period. During the overall study period, 15/20 patients (75%) were positive for antibodies against serotonin, gangliosides and/ or CNS-tissue at least at one time point.

Conclusions: Patients with MWS can have ANAs and antibodies against serotonin, gangliosides and CNS-tissue. IL-1 blockade may increase the formation of autoantibodies in previously antibody-negative patients. The clinical relevance of the presence of autoantibodies in patients with MWS is still unclear.

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Canakinumab (ILARIS®) Provides Rapid Response and Sustained Remission in Cryopyrin-Associated Periodic Syndrome (CAPS) Patients across All Severity Phenotypes. H. J. Lachmann[12], J. B. Kuemmerle-Deschner[6], E. Hachulla[3], R. Cartwright[1], I. Kone-Paut[4], J. Hoyer[2], P. Quartier[11], J. Smith[14], M. Gattorno[5], K. Leslie[10], J. Braun[9], A. Widmer[7], N. Patel[8], R. Preiss[8] and P. N. Hawkins[13]. [1]Allergy Center at Brookstone, Columbus, GA, [2]Department of Internal Medicine and Nephrology, Universitaetsklinikum Giessen und Marburg GmbH, Marburg, Germany, [3]Hôpital Claude Huriez CHRU, Lille Cedex, France, [4]Hôpital Kremlin Bicetre, CEREMAI, Le Kremlin Bicetre, France, [5]Istituto Giannina Gaslini, Genova, Italy, [6]Klinik fuer Kinder-und Jugendmedizin, Universitaetsklinikum, Tuebingen, Germany, [7]Novartis Pharma AG, Basel, Switzerland, [8]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [9]Rheumazentrum Ruhrgebiet, Herne, Germany, [10]UCSF School of Medicine, San Francisco, CA, [11]Unit'e d'Immunologie, Hematologie et Rhumatologie Pediatrique, Hopital Necker-Enfants Malades, Paris, France, [12]University College London Medical School, London, United Kingdom, [13]University College London Medical School, London, United Kingdom, [14]University of Wisconsin Hospital and Clinics, Madison, WI

Background: CAPS (a disease spectrum consisting of familial cold auto-inflammatory syndrome [FCAS], Muckle-Wells syndrome [MWS], neonatal-onset multisystem inflammatory disease [NOMID]) is a rare systemic inflammatory disease associated with mutations in NLRP3 causing excessive production of interleukin-1β (IL-1β). The fully human monoclonal antibody canakinumab provides prolonged selective blockade of IL-1β. This study evaluated the long-term efficacy and safety of canakinumab subcutaneous (sc) injections every 8 weeks in a large cohort of CAPS patients.

Methods: Patients enrolled in this open-label, multi-center study were canakinumab-naive or rolled-over from earlier studies. Patients received canakinumab 150 mg sc or 2 mg/kg sc (body weight ≤40 kg) every 8 weeks. The primary objective was to assess the long-term safety and tolerability of canakinumab in CAPS patients. Secondary objectives included assessment of response (for naive patients), maintenance of response for those patients who had achieved a complete response, percentage of patients requiring dose adjustment. Complete response was defined as: physician's global assessment of disease activity and skin assessment score ≤minimal and normal CRP and/or SAA values (<10 mg/L). Relapse was defined as: serum levels of CRP and/or SAA >30 mg/L and physician's global assessment of disease activity >minimal or physician's global assessment of disease activity minimal along with the assessment of skin disease >minimal.

Results: 166 (47 pediatric) patients aged 3–91 years were enrolled (30 FCAS; 103 MWS; 32 MWS/NOMID [14 NOMID]; 1 child did not have CAPS and was discontinued [protocol violator]). 109 patients were canakinumab-naive, while 57 had been pre-treated with canakinumab. 151 (91%) patients completed the study and 15 patients discontinued (4 due to adverse events [AEs]). Median duration of exposure to canakinumab was 414 days (range 29–687 days) and the mean number of injections per patient was 7.2. A complete response (CR) was achieved in 85/109 (78%) canakinumab-naive patients (80 patients achieved CR within 8 days, the others achieved CR within 21 days). Of the 141 patients who were included in the relapse assessment, 127 (90%) had no relapse, while 14 (10%) experienced a relapse. Dose adjustments were required in 36 (22%) patients (17% adults vs 34% children). In canakinumab-naive patients median CRP and SAA levels rapidly decreased within 7 days (2.5 and 4.9 mg/L [baseline levels were 19.6 and 35.6 mg/L, respectively]) and these levels were maintained within normal levels (<10 mg/L) during the study in the entire patient cohort. Predominant AEs were infections (65%), mostly mild to moderate in severity. Most frequent AEs were nasopharyngitis, headache and rhinitis. Serious AEs were reported in 18 patients. Majority of patients (92%) had no injection site reactions, 8% reported reactions which were all mild or moderate.

Conclusions: Canakinumab 150 mg sc every 8 weeks provided rapid improvement of symptoms and sustained remission in a large cohort of CAPS patients across different severity phenotypes. Long-term safety profile was comparable to that established in earlier trials of shorter duration.

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Celecoxib Analogue Lacking COX-2-Inhibitory Activity Inhibits Arthritis by Supressing IL-23 and Inflammatory Cytokines. Asako Chiba[2], Ryohsuke Tajima[2], Miho Mizuno[2], Chiharu Tomi[2], Iraide Alloza[3], Takashi Yamamura[2], Koen Vandenbroeck[3] and Sachiko Miyake[1]. [1]Department of Immunology, National Institute of Neuroscience, NCNP, Kodaira Tokyo, Japan, [2]Department of Immunology, National Institute of Neuroscience, NCNP, [3]Neurogenomiks Laboratory, Ikerbasque and Universidad Del País Vasco (UPV/EHU), Parque Tecnológico de Bizkaia

Background: Previously we reported that a trifluoromethyl analogue of celecoxib (TFM-celecoxib) lacking COX-2-inhibitory activity induces cellular retention of IL-12 and IL-23. Because these cytokines are involved in autoimmune or inflammatory diseases, we asked whether TFM-celecoxib suppresses animal models of arthritis.

Methods: To induce collagen-induced arthritis (CIA), DBA1/J mice were immunized with bovine type II collagen (CII) (150μg) in Freund's complete adjuvant containing 250μg of H37Ra *Mycobacterium tuberculosis* on day 0 and CII in IFA on day 21. Antibody-induced arthritis (AIA) was induced in C57BL/6 mice by injecting a mixture of anti-CII antibodies followed by lipopolysaccharide (LPS) administration 2 days later. Experimental autoimmune encephalomyelitis (EAE) was induced in C57BL/6 mice by immunizing with MOG_{35-55}-peptide (100μg) in CFA followed by pertussis toxin administration. Peritoneal recruitment of leukocytes was induced by injecting 1ml of 4% thioglycollate. Mice recieved 10μg/kg of TFM-celecoxib (TFM-C) every other day from day 1 in EAE and AIA experiments, every day from day 21 in CIA experiments. The control animals were injected with vehicle alone, and in some experiments another group of mice were treated with celecoxib. Bone marrow-derived dendritic cells (BMDCs) or splenic macrophages from mice treated with TFM-C were stimulated by LPS in vitro in the presense or absence of TFM-C, and cytokine consentration in the culture supernatants was measured by ELISA

Results: TFM-C strongly suppressed CIA and AIA, although celecoxib did not inhibit these models. Histopathological analysis of arthritic joints revealed that TFM-C treatment inhibited mast cell degranulation whereas celecoxib treatment failed to suppress mast cell activation. TFM-C suppressed mast cell-dependent neutrophil influx into peritoneal cavity after injection of thioglycollate. TFM-C treatment in vivo inhibited inflammatory cytokines production from macrophages. Moreover, TFM-C suppressed the clinical and pathological features of EAE in association with the reduction of IL-23 production by dendritic cells, which subsequently suppressed IL-17 production by lymph node cells when re-challenged by MOG in vitro.

Conclusion: TFM-C suppressed murine models of arthritis by suppressing innate immune cell activation and autoreactive T cell responses, high-

lighting the therapeutic potential of TFM-C for autoimmune diseases such as rheumatoid arthritis and multiple sclerosis.

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Comprehensive Analyses of MEFV, TNFRSF1A, MVK, and CIAS1 Mutations in 63 Patients with Clinically Periodic Fever Syndrome in Japan. Sayuri Kataoka[2], Manabu Kawamoto[1], Yasushi Kawaguchi[3], Takahisa Gono[1], Masanori Hanaoka[1], Hisae Ichida[1], Yasuhiro Katsumata[1], Yuko Okamoto[4], Yuko Ota[2], Ikuko Masuda[1] and Hisashi Yamanaka[1]. [1]Tokyo Women's Medical University, [2]Tokyo Women's Medical University, Japan, [3]Tokyo Women's Medical University, [4]Tokyo Womens Med Univ

Purpose: Periodic fever syndrome refers to a group of autoinflammatory disease sharing similar symptoms and characterized by recurrent unprovoked inflammation in the absence of infection. These diseases primarily include familial Mediterranean fever (FMF), TNF receptor-associated periodic syndrome (TRAPS), hyperimmunoglobulinemia D syndrome (HIDS), and cryopyrin-associated periodic syndrome (CAPS). The genetic studies revealed predominant mutations of MEFV gene in FMF, TNFRSF1A gene in TRAPS, MVK gene in HIDS, and CIAS1 gene in CAPS. A number of studies about hereditary autoinflammatory disease have already established in Europe and USA, while it has not been fully understood in the Japanese population. In the present study, we investigated a comprehensive analysis of mutations in MEFV, TNFRSF1A, MVK and CIAS1 in patients with clinically periodic fever syndrome.

Methods: We have defined clinically periodic fever syndrome as recurrent episodes of systemic inflammation in the absence of pathogens (i.e.: bacterial infection, viral infection), autoantibodies (i.e.: collagen diseases), or antigen specific T cells (i.e.: malignancy, allergy). Sixty-three patients were matched to those criteria and enrolled in the present study. All patients were Japanese. The median (range) of age was 13 years old (3 to 36), and the ratio of female/male was 29/34. All genotyping of exon 3 and exon 10 in the MEFV gene, exon 2 to exon 5 in the TNFRSF1A gene, exon 10 and exon 11 in the MVK gene, and exon 3 in the CIAS1 gene were determined by direct sequencing using ABI PRISM3100.

Results: The mutations of M694I and P369S + R408Q in the MEFV gene were found in 4 and 5 patients with clinically periodic fever syndrome, respectively. In the TNFRSF1A gene, the mutations of C30R and T61I were found in 1 and 3 patients, respectively. In the MVK gene, one patient was observed rare mutation of G326R, and E304K mutation in the CIAS1 gene was detected in one patient. Those 15 patients had only a mutation described above, while one patient had two mutations of the MEFV (M694I) and TNFRSF1A (T61I) genes. Finally, we detected gene mutations in 16 out of 63 patients with clinically periodic fever syndrome by these methods. Interestingly, only two in 16 patients had the family history of periodic fever: one has sister and one has brother and mother. Fourteen patients had no family history.

Conclusion: This comprehensive analysis can detect 16 patients (25%) with hereditary periodic fever syndrome, as a result of evaluating 63 patients with clinically periodic fever syndrome. These observations suggest FMF and TRAPS were common in the Japanese population, although it has been believed that hereditary periodic fever syndrome was a very rare disease in Japan.

Table 1. Summary of mutations in patients with clinically periodic fever syndrome

Mutation	Number of patient
MEFV	
P369S + R408Q	5
M694I	4
TNFRSF1A	
C30R	1
T61I	3
MVK	
G326R	1
CIAS1	
E304K	1
MEFV (M694I) + TNFRSF1A (T61I)	1
Total	16

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Defining the Aromatase Inhibitor Musculoskeletal Syndrome: A Prospective Trial. Ora Singer[1], Alana B. Levine[1], Tessa Cigler[3], Anne B. Moore[2], Huong T. Do[1] and Lisa A. Mandl[1]. [1]Hospital for Special Surgery, New York, NY, [2]NY Presbyterian - Weill Cornell Medical Center, New York, NY, [3]NY Presbyterian-Weill Cornell Medical Center, New York, NY

Background: Aromatase Inhibitors (AIs) are standard of care therapy for post-menopausal breast cancer, AIs have been associated with debilitating musculoskeletal symptoms, predominantly in the hands and wrists. Up to 15% of symptomatic patients discontinue this potentially life saving therapy. The purpose of this study is to define the AI syndrome.

Methods: Post-menopausal women with hormone-sensitive, non-metastatic breast cancer and no rheumatic disease were included in this prospective cohort study. Subjects were evaluated by a rheumatologist before starting AIs and at 6 months. Women who reported new or worsening musculoskeletal symptoms were classified as "symptomatic." The primary outcome was grip strength; secondary outcomes included 66/68 swollen and tender joint count, HAQ-DI, SF-36, AUSCAN Hand Index, and serum testing for CPK, CRP, ESR, CCP, SSA, SSB, RF, ANA. Contrast enhanced MRIs of the hands and wrists were performed at baseline and 6 month or at symptom onset. MRIs were read by two blinded radiologists using the OMERACT Rheumatoid Arthritis MRI Scoring with Tenosynovitis subscale (RAMRIS-TS).

Results: Of 35 women enrolled, 19 (54%) were symptomatic and of these 2 (5.7%) discontinued the AI. Mean time to onset of symptoms was 6 weeks (range 2 to 18). Fifty-eight percent of symptomatic subjects had involvement of the hands. Two had De Quervain's TS, 4 had tenderness over the flexor digitorum tendons, including 1 trigger finger, and 5 had generalized bilateral hand and wrist stiffness. Three subjects had ball of the foot and/or heel pain with weight bearing. Cancer stage was the only significant predictor of symptom development, (OR 5.9; 95% CI 1.2, 28.1) There was no difference in the mean change in grip strength between the symptomatic and asymptomatic groups, (−2.3 kg vs −1.4 kg, p-value=0.97). There were also no differences in the mean change in HAQ, SF 36, 66/68 tender and swollen joint counts and laboratory values. There was a statistically significant worsening of the AUSCAN pain, stiffness and total subscales in the symptomatic group (P-values = 0.004, 0.001 and 0.001, respectively). Although some symptomatic subjects with hand/wrist involvement had MRI abnormalities, there was no significant change in any RAMRIS score. ICC's were 0.8, 0.76, 0.19 and 0 for erosion, edema, synovitis and TS RAMRIS scores respectively

Conclusions: In this prospective study, more than half of subjects reported new or worsening musculoskeletal complaints on AIs. Later stage cancer increased the risk of developing pain, and clinical exam suggested underlying tenosynovial pathology. While TS was detected on MRI in some symptomatic subjects, the RAMRIS, developed for inflammatory arthritis, was not able to differentiate symptomatic from asymptomatic women. There was no difference in serum findings between the two groups. These findings suggest the AI syndrome is not due to the triggering of an autoimmune or systemic inflammatory process. Although symptoms were not limited to the hands and wrists, the AUSCAN was associated with increased pain, suggesting this instrument may be discriminative in diseases other than OA.

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Hearing Loss in Muckle-Wells-Syndrome. Assen Koitschev[1], Katharina Gramlich[3], Sandra Hansmann[3], Susanne M. Benseler[5], Stefan Plontke[2], Christiane Koitschev[2], Ina Koetter[4] and Jasmin Kuemmerle-Deschner[3]. [1]Department of Otorhinolaryngology, Klinikum Stuttgart, Germany, [2]Department of Otorhinolaryngology, University Hospital Tübingen, Germany, [3]Division of Pediatric Rheumatology, Department of Pediatrics, University Hospital Tübingen, Germany, [4]Division of Rheumatology, Department of Internal Medicine, University Hospital Tübingen, Tuebingen, Germany, [5]The Hospital for Sick Children, Toronto, ON, Canada

Background: Muckle-Wells syndrome (MWS) is an inherited autoinflammatory disease associated with excessive Interleukin-1 (IL-1) release caused by NLRP3 gene mutations. MWS patients are at high risk of

developing devastating sensorineural deafness. The study aims to report the otologic characteristics in severe MWS.

Patients and Methods: A single center observational cohort study of consecutive children and adults diagnosed with MWS between 2000 and 2008 was performed. Genetic testing of the NLRP3 gene was completed. All patients had standardized neurotologic assessments including hearing threshold and speech audiograms, caloric vestibular testing and a structured tinnitus questionnaire. The audiograms of members of the same family were compared in order to describe the family specific risk of progressive hearing loss.

Results: A total of 19 MWS-patients ages 3–72 years from 4 families with 3 different NLRP3 gene mutations were included. Almost all patients (89 %, 17/19) presented with sensorineural hearing loss of different range compared to normal hearing threshold of a same age population. 15 of 19 patients had symmetric bilateral hearing thresholds. In 3 patients minimal asymmetry of the hearing threshold in the higher frequencies was demonstrated. One female patient age 19 appeared deaf since birth on the left side. Hearing thresholds uniformly decline toward the higher frequencies starting with an isolated pitch above 4 kHz in younger patients. Increasing age was significantly associated with worsening hearing impairment. The vestibular caloric reactivity was normal in all, including patients with profound hearing loss. Non-debilitating intermittent or permanent tinnitus was reported by half of the adult patients. In this cohort, patients with the mutation V198M were the least affected by hearing loss, patients with the T348M mutation were severely affected.

Conclusion: Progressive sensorineural hearing loss without vestibular involvement is the characteristic symptom of MWS. Progression is age dependent with large variation by intra- and interfamilial comparison. Different mutations appear to be associated with different risk levels of hearing loss, T348M mutation being most severely affected. Early diagnosis and specific therapy by IL-1 inhibition may be essential to prevent severe disease consequences.

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Hearing Loss in Muckle-Wells-Syndrome—Effects of IL-1 Inhibitiony. Assen Koitschev[1], Katharina Gramlich[3], Sandra Hansmann[3], Susanne Benseler[4], Stefan Plontke[2], Christiane Koitschev[2], Ina Koetter[6], Ralph Preiss[5] and Jasmin Kuemmerle-Deschner[3]. [1]Department of Otorhinolaryngology, Klinikum Stuttgart, Germany, [2]Department of Otorhinolaryngology, University Hospital Tübingen, Germany, [3]Division of Pediatric Rheumatology, Department of Pediatrics, University Hospital Tübingen, Germany, [4]Division of Rheumatology, Department of Pediatrics, The Hospital for Sick Children, Toronto, Canada, [5]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [6]University Hospital, Tuebingen, Germany

Background: Muckle-Wells syndrome (MWS) is a rare inherited autoinflammatory disease. The most devastating symptoms are sensorineural deafness and amyloidosis. NLRP3 gene mutations are associated with excessive Interleukin-1 (IL-1) release. Specific Il-1 inhibition has been shown to be safe and effective in the treatment of MWS. The study aims to systematically evaluate the effect of IL-1 inhibition on hearing in MWS.

Patients and Methods: A single center observational cohort study of consecutive children and adults with confirmed MWS was performed. Prospective standardized audiologic assessments were conducted at baseline and during treatment with the IL-1 receptor antagonist Anakinra or the fully human monoclonal IL-1β-antibody Canakinumab. Comparison was based on pure tone thresholds at 500, 1000, 2000 and 4000 Hz and defined as an increase or decrease of 20 dB in hearing threshold at one or more frequencies, or of 10 dB at two or more consecutive frequencies.Comparisons were made using paired t-tests, chi-squares or Fishers exact test, when appropriate.

Results: A total of 19 patients with MWS, ages 3–72 years from 4 families with 3 different mutations of the NLRP3 gene were included. At baseline, 13 patients (68%) indicated subjective hearing loss, 4 (21%) showed high frequency hearing loss without subjective impairment and two (11%) had normal hearing threshold. Treatment with Anakinra significantly improved hearing in 2/12 patients (16 and 44 years). Hearing did not deteriorate in 10/12 (83%) patients during a median treatment course of 12 months (range 5–14). Canakinumab therapy was given to 14 patients. Hearing improved in 1/14 patient (19 years). No deterioration of hearing loss was observed in 13/14 (93%) patients during a median treatment course of 11 months (range 6–15).

Conclusion: lL-1 inhibition in MWS prevented progression of hearing loss in all MWS patients. Reversal of hearing loss occurred in a small group. Factors associated with reversal have to be explored in order to optimize therapy and improve long-term outcome of MWS patients.

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Inflammatory Arthritis Associated with Isolated Anti-CBir1 Antibodies: Part of the Spectrum of "Seronegative" Arthritis? Melissa A. Peda[1] and Stanford L. Peng[2]. [1]Benaroya Research Institute, [2]Benaroya Research Institute and Virginia Mason Medical Center, Seattle, WA

Background: Despite serological advances in the diagnosis of inflammatory polyarthritis (iPA) conditions, such as anti-CCP antibodies in RA, current rheumatological practice continues to encounter many patients with "seronegative" arthritis. Such patients are often treated as seronegative rheumatoid arthritis; however, further insight regarding the classification of such patients could help guide investigations into pathogenesis and/or treatment. Since some inflammatory arthritis conditions, especially spondyloarthropathies, have been associated with subclinical bowel inflammation, this study sought to explore the potential utility of the inflammatory bowel disease (IBD)-associated toll-like receptor (TLR) 5 ligand flagellin antibody, anti-CBir1, in the classification of "seronegative" inflammatory arthritis.

Methods: We performed a retrospective chart review of patients seen in the rheumatology clinic at the Virginia Mason Medical Center in Seattle, WA between Q4 2009–Q1 2010. Records of patients who had been tested for anti-CBir1 reactivity via the Prometheus® IBD Serology 7 panel, which includes also anti-*Saccharomyces cerevisiae* antibodies (ASCA) and outer membrane porin C (OmpC) specificities (San Diego, CA), were reviewed.

Results: In the timeframe specified, 132 patients had been tested with the IBD Serology 7 panel. Of these, 81 (61%) had at least one positive IBD serological marker (61%); the most prevalent was anti-CBir1, which was positive in 36 (27%), compared to ASCA (12.9% positive for IgA, 6% positive for IgG) and OmpC (10.6% positive). Interestingly, 7 of these CBir1-positive patients were otherwise "seronegative," with negative ANA, RF, anti-CCP, ANCA, Celiac serology, and HLA-B27: these patients generally exhibited synovitis of the medium and/or large joints. Clinical evidence of psoriasis, inflammatory bowel disease, or antecedent infection was absent in all patients. Interestingly, these patients seemed to respond to treatments often used in spondyloarthropathies, such as NSAIDs, sulfasalazine, or etanercept.

Patient	Age	Gender	Right knee, Left sternoclavicular	Anti-CBir1 (EU/mL)	Treatment Response
1	71	F	Bilateral shoulders and ankles	21.1	Prednisone
2	74	M	Right ankle, knee and wrist	31.7	Sulfasalazine
3	55	F	Right wrist	87.6	Etanercept
4	77	M	Bilateral knees and shoulders	36.6	Ibuprofen
5	62	M	Right knee, Left sternoclavicular joint	23.8	Indomethacin
6	66	M	Right wrist and knee, bilateral shoulders	22.2	Etanercept
7	89	M	Bilateral wrists; right knee	29.7	Sulfasalazine

Conclusions: Anti-CBir1 positivity may identify a subset of otherwise seronegative iPA patients, perhaps within the spectrum of inflammatory spondyloarthropathies. The bowel flora flagellin specificity of CBir1 reactivity raises the possibility of a linkage between bowel inflammation and arthritis: as a result, not only might CBir1 and/or other IBD-associated biomarkers be useful in the diagnosis of iPA, they may also provide further insight into the pathogenesis of these inflammatory disorders. Systematic investigation is therefore warranted to ascertain the clinical relevance of CBir1 reactivity in the diagnosis or classification of rheumatic conditions.

Disclosure: M. A. Peda: None; **S. L. Peng:** None.

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Long Term Treatment with Anakinra in Patients with Adult-Onset Still Disease. Giampietro Cecilia[1], Ridene Meriem[2], Fautrel Bruno[3], Bourgeois Pierre[3] and CRI. [1]University of L'Aquila, L'Aquila, Italy, [2]University of Tunis, Tunis, Tunisia, [3]University Paris 6–Pierre et Marie Curie University; Rheumatology, Pitie-Salpêtriere Hospital, Paris, France

Background: Adult-onset Still disease (AOSD) is a rare systemic inflammatory disorder. Aetiology is still unknown, however recent advances suggest IL-1 to play a pivotal role in his pathogenesis.

Several observations have demonstrated the rapid efficacy of the anti-IL1 receptor antagonist anakinra in refractory cases treatment, but other studies are needed to evaluate his long term effects.

Objective: To assess the long term efficacy and safety of anakinra treatment in patients with AOSD.

Methods: Patients were identified by their participation to a precedent study and by a survey conducted in the CRI website.

19 patients affected by AOSD as defined by Yamaguchi diagnostic criteria and treated with anakinra were recruited contacting by mail all departements of rheumatology and internal medicine in France. Medical informations were retrospectively collected using a standardised questionnaire.Anakinra was given subcutaneusly at a daily dose of 100mg.

Patients were classified at remission if all symtoms of AOSD were disappeared, partial response if some general or articular signs persisted and failure if no response were observed.

Results: Patients were mean aged 40.6 ± 11.5 years (range 23 to 73), with mean disease duration at anakinra start of 9.4 years. Clinical expression was predominantely systemic in 6 patients and polyarticular in 13. All patients have previously failed to corticosteroids, synthetic DMARDs and for 10 of them to anti-TNFα and anti-CD20.

Anakinra was well tolerated in patients with AOSD and adverse events were rated as mild. The most common adverse event observed was a rash at the site of injection. It motived treatment discontinuation in only 1 patient. No augmentation of infection rate was observed.

At a mean follow up of 30.7 months, complete remission occurred in 13 cases. Partial response was observed in 4 cases. The symptoms that persisted were mainly articular manifestation whereas systemic ones disappeared early in the cours of treatment. 2 patients experienced a loss of efficacy after a mean of 15 months.

Anakinra allowed corticosteroid sparing and reduction of dose of eventually associated DMARDs. At the last visit, 4 patients withdrawn treatment because remission has been obtained and reduction of anakinra dose was possible in 4 cases without observed relapse of disease.

Evolution in Long-term Follow-up

Complete remission (n = 13) (68.4%)	Anakinra discontinued without relapse (n = 4) (21%)
	Dose reduction without relapse (n = 4) (21%):
	- 1 subcutaneous injection 3 time a week (n = 1)
	-1 subcutaneous injection 2 time a week (n = 2)
	- 1 subcutaneous injection 6 time a week (n = 1)
	Same dose continued (n = 5) (26.3%)
Partial response (n = 4) (21%)	Desappearance of systemic manifestations
	Persistence of articular manifestations
Loss of efficacy (n = 2) (10.5%)	Switch to anti-IL6 (1 infusion/4 weeks) with remission

Conclusion: AOSD patients experience a drastic response to Anakinra. In our long term study this efficacy is maintained without relapse or serius side effects.

Disclosure: G. Cecilia: None; **R. Meriem:** None; **F. Bruno:** None; **B. Pierre:** None; **CRI:** None.

903

Lymph Node and Bone Marrow Expression of Macrophage Migration Inhibitory Factor and IL18 in Adult-Onset Still's Disease. Sung-Hoon Park[1], Hwa-Jeong Lee[2], Seong-Kyu Kim[2] and Jung-Yoon Choe[2]. [1]Catholic University of Daegu, School of Medicine, Arthritis and Autoimmunity Research Center, Daegu, Korea, Republic of, [2]Catholic University of Daegu, School of Medicine, Arthritis and Autoimmunity Research Center

Background: Adult-onset Still's disease(AOSD) is a systemic inflammatory disorder, involving dysregulated production of proinflammatory cytokine. In the previous studies, although its mechanism is not precise, serum IL18 and macrophage migration inhibitory factor(MIF) level was significantly elevated in the disease patients and was shown to be correlated with disease activity. In this study, we investigated a expression of macrophage MIF and IL18 in lymph node(LN) and bone marrow(BM) specimen of AOSD patients and compared it with normal marrow or reactive lympadenopathy.

Methods: LN or BM section of 13 AOSD patients were prepared(both LN and BM in 6 of them). 3 of 6 patients showed a features of the macrophage activation syndrome(MAS), and were underwent both LN and BM biopsy. Immunohistochemical stain using anti-MIF antibody(Abcam, Cambridge, UK) and anti-IL18 monoclonal antibody(R&D Systems, Minneapolis, MN, USA) was done according to the recommendations of the manufacturer's instructions. 3 specimens of normal BM section and 3 specimens of reactive lymphadenitis were compared as control group. Correlation of serum ferritin and C-reactive protein(CRP) level with tissue cytokine expression was investigated.

Results: After staining with anti-MIF antibody and anti-IL18 monoclonal antibody, the staining intensity was measured by counting a total number of reactive cells(positive dot) in $100\times100\mu$m field manually. All cell counts were performed by the same observer for the entire study and verified by a second observer blinded to the study group. Mean age of LN group was 43.56±12.45 years old(2 male and 11 female patients) and 41.03±18.79 years old(3 male and 5 female patients) in BM group. Stain intensity of IL18 and macrophage MIF in LN group was significantly higher than reactive LN group. BM of AOSD patients expressed stronger IL18 and macrophage MIF than normal BM. Both IL18 and macrophage MIF overexpressed in MAS patients group, but there was no statistically significant difference($p=0.065$) compared with other AOSD patients without MAS(Table 1). Serum ferritin and CRP level was not quantitatively correlated with stain intensity.

Table 1 LN and BM immunohistochemical stain intensity

	LN N = 13	BM N = 8	Reactive LN N = 3	Normal BM N = 3	MASLN N = 3	MAS BM N = 3
Mean age, year	43.56 ± 12.45	41.03 ± 18.79				
Sex, M/F	2/113/5	0/3	1/2	1/2	1/2	
IL 18 stain	198.66 ± 91.36	142.32 ± 74.28	15 ± 12.31	11 ± 8.01	210.52 ± 42.23	148.74 ± 25.17
MIF statin	122.64 ± 110.11	102.46 ± 123.20	9 ± 16.14	5 ± 9.22	132.74 ± 46.04	114.24 ± 56.91

Conclusion: Tissue IL18 and macrophage MIF was overexpressed in both LN and BM of AOSD patients. Their pathophysiologic correlation and therapeutic implication should be elucidated.

Disclosure: S.-H. Park: None; **H.-J. Lee:** None; **S.-K. Kim:** None; **J.-Y. Choe:** None.

904

New Onset of Uveitis under Anti TNF Therapy. A Nationwide Series. Daniel Wendling, Julien Paccou, René-Marc Flipo, Emmanuelle Dernis, Guillaume Direz, Veronique Ferrazzi, Séverine Guillaume, Jean-Michel Ristori and Club Rhumatismes et Inflammation (CRI). Rheumatology, University Hospital, Besançon, Besançon, France

Background: Uveitis may be associated with various inflammatory diseases. Previous reports suggested that TNF blockers, especially anti TNF monoclonal antibodies, may reduce the incidence of uveitis flares in those diseases. Under these circumstances, de novo occurrence, i.e. new onset of the first episode of uveitis under anti TNF therapy is uncommon.

Aim: The aim of this study was to collect cases of new onset of uveitis under anti TNF therapy, using a nationwide network, and to describe such cases.

Methods: All French rheumatologists and internal medicine practitioners registered on the Club Rhumatismes et Inflammation web site (1,400 physicians) were contacted by 3 electronic newsletters in an attempt to declare the cases of new onset of uveitis, diagnosed by an ophthalmologist, in patients treated with TNF blockers. A previous episode of uveitis before anti TNF therapy was an exclusion criteria. Informations were recorded about the patient (age, gender), the disease (diagnosis, duration), the TNF blocker (type, duration), the uveitis (type, severity, outcome).

Results: Thirteen cases were recorded, 7 men, mean age 43 (5–70) years. Other causes of uveitis were excluded (e.g. infection). The underlying disease was ankylosing spondylitis (6 cases, 5 HLA-B27 positive), psoriatic arthritis (3 cases), rheumatoid arthritis (2 cases), juvenile spondyloarthritis, psoriatic spondyloarthritis (1 case each). The mean duration of the disease was 13.5 (1.5–35) years. The TNF blocker at time of uveitis was etanercept 9 times (3 cases after adalimumab), adalimumab 2 times (with previous infliximab and etanercept), infliximab 2 times (one with previous etanercept). The mean duration of exposure to anti TNF agents was 28.3 (4–65) months at uveitis occurrence. Eleven of the patients were good responders to TNF blockers at time of uveitis onset. Uveitis was acute anterior in 12 cases (bilateral in 2), and one bilateral chronic anterior uveitis. Uveitis was treated locally in 12 cases, and with systemic steroids in one case. The cases of acute anterior uveitis resolved within one month, TNF blocker was stopped in two cases,

and maintained in the others. Uveitis recurrence occurred in 5 cases, with sequelae in one case, with a mean follow-up of 16.9 (1– 77) months.

Conclusion: Uveitis occurs de novo under anti TNF therapy mainly in spondyloarthropathies, but also in rheumatoid arthritis patients; this new onset seems more frequent under etanercept and uveitis is time-limited without discontinuation of the TNF blocker in most of the cases. This illustrates a new possibility of paradoxical effects of anti TNF agents, and rheumatologists should be aware about this event.

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905

Preliminary Scores for the Evaluation of Disease Activity in Familial Mediterranean Fever, Mevalonate Kinase Deficiency, TNF-Receptor Associated Periodic Syndrome and Cryopyrin-Associated Diseases: Results from the AIDAI Consensus Conference. Maryam Piram[1], Joost Frenkel[11], Marco Gattorno[13], Seza Ozen[15], Helen Lachmann[16], Rafaela Goldbach-Mansky[17], Anna Simon[3], Veronique Hentgen[10], Benedicte Neven[7], Katia Stankovic-stojanovic[18], Jasmin Kuemmerle-Deschner[14], Hal Hoffman[8], Sylvia Stojanov[4], Agnes Duquesne[6], Pascal Pillet[9], Alberto Martini[12], Jacques Pouchot[5] and Isabelle Kone-Paut[2]. [1]CEREMAI, Pediatric Rheumatology, Bicêtre Hospital, Paris University of Medicine, Le Kremlin Bicêtre, France, [2]CEREMAI, Pediatric Rheumatology, Bicêtre Hospital, Paris University of Medicine, Le Krelmlin Bicêtre, France, [3]Department of General Internal Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, [4]Department of Infectious Diseases and Immunology, University Children's Hospital, Munich, Germany, [5]Department of Internal Medicine, European Georges Pompidou Hospital, Paris-Descartes University, [6]Department of Nephrology and Pediatric Rheumatology, Hôpital Femme Mere Enfant, Hospices Civils de Lyon, Lyon, France, [7]Department of Pediatric Immuno-Hematology and Pediatric Rheumatology, Necker-Enfants Malades Hospital, Paris, [8]Department of Pediatrics and Medicine, University of California at San Diego, Rady Children's Hospital of San Diego, [9]Department of Pediatrics, Children's Hospital of Bordeaux, France, [10]Department of Pediatrics, National Reference Center for Auto-inflammatory Disorders, Versailles-Le Chesnay Hospital, France, [11]Department of Pediatrics, University Medical Center Utrecht, Utrecht, The Netherlands, [12]Department of Pediatrics, University Medical Center Utrecht, Utrtecht, The Netherlands; 3UO Pediatria II and Department of Pediatrics, "G. Gaslini" Institute and University of Genoa, Italy, [13]Department of Pediatrics, University Medical Center Utrecht; 3UO Pediatria II and Department of Pediatrics, "G. Gaslini" Institute and University of Genoa, Genoa, Italy, [14]Division of Pediatric Rheumatology, Department of Pediatrics, University Hospital Tübingen, Germany, [15]Hacettepe University Faculty of Medicine, Ankara, Turkey, [16]National Amyloidosis Centre, University College London Medical School, London, UK, [17]National Institute of Arthritis Musculoskeletal and Skin Disease, NIH, Bethesda, MD, [18]National Reference Center for Inflammatory Amyloidosis and Familial Mediterranean Fever, Department of Internal Medicine, Tenon University Hospital, Université Pierre et Marie Curie Paris 6, Paris, France

Introduction: While auto-inflammatory disorders [AIDs] affect clinically the same organs with a variable intensity or frequency, we hypothesized that a common effort to define disease activity scores could make sense and would help simplify the decision tree in the management of these diseases. Moreover standardized activity score are needed to better capture the efficacy of new medications.

Objective: To develop preliminary activity scores for four auto-inflammatory diseases: Familial Mediterranean fever [FMF], Mevalonate Kinase deficiencies [MKD], TNF-receptor associated periodic syndrome [TRAPS] and Cryopyrin associated diseases [CAPS].

Methods: The study was conducted by using well-recognized consensus formation methodology, specifically designed to combine opinions from a group of experts in a particular field: the Delphi Technique and Nominal Group Technique (NGT). Results from a two steps web-survey plus data from parents/patients interviews provided an agenda for a consensus conference aimed to build provisional core sets for each diseases.

Results: Twenty-four of 65 pediatric and adult AIDs experts (PRES/EUROFEVER network and ISSAID society) from 20 countries answered the web questionnaire and 16 attended the consensus conference. Consensus was obtained to develop separate activity scores for each diseases but on the same format. All participants agreed for a patient designed diary scored 0 to 1 for fever >38 and any pain relief taken. A 0-to 3 score was applied for each clinical variables (according to the diseases). Then, three-month scores are calculated as Score = Σ (n variables) for each month divided by the number of days in the trimester. Mean scores vary from 0 to 16 (0 to 13 for CAPS). According to consensus vote, a final four-domain (clinical and visual global assessment, rescue treatment, biological, QoL) composite score was built-up for purpose of clinical studies. We included a damage scale for severe CAPS that will not be counted in these scores but will serve for targeted clinical trials.

Conclusion: Using consensus formation techniques, we formulated preliminary scores to measure disease activity in four main AIDs. The prospective validation will follow.

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906

Prevalence and Clinical Significance of Cryofibrinogenemia in Patients with Renal Disorders. Benjamin Terrier, Hassan Izzedine, Lucile Musset, David Saadoun and Patrice Cacoub. Pitié-Salpétrière

Background: Cryofibrinogenemia (CryoFg) is an under-recognized cryoprotein that can be life-threatening when untreated. Symptoms of CryoFg are mainly cutaneous including purpura, ecchymosis, ulcerations, livedo and ischaemic necrosis. Renal lesions rarely develop in patients with CryoFg, but the detection of CryoFg was identified in patients with nephropathy.

Objective: Our aim was to describe the prevalence and the significance of CryoFg in patients with renal disorders.

Methods: 101 consecutive patients (mean age 58 $\pm$ 18, female/male 35/66) admitted in the Nephrology Department of a single university hospital for the management of renal disorders (mean age 58 $\pm$ 18, female/male 35/66) were consecutively included in the study and tested for cryoglobulinemia and CryoFg. Anticoagulant-free tubes for cryoglobulin detection or citrated tubes for CryoFg detection were collected. When positive, CryoFg quantification was performed. Patients who were CryoFg positive were defined as having plasma CryoFg over 0.05 g/L. We analyzed clinical and biological factors associated with the presence of CryoFg.

Results: Among the 101 patients, 11 patients had positive CryoFg without detectable cryoglobulin (11%). Median CryoFg level was 0.07 g/L (0.05–1.16). Main epidemiological features and causes of nephropathy, in particular vascular nephropathies, were similar between CryoFg- and CryoFg+ patients. No biological difference (hematuria, proteinuria, creatinine level and glomerular filtration rate using MDRD) was found between CryoFg- and CryoFg+ patients. In contrast, CryoFg+ compared to CryoFg- patients had more frequently severe thrombotic events (36 vs. 0%, $p<0.0001$). Severe thrombotic events included renal arteries thrombosis in 2 patients, recurrent arteriovenous fistula thrombosis in 1, and recurrent dialysis catheter thrombosis with superior vena cava obstruction in 1. The presence of CryoFg was not associated with other manifestations, in particular cutaneous manifestations.

Conclusion: Cryofibrinogenemia is detected in up to 11% of patients with renal disorders. In such patients, the presence of CryoFg is associated with thrombotic events.

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907

Pseudo-Hypertrophic Osteoarthropathy in Lung Transplant Recipients on Long Term Voriconazole Therapy. Rajan Saggar[1], Tisha Wang[3], Rajeev Saggar[3] and Roy D. Altman[2]. [1]UCLA, Los Angeles, CA, [2]UCLA, Agua Dulce, CA, [3]UCLA

Objective: Report a series of patients with a newly described syndrome

Method: Seven cases of lung transplant recipients on long term voriconizole developed a musculoskeletal syndrome.

Results: Lung transplantation was undertaken for end-stage emphysema, sarcoidosis, and idiopathic pulmonary fibrosis. Oral voriconazole was initiated as prophylaxis after isolation of Aspergillus spp. after surveillance bronchoscopy. After 6 to 26 months of therapy with vori-

conizole (200mg bid), this subset of patients presented with non-specific, diffuse bony pain involving arms, shoulders, thighs, knees and shins. Serum alkaline phosphatase was elevated to 1.1 to 7 times the upper limit of normal. Bone scanning with Tc-99m revealed localization of the nuclide to long bones in a spotty distribution atypical for hypertrophic osteoarthropathy. None of the cases had associated clubbing. 2 cases demonstrated periostitis on plain radiograph. Symptoms remised within 2–4 weeks of discontinuation of voriconazole. Repeat bone scan within 6 weeks of voriconazole discontinuation demonstrated significantly reduced accumulation of nuclide.

Conclusion: A syndrome of diffuse extremity pain with periostitis can be seen in lung transplant patients on long term voriconizole. It is suspected that this syndrome may also be seen with azole therapy in long term use for other transplant recipients.

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QuantiFERON®-TB Gold In-Tube Test Versus Tuberculin Skin Test across RA, PsA, and AS Patients Prior to Treatment with Golimumab, a Human Anti-TNF Antibody. Elizabeth C. Hsia[5], Neil Schluger[6], John J. Cush[1], Richard E. Chaisson[7], Eric L. Matteson[8], Anna Beutler[3], Mittie K. Doyle[2], Benjamin L. Hsu[4] and Mahboob U. Rahman[5]. [1]Baylor Research Institute, Dallas, TX, [2]Centocor Research and Development, Inc., Malvern, PA, [3]Centocor Research and Development, Inc., Collegeville, PA, [4]Centocor Research and Development, Inc./Univ. of Pennsylvania School of Medicine, Wynnewood, PA, [5]Centocor Research and Development, Inc./Univ. of Pennsylvania School of Medicine, Malvern, PA, [6]Columbia University College of Physicians & Surgeons, [7]Johns Hopkins University, [8]Mayo Clinic, Rochester, MN

Background: Screening for latent tuberculosis infection (LTBI) prior to use of tumor necrosis factor (TNF) blockers is recommended to decrease the risk of tuberculosis (TB) reactivation. The standard screening tuberculin skin test (TST) is limited by positive (+) results due to cross-reactivity with Bacillus Calmette-Guérin (BCG) vaccine and false-negative (−) results, especially in the immunocompromised. More recently developed blood tests, eg, QuantiFERON®-TB Gold test In-Tube (QFT), offer the possibility of improved LTBI detection, but performance data in patients (pts) with autoimmune inflammatory disease is limited.

Objectives: Compare QFT vs TST performance for LTBI screening prior to golimumab (GLM) use across 5 pt populations with rheumatic disease.

Methods: All pts were screened by QFT and TST in each of the 5 Phase 3 trials of subcutaneous GLM that included pts with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis enrolled from North & South America, Europe (Western+Eastern), Australia/New Zealand, and Asia. TST (Mantoux method) was deemed + according to local country guidelines for immunosuppressed host, or if ≥5mm if no guidelines existed. Any initially indeterminate (IND) QFT results were repeated, and final results were used. IND QFT results were considered discordant with TST results. QFT and TST results were tabulated overall and by known BCG vaccination status.

Results: Of the 2294 pts in this pooled analysis, at least 1 test was + in 13.9%. Of these, 9.4% were TST +, 7.1% were QFT +, and 2.6% QFT + and TST + (Table). QFT IND rate was 1.8%. Agreement of TST and QFT results was 87.1%, and Kappa coefficient was 0.257 (95% CI: 0.192 to 0.321; p=0.021). Among QFT + tests only 36.2% were TST +; among TST + tests only 27.4% were QFT +. 784/2294 pts had prior BCG. The TST + rate was 3-fold higher in BCG + vs BCG − (15.2% vs 4.9%), which was not seen with QFT + tests (9.1% vs 6.0%), supporting the use of QFT in BCG + pts. The slightly higher QFT + rate among BCG + vs BCG − pts might be explained by the higher endemic TB rate in the regions in which this group of pts resides rather than being false +. Despite the known greater cross-reactivity of TST with non-TB mycobacteria among BCG − pts, the QFT + rate was slightly greater than the TST + rate suggesting the possibility of higher sensitivity of QFT. By repeating initially IND results, the QFT IND rate was much lower than in previous reports.

Conclusions: In the absence of a true gold-standard test for LTBI, results of this large comparison of QFT and TST in pts with rheumatic disease suggest that QFT provides greater sensitivity and specificity than TST.

Table. Screening TST results by QFT and BCG vaccination status

		Screening TST result	
	QFT result (n)	+ (n)	− (n)
All GLM Phase 3pts (n = 2294)	+(163)	59	104
	−(2089)	150	1939
	IND (42)	6	36
BCG + pts (n = 784)	+(7l)	28	43
	−(703)	91	612
	IND (10)	0	10
BCG − pts (n = 1257)	+(75)	24	51
−(1158)	32	1126	
	IND (24)	6	18

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Regulatory T-Cells in Familial Mediterrnean Fever (FMF). Doron Rimar[2], Itzhak Rosner[3], Gleb Slobodin[3], Nina Boulman[3], Aharon Kessel[1], Elias Touby[1] and Michael Rozenbaum[3]. [1]Immunology Unit, Bnai-Zion Medical Center, Haifa, Israel, [2]Rheumatology Unit, Bnai-Zion Medical Center, Haifa, Israel, [3]Rheumatology Unit, Bnai-Zion Medical Center, Haifa, Israel

Introduction: The role of regulatory T cells (T-regs) in FMF is yet to be evaluated. Preliminary studies suggest a rise in the number of regulatory T cells after FMF attacks, reaching maximal level at 7 days.

Aim: To investigate the role of T-regs in FMF.

Methods: 5 patients with refractory FMF (defined as at least 1 attack per month despite colchicine therapy of at least 2 mg per day) were evaluated. Seven days after each FMF attack, the number of T-regs and expression of FOX P3 was estimated by flow cytometry after staining for CD4, CD25 bright, and FoxP3 and compared to the level after 14 or more days of remission.

Results: Three females and 2 males were included. All patients had definite FMF according to the TEL HASHOMER criteria with high severity scores, mean 2.8. The patients were of different ethnic origins: 1 Jew, 2 Arabs and 2 Druzes. Their mean age was 31.6±6.2 yrs. Mean age at onset of FMF was 9.3±9.3 yrs. Mean colchicine dose was 2.6mg ± 0.4. Six FMF attacks were assessed. The expression of FOX P3 on CD 4 CD25 bright T cells 7 days after the attacks was significantly higher than at remission, mean fluorescence intensity (MFI) of 10.68±1.6 vs. 4.26±0.9 (p = 0.0002). There was no difference between the percent of CD4, CD25 bright T cells 10.08% ± 3.18 vs. 11.23% ± 4 respectively (p>0.05).

Conclusion: The expression of FOX P3 by T-regs increases after attacks of FMF, yet the percentage of T regs remain unchanged. Anti-inflammatory cytokines interleukin-10 and TGF-β have been (paradoxically?) reported to increase in FMF attacks along with pro-inflammatory cytokines. These anti-inflammatory cytokines are known to activate T-regs, in line with the present findings. It is suggested that T-regs may have a role in terminating FMF attacks.

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910

Safety of Arthrocentesis in Patients on Chronic Warfarin Therapy with Therapeutic INR. Imdad Ahmed[2] and Elie Gertner[1]. [1]Regions Hospital, St Paul, MN, [2]Regions Hospital

Introduction: Patients often need arthrocentesis for diagnostic and therapeutic reasons while on chronic warfarin therapy. Often the procedure is delayed or avoided because of concern about bleeding. The aim of this retrospective study was to determine the safety of arthrocentesis in patients on chronic oral warfarin therapy with INR≥2.0.

Methods: From 01/ 2001 to 11/2008, we reviewed records at Regions Hospital and HealthPartners Medical Group of 514 consecutive patients on chronic warfarin therapy who underwent 640 joint aspiration procedures. Total of 456 procedures were performed with INR ≥2.0 (Group A) and 184 procedures were performed with INR <2.0 (Group B).

The end points were: (1) clinically significant bleeding,(2) infection of the joint (3) pain in the joint needing emergency room, urgent care or physician visits. The end points were both early (within 24 hours post-procedure) and late (within 30-days). Indications for arthrocentesis were usually pain/effusion in patients with diseases such as rheumatoid arthritis, osteoarthritis, gout etc.

Results: There were no significant differences in age, sex, body mass index and concurrent use of antiplatelet agents between the two groups. Groups were also comparable among all medical co-morbidites examined (diabetes mellitus, hypercoagulability, hypertension, liver failure, renal failure and smoking status). Mean INR at the time of procedure for group A was higher than group B (2.7±0.03 vs.1.6±0.02). [Table 1] shows the early and late complications in both groups.

Table 1. Early and late complications between two groups

Complications	Group A INR > 2.0 N = 456	Group B INR < 2.0 N = 184	P Value
Clinically significant bleeding (early)	1 (0.2%)	0	NS
Clinically significant bleeding (late)	0	0	NS
Infection (early)	1 (0.2%)	0	NS
Infection (late)	1 (0.2%)	0	NS
Pain causing physician visit	3 (0.7%)	0	NS

NS = non significant.

There was no statistically significant difference in the overall complication rate between patients with INR ≥2.0 (Group A) and patients with INR<2.0 (Group B) (p=0.708). Receiver operating characteristic [Figure-2] analysis showed that INR offered modest value as a predictive instrument, with a c-statistic of 0.615.

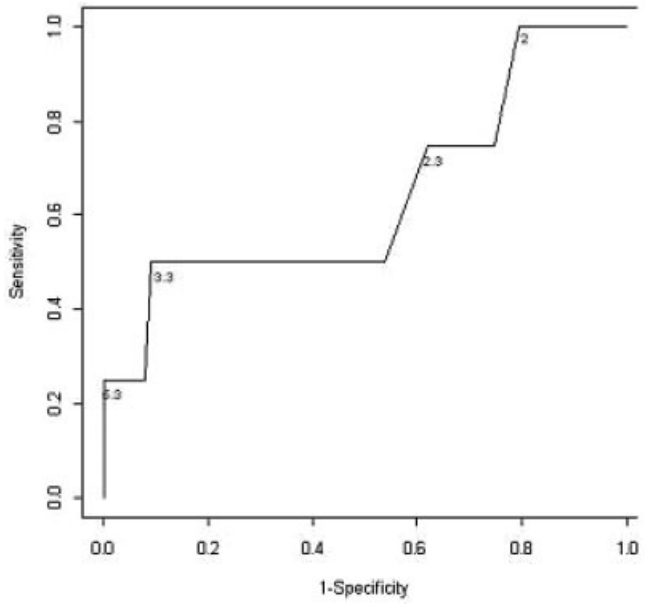

Figure 1. Receiver operating characteristic (ROC) analysis.

Conclusions: Arthrocentesis in patients on chronic warfarin therapy with therapeutic INR appears to be safe without an increased risk of bleeding complications. This approach simplifies the peri-procedural management of anticoagulation, and could lead to improved outcomes and reduced health care costs.

Disclosure: I. Ahmed: None; **E. Gertner:** None.

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Standardization of Antinuclear Antibody Assessment on HEp-2 Cells by Automated Interpretation. Karl Egerer[1], Dirk Roggenbuck[4], Rico Hiemann[6], Max-Georg Weyer[5], Barbara Lehmann[3], Eugen Feist[3] and Gerd R. Burmester[2]. [1]Charite-University Medicine, Berlin, Germany, [2]Charite-University Medicine, Berlin, Germany, [3]Charite-University Medicine, [4]Medipan GmbH, Berlin Dahlewitz, Germany, [5]Medizinisches Versorgungszentrum für Laboratoriumsmedizin, Mikrobiologie, Virologie und Infektionsepidemiologie, Hygiene und Umweltmedizin, [6]University of Applied Science Lausitz

Introduction: Analysis of antinuclear antibodies (ANAs) by indirect immunofluorescence (IIF) is a basic tool for the serological diagnosis of systemic rheumatic disorders. Automation of ANA IIF interpretation including pattern recognition can improve assay reproducibility and intra- and inter-laboratory variability. Automation of ANA reading meets the demand for cost-effective assessment of large numbers of samples in routine laboratories. Comparing automated and visual interpretation of ANA patterns, the usefulness for laboratory diagnostics was investigated.

Methods: Antinuclear antibody detection by IIF on human epithelial-2 (HEp-2) cells including pattern recognition was performed in a total of 1222 consecutive sera of patients with suspected systemic rheumatic diseases from a university routine laboratory (n=924) and a private referral laboratory (n=298). IIF reading results obtained in routine diagnostics were compared with findings by a novel automated interpretation system employing mathematical pattern recognition algorithms.

Results: Visual and automated interpretation of ANA showed a very good agreement regarding positive / negative discrimination (kappa=0.828). Only 98 (8.0%) of 1222 sera demonstrated discrepant results in the differentiation of positive from negative samples. The contingency coefficient of Chi-square statistics was 0.646 for the university laboratory cohort with an agreement of 93.0% and 0.695 for the private laboratory cohort with an agreement of 90.6%, p<0.0001, respectively. According to the McNemar test, there was no significant difference in the university cohort (1.08%, p=0.25).

Comparing respective immunofluorescence patterns, 111 (15.3%) sera yielded differing results in both cohorts. Discrepant results were mainly obtained when the AKLIDES algorithms assessed cytoplasmic signals as nuclear staining due to superposition.

Conclusions: Automated interpretation of ANA by IIF on HEp-2 cells using an automated reading system is a reliable and robust method for positive/negative differentiation of IIF findings. Employing novel mathematical algorithms, automated interpretation provides reproducible detection of specific immunofluorescence patterns on HEp-2 cells. Automated interpretation can reduce drawbacks of ANA detection by IIF in routine diagnostics providing more reliable data for clinicians.

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The CIRAS Study: A Case Control Study To Define the Clinical, Immunologic and Radiographic Features of the Aromatase Inhibitor Arthralgia Syndrome. Victoria K. Shanmugam[3], James McCloskey[1], Elizabeth Elston[4], Sandra J. Allison[2], Claudine Isaacs[5] and Jennifer Eng-Wong[5]. [1]Department of Internal Medicine, Georgetown University Medical Center, Washington, DC, [2]Department of Radiology, Georgetown University Medical Center, Washington, DC, [3]Division of Rheumatology, Immunology and Allergy, Georgetown University Medical Center, Washington, DC, [4]Georgetown University, [5]Lombardi Cancer Center, Georgetown University Medical Center, Washington, DC

Background: Aromatase inhibitors (AIs) reduce recurrence in postmenopausal hormone-receptor positive breast cancer. However, development of joint pains (Arthralgia Syndrome) limits compliance. The pathophysiology of this syndrome is unknown, but morning stiffness suggests an inflammatory etiology. Associations have been reported with tenosynovitis and autoimmune diseases. The CIRAS study was designed to determine the evidence for an inflammatory etiology.

Methods: Postmenopausal breast cancer patients followed at Lombardi Cancer Center with hand pain but without known autoimmune disease were recruited. Subjects receiving AIs were cases (n=25) while those not receiving AIs were controls (n=23).

Subjects were evaluated after abstaining from non-steroidal anti-inflammatory drugs for 48 hours. They completed a health assessment questionnaire (PROMIS-HAQ). The rheumatologist completed a history and physical, and disease activity score (DAS-28). Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibody (ANA), rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP), vitamin D and cytokine levels were tested. Bilateral hand radiographs and ultrasound were performed. The hand ultrasound was scored for presence of flexor tenosynovitis, fluid in the metacarpophalangeal joints, tissue edema, and tendon sheath enhancement for each digit on both hands, and a total ultrasound score was computed. The rheumatologist and radiologist were blinded as to study group. Data was analyzed using t-test and Fisher's exact test.

Results: Patients in both groups were predominantly Caucasian and of similar age. Neither the DAS-28 nor the ESR was significantly different between cases and controls.

Table 1. Results of the CIRAS study

		CASE (n = 25)	CONTROL (N = 23)	p value
Symptoms:	PROMIS-HAQ (mean ± SEM)	9.700 ± 1.832	10.05 ± 2.529	0.5091
	PROMIS-HAQ Global (mean ± SEM)	51.04 ± 7.141	54.43 ± 7.714	0.7478
	Pain score (mean ± SEM)	34.88 ± 5.451	42.83 ± 5.506	0.3111
	Duration of morning stiffness/ hours (mean ± SEM)	2.400 ± 0.4203	1.435 ± 0.2937	0.0704
Inflammatory indices:	DAS-28 (mean ± SEM)	2.311 ± 0.1469	2.29 ± 0.1393	0.9182
	ESR mm hr (mean ± SEM)	17.08 ± 3.036	18.50 ± 2.936	0.7399
Vitamin D	Vitamin D ng/ml (mean ± SEM)	30.17 ± 2.537	33.35 ± 2.576	0.3848
Autoimmune features	ANA positive (n)	4	6	0.3900
	Autoimmune disease (n)	4	6	0.3900
X-ray	Degenerative joint disease (n)	15	14	0.9509
Other medication:	Bisphosphonate (n)	11	8	0.5661
	Tamoxifen (n)	7 current use	9 prior use	
Ultrasound findings:	Total ultrasound score (mean ± SEM)	6.600 ± 1.049	4.909 ± 1.040	0.2606
	Tendon nodules (n)	3	0	0.2354
	DeQuervain's tenosynovitis (n)	4	2	0.6681
	Ganglion cysts (n)	8	8	1.0000
	Flesor tenosynovitis (n)	14	10	0.5639

Hypovitaminosis D was found in 1 case and 5 controls (p 0.06).There was no significant difference in mean vitamin D. In each group two subjects had previously undiagnosed autoimmune disease (8.3%). A positive ANA was identified in 6 controls and 4 cases (20.8%). While cases experienced more prolonged morning stiffness, this did not reach statistical significance (p= 0.07). PROMIS-HAQ, global-HAQ and mean pain scores were not significantly different. There was no difference in ultrasound score or tendon nodules, Dequervain's tenosynovitis, ganglion cysts or flexor tenosynovitis. Several patients in the control arm had a similar constellation of symptoms to those receiving AIs.

Conclusions: The arthralgia syndrome may not be unique to patients receiving AIs. This syndrome warrants further investigation since development affects compliance with AI therapy.

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ACR Poster Session B
Muscle Biology, Myositis and Myopathies: New Developments in the Diagnosis, Pathogenesis and Treatment of Myositis
Tuesday, November 9, 2010, 9:00 AM–6:00 PM

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A Negative Anti-Nuclear Antibody Does Not Indicate Autoantibody Negativity. Rohit Aggarwal[2], Noreen Fertig[2], Dana P. Ascherman[3], Elaine A. Cassidy[1] and Chester V. Oddis[2]. [1]Children's Hospital Pittsburg, Pittsburgh, PA, [2]University of Pittsburgh, Pittsburgh, PA, [3]University of Pittsburgh, Pittsburgh, PA

Purpose: To evaluate the diagnostic utility of anti-cytoplasmic autoantibody (anti-cytAb) staining by indirect immunofluorescense (IIF) on Hep 2 substrate in anti-synthetase antibody positive (anti-synAb+) patients and to compare it with Anti-nuclear antibody (ANA) testing.

Methods: Using the Pittsburgh database of myositis and systemic sclerosis (SSc), anti-synAb+ patients were evaluated for ANA and anti-cytAb positivity. Anti-synAb+ patients included both Jo-1 and non-Jo-1 patients. SSc patients without anti-synAb were the control group. The following test characteristics of anti-cytAb and ANA were assessed in the anti-synAb+ patients: a) sensitivity [true positive (TP)/TP + false negative (FN)], b) specificity [true negative (TN)/ TN + false positive (FP)], c) positive predictive value (PPV; TP/TP + FP), d) negative predictive value (NPV; TN/TN + FN) and e) accuracy (TP + TN/ total number of patients tested). Anti-cytAb testing was done using the same method as ANA testing by IIF on Hep2 cell. Both were reported simultaneously on each patient sample. Anti-synAb status was not known before the ANA and anti-cytAb determination.

Results: All anti-synAb+ patients [n=202; Jo-1=122 patients; non-Jo-1=80 patients] between 1985–2009 with available serum samples were assessed. Non-Jo-1 included: anti-PL-12, anti-PL-7, anti-EJ, anti-OJ, anti-KS. Anti-cytAb showed high sensitivity (72%), specificity (91%), NPV (91%) and accuracy, but only modest PPV (44%) for anti-synAb positivity (Table 1). Similar sensitivity results were seen for Jo-1 and non-Jo-1 (PL-12, PL-7 and KS) autoAb subgroups. In contrast, the ANA showed only modest sensitivity (50%) as well as poor specificity (0.6%), PPV (5%), NPV (10%) and accuracy (5%). Positive anti-cytoplasmic staining was significantly greater in the anti-synAb+ patients than ANA positivity (72% vs. 50%, p<0.001). Moreover, 81/99 (82%) of ANA negative patients in the anti-synAb+ cohort had positive anti-cyt staining-Ab. In contrast, the control group of SSc (n=1946) showed high positive rates for ANA (1935/1946, 99%), but very low positive rates for anti-cytAb (180/1946, 9%). Combining anti-cytAb or ANA positivity to identify anti-synAb+ patients increases the sensitivity to 90% (177/196), but specificity decreases dramatically (0.4%). Finally, the combination of anti-cytAb or Jo-1 positivity shows high sensitivity (181/196, 92%) and specificity (91%) for identification of anti-synAb+ patients.

Table 1. Anti-cytAb and ANA sensitivity, specificity, NPV, PPV, and accuracy for anti-synAb+ patients

Test Statistic	ANA	Anti-cytAb	p value
Sensitivity			
All anti-synAb patients	100/199 (50%)	142/196 (72%)	p<0.001
All Jo-1	62/119 (52%)	77/116 (66%)	p=0.026
All non-Jo-1	38/80 (48%)	65/80 (81%)	p<0.001
PL-12	17/35 (49%)	30/35 (86%)	p<0.001
PL-7	13/25 (52%)	23/25 (92%)	p<0.001
EJ	3/9 (33%)	4/9 (44%)	NS
KS	2/6 (33%)	6/6 (100%)	p=0.013
OJ	3/5 (60%)	2/5 (40%)	NS
Specificity*	0.60%	91%	
NPV*	10%	91%	
PPV*	5%	44%	
Accuracy*	5%	89%	

*All anti-synAb group NS = not significant

Conclusions: Assessing patients for anti-cytAb staining using similar techniques to current ANA testing has excellent diagnostic utility for anti-synAb+ patients while ANA testing alone has poor test characteristics. Cytoplasmic staining should therefore be assessed and reported for patients suspected of having a rheumatic disease (RD), and a negative ANA should not be used to exclude a RD diagnosis.

Disclosure: R. Aggarwal: None; **N. Fertig:** None; **D. P. Ascherman:** None; **E. A. Cassidy:** None; **C. V. Oddis:** None.

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A Novel Form of an Autosomal Dominant Vacuolar Hereditary Myopathy. Christine Castro[5], Ivona Aksentijevich[6], Elaine Remmers[6], Elisabeth Rushing[1], Simona Bianconi[3], Marjan Huizing[4], Mildred Wilson[6], Thomas Markello[2], Daniel Kastner[6] and Mark Gourley[6]. [1]Armed Forces Institute of Pathology, [2]National Institues of Health/National Human Genome Research Institute/Medical Genetics Branch, [3]National Institutes of Health, [4]National Institutes of Health, National Human Genome Research Institute, Medical Genetics Branch, [5]National Institutes of Health, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD, [6]National Institutes of Health, National Institute of Arthritis and Musculoskeletal and Skin Diseases

Background: Inclusion body myositis (IBM) is a slowly progressive skeletal muscle disease of unknown etiology with both sporadic and familial forms. The disease is characterized by proximal and often asymmetric distal muscle weakness, often with quadriceps atrophy. Muscle biopsy often shows degenerating and regenerating muscle fibers, perimyofiber distribution of inflammatory cells, and occasional red-rimmed vacuoles on Gomori trichrome staining. The most distinguishing feature is lack of response to immunomodulatory therapy. In familial IBM, disease onset often occurs in the late-teens to mid-20s; a Finnish form occurs in the 40s. Conversely, the sporadic form often occurs in those over age 50.

Purpose: We identify what we believe is a new familial form of IBM in one family with 3 generations demonstrating onset after age 50. In the third generation, 5 of 10 siblings are clinically affected, suggesting autosomal dominant inheritance. Results of muscle biopsy, EMG and MRI are consistent with IBM.

Methods and Materials: Subjects include 10 siblings (5 affected) ages 47 to 64, their unaffected father (age 86) and affected mother (age 70). They are of German and Dutch descent. Blood samples were obtained from all siblings and from the father. (A histology block of an endometrial biopsy from many years ago was obtained from the deceased mother.) MRI of bilateral thighs (T1-weighted and STIR images) was performed on 7 siblings. Muscle biopsy of the right quadriceps was done on 7 siblings and sent to Armed Forces Institute of Pathology for processing. DNA was extracted from blood of the 10 siblings, from their father, and the endometrial biopsy of the mother (later not used due to poor quality). Linkage analysis was performed and genotype data was analyzed via a program designed to identify the maternal haplotype transmitted to each child. Selected genes from the candidate interval were sequenced.

Results: MRI images from the 5 affected subjects showed edema, fatty replacement, muscle atrophy and/or fascial enhancement. The 2 unaffected subjects were normal. Histology revealed abnormalities including vacuoles on Gomori trichrome stain, degenerating and regenerating muscle fibers, fiber size variation, and presence of angular atrophic fibers in all 7 siblings. Through genetic analysis, a 3 megabase region of interest was found on chromosome 12. To date, no genes have been located.

Conclusion: We present a family with a seemingly autosomal dominant late onset vacuolar myopathy. Linkage analysis and gene sequencing has led us to chromosome 12 where a 3 megabase region peaks our interest. However, we have not yet isolated a gene. Characterization of this family's disease is of great interest because hereditary or familial forms of any IIM provide genetic information to further our understanding of this disease process as well as identify individuals who would be most affected by such diseases.

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Anti-SRP Auto-Antibody Titers Correlate with Serum Creatine Kinase in Necrotising Myopathy. Olivier Benveniste[1], Laurent Drouot[3], Fabienne Jouen[3], Serge Herson[2], Jean-Luc Charuel[2], Coralie Bloch[2], Anthony Behin[2], Zahir Amoura[2], Isabelle Marie[4], Bruno Eymard[2], Danièle Gilbert[3], François Tron[3], Lucile Musset[2] and Olivier Boyer[3]. [1]Assistance Publique - Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, Paris, France, [2]Assistance Publique - Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, France, [3]Inserm, U905, Rouen University, France, [4]Rouen University Hospital, Department of Internal Medicine, France

Objective: Anti-signal recognition particle (SRP) auto-antibodies (aAbs) are associated with severe, generally treatment-resistant forms of acquired necrotising myopathies. The physiological role of the SRP complex is to guide the translocation of nascent polypeptides into the endoplasmic reticulum during protein synthesis. Since the expression of SRP is ubiquitous, the role of anti-SRP aAbs in myopathies remains elusive. Notably, clinical studies have been hampered by the lack of a quantitative assay for the longitudinal follow-up of anti-SRP aAb titers. To this end, we developed a Luminex™-based quantitative test of anti-SRP aAb, referred to as Fluorescence Microsphere Immunoassays for quantification of SRP54-specific aAb (FMI-SRP54), and asked whether there was a correlation between anti-SRP aAb titers and serum creatine kinase (CK) levels.

Methods: The diagnostic value of the test was determined by comparing serum titers from 31 anti-SRP aAb positive patients to that of 190 healthy blood donors and 167 control patients with different inflammatory/autoimmune conditions including 80 rheumatoid arthritis, systemic sclerosis or lupus, 30 anti-tRNA synthetase aAb positive myositis, 30 inclusion body myositis and 27 patients with polyclonal hypergammaglobulinemia. Among the 31 anti-SRP aAb positive patients, 8 were sampled over time for monitoring of anti-SRP aAb titers and CK levels (at least 3 times consecutively with a mean follow-up of 722 days). The date of the first sample corresponded to the initiation of treatment (for naive patients) or restart of a modified one (for relapsing patients). The relationship between anti-SRP aAb titers and CK levels was tested using a linear mixed model.

Results: The specificity of the assay was 100% with a confidence interval of [98%–100%] and the sensitivity was 100% [89%–100%]. There was a clear predominance of the IgG1 and IgG4 isotypes among anti-SRP54 aAbs. FMI-SRP54 permitted to measure the degree of aAb depletion after plasma exchanges that repeatedly reduced anti-SRP54 aAb titers by more than 2-fold in one patient studied. Importantly, the longitudinal follow-up of the 8 patients revealed a striking correlation between the degree of myolysis under therapy measured by CK levels and the anti-SRP54 aAb titers ($p<0.005$).

Conclusion: Anti-SRP aAb positive myopathy appears as one of the few human autoimmune diseases in which specific aAb titers correlate with surrogate disease activity markers. These results may also suggest a pathogenic role for anti-SRP aAbs and prompts to evaluate B-cell targeting therapies in patients with this particular form of necrotising myopathy.

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Clinical Manifestation and Prognostic Factor in Anti-Melanoma Differentiation-Associated Gene 5 Antibody-Associated Interstitial Lung Disease as a Complication of Dermatomyositis. Takahisa Gono[5], Yasushi Kawaguchi[3], Takashi Satoh[2], Masataka Kuwana[1], Yasuhiro Katsumata[5], Kae Takagi[5], Ikuko Masuda[3], Sayumi Baba[5], Masanori Hanaoka[5], Yuko Okamoto[5], Yuko Ota[5], Sayuri Kataoka[5] and Hisashi Yamanaka[4]. [1]Keio University School, Tokyo, Japan, [2]Keio University School, [3]Tokyo Women's Medical University, Tokyo, Japan, [4]Tokyo Women's Medical University, Shinjuku-ku, Tokyo, Japan, [5]Tokyo Women's Medical University

Purpose: The aim of the present study is to evaluate the clinical manifestation and prognostic factors of anti-melanoma differentiation–associated gene 5 (MDA5) antibody-associated interstitial lung disease (ILD) with dermatomyositis (DM).

Methods: Fourteen patients who presented with anti-MDA5 antibody and 10 patients with anti-aminoacyl-tRNA synthetase (ARS) antibody were enrolled. All of patients were diagnosed as having DM with ILD. Clinical manifestations in the patients with anti-MDA5 antibody were compared to those in the patients with anti-ARS antibody.

Results: The age at onset was 43.6 ± 14.6 years (mean ± SD), with no significant difference between each subset. The frequency of clinically amyopathic dermatomyositis (57%) was significantly higher ($P = 0.033$) in the subset with anti-MDA5 antibody. The creatine kinase (CK) value (median, 198 IU/ml) was significantly lower ($P = 0.01$) and ferritin values (median, 680 ng/ml) were significantly higher ($P = 0.016$) in the subset with anti-MDA5 antibody. The frequencies of acute/subacute interstitial pneumonia was significantly higher ($P = 0.036$) in the subset with anti-MDA5 antibody (71%) than the subset with anti-ARS antibody (20%), although pulmonary function showed no significant differences between each subset. Significant correlations were found between A-a$DO_2$and KL-6 ($r_s = 0.73$, $P = 0.016$), and A-aDO_2 and ferritin ($r_s = 0.66$, $P = 0.013$) in the subset with anti-MDA5 antibody. Clinical manifestations were compared between the surviving and non-surviving patients who had ILD with anti-MDA5 antibody.

The followings were significantly higher in the non-surviving patients with anti-MDA5 antibody: age at onset ($P = 0.045$), A-aDO_2 ($P = 0.045$), AST ($P = 0.027$), γ-GTP ($P = 0.028$), and ferritin ($P = 0.016$). Age- and sex-adjusted Cox regression analysis was performed to identify a prognostic factor for ILD with anti-MDA5 antibody. The most significant prognostic factor was serum ferritin (Hazard ratio per unit 1.005, 95% confidential interval 1.004–1.014, $P = 0.027$). The cumulative 60-month survival rates were significantly lower ($P = 0.042$) in the subset with anti-MDA5 antibody (62.9%) than in the subset with anti-ARS antibody (100%). Additionally, the cumulative survival rate was significantly lower ($P < 0.0001$) in the subset with ferritin ≥ 1600 ng/mL than that in the subset with ferritin <1600 ng/mL in anti-MDA5 antibody-associated ILD.

Conclusion: Both serum ferritin and anti-MDA5 antibody are powerful indicators for the early diagnosis of A/SIP with DM. Serum ferritin also predicts disease severity and prognosis for patients with anti-MDA5 antibody.

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Efficacy and Tolerance of Rituximab in Refractory Idiopathic Inflammatory Myopathy. Data of the AIR Registry. Marion Couderc[3], Jacques E. Gottenberg[12], Xavier Mariette[2], Eric Hachulla[9], Jean Sibilia[11], Olivier Fain[6], Arnaud Hot[8], Maxime Dougados[5], Liana E. Euller-Ziegler[7], Pierre Bourgeois[10], Claire Larroche[10], Anne Tournadre[3], Zahir Amoura[10], Bernard Mazieres[14], P. Arlet[13], Michel De Bandt[1], Thierry Schaeverbeke[4] and Martin Soubrier[3]. [1]Aulnay Hospital, Carrieres Sur Seine, France, [2]Bicetre Hospital/Paris Univ, Le Kremlin Bicetre, France, [3]Clermont-Ferrand Hospital, [4]Groupe Hospitalier Pellegrin, Bordeaux, France, [5]Hospital Cochin, Paris, France, [6]Jean Verdier Hospital, Paris University, [7]L'Archet Hospital (University), Nice, France, [8]Lyon Hospital, [9]National Scleroderma Centre, Lille Cedex, France, [10]Paris Hospital, [11]Strasbourg Hospital, Strasbourg, France, [12]Strasbourg Hospitals, Strasbourg, France, [13]Toulouse Hopsital, [14]Toulouse Hospital

Objective: To assess the efficacy and tolerance of Rituximab (RTX) in patients with refractory idiopathic inflammatory myopathies.

Methods: Adult patients from the Auto-Immunity and Rituximab (AIR) french registry treated by RTX for polymyositis (PM), dermatomyositis (DM) or antisynthetase syndrome (AS) were prospectively included. Efficacy was evaluated on the basis of CPK level, daily corticosteroid dose (CS), concomitant immunosuppressor treatment (IS) dose and physicians' opinion. A patient was considered as a responder if there was improvement in at least 2 of these 4 criteria and no aggravation in the 2 others.

Results: Thirty patients were studied (21 women (70%), mean age 52.5 years), 12 with PM, 6 with DM and 12 with AS. Mean disease duration was 6.1 years. All had received IS agents. Twenty-five patients received two doses of 1 gram of RTX 2 weeks apart and 5 patients received four weekly infusions of 375 mg/m2 of RTX. RTX was given alone to 9 patients and in combination with IS to the others. Twenty eight patients received associated CS (mean daily dose 21.4 mg/day). The mean follow up period was 17.2 months.

Twelve adverse events corresponding to 27.9 adverse events per 100 patient-years were reported: two acute infusion reactions of moderate severity, two episodes of undetermined fever, and eight infectious events (18.6 for 100 patients-year) in 7 patients of which seven were mild to moderate, and only one serious (pyelonephritis). Most of these infectious events occurred in the initial 6 months (87.5%).

Efficacy was observed in 21 patients (70%): 8 PM (66.7%), 5 DM (83.3%), 8 AS (66.7%). The mean daily corticosteroid dose (CS) decreased from 21.2 +/− 19.5 to 9.9 +/− 8.5 mg/day. Daily CS dose decreased in 20 patients, increased in 3, and remained unchanged in 7 patients. In patients with elevated CPK level (n=24), it decreased in 19 patients, increased in 5 patients and the mean CPK level decreased from 20,7 ± 29,9 to 11 ± 24,6 times the normal range. Physician opinion on RTX efficacy was favourable for 20 patients and unfavourable for 10. Three patients were considered to be in complete remission with normal CPK level, discontinuation of corticosteroids and in 2 of them discontinuation of IS therapies. Efficacy was not significantly different between patients with or without inflammatory myopathy antibodies [14/17 (82.3%)] [7/13(53.8%)] (p = 0.12)]. Mean duration of efficacy in responders was 15.5 months. Ten patients received a second course of RTX; efficacy was observed in 8 with a mean duration of 7.4 months, 1 patient was not evaluated and 1 did not respond.

Conclusions: Rituximab seems to be an effective and well-tolerated treatment in patients with idiopathic inflammatory myopathies.

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Efficacy of Allogeneic Mesenchymal Stem Cells Transplantation in Patients with Drug-Resistant Polymyositis and Dermatomyositis. Lingyun Sun[1], Dandan Wang[2], Huayong Zhang[2], Jun Liang[2] and Xuebing Feng[2]. [1]Department of Rheumatology and Immunology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, Jiangsu, China, [2]Department of Rheumatology and Immunology, The Affiliated Drum Tower Hospital of Nanjing University Medical School

Objective: To assess the safety and clinical efficacy in ten patients with drug-resistant polymyositis (PM) or dermatomyositis (DM) treated by allogeneic mesenchymal stem cells transplantation (MSCT).

Methods: A single-arm trial involved 10 DM/PM patients, 4 for DM and the other 6 for PM, aged from 19 to 44 years old, that were refractory to standard treatment and/or with severe systemic involvement. Average disease duration was 7.5 months (6 to 60 months). All the patients met the Bohan and Peter criteria for DM or PM. Three patients received bone marrow (BM) derived MSC, two of which were given a second umbilical cord (UC) derived MSC due to disease relapse. The other 7 patients were transplanted with UC-MSC only once time. BM MSC were aspirated from related healthy donors and expanded in vitro, and UC MSC were obtained from Stem Cell Center of Jiangsu Province of China. All the infused MSC were derived from passage 2 to passage 4, with rigorous purification and quality control. The clinical manifestations and laboratory parameters were compared pre- and post-MSCT, with a mean follow-up of 12 months (range, 6 to 18 months). Advert events were monitored all the time during and post-MSCT.

Results: Serum creatine kinase (CK) for all the patients decreased significantly at the first 6 months (baseline: 2380.0±673.8U/L; 1m: 1027.0±266.7U/L; 2m: 486.2±143.1U/L; 3m: 92.9±19.5U/L; 6m: 248.8±135.6U/L, all $p<0.05$ vs baseline value), and continued to decreased to 106.0±39.4U/L for 5 patients completed 1 year visit, in paralleled with the amelioration of serum CK-MB levels at the same visit. Meanwhile, patient's global assessment by VAS and detection for the Manual Muscle Test (MMT) also ameliorated with improved disease. In addition, MRI confirmed alleviated inflammation in the thigh muscles 3 months after BM MSC infusion for one patient. Six patients were complicated with moderate-to-severe ILD, shown as interstitial pneumonia. High-resolution CT scans manifested obvious amelioration in 3 patients, and at least no progression in 2 patients 6 months post-MSCT. Furthermore, for one patient with refractory skin ulcers on both knees, elbows and proximal interphalangeal joints, matter plus decreased and new granulation tissues appeared at 2 months visit, and almost healings of the ulcers 6 months after UC MSCT. Disease relapsed in 3 patients at 5, 6, 8 months post-MSCT respectively, 2 of which received second UC MSC infusion, also due to ineffective to standard treatments. Unfortunately, one patient was unresponsive to second MSCT, and the other died 5 months later due to rapid progression of disease and severe myocarditis induced by a common cold. Another patient died 7 months post-MSCT, due to uncontrolled pulmonary infection. No transplant related mortality or any significant toxicity was observed during or after MSC infusion.

Conclusion: We provide evidence that allogeneic BM or UC MSC infusion is safe and effective in drug-resistant DM/PM patients. However, further observation with more patients included and longer periods of follow-up will be needed to determine the efficacy and safety of this novel approach to the treatment of DM/PM.

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ESR and CRP Do Not Correlate with Extent of Muscle Injury but Their Elevation Is Associated with Pulmonary Involvement in Idiopathic Inflammatory Myopathy. Jin Kyun Park[4], Michael George[2], Sonye K. Danoff[3], Marzouq A. Qubti[4], Allan C. Gelber[1] and Lisa Christopher-Stine[5]. [1]Baltimore, MD, [2]Department of Medicine, University of Pennsylvania, [3]Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, [4]Division of Rheumatology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, [5]Johns Hopkins University, Baltimore, MD

Background: Although Idiopathic Inflammatory myopathies (IIM) are systemic autoimmune diseases with muscle as the main target, the clinical implication of Erythrocyte Sedimentation Rate (ESR) is not well defined to date. From our clinical experience, we hypothesized that ESR is elevated in IIM subsets with interstitial lung disease (ILD).

Methods: Clinical and laboratory data from 50 patients with IIM who visited our Center between March 2007 and April 2009 were collected. All patients underwent routine CT scanning in a standard protocol to assess malignancy and ILD status. ESR (normal<30mm/hr), C-reactive protein (CRP; normal <0.5 mg/dL), creatine phosphokinase (CPK) and aldolase level were measured at the time of diagnosis. ILD was defined by presence of typical radiographic changes. Mann-Whitney test for continuous variables and 2 sided Fisher's exact test for dichotomous variables were performed. Rho and P values were generated using Spearman's correlation analysis. These associations were also examined in analyses stratified by the presence (vs. absence) of ILD. P-values of <0.05 were considered statistically significant.

Results: ESR and CRP did not correlate significantly with CPK (ESR, r_s= 0.106, p=0.465; CRP, r_s =0.031, p=0.878) or aldolase (ESR, r_s= 0.034, p= 0.827; CRP, r_s=0.076, p=0.719), while CPK and aldolase showed high correlation with each other (r_s=0.784, p<0.001) as expected. Notably, there were 21 patients with 29 without ILD. Age, gender and race did not differ significantly between both groups. CPK and aldolase did not differ between IIM without versus with ILD (CPK 1028 +/− 2567 IU/L vs. 1227 +/−2804 IU/L, p=0.723; aldolase 16.9 +/− 22.2 IU/L vs. 22.7 +/− 35.6 IU/L, p=0.914). However, within the IIM stratum with ILD, ESR was significantly higher (18.3 +/−15.7 mm/hr vs. 44.9 +/− 36 mm/hr, P= 0.001). CRP was similarly higher in ILD groups (0.71 +/− 0.57 mg/dL vs. 0.23 +/− 0.185 mg/dL, p=0.045). Further, 5 (17.2 %) out of 29 patients without ILD had elevated ESR as compared to 12 (57.1 %) out of 21 with ILD (p= 0.0059). CRP was elevated in 1 (7.7 %) of 13 IIM without ILD, and in 7 (50 %) of 14 IIM with ILD (p=0.035).

Conclusion: Here, we provide evidence that: i.) ESR and CRP do not correlate with biochemical muscle injury and ii.) elevation of ESR or CRP is associated with the presence of ILD. Therefore, any elevation of systemic inflammatory markers should prompt clinicians to evaluate for the presence of an ILD.

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Evaluation of Reliability, Validity, and Responsiveness of the CDASI and CAT-BM. Renato Goreshi[8], Joyce Okawa[8], Matt Rose[8], Rui Feng[1], Lela Lee[6], Christopher Hansen[10], Carolyn Bangert[9], Kari Connolly[5], Mark Davis[2], Jeff Callen[7], Nicole Fett[8], Steven Fakharzadeh[4], Jennie Clarke[3] and Victoria Werth[8]. [1]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, [2]Mayo Clinic- Rochester, [3]Penn State Hershey, School of Medicine, [4]Philadelphia VA Medical Center, [5]University of California-San Francisco, School of Medicine, [6]University of Colorado, School of Medicine, [7]University of Louisville, School of Medicine, [8]University of Pennsylvania, School of Medicine, [9]University of Texas, School of Medicine, [10]University of Utah, School of Medicine

To properly evaluate therapies for cutaneous dermatomyositis (DM) it is essential to administer an outcome instrument that is reliable, valid, and responsive, particularly when measuring disease activity. The purpose of this study is to compare two skin-severity DM outcome measures, the Cutaneous Disease and Activity Severity Index (CDASI) and the Cutaneous Assessment Tool-Binary Method (CAT-BM), with the Physician Global Assessment (PGA) as the 'gold standard'. In a one-day session, ten dermatologists evaluated fourteen patients with DM using the CDASI, CAT-BM, and PGA scales, which were used as the 'gold standard' for comparison. Inter- and intra-rater reliability was assessed by intraclass correlation coefficients (ICC) and paired t-tests. Construct validity was determined by using a linear mixed model. Content validity was determined by administering a Physician Exit Questionnaire, specifically asking if any outcome instrument was missing an appropriate measure for the evaluation of DM. Responsiveness was assessed from a different study population, where one physician determined CDASI, CAT-BM, and PGA scale scores, including a qualitative perception from the physician if the patient had improved, worsened, or had no change from their previous visit. A standard response mean (SRM), or mean change:standard deviation of change between visits, of the activity scores of each outcome instrument was determined by choosing the largest change in PGA scale scores between two visits, when the physician noted a change between visits. Difference in completion time of each instrument was assessed by a paired t-test. The CDASI was found to have a higher inter-rater reliability (ICC: CDASI Activity 0.748, CAT-BM Activity 0.546) and a higher intra-rater reliability (ICC: CDASI Activity 0.868; CAT-BM Activity 0.714). To assess construct validity, both the CDASI and the CAT-BM were found to be significant predictors of the the PGA scales (p<0.001). All physicians felt that the CDASI was not missing any measure to sufficiently assess DM. 90% of physicians felt the same with the CAT-BM, with one physician feeling that the CAT-BM did not adequately assess the scalp. The CDASI had the highest SRM among all outcome instruments (CDASI: 1.25, CAT-BM: 0.93, PGA-Activity: 1.03, PGA-Activity Likert: 0.61). The CDASI had a statistically longer completion time than the CAT-BM (Completion Time: CDASI 4.76 minutes; CAT-BM 3.19 minutes; p<0.001) with a mean time difference of 1.58 minutes. We conclude that the CDASI is a better clinical tool to assess skin severity in DM, especially in regards to responsiveness.

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Fasciitis Is a Common Lesion of Dermatomyositis Demonstrable Early after Disease Onset by *En Bloc* Biopsy Combined with Magnetic Resonance Imaging. Ken Yoshida[2], Daitaro Kurosaka[2], Kensuke Joh[1], Eigo Takahashi[2], Kenichiro Hirai[2], Kentaro Noda[2], Taro Ukichi[2], Kazuhiro Furuya[2], Maimi Yanagimachi[2], Isamu Kingetsu[2] and Akio Yamada[2]. [1]Division of Pathology, Sendai Shakai Hoken Hospital, [2]Division of Rheumatology, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan

Purpose: To investigate the incidence of fasciitis in dermatomyositis (DM), and to analyze the process of myositis progression.

Methods: *En bloc* biopsy combined with Short tau inversion recovery or fat-suppressed T2-weighted magnetic resonance imaging (MRI) was performed on fourteen patients with newly diagnosed adult-onset DM. Vascular inflammation score (VIS) was defined as the number of aggregates of ≥50 inflammatory cells infiltrating around a small blood vessel or vessels per 4 mm^2 area of tissue. Total vascular inflammation score (TVIS) was defined as the summation of VIS in three fields with the most remarkable perivascular infiltrates. Fasciitis was defined as TVIS of the fascia ≥3 to exclude very mild inflammation. The grade and distribution of perivascular inflammatory changes were evaluated in the fascia and muscle using TVIS. *En bloc* biopsy was also performed on six patients with other rheumatic diseases including three patients with polymyositis (PM). These subjects constituted a comparison group. Immunohistochemistry was performed to identify T lymphocytes (CD3), CD4+ cells, CD8+ cells, B cells (CD20, CD79a), and macrophages (CD68).

Results: In all patients with DM, MRI revealed abnormal hyperintensity in the fascia and in marginal sites of the muscle predominantly over central sites. In Case 11, abnormal hyperintense areas were detected on the first MRI in the fascias, and on the second MRI two months later, the hyperintense areas had progressed from the fascias to marginal sites of the muscles. *En bloc* biopsy revealed fasciitis evidenced by inflammatory infiltrates around the fascial small blood vessels in most of the patients with DM. However, inflammatory infiltrates around the intramuscular small blood vessels were not detected in four patients with DM. In those who underwent *en bloc* biopsy earlier than two months after the appearance of muscle symptoms, TVIS of the fascia was significantly higher than TVIS of the muscle. In contrast, in those who underwent *en bloc* biopsy at two months or later, TVIS of the

fascia did not differ significantly from TVIS of the muscle. Immunohistochemistry showed that CD3+ T lymphocytes, CD4+ cells and CD20+ B cells were mainly present among inflammatory cells. The CD4/CD8 cell ratio was >1 in almost all specimens from the patients with DM. In any one of the patients with other rheumatic diseases, MRI revealed no significant hyperintense areas in the fascias and none of specimens from other rheumatic diseases histopathologically revealed fasciitis.

Conclusions: Fasciitis was histopathologically confirmed in most of the patients with adult-onset DM and recognized as a common lesion that appears early after the onset of muscle symptoms in DM. Our results suggest that the fascial microvasculature is the primary site of inflammatory cell infiltration in DM. The results of MRI suggest that inflammation in myopathy accompanying DM progresses from the fascia into the muscle. Muscle symptoms such as myagia in DM may be attributed to fasciitis if muscle biopsy reveals no myositis. Fasciitis may be a lesion specific to DM rather than to PM.

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Immunosuppressive Treatments Do Not Alter Natural History of Sporadic Inclusion Body Myositis: The Paris/Oxford Study on 136 Patients. Benveniste Olivier[2], Guiguet Marguerite[5], Jane Freebody[4], Serge Herson[2], Odile Dubourg[3], Waney Squier[4], Pascal Laforet[1], Isabel Leite[4], Bruno Eymard[1] and David Hilton-Jones[4]. [1]Assistance Publique-Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, Institut de Myologie, France, [2]Assistance Publique-Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, Médecine Interne, France, [3]Assistance Publique-Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, Neuropathologie, France, [4]Department of Neurology, West Wing, John Radcliffe Hospital, Oxford, United Kingdom, [5]INSERM–UPMC UMR S 943, Biostatistique, Paris, France

Objective: Sporadic inclusion body myositis (sIBM) is characterized by slowly progressive, asymmetric atrophy and weakness of both proximal and distal muscles, most prominently affecting the finger and wrist flexors and quadriceps. Although drugs such as corticosteroids, methotrexate, cyclophosphamide, and IVIg may reduce the degree of inflammation on biopsy and lower serum creatine kinase levels, clear clinical improvement has not been demonstrated. The aim of the study was to evaluate whether immunosuppression alters the course of progression of sIBM.

Methods: Two cohorts of patients, one from Paris and the other from Oxford were included. The same clinical-research form was used in both centers for data collection and was completed either during a clinic visit (52%), or by extraction from previous medical records (48%).

Results: 136 patients (57% males, 61 [55–69] years at onset) were included. sIBM was diagnosed on the basis of accepted clinical and pathological criteria; 97 patients (72%) were considered to have definite sIBM, 39 patients (28%) had probable sIBM. At the last visit all patients had muscle weakness (proximal MRC $\leq$ 3/5 in 47%, distal MRC $\leq$ 3/5 in 38%) and half of them reported swallowing problems. During their follow-up, 75% of patients had significant walking difficulties and 37% used a wheelchair (after a median duration from onset of 14 years). The risk of death was only influenced by older age at onset of first symptoms. 71 (52%) patients received immunosuppressive treatments (prednisone in 91.5% associated (in 64.8%) with other immunomodulatory drugs (intravenous immunoglobulins, methotrexate or azathioprine) for a median duration of 41 months). At the last assessment, patients who had been treated were more severely affected on a sIBM weakness composite index ($p=0.03$) and disability scales (Walton $p=0.007$, RMI $p=0.004$).

Conclusion: This study showed that in our population, sIBM started on average in the 6th decade of life and is then slowly progressed. It took a median of 14 years to get from first symptoms to the need to use a wheelchair, but also, that this disease is not usually the cause of death. Furthermore, it could not be excluded that conventional immunosuppressant treatment is not only ineffective but might also hasten progression. The findings of this study include important messages for the design of the future trials.

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Interleukin-18 Is a Key Mediator in Dermatomyositis: Contribution to Development of Interstitial Lung Disease. Takahisa Gono[2], Yasushi Kawaguchi[1], Tomoko Sugiura[2], Kae Takagi[2], Ikuko Masuda[1], Hisae Ichida[2], Yasuhiro Katsumata[2], Akiko Tochimoto[2], Sayumi Baba[2], Masanori Hanaoka[2], Yuko Okamoto[2], Yuko Ota[2], Sayuri Kataoka[2] and Hisashi Yamanaka[3]. [1]Tokyo Women's Medical University, Tokyo, Japan, [2]Tokyo Women's Medical University, [3]Tokyo Womens Med Univ, Shinjuku-ku, Tokyo, Japan

Purpose: The aim of the present study is to determine whether interleukin (IL)-18 is involved in the inflammation of dermatomyositis (DM) and polymyositis (PM).

Methods: Thirty-three patients with DM were enrolled in this study, including 25 with interstitial lung disease (ILD). In addition, 16 patients with PM were enrolled, including 6 with ILD. All patients were admitted to our hospital as a result of their condition requiring treatment, and clinical laboratory data including serum creatine kinase (CK), ferritin and IL-18 were recorded on admission.

Results: The level of CK was significantly ($P = 0.01$) higher in PM patients (median, 2174 IU/ml) than in DM patients (median, 375 IU/ml). Although CRP levels were not significantly different, ferritin was significantly ($P = 0.003$) higher in DM patients (median, 236 ng/ml) than in PM patients (median, 55 ng/ml). The median levels (range) of serum IL-18 were 552 pg/mL (141–4850), 256.5 pg/mL (119–2190), and 50.5 pg/mL (18–121) in DM patients, PM patients, and healthy controls (n = 30), respectively. The levels of IL-18 were significantly higher in DM and PM patients than in healthy controls ($P < 0.0001$ for both comparisons), and were significantly ($P = 0.0044$) higher in DM than in PM patients. Additionally, ferritin and IL-18 were significantly ($P = 0.023$ and 0.034, respectively) higher in DM patients with ILD (median, 320 ng/ml and 625 pg/ml, respectively) than in DM patients without ILD (median, 82 ng/ml and 328 pg/ml, respectively), but the CK and CRP levels were not significantly different. By contrast, the median values of IL-18 were 382.5 pg/mL and 234.5 pg/mL in PM with ILD and PM without ILD patients, respectively. There were no significant differences between PM with and without ILD for the measured parameters. Significant positive correlations were found between CK and ferritin ($r_s = 0.39$, $P = 0.024$), CK and IL-18 ($r_s = 0.48$, $P = 0.005$), and IL-18 and ferritin ($r_s = 0.54$, $P = 0.0012$) in the DM group as a whole, although correlations between CRP and CK, CRP and IL-18, and CRP and ferritin were not found. These findings were especially notable in the DM with ILD subset. Significant positive correlations were found between CK and ferritin ($r_s = 0.40$, $P = 0.047$), CK and IL-18 ($r_s = 0.63$, $P = 0.0008$), and IL-18 and ferritin ($r_s = 0.41$, $P = 0.042$) in the DM with ILD subset. By contrast, there was no significant correlation with PM.

Conclusion: Serum IL-18 was strikingly elevated in patients with DM, and was associated particularly with disease activity and ILD complication in DM.

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KL-6: A Serological Biomarker for Interstitial Lung Disease and Pulmonary Function in Patients with Polymyositis and Dermatomyositis. Sevim Barbasso Helmers[3], Maryam Fathi[1] and Ingrid E. Lundberg[2]. [1]Department of Respiratory Medicine and Allergy, Karolinska Institutet, Stockholm, Sweden, [2]Karolinska Institutet, Stockholm, Sweden, [3]Rheumatology Unit, Dpt. of Medicine, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden

Background: Interstitial lung disease (ILD) is reported in up to 78% of polymyositis (PM) and dermatomyositis (DM) patients, but pulmonary function tests are not always easily available and repeated radiological examinations are restricted by the irradiation. One interesting biomarker for ILD is Krebs von den Lungen-6 (KL-6), a glycoprotein secreted by type II alveolar pneumocytes and bronchiolar epithelial cells. A few studies with a limited number of patients have reported elevated serum levels of KL-6 in patients with myositis associated ILD. These need replication and it is unknown whether KL-6 serum levels vary over time in PM/DM patients.

Objectives: To investigate whether Caucasian patients with PM/DM and ILD have elevated serum levels of KL-6 compared to healthy controls and

whether KL-6 could be used as a marker for disease activity and prognosis of ILD in PM/DM.

Methods: Thirty PM/DM patients (19 women, 11 men; median 54 years, range 22–74,) and 17 age- and gender matched healthy controls were included in a cross-sectional analysis. Twelve patients with less than one month in between multiple serum samples and lung function tests were included for longitudinal evaluation. KL-6 serum levels were analyzed using a sandwich enzyme immunoassay kit (Sanko Junyaku Co., Ltd, Tokyo, Japan). ILD was defined as restrictive lung function impairment, total lung capacity (TLC) and diffusing capacity for carbon monoxide (DLco) l<80% of predicted, with radiographic signs of ILD on chest X-ray /or high resolution computerized tomography. Groups were compared by Mann Whitney test. Spearman's correlation r-value > 0.5 or < -0.5, and p-values ≤ 0.05 were considered significant.

Summary of Results: Patients with PM or DM had significantly higher KL-6 serum levels compared to healthy controls (median, range; 400, 132–2318 U/ml versus 225, 136–519 U/ml, p=0.01). The patients with ILD (n=7) had significantly higher median serum concentrations of KL-6 compared to those without (n=23) (995, 533–2318 U/ml versus 322, 132–1225 U/ml, p=0.0002). At KL-6 cut-off level of 549 U/ml (mean ±2.5 SD of controls) we found a sensitivity and specificity of 84% and 80% respectively for diagnosis of ILD. A significant inverse correlation between KL-6 serum levels and results of pulmonary function tests was demonstrated in the cross sectional part: forced expiratory volume in one second (FEV1)% (r=−0.60), vital capacity (VC)% (r=−0.54), TLC% (r=−0.59), Forced VC (FVC)% (r=−0.64) and DLco% (r=−0.52). In the patients with longitudinal follow up, this inverse correlation increased: FEV1% (r=−0.801), VC% (r=−0.788), TLC% (r=−0.788), FVC% (r=−0.784) and DLco% (r=−0.653). The changes of KL-6 serum levels showed a significant inverse correlation with changes of the pulmonary function tests: FEV1% (r=−0.570), TLC% (r=−0.530), DLco% (r=−0.530) and RV (r=−0.525). There was no significant correlation between serum levels of KL-6 and CRP or creatine kinase (CK) levels.

Conclusion: These results support the usefulness of serum measurements of KL-6 in the diagnostic evaluation and establishment of severity, as well as in evaluation of response to therapy in patients with ILD and myositis.

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Longitudinal Assessment of Activity and Damage in a Synthetase Positive Cohort. Elaine A. Cassidy[1], Rohit Aggarwal[3], Noreen Fertig[4], Dana P. Ascherman[3] and Chester V. Oddis[2]. [1]Children's Hospital Pittsburgh Division of Rheumatology, Pittsburgh, PA, [2]University of Pittsburgh, Pittsburgh, PA, [3]University of Pittsburgh School of Medicine Division of Rheumatology and Clinical Immunology, Pittsburgh, PA, [4]University of Pittsburgh School of Medicine Division of Rheumatology and Clinical Immunology

Purpose: To compare disease activity and damage in a longitudinal cohort of Jo-1 and non Jo-1 anti-tRNA synthetase autoantibody (anti-synAb) positive patients (pts).

Methods: Since 2002 one investigator (CVO) has prospectively completed the Myositis Disease Activity Assessment Tool (MDAAT) and Myositis Damage Index (MDI) on pts with the data entered into the Myositis Data Management System (MDMS). All anti-synAb+ pts in MDMS were included in this analysis. The MDAAT includes an intention to treat component but only the visual analog scale (VAS) assessing disease activity at last visit in constitutional, cutaneous, skeletal, pulmonary, extramuscular global, muscle and overall global categories were used in this study. VAS activity scores were designated as: none=0; minimal (0<VAS≤1); mild (1<VAS≤3); moderate (3<VAS≤7) and severe (VAS>7). The groups were compared using Kruskal Wallis test for VAS scores, and the Chi-square test for ordinal VAS values. The MDI assesses organ system damage using a VAS and a dichotomous variable, and the 2 groups were compared using the last recorded organ system VAS score (Kruskal Wallis) and the presence or absence of organ damage using Chi-square test for skeletal, muscle, pulmonary, and global categories. Regression analysis was used to control for time from diagnosis and first visit to assessment of activity or damage.

Results: Activity was assessed in 59 anti-synAb+ pts (41 Jo-1; 18 non-Jo-1) having at least 2 MDAATs in 1 year, or >3 over any time period. Damage was assessed in 71 pts (50 Jo-1; 21 non-Jo-1) that had >1 MDI. The Jo-1 and non-Jo-1 groups were similar in terms of gender and ethnicity. Median time in yrs (IQR) from diagnosis to last completed MDAAT was 5.8 (2.2–3.9) vs. 4.2 (2.0–8.7) for Jo-1 and non-Jo-1 pts (p=NS). The skeletal activity at last assessment was worse in Jo-1 pts as 71% had VAS = 0 compared to 95% of non Jo-1 pts (p=0.03). This remained significant after controlling for time from diagnosis or first visit to assessment (p=0.03). There were no differences in disease activity at last visit between Jo-1 and non Jo-1 pts in the other categories. Regarding damage, non-Jo-1 patients had significantly more damage from pulmonary hypertension (PHT) at last MDI (40% non-Jo 1 vs. 11% Jo-1 pts; p=0.005) which remained significant after controlling for time from diagnosis or first visit (p=0.006). Forty-two of 71 anti-synAb+ pts had pulmonary function tests at last MDI and %predicted FEV-1 (75 +/− 16 vs. 74 +/− 25) and %predicted DLCO (57 +/− 23 vs. 52 +/− 25) were similar for Jo-1 and non-Jo-1 pts (p=NS). There was no difference between groups in global disease damage at last visit [median VAS (IQR): 1.8 (0.65–3.25) and 2.2 (1.4–3.8), respectively]. No differences in damage between Jo-1 and non Jo-1 pts were noted in the other categories.

Conclusions: Jo-1 and non-Jo-1 anti-synAb+ pts have similar activity and damage scores at last follow-up for multiple organ systems. Jo-1 pts have increased arthritis activity while non-Jo-1 pts have increased PHT-related damage. Comparing these results to other autoantibody and myositis subsets will further validate the usefulness of these activity and damage indices.

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Longitudinally Followed Serum Levels of B-Cell Activating Factor of the TNF Family Correlate with Disease Activity in Anti-Jo-1 Positive Patients with Myositis. Olga Krystufkova[1], Marta Mitterwald-Modra[2], Herman Mann[2], Louise Ekholm[5], Hana Hulejova[2], Ingrid E. Lundberg[4] and Jiri Vencovsky[3]. [1]Institute of Rheumatology, Prague, Czech Republic, [2]Institute of Rheumatology, [3]Institute of Rheumatology and Dept of Rheumatology of the 1st Faculty of Medicine, Charles University, Prague, Prague, Czech Republic, [4]Karolinska Institutet, Stockholm, Sweden, [5]Karolinska Institutet, Sweden

Purpose: A role of B cells in pathogenesis of myositis is supported by common occurrence of autoantibodies. Anti-histidyl-tRNA synthetase (anti-Jo-1) is the most frequent myositis specific autoantibody, associated with a distinct clinical phenotype. Its observation before onset of clinical symptoms suggests a role in the pathogenesis of this subset of myositis. B-cell activating factor of the TNF Family (BAFF) plays a role in autoantibody production. In a previous cross-sectional study we found elevated serum levels of BAFF in patients with anti-Jo-1 positive polymyositis (PM) and in dermatomyositis (DM) and there was a correlation with serum creatine kinase (CK) levels.

The aim of the study was to investigate if serum levels of BAFF change over time and if there is a relation to disease activity measures in anti-Jo-1 positive myositis.

Methods: Sixty-seven anti-Jo-1 autoantibody positive patients from two centers were included. Paired serum samples from two time points (mean interval 28 months) in 50 patients (21 DM and 29 PM) were evaluated. Anti Jo-1 positivity was confirmed by line-blot and western blot assays. BAFF levels in serum were measured by ELISA. Serum levels of CK, myoglobin, aminotransferases (ALT, AST) and C-reactive protein (CRP) were retrieved from patients' records or measured in the same sera. Clinical disease activity was assessed by the score of the core set tool according to the IMACS Group, including both extramuscular, muscular and the physician's score of overall disease activity.

Results: The baseline BAFF levels correlated positively with serum levels of CK (rs=0.49, p<0.0001), myoglobin, (rs=0.37, p=0.005), AST (rs=0.46, p=0.0001) and CRP (rs=0.42, p=0.0006) and with cutaneous disease activity (rs=0.26, p=0.04). Levels of BAFF and myoglobin had decreased significantly at the second visit (paired test p<0.05), while p value for CK was 0.09. A significant improvement of cutaneous, skeletal, pulmonary, muscle and global disease activities was also recorded (p<0.05 for all). A positive correlation between changes of serum BAFF levels and changes of CK (rs=0.7, p=0.0001), myoglobin (rs=0.6, p<0.0001), ALT (rs=0.52, p=0.0001), AST (rs=0.62, p<0.0001) and CRP (rs=0.29, p=0.049) levels in serum or skeletal (rs=0.45, p=0.003), muscle (rs=0.32, p=0.04) and global (rs=0.37, p=0.02) disease activities was also recorded.

Conclusions: The correlation between serum levels of BAFF and markers of muscle involvement or clinical measures of disease activity as well as a correlation of their changes over time might indicate a role of BAFF in the pathogenesis of myositis with anti-Jo-1 autoantibodies. BAFF could thereby be a novel potential target of intervention in this subset of myositis.

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MHC Classes I and II Expressions in Membrane and Cytoplasm of Muscle Fibers in Untreated Juvenile and Adult Dermatomyositis. Adriana Maluf Elias Sallum, Samuel Katsuyuki Shinjo, Mary Souza Carvalho, Clóvis Artur Almeida da Silva, Maurício Levy-Neto and Suely Kazue Nagahashi Marie. Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

Background: Recently, we have shown that MHC I expression in muscle fibers is a premature and late marker of treated and untreated juvenile dermatomyositis (JDM). However this alteration was not systematically studied in adult DM (ADM). Moreover, simultaneous assessment of MHC I and II expressions in fibers membrane and cytoplasm in both untreated diseases has not been performed.

Objectives: To assess the MHC I and II expressions in fibers membrane and cytoplasm in untreated ADM and JDM and to correlate to clinical, laboratorial, and treatment outcome features.

Patients and Methods: Twenty-seven ADM and 34 JDM patients, fulfilling Bohan and Peter criteria diagnosed from 1990 to 2010, were included in this study. Routine histochemistry and immunohistochemistry (StreptABComplex/HRP) for MHC I and II (Dakopatts) were performed on serial frozen muscle sections. Each biopsy specimen was coded and analyzed concomitantly by two investigators (AMES and SKS). The pathology readers were blinded to diagnosis, clinical status and therapy when the biopsies were evaluated. Expressions of MHC I and II were assessed as negative or positive stained fibers.

Results: The mean age at disease onset was significantly higher in ADM than in JDM (42.7±18.3 vs. 8.2±3.8 years, $p<0.001$), whereas the symptoms duration before muscle biopsy were similar in both groups (9.8±13.3 vs. 7.1±10.7 months; $p=0.388$). No statistical differences were observed regarding gender, ethnicity, frequency of constitutional symptoms, disease severity, organ involvement (articular, pulmonary, cardiac or gastrointestinal), comorbidities, laboratorial (CK and aldolase levels) and treatment (prednisone, intravenous methylprednisolone and immunosuppressive drugs) ($p=0.050$), except for the lower frequency of Gottron signal in ADM compared to JDM patients (85.2 vs. 100.0%, $p=0.034$). Regarding the immunohistochemical analysis, the frequency of MHC I expression in fibers membrane (85.2 vs. 100.0%, $p=0.034$) and cytoplasm (74.1 vs. 97.1%, $p=0.017$) was significantly lower in ADM than JDM. In contrast, the MHC II expressions in fibers membrane (70.4 vs. 35.3%; $p=0.010$) and the cytoplasm (44.5% vs. 17.7%, $p=0.028$) were higher in ADM than JDM. Additionally, the MHC I and II expressions were not correlated to demographic data, clinical and laboratorial features, including CK levels and disease duration before muscle biopsy.

Conclusions: The MHC I and II expressions differ in muscle fiber in JDM and ADM. These diagnostic tools can be routinely used independent of period of time until muscle biopsy.

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MicroRNA Expression in Juvenile Dermatomyositis (JDM): Clues to Disease Pathogenesis and Chronicity. Simone Sredni, Peter Hendrickson, Sheela Shrestha and Lauren M. Pachman. Children's Memorial Research Center, Chicago, IL

Background: Juvenile dermatomyositis (JDM) is an autoimmune vasculopathy targeting small blood vessels. We found that: (1) untreated chronic inflammation lasting >2 mos has a strong influence on disease prognosis and molecular pathophysiology, (2) proinflammatory cytokines, IFN-α and TNF-α are increased in JDM sera and tissue damaging endothelial cells and (3) JDM patients have immune activation of VCAM-1, a soluble gatekeeper for leukocyte migration localized in high concentration on endothelial cells. It is also known that the A polymorphism of TNF-α-308 promoter region contributes to the inflammatory microenvironment in JDM, but the mechanism is not well understood. Moreover, due to absence of inflammatory process biomarkers and disease severity prognostic indicators, there are no surrogate indicators of immune activation that can guide effective treatment for JDM, as muscle enzymes normalize rapidly.

MicroRNAs (miRNAs) are non-coding RNAs usually 18–25bp long that regulate several messenger RNAs simultaneously by mechanisms such as incomplete base pairing and post-transcriptional gene silencing. Modulation of levels of key miRNAs can affect regulation of several physiological and pathological functions offering a new prototype for therapeutic intervention.

Methods: After obtaining informed consent, miRNA expression profiles in diagnostic muscle biopsies (MBx) from 2 groups of children with definite/probable JDM and age/gender-matched controls were tested: (1) short duration of untreated disease (SDD), <2 mos prior to MBx; (2) long disease duration (LDD), ≥2 mos of symptoms, using microarrays with locked nucleic acid technology (miRCURY LNA™ microRNA Array Exiqon, Vedbaek, Denmark). Selected dysregulated genes were confirmed by qRT-PCR and immunohistochemistry.

Results: We found significant differential expression of: (1) miR-10b ($p=0.03$) in JDM vs. controls, (2) miR-146b ($p=0.02$), miR-126 ($p=0.014$) and miR-23a ($p=0.04$) when comparing SDD and LDD and (3) miR-34a ($p=0.02$) when comparing SDD vs LDD patients with TNF-α-308 G allele. Expression of miRNAs (23a, 126 and 146b) and of possible interactive targets (IL1B, TNF-α, VCAM-1) was verified by qRT-PCR and immunohistochemistry.

Discussion: MiR-10b, down regulated in JDM vs. controls, modulates HOXD10 expression. HOXD10 controls OPN, which is important in T cell regulation/regeneration and is present in dystrophic calcifications associated with chronic cutaneous inflammation. When comparing JDM MBx of SDD vs LDD miR-23a, miR-126 and miR146b were differentially expressed. MiR-126 regulates VCAM-1 (increased in SDD) and might be a key component of vascular damage. Increase in miR-146b expression by cytokines IL-1B and TNF-α may be important in molding the phenotype of children who have had untreated chronic inflammation for a longer period.

Conclusion: In JDM, critical processes affecting vascular system formation/function and inflammation are modulated by miRNAs. Identification of key miRNAs will give us clues not only to JDM pathogenesis and chronicity but may reveal new potential therapeutic targets.

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Non-Jo-1 Anti-Synthetase Autoantibodies Are Not Specific for Myositis and Are Associated with Poor Survival. Elaine A. Cassidy[1], Rohit Aggarwal[3], Noreen Fertig[3], Mary Lucas[3], Dana P. Ascherman[3] and Chester V. Oddis[2]. [1]Children's Hospital of Pittsburgh Division of Rheumatology, Pittsburgh, PA, [2]University of Pittsburgh, Pittsburgh, PA, [3]University of Pittsburgh School of Medicine Division of Rheumatology and Clinical Immunology, Pittsburgh, PA

Purpose: To compare clinical features and outcome in patients (pts) with Jo-1 vs. non-Jo-1 anti-tRNA synthetase autoantibodies (anti-synAb).

Methods: All anti-synAb positive pts in a Connective Tissue Disease (CTD) Registry were included regardless of initial or subsequent CTD diagnosis. Demographic and clinical data were collected from the medical record and registry. Current status and cause of death was determined by query of the National Death Index or Social Security Death Index, and medical record. For lung survival an endpoint of lung transplant or death was used. Survival was compared by Kaplan-Meier and log rank test. Cox proportional hazards ratios were calculated to compare survival after controlling for co-variates.

Results: 202 of 3880 (5.2%) CTD pts were anti-synAb positive [122 Jo-1; 80 non-Jo-1 (35 PL-12; 25 PL-7; 9 EJ; 6 KS; 5 OJ]. Both groups had similar demographic features (Table 1), but non-Jo-1 pts had a greater delay in diagnosis, and a diagnosis at 1st visit in 60% that did not include PM or DM.

Table 1. Demographic and Clinical Features of Synthetase Cohort

	Mean Age at Symptom Onset (yrs)	% Female	% Caucasian	Myositis (%)	Diagnoses at First Visit Overlap or UCTD (%)	SSc (%)	Median Delay in Dx from 1st CTD Symptom (mths; IQR)
Jo-1 (n = 122)	45	67	82	83	PM 58 DM 25	17 0	6 (2–13)
non-Jo-1 (n = 80)	46	70	75	40	PM 23 DM 17	49 11	9 (3–24)
p value	NS	NS	NS	p < 0.0002			p = 0.03

NS = not significant; IQR-interquartile ratio; UCTD = undifferentiated connective tissue disease

Sixty-six pts are deceased with pulmonary fibrosis and pulmonary hypertension the most common causes. Twelve pts (7 Jo-1; 5 non-Jo-1) underwent lung transplantation. Although a pulmonary cause of death was similar between Jo-1 and non-Jo-1 cohorts, the 5 and 10 yr unadjusted cumulative and median survival was significantly different.

Table 2. Outcome and Survival of Synthetase Cohort

	Deceased (%)	Mean Age at Death (yrs)	Pulmonary Cause of Death: Fibrosis PHT	Cumulative Survival: 5 year (%)	Cumulative Survival: 10 year (%)	Median Survival (yrs; IQR)
Jo-1 (n = 122)	36 (30%)	58 +/−14	19/36 16/36 3/36	90	74	15 (7.9–21.3)
non-Jo-1 (n = 80)	30 (38%)	62 +/−14	20/30 16/30 4/30	70	48	9 (4.3–18)
p value	NS		NS	P <0.01		P <0.01

PHT = pulmonary hypertension

After adjusting for gender, ethnicity and age at diagnosis, non-Jo-1 pts had decreased survival (HR 1.86; p=0.02; 95% CI 1.10–3.14) and lung survival (HR 1.96; p= 0.008; 95% CI 1.19–3.23) compared to Jo-1 pts. After adjusting for diagnosis delay, non-Jo-1 pts had decreased lung survival (HR 1.77; p= 0.03; 95% CI 1.06–2.97), and a trend toward decreased cumulative survival (HR 1.71; p =0.051; 95% CI 1.00– 2.96). Non-Jo-1 PM pts had the worst cumulative survival (HR 3.75; p=0.02; 95% CI 1.21– 11.68) and lung survival (HR 2.84; p=0.01; 95% CI 1.23–6.52).

Conclusions: In the largest reported anti-synAb+ cohort to date, the previously described myositis specificity of non-Jo-1 anti-synAb was not supported. Non-Jo-1 pts have decreased cumulative survival and lung survival compared to Jo-1 pts, with non-Jo-1 pts with PM having the worst cumulative and lung survival. The difference in survival may be attributable to a delay in diagnosis in the non-Jo-1 group due to nonspecific symptoms at presentation and negative commercial antibody testing. Increased awareness of this CTD subset among rheumatologists and pulmonologists is emphasized.

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Predictors of Survival in Patients with Anti-Synthetase Autoantibodies.

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Purpose: To evaluate baseline clinical, laboratory, serologic, radiographic and functional predictors of survival in patients (pts) with anti-synthetase autantibodies (anti-synAb) from a single tertiary care center.

Methods: All anti-synAb+ pts from a single referral center between1985–2009 were included regardless of their initial or subsequent connective tissue disease (CTD) diagnosis. All data were collected from the registry database and medical record. Current status and cause of death was determined by query of the National Death Index or Social Security Death Index, and record review. For lung survival an endpoint of lung transplant or death was used. Each baseline characteristic was evaluated for prediction of overall and lung survival using Cox-proportional hazard in a univariate fashion. Only clinical data available at first visit was used in the model.

Results: Of the 3880 CTD pts in the registry from 1985–2009, 202 (5.2%) were anti-synAb+ [122 Jo-1; 80 non Jo-1 (35 PL-12; 25 PL-7; 9 EJ; 6 KS; 5 OJ)]. Eighty-nine (44%) had PM, 44 (22%) DM, and 69 (34%) had undifferentiated or overlap CTD. Demographic features predicting survival included age at diagnosis and symptom onset, and a diagnosis delay (Table 1). PM pts had worse survival. Among other variables only arthralgia, pleurisy, dermatomyositis V neck or trunk rash, and telangiectasia had worse survival while Gottron papules had better survival. Raynaud, sicca symptoms, dyspnea, fever, muscle weakness, dysphagia, puffy fingers, mechanic hands, heliotrope rash, physician global assessment of active disease, capillary microscopy, digital abnormality, and calcinosis did not predict survival. Among lab and serologic parameters only non-Jo1 anti-synAb positivity, particularly anti-PL-7 and anti-EJ predicted worse survival, while SSA antibody was protective. ANA positivity, muscle enzymes, hemoglobin, platelet and ESR had no impact on survival. The % predicted FVC and DLCO along with pulmonary hypertension (PHT) by echocardiography and secondary PHT at baseline predicted survival. High resolution CT (HRCT) evidence of pulmonary fibrosis did not predict survival as most pts had some evidence of fibrosis by routine chest radiography or HRCT.

Table 1. Univariate predictors of overall and lung survival in a synthetase cohort

	Overall survival Hazzard ratio (C.I.)	p value	Lung survival Hazard ratio (C.I.)	p value
Demographic				
Gender (male)	0.82 (0.47–1.44)	0.57	0.82 (0.48–1.43)	0.47
Ethnicity (AA)	0.92 (0.43–1.96)	0.87	1.0 (0.49–2.04)	0.98
Age at diagnosis (yrs)	1.03 (101–1.05)	<0.001	1.03 (1.01–1.05)	<0.001
Age at symptoms (yrs)	1.02 (1.0–1.04)	0.07	1.02 (1.0–1.03)	0.01
Diagnosis delay (yrs)	1.03 (1.0–1.06)	0.04	1.01 (1.0–1.01)	0.008
Clinically history				
Clinical diagnosis	PM: 2.4 (1.08–5.53)	0.032	PM: 2.73 (1.21–6.15) UCTD 2.54 (1.11–5.84)	PM: 0.015 UCTD 0.27
Inflammatory arthralgia	1.84 (1.08–3.15	0.02	1.78 (1.08–2.95)	0.02
V neck trunk rash	2.9 (1.14–7.32)	0.02	2.64 (1.05–.6.65)	0.04
Gottron papules	0.33 (0.14–0.78)	0.01	0.32 (0.14–0.71)	0.005
Telangiectasia	2.6 (1.4–4.8)	0.003	2.93 (1.64–5.25)	<0.001
Pleurisy	1.88 (1.02–3.48)	0.04	1.97 (1.06–3.63)	0.03
All non-Jo1	1.67 (1.05–2.68)	0.03	1.64 (1.03–2.63)	0.04
Anti-PL-7	2.45 (1.31–4.56)	0.005	2.55 (1.37–4.73)	0.003
Anti-EJ	3.29 (1.27–8.49)	0.01	3.14 (1.22–8.09)	0.01
SSA (n = 81)	0.11 (0.15–0.85)	0.04	0.10 (0.13–0.76)	0.03
Pulmonary Function Testing Other				
%FVC 1	0.97 (0.96–0.99)	0.03	0.97 (0.95–0.98)	0.001
%DLCO	0.96 (0.94–0.98)	0.006	0.96 (0.94–0.99)	0.006
Elevated PAP	3.1 (1.3–70)	0.006	3.2 (1.53–6.74)	0.002
Secondary PHT	3.46 (1.65–7.27)	0.001	3.34 (1.59–7.0)	0.001
O_2 requirement at baseline	2.43 (1.38–4.26)	0.002	2.42 (1.37–4.21)	0.002

CI = confidence interval, AA = African American, PAP = Pulmonary artery pressure

Conclusion: The myositis clinical subset (i.e. PM), anti-synAb positivity, pulmonary function parameters, secondary PAH, joint involvement, pleurisy, various DM rashes and telangiectasia help predict overall survival and lung survival in anti-synAb+ pts. Some findings can be explained on the basis of their known myositis subset associations, such as Gottron papules in DM (which has a better prognosis than PM) and telangiectasias in UCTD (worse survival due to non-Jo-1 association). However, others require further study to confirm their association with survival (e.g. SSA positivity).

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Pulmonary Manifestations of Polymyositis and Long-Term Outcomes—A Retrospective Study.

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Background: Polymyositis (PM) is a systemic inflammatory disorder which primarily affects striated muscles; however, other organ systems, including the lungs, may be involved. While the interstitial lung disease (ILD) associated with polymyositis (ILD-PM) carries significant morbidity and mortality, the clinical factors impacting outcome of patients with ILD-PM are unclear.

Methods: A single-center retrospective study of well-defined patients with PM (Peter and Bohan criteria) and ILD evaluated and followed by an ILD expert (GR). Baseline demographics, serial pulmonary function tests (PFTs), estimates of pulmonary arterial hypertension (PAH) based on echocardiogram results, high resolution computed scan (HRCT) images of the chest, and treatment regimen were assessed to determine long term outcome of patients. Statistical analyses were performed using STATA v.11.

Results: 25 patients met inclusion criteria; baseline demographics are shown.

Table 1. Baseline Patient Demographics and Follow-Up Data

Women: n (%)	15 (60%)	
Men: n (%)	10 (40%)	
Mean Age (range)	59 (39–82)	
ILD/IIP as initial presentation (prior to PM)	12 (48%)	
Current smoker	2/25	
Past smoker	11/25	
Never smoker	12/25	
Jo - 1 Ab positivity	6/17 (35%)	
ANA positivity	5/15 (33%)	
Pulmonary Function Testing	Baseline	Last Recorded
Mean DLCO	39% (+/−16)	38% (+/−17)
Mean FVC	58% (+/−16)	61% (+/−20)
Mean FEV1	57% (+/−14)	55% (+/−18)
Mean FEV1/FVC	.77 (+/−.13)	.76 (+/−.15)

(+/−) denotes standard deviation. IIP: Idiopathic Interstitial Pneumonia

Twelve of the 25 patients (48%) manifested ILD/idiopathic interstitial pneumonia (IIP) before the overt manifestation of PM, and an average of 18.2 months elapsed prior to diagnosis of PM. Mean duration of follow up was 7.2 years; 4 patients died during this period (16% mortality rate). HRCT images confirmed ILD/IIP in all patients; ground glass opacification was the most common pattern (n=7), followed by honeycombing (n=4). Estimated systolic pulmonary artery pressure > 35mm Hg was observed in three of six patients subjected to echocardiogram. Microscopic features of nonspecific interstitial pneumonia (n=2), usual interstitial pneumonia (n=1), organizing pneumonia (n=1), and unclassifiable fibrotic pattern (n=2) were present in six patients subjected to surgical lung biopsy. Although history of cigarette smoking did not influence the baseline PFTs, ever smokers had a lower last recorded DLCO (p=0.045, adjusted for age and gender). Treatment regimens included methotrexate (MTX) (n=11), azathioprine (n=17), mycophenolate (n=2), and prednisone in all of the patients. The means of the last recorded DLCO and FVC for patients treated with MTX were 29.9% and 47.8% of predicted values respectively, compared with 43.7% and 68% for those who were never treated with MTX. The last recorded DLCO was more frequently <30% of predicted values in patients treated with MTX compared to those treated with azathioprine or mycophenolate (logistic regression; p< 0.001), even when controlled for age, gender, and smoking status.

Conclusions: 1) 48% of patients with ILD-PM present with ILD/IIP prior to overt manifestation of PM.

2) History of cigarette smoking confers a poor prognosis based upon worsening of DLCO measurements during the course of ILD-PM.

3) 16% of patients with ILD-PM died during follow up (mean duration=7.2 yrs).

4) Patients treated with MTX had a poor outcome based on the worsening of DLCO to < 30% predicted at last follow up.

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Skin Ulcer Is a Prognostic Factor of Respiratory Failure in Interstitial Lung Disease in Patients with Polymyositis or Dermatomyositis. Kazuyoshi Ishigaki[3], Yasunobu Takizawa[4], Junko Maruyama[4], Ran Nakashima[1], Tsuneyo Mimori[2] and Keigo Setoguchi[4]. [1]Department of Rheumatology and Clinical Immunology, Kyoto University Graduate School of Medicine, Japan, [2]Department of Rheumatology and Clinical Immunology, Kyoto University Graduate School of Medicine, Japan [3]Tokyo Metropolitan Komagome Hospital, Bunkyo-ku, Tokyo, Japan, [4]Tokyo Metropolitan Komagome Hospital

Objective: To elucidate prognostic factors of interstitial lung disease (ILD) in Japanese patients with polymyositis or dermatomyositis including clinically amyopathic dermatomyositis (CADM).

Methods: We reviewed the medical records of 59 consecutive polymyositis and dermatomyositis patients who were seen at Tokyo Metropolitan Komagome Hospital from January 2000 to December 2009.

Results: Eighteen patients had polymyositis; 41 patients had dermatomyositis, of whom 15 had CADM. Thirty-one patients (53%) developed ILD; 13 cases were indolent, 18 were acutely progressive, and 6 led to respiratory failure (demographic data in Table 1). Univariate analysis identified associations between respiratory failure and normal muscle strength, skin ulcers, pneumomediastinum, CRP level at or above 2.0 mg/dl, ferritin level at or above 200 ng/ml, and LDH/CPK ratio at or above 2.0. Multivariate analysis identified associations only between respiratory failure and skin ulcers (odds ratio (OR) 12.1, 95% confidence interval (CI) 1.42–104, p=0.022) and elevated CRP level at or above 2.0 mg/dl (OR 14.9, 95%CI 1.34–167, p=0.028) (Table 2). Ferritin level was excluded from multivariate analysis because 33 values were missing. Four of 7 serum samples from CADM patients were positive for anti-CADM 140 antibody, which is reportedly associated with CADM. Three of the 4 antibody-positive patients subsequently underwent respiratory failure (p=0.371, not significant). Skin biopsy was done in 7 of the 10 patients with skin ulcers, but no signs of vasculitis were detected in any.

Conclusion: Skin ulcers and high CRP level are independent prognostic factors of respiratory failure in ILD in patients with polymyositis or dermatomyositis. Although we found no pathological evidence linking skin ulcers to vasculitis, we suspect systemic vasculopathy may contribute to the poor prognosis. Aggressive immunosuppressive therapy should be considered to prevent respiratory failure in patients with skin ulcers and high inflammatory marker levels.

Table 1. Categorical data are n (%) and age data are mean ± SD

Classification	PM (n = 18)	DM (n = 26)	CADM (n = 15)	Total (n = 59)
Age at onset (years)	59.8 ± 14.3	61.5 ± 11.4	54 ± 16.5	59.1 ± 14.1
Female	10 (55.5)	19 (73)	9 (60)	38 (64.4)
Muscle weakness	18 (100)	26 (100)	0	44 (74.5)
Skin ulcer	0	7 (26.9)	3 (20)	10 (16.9)
Malignancy	5 (27.7)	12 (46.1)	1 (6.6)	18 (30.5)
Interstitial lung disease				
None	13 (72.2)	13 (50)	2 (13.3)	28 (47.4)
Slowly progressive	2 (11.1)	5 (19.2)	6 (40)	13 (22)
Acutely progressive	3 (16.6)	8 (30.7)	7 (46.6)	18 (30.5)
Respiratory failure	0	2 (7.6)	4 (26.6)	6 (10.1)
Death	0	1 (3.8)	2 (13.3)	3 (5.0)

PM: polymyositis, DM: dermatomyositis (not including CADM), CADM: clinically amyopathic dermatomyositis.

Table 2. Results of univariate and multivariate analysis.

		Univariate analysis		Multivariate analysis	
		Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Muscle strength	normal	7.63 (1.23–47.2)		–	
	weak	1.00	0.029		
Skin ulcer	+	15.6 (2.34–104)		12.1 (1.42–104)	
	−	1.00	0.004	1.00	0.022
Pneumomediastinum	+	16.6 (2.30–120)		-	
	−	1.00	0.005		
CRP [mg/dl]	≥2.0	17.2 (1.82–163)		14.9 (1.34–167)	
	<2.0	1.00	0.013	1.00	0.028
Ferritin [ng/ml]	≥200	9.98 (1.01–98.6)			
	<200	1.00	0.049		
LDH/CPK ratio	≥2.0	7.16 (1.16–43.9)		-	
	<2.0	1.00	0.033		

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The Anti-Oxidant Function of High Density Lipoprotein and Paraoxanase-1 Are Abnormal in Patients with Dermatomyositis. Christina Charles-Schoeman[2], Yuen Yin Lee[3], John D. FitzGerald[4], Veena K. Ranganath[1] and Srinivasa T. Reddy[3]. [1]UCLA School of Med Rehab 32–59, Los Angeles, CA, [2]UCLA School of Medicine, Los Angeles, CA, [3]UCLA School of Medicine, [4]UCLA School of Medicine Rehabilitation, Los Angeles, CA

Purpose: Damage to the vascular endothelium is implicated in the pathogenesis of dermatomyositis (DM) and to a lesser degree in other idiopathic inflammatory myopathies (IIM). Normal high density lipoprotein (HDL) protects the vascular endothelium from damage due to oxidized phospholipids, which accumulate under conditions of oxidative stress. During acute and chronic inflammatory states, enzymes such as myeloperoxidase (MPO) produce increased amounts of oxidized phospholipids, which impair this function of HDL. The current work evaluates the function of HDL and its associated protein, paraoxanase 1 (PON-1), in patients with IIM.

Methods: Plasma samples were collected from 26 patients with DM, 20 patients with polymyositis (PM), and 23 healthy controls. HDL's anti-oxidant function was measured by a cell free assay which assesses the ability of patient HDL to inhibit oxidation of a stock LDL. PON-1 activity was measured by the arylesterase assay and MPO activity was assessed using a commercial kit. HDL and LDL cholesterol levels were measured by standard methods and apolipoprotein A-1 (apoA-1) levels were assessed by ELISA.

Results: The anti-oxidant function of HDL as measured by its ability to inhibit oxidation of LDL was significantly worse in patients with DM when compared to age and sex matched healthy controls (see table). Plasma MPO activity was significantly higher in DM patients compared to controls and was correlated with HDL function, ($r = 0.43$, $p=0.0003$ all patients; $r= 0.44$, $p=0.02$ DM only); higher plasma MPO activity was associated with worse HDL function. PON-1 activity was significantly lower in both DM and PM patients compared to controls and there was a trend for an association with HDL function ($r= -0.20$, $p=0.11$); lower PON-1 activity associated with worse HDL function.

Group	HII	Age (yrs)	F (%)	HSCRP (mg/L)	ESR (mm/h)	HDL (mg/dL)	LDL (mg/dL)	ApoA-1 (ug/ml)	MPO (ng/ml)	PON (mOD/min)
DM n = 26	0.73 ± 0.55*	46 ± 14	92†	7.3 ± 10.6*	30 ± 29*	53 ± 16	101 ± 32	305 ± 141	31 ± 17*	3.3 ± 1.3*
PM n = 20	0.61 ± 0.73	54 ± 12*	60	6.4 ± 9.4*	31 ± 25*	62 ± 33	117 ± 49	239 ± 143	27 ± 22	3.5 ± 1.1*
Controls n = 23	0.34 ± 0.14	45 ± 13†	73	1.3 ± 1.7†	11 ± 9†	55 ± 13	101 ± 31	259 ± 64	22 ± 18	4.4 ± 1.3†

HII = HDL Inflammatory Index; F = Female; HSCRP = High Sensitivity C Reactive Protein, ESR = Erythrocyte Sedimentation Rate; *p value < 0.05 compared to controls; †p value < 0.05 compared to PM.

Conclusions: The anti-oxidant function of HDL and its associated protein PON-1 are abnormal in patients with DM compared to healthy controls. Because HDL normally protects the vascular endothelium from oxidative damage, these findings may warrant further investigation of therapies that remove oxidized phospholipids and improve the function of HDL, such as apoA-1 mimetic peptides, for the treatment of DM and other IIM associated with vascular injury.

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The Interferon Signature in Myositis Is Associated with RNA-Binding Protein Autoantibodies. Hatice Bilgic[4], Joseph Wilson[4], Thearith Koeuth[4], Kelly T. McNallan[2], Steven R. Ytterberg[1], Erik J. Peterson[3], Ann M. Reed[1] and Emily C. Baechler[4]. [1]Mayo Clinic, Rochester, MN, [2]Mayo Clinic, Rheumatology, Rochester, MN, [3]University of Minnesota Department of Medicine, Minneapolis, MN, [4]University of Minnesota Department of Medicine, Minneapolis, MN

Background: Several autoimmune diseases are characterized by elevated expression of type I interferon (IFN)-regulated transcripts and proteins in peripheral blood. This IFN signature' is a marker for disease activity in patients with dermatomyositis (DM), and IFN pathway activation is proposed to play a role in the pathogenesis of this disease. The IFN signature in systemic lupus erythematosus is associated with the presence of autoantibodies against RNA binding proteins (RBP), which are commonly observed in lupus patients. However, anti-RBP antibodies are found less frequently in patients with DM.

Methods: We compared blood IFN signatures and autoantibody profiles in 126 patients with inflammatory idiopathic myopathies (IIM), including 76 DM patients (46 adult and 30 pediatric) and 50 patients with other types of IIM (24 polymyositis (PM), 9 inclusion body myositis (IBM), and 17 with uncharacterized myositis). IFN gene signatures were measured from whole blood RNA using TaqMan quantitative real-time RT-PCR to detect the levels of 3 IFN-regulated transcripts (G1P2, IFIT1, and IRF7). For each subject, an IFN gene score' was calculated from the levels of these 3 transcripts. Serum levels of IFN-regulated chemokines (IP-10, I-TAC, and MCP-1) were measured using a multiplexed ELISA (SearchLight, Aushon Bioscience), and a chemokine score' was calculated for each patient using the normalized levels of the 3 chemokines. A bead-based immunoassay (Luminex) was used to detect anti-Sm, -RNP, -SS-A 60, -SS-A 52, -SS-B, -Scl-70, -Jo-1, -Ribosome P and -Chromatin antibodies in serum. Spearman's rank method was used to for correlation and the Mann-Whitney test was used for group comparisons.

Results: Out of 126 myositis patients, 33 were positive for at least one RBP antibody (anti-Sm, -RNP, -SS-A, or –SS-B). Both chemokine scores ($p=0.04$) and IFN gene scores ($p=0.003$) were significantly higher in RBP+ patients compared to RBP- patients. The IFN gene score was significantly correlated with the number of RBP antibodies ($r=0.31$, $p=0.002$), and with the levels of individual autoantibodies (anti-RNP, $r=0.28$, $p=0.004$; SS-A 60, $r=0.23$, $p=0.02$; and SS-A 52, $r=0.35$, $p=0.0004$). The chemokine score was positively correlated with anti-SS-A ($r=0.20$, $p=0.02$) but negatively correlated with anti-Sm ($r = -0.18$, $p=0.04$). When the analysis was repeated in the DM and other myositis' (PM, IBM, uncharacterized IIM) groups separately, IFN gene scores of RBP+ and RBP- groups were significantly different in both the DM and other myositis' subgroups ($p=0.01$ for both). IFN gene and chemokine scores were significantly correlated in the DM subgroup ($r=0.61$, $p<0.001$) but not in the others ($r=0.11$, $p=0.59$).

Conclusions: These results suggest that the IFN gene signature is associated with the presence of anti-RBP antibodies in patients with myositis. The presence of these autoantibodies, together with elevated IFN signatures, may promote identification of patients with myositis overlap syndromes.

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The Role of Innate Immunity in a Model of HRS-Induced Myositis. Makoto Soejima[4], Eun Ha Kang[1], Yasuhiro Katsumata[2], Xinyan Gu[3], Paula Clemens[3] and Dana Ascherman[3]. [1]Seoul National University College of Medicine, [2]Tokyo Women's Medical University, [3]University of Pittsburgh, [4]University of Pittsburgh, Pittsburgh, PA

Aim: The aim of this study was to clarify the contribution of innate immunity in a model of histidyl-tRNA synthetase (HRS)-induced myositis.

Background: Previous studies have suggested an important role for the autoantigen HRS in the pathogenesis of myositis. While most investigations have focused on the ability of HRS to trigger adaptive immune responses, *in vitro* studies clearly indicate that HRS possesses intrinsic immunostimulatory properties that may operate through the innate immune system.

Methods: We immunized different strains of mice (C57BL/6, B6.G7, NOD.*Idd3/5*, DO11.10/Rag2$^{-/-}$, and C3H/HeJ) with soluble HRS (Jo-1) or appropriate control proteins (maltose binding protein; MBP) via the intramuscular (IM) route. To evaluate the resulting immune response, we determined IgG anti-Jo-1 and anti-MBP antibody levels in the sera of mice immunized with different proteins using standard solid phase ELISA. As a measure of *in vitro* T cell proliferation, we CFSE labeled splenocytes or LN cells derived from these mice and then co-cultured cells with various antigens for 96 hours before flow cytometric assessment of CFSE dilution. Immunohistochemical staining of cell surface markers (CD3, CD4, CD8, CD44, CD11c, F4/80, B220, CCR5) permitted characterization of inflammatory infiltrates resulting from our IM immunization protocol. Quantification of antigen-induced muscle inflammation was based on a scoring system combining the relative intensity and distribution of lymphocytic infiltrates in multiple fields viewed under high power magnification, where 0=no inflammation, 1=minimal inflammation, 2=moderate inflammation, and 3=severe inflammation. Severity scores for muscle inflammation were compared using the Mann-Whitney *U*-test.

Results: IM immunization with a murine HRS fusion protein induced significant muscle inflammation (relative to MBP control protein) in multiple congenic strains of C57BL/6 and NOD mice. Infiltrates occurred as early as 7 days post immunization and persisted as long as 7 weeks following a single administration of soluble HRS protein. Immunohistochemical staining indicated that these infiltrates were composed primarily of CD3+CD44+CCR5+ lymphocytes admixed with smaller numbers of B cells and macrophages. Corresponding to these histopathologic findings, ELISAs demonstrated class-switched antibody responses to HRS at each of these time points. Measurement of T cell responses to immunizing antigens through CFSE proliferation assays also revealed a level of antigen-specific priming. Parallel experiments in DO11.10/Rag2$^{-/-}$ (OVA-specific TCR transgene) and C3H/HeJ (TLR4$^{-/-}$) mice showed that HRS could induce exuberant muscle inflammation in the absence of TCR or TLR4 signaling, further implicating alternative components of the innate immune response.

Conclusion: Based on IM immunization with a soluble derivative of murine HRS, the reported experiments demonstrate that this putative autoantigen can trigger innate immune responses which bypass BCR and TCR signaling to generate significant muscle inflammation in a novel model of idiopathic inflammatory myopathy.

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13-Week Efficacy and Safety Evaluation of Naproxcinod, a Cyclooxygenase Inhibiting Nitric Oxide Donator (CINOD), in Patients with Osteoarthritis of the Hip. Christoph Baerwald[3], Hayet Frayssinet[1], Thierry Ferreira[1], Brigitte Duquesroix[1] and Thomas Schnitzer[2]. [1]NicOx, SA, [2]Northwestern University, [3]Universitätsklinikum Leipzig

Purpose: Naproxcinod is a Cyclooxygenase Inhibiting Nitric Oxide Donator (CINOD) under development for the relief of signs and symptoms of osteoarthritis (OA).

Methods: 810 patients with primary hip OA experiencing pain flare at baseline were randomized to naproxcinod 750mg, placebo or naproxen 500mg (all *bid*) in a 2:2:1 ratio. 3 co-primary efficacy endpoints: change from baseline in WOMAC™ pain and function subscales, and patients' overall rating of disease status at Week 13. The primary efficacy variables were analyzed using an ANCOVA model with treatment group and site as factors, and baseline value as a covariate. Non-inferiority naproxcinod versus naproxen was tested post-hoc. Safety assessments included adverse events (AEs) and office blood pressure (BP) monitoring (2 to 4 hours post-dose).

Results: 810 patients randomized. Naproxcinod was statistically superior to placebo for all 3 co-primary endpoints ($p<0.0001$), while similar to naproxen. Treatments were well tolerated. Most AEs were mild or moderate and SAEs were low and similar between groups. The mean change (SD) from Baseline at Week 13 in Systolic BP was −2.60 (11.33) mm Hg in the naproxcinod 750 mg bid group, −2.49 (11.64) mm Hg in the placebo bid group, and −0.49 (12.32) mm Hg in the naproxen 500 mg bid group.

Conclusion: Naproxcinod efficacy was statistically superior to placebo in all 3 co-primary efficacy variables. Naproxcinod was well tolerated with a BP profile that tended to be different from that of naproxen.

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A Fixed-Dose Combination of Naproxen and Esomeprazole Magnesium (VIMOVO™) Has Comparable Efficacy and Tolerability to Celecoxib in Patients with Osteoarthritis (OA) of the Knee: Results from Two Randomized, Controlled Trials. Marc C. Hochberg[4], Byron Cryer[5], John G. Fort[3], Clara Hwang[1], Ola Svensson[2] and Mark B. Sostek[1]. [1]AstraZeneca, Wilmington, DE, [2]AstraZeneca, Sodertalje, Sweden, [3]POZEN, Inc, Chapel Hill, NC, [4]University of Maryland, Baltimore, MD, [5]University of Texas Southwestern Medical Center, Dallas, TX

Background: It is recommended that patients (pts) at risk for serious NSAID-associated upper gastrointestinal (UGI) toxicity should receive a COX-2 selective inhibitor, or a nonselective NSAID plus gastroprotection. The efficacy and tolerability of a fixed-dose combination (FDC) of enteric-coated naproxen 500mg and immediate-release esomeprazole magnesium 20mg was compared with celecoxib 200mg in 2 identical, non-inferiority studies in pts with OA.

Methods: Two double-blind, double-dummy, placebo-controlled, multicenter Phase 3 studies (307/309) enrolled pts aged ≥50 years with symptomatic OA of the knee. Following an OA flare, pts were randomized 2:2:1 to receive FDC naproxen/esomeprazole BID, celecoxib 200 mg QD, or placebo for 12 weeks. The primary endpoints were mean change from baseline to Week 12 in WOMAC pain, WOMAC function, and Patient Global Assessment (PGA) of OA using a visual analog scale (VAS, 0–100mm); each endpoint had prespecified non-inferiority margin of 10mm between active treatments. Tolerability endpoints included the modified Severity Of Dyspepsia Assessment (mSODA), heartburn severity, and predefined NSAID-associated UGI adverse events (AEs).

Results: Study 307: 619 pts were randomized, 614 were treated, and 521 completed; Study 309: 615 pts were randomized, 610 were treated, and 489 completed. Baseline demographics were similar between treatment groups in both studies; mean age was 62 years and >60% were women. Improvements in WOMAC pain and function, and PGA were seen with naproxen/esomeprazole and celecoxib in both studies. Naproxen/esomeprazole was non-inferior to celecoxib for each primary endpoint; upper/lower limits of 95% CI of treatment differences were <5mm (table). Both active treatments showed significantly greater efficacy vs placebo in Study 307 ($p<0.05$), while only naproxen/esomeprazole was significantly superior to placebo in Study 309 ($p<0.05$). The incidence of UGI AEs was 17.3% in Study 307 and 20.3% in Study 309, and was similar between treatment groups. UGI AEs reported by ≥3% of pts were dyspepsia, nausea, and upper abdominal pain. In Study 307, 1.2%, 1.6%, and 2.4% of pts discontinued due to UGI AEs in the naproxen/esomeprazole, celecoxib, and placebo groups, respectively; in Study 309, 0.8%, 3.7%, and 2.5% withdrew, respectively. Improvements in mSODA scores were similar across treatment groups in both studies, with no significant differences between active treatments (table). Pts treated with naproxen/esomeprazole had significantly more heartburn-free days vs those treated with celecoxib (95% CIs: Study 307: 2.1, 12.7; Study 309: 2.5, 13.4) and placebo (95% CIs: Study 307: 6.4, 19.2; Study 309: 1.1, 14.4).

	Study 307			Study 309		
	Naproxen/ esomeprazole (N=246)	Celecoxib (N=243)	Naproxen/ esomeprazole – celecoxib	Naproxen/ esomeprazole (N=241)	Celecoxib (N=244)	Naproxen/ esomeprazole – celecoxib
WOMAC pain,[a] n	226	221		213	220	
LS mean change from baseline to Week 12	-42.0	-41.8	-0.2	-44.2	-42.9	-1.3
95% CI			-4.8, 4.3			-5.9, 3.3
WOMAC function,[a] n	226	221		213	220	
LS mean change from baseline to Week 12	-36.4	-36.3	-0.1	-38.9	-36.8	-2.1
95% CI			-4.6, 4.4			-6.8, 2.6
PGA-VAS,[a] n	242	230		235	234	
LS mean change from baseline to Week 12	21.2	21.6	-0.5	29.0	25.6	3.5
95% CI			-5.1, 4.1			-1.4, 8.3
mSODA, n	245	237		238	241	
LS mean change from baseline to Week 12	-3.8	-4.6	0.8	-4.0	-3.4	-0.6
95% CI			-0.4, 1.9			-1.8, 0.6

ITT population analysis with last observation carried forward. [a]Non-inferiority was established if the upper bound of a 95% CI was ≤10 mm for WOMAC pain and function, and if the lower bound was ≥-10 mm for PGA-VAS. CI, confidence interval; ITT, intent-to-treat; LS, least squares.

Conclusions: With non-inferior efficacy and comparable UGI tolerability to celecoxib, naproxen/esomeprazole may offer an effective and well-tolerated treatment option for pts with knee OA at risk for serious UGI AEs.

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Chondroitin Sulfate Treatment Is Effective at Reducing Cartilage Loss in the Tibiofemoral Compartment in Knee OA as Assessed by Magnetic Resonance Imaging (MRI). Jean-Pierre Pelletier[8], Lukas M. Wildi[5], Jean-Pierre Raynauld[5], André Beaulieu[3], Louis Bessette[4], Frédéric Morin[1], François Abram[6], Marc Dorais[7] and Johanne Martel-Pelletier[2]. [1]Centre de Recherche Musculo-squelettique, Trois-Rivières, [2]CR-CHUM, Notre-Dame Hospital, Montreal, QC, Canada, [3]Faculty of Medicine, University of Laval, QC, [4]Groupe de Recherche en Rhumatologie et Maladies Osseuses, Sainte-Foy, [5]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, [6]Research and Development, ArthroVision Inc., Montreal, [7]StatSciences Inc., Notre-Dame de l'Ile-Perrot, [8]University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC, Canada

Background: The osteoarthritis (OA) disease-modifying effect of chondroitin sulfate (CS) has been demonstrated by X-ray in knee OA after two years of treatment [1,2]. We further explored by performing a randomized, double-blind, placebo-controlled study using a more sensitive imaging technique, quantitative MRI, the effect of CS treatment on cartilage volume loss in knee OA. We also investigated, for the first time, the effect of CS on bone marrow lesion (BML) size and the severity of synovitis.

Methods: Knee OA patients were treated with CS (800 mg once daily) or placebo for 6 months, followed by an open-label period of 6 months in which patients from both groups received CS. Patients with primary knee OA, Kellgren-Lawrence grades 2–3, and clinical as well as MRI signs of synovitis were included. MRI was performed at baseline, 6, and 12 months. Global cartilage volume and sub-regions were quantified using a specially developed computer program. The BML size was assessed using a semi-quantitative scoring system. Synovial membrane thickness (synovitis) was measured in mm, and joint swelling incidence was evaluated. Statistical analyses were assessed by ANCOVA for the cartilage volume, Wilcoxon Mann-Whitney

tests for BML, ANOVA for synovitis, and Fisher's exact test for joint swelling.

Results: Knee OA patients were treated with CS (n=35) or placebo (n=34). Patients on CS treatment (12 months CS) compared to the patients in the placebo group (6 months placebo followed by 6 months CS) experienced a significant reduction in global cartilage volume loss at 6 (p=0.064 for a trend) and 12 (p=0.025) months, in the lateral tibiofemoral compartment (p=0.015; p=0.004), as well as in the tibial plateau (p=0.002; p=0.017). Interestingly, there was also a reduction in BML score in the global knee and lateral tibiofemoral compartment at 12 months (p=0.060; p=0.035, respectively). Although there was no statistically significant difference in synovial thickness between the 2 treatment groups at 6 months, discrimination between patients showed that those who received concomitant NSAID treatment demonstrated a statistically significant reduction in the CS group compared to the placebo group (p=0.029), as well as lower incidence of joint swelling (p=0.092).

Conclusion: Data showed that CS treatment can rapidly and significantly reduce the cartilage loss in symptomatic knee OA patients. This protective effect was associated with a decrease in BML size, supporting their role in cartilage loss. Moreover, data revealed that CS in combination with NSAIDs exerts an additional clinically relevant anti-inflammatory activity.

References:

1. Michel BA, et al. Arthritis Rheum 2005;52:779-86. 2. Kahan A, et al. Arthritis Rheum 2009;60:524–33.

Disclosure: J.-P. Pelletier: ArthroVision Inc., 1, 5, Bioiberica S.A. (Spain), 1, 5; **L. M. Wildi:** None; **J.-P. Raynauld:** ArthroVision Inc., 5; **A. Beaulieu:** Bioiberica S.A., 2; **L. Bessette:** Bioiberica S.A., 2; **F. Morin:** Bioiberica S.A., 2; **F. Abram:** ArthroVision Inc., 3; **M. Dorais:** ArthroVision Inc., 5; **J. Martel-Pelletier:** ArthroVision Inc., 1, 5, Bioiberica S.A., 1, 5.

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Chronic Pain Associated with Obesity in the Elderly Is in Part Explained by the Presence of Osteoarthritis. Irene Blanco[2], Richard B. Lipton[2], Chaim Putterman[1] and Carol A. Derby[2]. [1]Albert Einstein College of Med, Bronx, NY, [2]Albert Einstein College of Medicine, Bronx, NY

Background: Up to 60% of the elderly report chronic pain. Our group has shown a significant association between chronic pain and obesity in the elderly. It is unclear if this association is due to being overweight or comorbidities associated with obesity such as diabetes and osteoarthritis. Therefore, we conducted a cross-sectional study to investigate if the link between obesity and chronic pain is mediated by other factors.

Methods: The Einstein Aging Study (EAS) is a longitudinal study of community residing elderly. Participants are recruited using Medicare beneficiary lists and voter registration records. Demographics and medical history are collected as well as the Geriatric Depression Scale (GDS), SF-36, and the Total Pain Index (TPI) which measures pain severity, location, duration and frequency over 3 months prior to the visit. Chronic pain is defined as pain intensity of ≥4/10 (moderate to severe intensity) in at least 1 body location. To investigate the role of osteoarthritis (OA) and several comorbidities in the relationship between chronic pain (CP) and obesity, unweighted logistic regressions were performed. Overweight was defined as a BMI ≥ 25.0 and obese as a BMI ≥ 30.0

Results: 423 participants screened between 2005–2009 were included. The median age of the group was 78.9y (IQR: 74.7–83.3) and 63.8% were female (270/423). Of these participants, 209/423 (49.4%) report having chronic pain. More women than men reported CP (55.2% v 44.8%, p<0.01). There was no association of CP with either age (p=0.32), race (p=0.47), education (p=0.187), depression (p=0.42) or a history of a hip replacement (p=0.37) or hip/femur/pelvis fracture (p=0.41). On univariate analyses, being obese conferred an increased risk of CP (OR=1.76, p=0.025). CP was also associated with a history of diabetes (OR=1.92, p=0.01) and a osteoarthritis (OR=3.27, p<0.01)

When adjusted for age, race, gender, education and the following comorbidities: diabetes, stroke, heart attack, COPD, hip replacement and hip/femur/pelvis fracture, being overweight or obese significantly increased the risk for chronic pain. (OR=1.57, p=0.038) However when the model was adjusted for a history of osteoarthritis, BMI was no longer significantly associated with CP (OR= 1.45, p=0.09). OA was associated with the presence of CP with a significantly increased odds ratio of 3.03 (p<0.01, 95%CI: 1.90, 4.84). When we stratified the model by OA status, being overweight or obese increased the risk of CP in those with OA, but it was not significant (OR=1.39, p=0.22). In the stratified model, females with OA continued to have a higher risk of CP (OR=2.05, p=0.01) and diabetes did confer a higher risk that trended towards significance (OR=1.86, p=0.063)

Conclusions: We continue to see a link between chronic pain and obesity in this population. It is likely secondary to the effects of obesity, particularly osteoarthritis. New research has linked adipokines to the pathogenesis of OA. It is unknown if these molecules are correlated with increased pain from OA. More studies are needed to elucidate the origins of pain in the elderly so that targeted interventions can be designed.

Disclosure: I. Blanco: None; **R. B. Lipton:** None; **C. Putterman:** None; **C. A. Derby:** None.

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Clinical Evaluation of Chondroitin 4&6 Sulfate (Condrosulf®) in the Treatment of Symptomatic Hand Osteoarthritis. A 6-Month Randomized Double-Blind, Placebo Controlled Study. Cem Gabay, Carole Medinger, Danielle Gascon and Axel Finckh. Univ Hosp of Geneva, Geneva, Switzerland

Background: Symptomatic hand osteoarthritis (OA) is a common cause of consultation for both primary care physicians and in rheumatologists. Severe forms may lead to advanced structural changes, joint deformity and disability. Despite its frequency and severity there are currently only a limited number of therapeutic options.

Objective: To examine the effect of chondroitin 4&6 sulfate (CS) 800 mg daily on pain and function in patients with hand OA.

Patients and Methods: This is an investigator initiated, randomized, placebo-controlled, single center, trial. Patients older than 40 years, with hand OA as defined by the ACR clinical and radiological criteria, suffering from regular joint pain (VAS ≥ 40/100 mm), and substantial functional impairment (functional index of hand OA (FIHAO): Dreiser score ≥ 6) were randomized to CS or placebo. Patients with other rheumatic conditions were excluded. The use of paracetamol, but not nonsteroidal anti-inflammatory drugs, was allowed during the study period. Primary end points included global spontaneous pain (VAS) and functional impairment (FIHOA). Secondary endpoints included global improvement (VAS improvement), grip strength, duration of morning stiffness, consumption of paracetamol, and drug safety. The investigators, independently from the pharmaceutical study sponsor, replicated both the data transcription and the statistical analysis.

Results: 163 patients were randomized, 81 in the CS and 82 in the placebo groups. One patient in the CS group was excluded from the ITT analysis for protocol violation. Demographic data including age, sex, BMI, blood pressure were perfectly matched in the two groups. Mean ± SD global pain VAS and Dreiser scores in the CS and placebo groups were 54.9 ± 14.2 and 11.0 ± 4.1 and 53.6 ± 14.2 and 10.3 ± 3.8, respectively. Other clinical characteristics including grip strength, number of days of painful flares, duration of morning stiffness was also balanced between the two groups. At six months, the improvement of global pain (VAS) and FIHOA were significantly more important in the CS group (−20 ± 26.6 mm and −2.9 ± 5.3) than in the placebo group (−11.3 ± 24.0 and −0.7 ± 4.8, significance P=0.03 and P=0.008, respectively). The evaluation of global improvement (VAS improvement) and duration of morning stiffness were also significantly better in the CS group (P=0.04), whereas grip strength and rescue medication were not significantly different. There was also no difference regarding the frequency of adverse events.

Conclusion: CS 800 mg daily is effective and safe in the treatment of symptomatic hand OA.

Disclosure: C. Gabay: None; **C. Medinger:** None; **D. Gascon:** None; **A. Finckh:** None.

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Controversies in the Use of Acupuncture for Osteoarthritis (OA). A Systematic Review of the Quality and Treatment Features of Randomized Clinical Trials (RCT). Maria F. Marengo[2], Christian A. Waimann[2], Maria A. Lopez-Olivo[2], Carol Looney[1] and Maria E. Suarez-Almazor[3]. [1]The University of Texas M. D. Anderson Cancer Center, [2]The University of Texas M. D. Anderson Cancer Center, Houston, TX, [3]University of Texas, MD Anderson Cancer Center, Houston, TX

Background: Acupuncture is one of the most frequently used non-pharmacological therapies for musculoskeletal disorders. There is conflicting evidence on its efficacy for the management of knee OA, which could potentially be attributable to the quality and variability of methodologies used

across RCTs. We conducted a systematic review of the evidence reported for acupuncture in the treatment of knee OA.

Methods: We electronically searched Embase, Medline, Web of Science and Cochrane Library up to June 9 2010, and manually searched the bibliography included in the identified systematic reviews and meta-analyses. We selected all RCTs which included patients with knee OA, compared needle acupuncture with a sham procedure, and reported pain outcomes. We excluded articles were the control group did not receive a sham intervention. We evaluated the quality of the trials using the Cochrane methods to assess risk of bias (0-worst to 11-best), and we also identified the characteristics of the trials, and specifically the modalities used for the acupuncture and sham treatments. Two authors independently agreed on eligibility and assessed the quality and methods.

Summary of the Results: We identified 6 systematic reviews. Of 14 RCTs, 9 included a sham intervention. Eight of the trials included the WOMAC as an outcome. A total of 1034 patients received acupuncture and 1127 sham intervention. Five of the 9 RCT reported statistically significant results with respect to pain. Six RCTs had a quality score of at least 7 points. The 3 with lower quality did not report statistically significant findings. Marked differences were observed with respect to trial characteristics, acupuncture treatment and sham procedures, with respect to use and number of points, duration and frequency of treatments and sham pricedures (penetrating versus non-penetrating needles). Negative trials were more likely to have used fewer acupuncture points, shorter duration and number of treatments, electric stimulation in the sham group. Very few studies controlled for the potential placebo effects of the interaction between acupuncturists and research staff with participants.

Conclusions: RCTs of acupuncture in the treatment of knee OA show variability in the results that does not appear to be related to quality of the trial, but is associated with the characteristics of the acupuncture treatment and the procedures used for the sham intervention.

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Disease Modifying Activity of Celecoxib on Articular Cartilage in Osteoarthritis?—A Randomized Clinical Trial. T. N. de Boer[2], S. C. Mastbergen[2], A. M. Huisman[3], A. A. Polak[1], J. W. J. Bijlsma[2] and F. P. J. G. Lafeber[2]. [1]Orthopedics, Sint Franciscus Gasthuis Rotterdam, Rotterdam, The Netherlands, [2]Rheumatology & Clinical Immunology, University Medical Center Utrecht, Utrecht, The Netherlands, [3]Rheumatology, Sint Franciscus Gasthuis Rotterdam, Rotterdam, The Netherlands

Background: Selective COX-2 inhibitors are frequently used in the treatment of osteoarthritis (OA) to control inflammation and relieve pain. *In vitro* and *ex vivo* research using human articular cartilage, demonstrated an inflammation independent chondroprotective effect of celecoxib. Such effects are difficult to verify in clinical trials because changes in OA cartilage are slow and evaluation by imaging and biomarker techniques are still hampered by their limited sensitivity. Therefore, patients were treated *in vivo* prior to joint replacement surgery. At the moment of surgery, cartilage was obtained and analyzed in detail *ex vivo*. Three recent studies using this approach demonstrated a beneficial effect of celecoxib at chondrocyte mRNA and protein level, and at the level of matrix integrity suggesting disease modifying characteristics of celecoxib. These positive results tempted us to perform a well designed and powered RCT to evaluate the disease modifying properties of celecoxib in treatment of end-stage OA.

Methods: Patients (n=172) with end-stage knee OA on the waiting list for knee replacement surgery were randomized to 4 groups and treated for at least 4 weeks prior to surgery: celecoxib 2dd200mg, naproxen 2dd250mg stopped 3 days prior to surgery (because of its platelet-inhibiting effect), celecoxib 2dd200mg also stopped 3 days prior to surgery, or no treatment. Cartilage and synovial tissue were collected during surgery and analyzed *ex vivo* fully blinded to the treatment until all data were obtained. The study was conducted according to the declaration of Helsinki and registered EudraCT nr 2007-004862-41.

Results: 4 patients withdrew their consent, 10 changed medications within 2 weeks, and of 20 patients insufficient tissue was obtained. Drop-outs were equally distributed over the 4 treatment arms. Data were analyzed by intention to treat as well as per protocol of the remaining 138 patients. At inclusion, age, gender, weight (BMI), and cartilage damage (X-ray, macroscopic or histological) did not differ between the 4 randomized groups. Unexpectedly, cartilage proteoglycan release was not different between the 4 treatments. Also the other biochemical cartilage parameters did not differ between the 4 groups. Furthermore, prostaglandin-E_2 and nitric oxide (NO) levels produced by the cartilage remained unchanged compared to the no-treatment group. The *ex vivo* release of inflammatory mediators IL-1β, TNFα, PGE_2 and NO by the synovial tissue only showed a statistical significant decrease in NO levels in the celecoxib treated group compared to the no-treatment group. Celecoxib treatment showed a slight improvement in WOMAC pain ($p<0.01$), function and total score compared to the no-treatment group.

Conclusions: No clear effect of celecoxib treatment on cartilage was evident in the present study. Also the effects on synovial inflammatory mediators were limited. Only a small beneficial effect on WOMAC scores was found. As such the reported *in vivo* disease modifying effects of celecoxib could not be confirmed in a sufficiently powered single blinded RCT.

Disclosure: T. N. de Boer: None; **S. C. Mastbergen:** None; **A. M. Huisman:** None; **A. A. Polak:** None; **J. W. J. Bijlsma:** None; **F. P. J. G. Lafeber:** None.

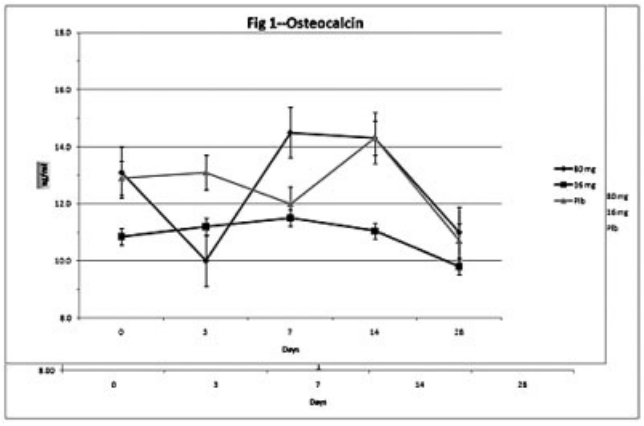
943

Effects of Intraarticular (IA) Corticosteroid Injections on Bone Markers and Endogenous Cortisol in Patients with Knee Osteoarthritis (OA), a Pilot Study. Aruna Baratham[3], Barbara P. Lukert[1] and Herbert B. Lindsley[2]. [1]Kansas City, KS, [2]Kansas University Med Ctr, Kansas City, KS, [3]KU Medical Ctr, Kansas City, KS

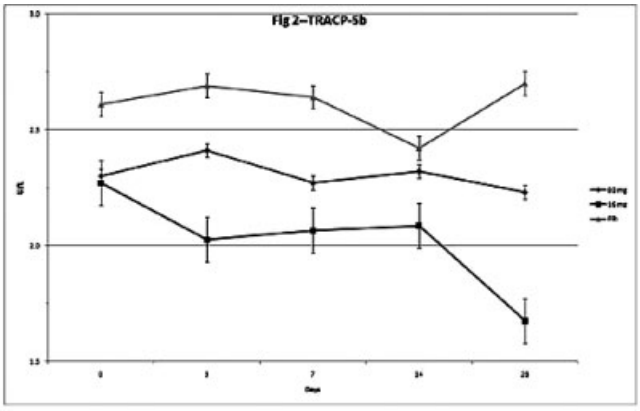
Purpose: IA steroids are used to treat knee OA. Little is known about the systemic effect of intraarticular steroid injections on bone or the pituitary-adrenal axis. There are some studies describing transient decreases in cortisol levels after IA injections in rheumatoid arthritis patients, but no data are published regarding IA steroid injections and their effect on bone turnover markers in OA patients.

Method: We describe a randomized, double blind, placebo controlled study to determine the effects of IA corticosteroid injections on bone turnover markers and endogenous cortisol. 25 subjects (20 females, 5 males) with knee OA, age range 40–80 years were identified from our clinical practice. They were not on any bisphosphonates for at least three years, no systemic illness, and not on oral glucocorticoids; their last IA glucocorticoid injection was given more than 3 months ago. They were randomized to one of three different groups injected in the more symptomatic knee on Day 0. Ten subjects (Group 1) were injected with Depo-methylprednisolone 80 mg plus lidocaine 20 mg, 10 additional subjects (Group 2) were injected with Depo-methylprednisolone 16 mg plus lidocaine 20 mg and 5 subjects (Group 3) was given normal saline with lidocaine 20 mg. Blood draws were performed five times (Days 0, 2–3, 7, 14 and 28).

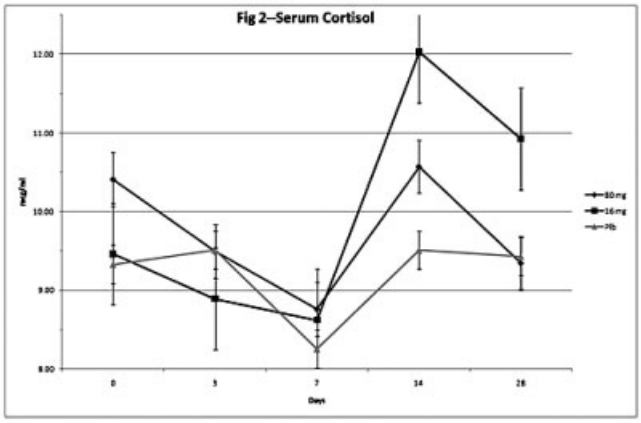
Results: Median levels of serum osteocalcin a bone formation marker, reached a nadir (10 ng/ml from baseline of 16 ng/ml) by Days 2–3 with recovery by Day 7 (15 ng/ml) after IA corticosteroids only for Group 1 ($p=0.003$). No change was seen in Groups 2,3.



In contrast the bone catabolic marker Tartrate-resistant Acid Phosphatase Form 5b (TRACP-5b) showed no consistent change for any of the three groups over 28 days (range 1.7–2.7 U/L).



Median baseline endogenous cortisol level was 9.5 mcg/dL, reached a nadir by Day and returned at least to baseline by day 14 (p=NS).



Conclusions: IA corticosteroids have a transient adverse effect on bone formation with significant recovery of osteocalcin levels by one week and no change in bone catabolism. Cortisol levels decrease slightly at one week of IA administration and rebound above baseline by two weeks. In contrast to daily oral corticosteroids, single doses of IA steroids have no persistent adverse effect on bone or the HPA axis.

Disclosure: A. Baratham: None; **B. P. Lukert:** Amgen Inc., 5; **H. B. Lindsley:** None.

944

Efficacy and Safety of the Lidocaine Patch 5% (Lidoderm®) When Used as Adjunct Treatment in Patients with Osteoarthritis of the Knee. Alan Kivitz[1], Ernest A. Kopecky[3], Yusong Chen[2], Steve Xiang[2], Matthew Wieman[2] and Errol M. Gould[2]. [1]Altoona Center for Clinical Research, Duncansville, PA, [2]Endo Pharmaceuticals Inc., Chadds Ford, PA, [3]Endo Pharmaceuticals Inc.

Purpose: To explore the sensitivity of a dual sequence, crossover design to estimate the treatment effect and safety of the lidocaine patch 5%, relative to placebo, as adjunctive therapy for knee osteoarthritis (OA).

Methods: This pilot study was a randomized, double-blind, placebo-controlled, 2-sequence, dual crossover, 3-period, multicenter trial in patients with moderate-to-severe pain from OA of the knee. Following an open-label, active run-in phase of up to 28 days (to achieve adequate, stable pain control without the use of rescue medication), patients were randomized to 1 of 2 treatment sequences: Sequence LPP (lidocaine patch 5%, placebo patch, placebo patch) or Sequence PLL (placebo patch, lidocaine patch 5%, lidocaine patch 5%). Two full patches were applied once daily to the knee, 1 on the front and 1 on the back of the knee. Patients maintained their existing OA analgesic regimen. Each treatment period was 4 weeks. The primary efficacy endpoint was time-to-exit from current study treatment; secondary efficacy measures included a Pain Intensity-Numerical Rating Scale (PI-NRS; 0 = no pain to 10 = worst possible pain) and Pain Relief Scale (PRS; 0 = completely worse to 8 = complete pain relief). Adverse events (AEs) were recorded.

Results: A total of 169 patients participated in the run-in phase; 93 patients aged 39 to 85 years were randomized. Correction of operational issues necessitated a modified intent-to-treat (MITT) population (n = 42). In the MITT population, the hazard ratio (95% confidence interval [CI]) for time-to-exit was 1.78 (0.89, 3.55), indicating that a patient on the lidocaine patch 5% has a 78% greater chance of remaining on treatment relative to the placebo patch at any time point during any 4-week treatment period. The odds ratio (95% CI) for exit status was 1.86 (0.86, 4.02), indicating that a patient on lidocaine patch 5% has an 86% greater likelihood of remaining on treatment relative to placebo. The LS means of the average of the last 2 daily PI-NRS or PRS scores favored the lidocaine patch 5% compared with placebo for all populations. PI-NRS scores were significantly improved for lidocaine patch 5% patients only in the MITT population (0.54-point difference compared with placebo [P = 0.02]). General disorders and administration site conditions were the largest group of treatment-related AEs in the run-in phase and double-blind treatment periods. Cutaneous AEs were mostly mild or moderate in severity and self-limited.

Conclusions: The small size of the MITT population did not allow for robust hypothesis testing, however the results suggest a beneficial treatment effect of the lidocaine patch 5% as add-on therapy in patients with OA of the knee. The lidocaine patch 5% was generally well tolerated in this population. Use of a dual sequence, crossover design may be a sensitive model for studying the effects of the lidocaine patch 5%.

Disclosure: A. Kivitz: None; **E. A. Kopecky:** Endo Pharmaceuticals Inc., 1, 3; **Y. Chen:** Endo Pharmaceuticals Inc., 1, 3; **S. Xiang:** Endo Pharmaceuticals Inc., 1, 3; **M. Wieman:** Endo Pharmaceuticals Inc., 1, 3; **E. M. Gould:** Endo Pharmaceuticals Inc., 1, 3.

945

Efficacy, Safety and Tolerability of HZT-501, Including Users of Low-Dose Aspirin, a Single-Tablet Combination of Ibuprofen-Famotidine: Results of Two Phase 3 Trials. Michael E. Weinblatt[2], Mark C. Genovese[5], Alan J. Kivitz[1], Alfonso E. Bello[4], Amy Grahn[3], Jeffrey W. Sherman[3] and Michael H. Schiff[6]. [1]Altoona Arthritis & Osteo Ctr, Duncansville, PA, [2]Brigham & Womens Hospital, Boston, MA, [3]Horizon Pharma, Inc., Northbrook, IL, [4]Illinois Bone & Joint Inst, Glenview, IL, [5]Stanford University, Stanford, Sunnyvale, CA, [6]University of Colorado, Denver, Greenwood Village, CO

Background: Gastrointestinal (GI) toxicity remains a major concern with non-steroidal anti-inflammatory drugs (NSAIDs) used in the treatment of OA, RA, and pain. Low-dose aspirin (LDA) is prescribed for prevention of cardiovascular events. LDA is a risk factor for upper GI (UGI) ulcers and UGI bleeding, with the risk increased when LDA is taken in combination with NSAIDs. Randomized trials have demonstrated that high-dose H_2 receptor antagonists (H_2RAs) reduce the incidence of ulcers in NSAID users and in LDA users, but their benefit in patients taking concomitant NSAIDs and LDA is uncertain. A combination tablet of a NSAID plus a high-dose H_2RA may both decrease ulcer disease in NSAID plus LDA users and improve compliance.

Methods: Two 24-wk double-blind, randomized trials of HZT-501, a single-tablet combination of ibuprofen (IBU; 800mg) and famotidine (FAM; 26.6mg) given three times daily were undertaken (REDUCE-1 and REDUCE-2). Patients 40–80 yrs expected to require daily NSAID therapy >= 6 mos with no history of ulcer complications, negative H. pylori stool test and baseline endoscopy (EGD) showing no ulcers and <5 erosions in the UGI tract were randomly assigned in a 2:1 ratio to HZT-501 or IBU 800 mg tablets. Concomitant LDA (<=325 mg daily) and oral anticoagulants (OAC) therapies were permitted. Randomization was stratified based on LDA/OAC therapy and prior ulcer history. Study EGDs were done at 8, 16 and 24 wks of therapy. The predefined population for primary analyses of ulcers was all patients with at least one on-study EGD. Additional safety data included treatment emergent adverse events (TEAEs), clinical laboratory assessments and physical exams.

Results: The studies included 906 and 627 patients. Total patients were1533, of which 1022 received HZT-501 and 511 received IBU. They included 121 of 812 and 79 of 570 LDA users in their primary analysis populations, respectively. A combined sub-group analysis of the LDA

users demonstrated a reduction in UGI ulcers (HZT-501: 14.0% vs. IBU: 34.5%; difference 20.5% [95% CI: 6.5, 34.6]). The Table shows the differences for HZT-501 vs. IBU in the life table estimates and crude proportions for all patients and for the LDA users developing UGI ulcers as well as discontinuation, serious adverse events (SAE) and TEAEs of interest over 24 wks. There were no clinically relevant differences between treatment groups in vital signs, hematology, biochemistry values or physical exams.

Table

	REDUCE 1 & 2		
	HZT-501 (N=1022)	**IBU (N=511)**	**p-value**
Discontinuation	31.0%	42.9%	<0.0001
TEAE	6.7%	7.6%	0.478
Dyspepsia[1]	0.6%	1.8%	0.014
SAEs	3.2%	3.3%	NA
TEAEs	55.0%	58.7%	0.162
GI Disorders	26.0%	28.4%	0.329
Dyspepsia[1]	4.7%	8.0%	0.009
Infections and Infestations	20.6%	20.7%	0.960
Cardiac Disorders	0.4%	1.0%	NA
UGI Ulcer: All	**HZT-501 (N = 930)**	**IBU (N = 452)**	**p-value**
Life table	14.1%	26.5%	<0.0001
Crude rate	11.0%	21.9%	<0.0001
UGI Ulcer: LDA Users	**HZT-501 (N=149)**	**IBU (N=58)**	**p-value**
Life table	14.0%	34.5%	0.004
Crude rate	12.8%	32.8%	0.002

[1]Preferred term for patient reported adverse event

Conclusion: HZT-501 reduces NSAID-associated UGI ulcers overall and in the subset of NSAID users taking LDA. TEAEs were balanced across both treatment groups except dyspepsia which was statistically lower for HZT-501 vs. IBU in line with known activity of FAM. Combination therapy may improve adherence and compliance in patients taking NSAIDs plus LDA who require gastroprotection.

Disclosure: M. E. Weinblatt: Horizon Pharma, Inc., 5; **M. C. Genovese:** Horizon Pharma, Inc., 5; **A. J. Kivitz:** Horizon Pharma, Inc., 2, 5; **A. E. Bello:** Horizon Pharma, Inc., 2, 5; **A. Grahn:** Horizon Pharma, Inc., 3; **J. W. Sherman:** Horizon Pharma, Inc., 3; **M. H. Schiff:** Horizon Pharma, Inc., 5.

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Long Term Safety of an NSAID with Built-in Gastroprotection for Treatment of Pain and Inflammation Related to OA and RA: Results from a One Year Safety Trial of a Single-Tablet Combination of Ibuprofen-Famotidine vs. Ibuprofen Alone. Michael H. Schiff[6], Mark C. Genovese[5], Alan J. Kivitz[1], Alfonso E. Bello[4], Jeffrey W. Sherman[3], Amy Grahn[3] and Michael E. Weinblatt[2]. [1]Altoona Arthritis & Osteo Ctr, Duncansville, PA, [2]Brigham & Womens Hospital, Boston, MA, [3]Horizon Pharma, Inc., Northbrook, IL, [4]Illinois Bone & Joint Inst, Glenview, IL, [5]Stanford University, Stanford, Sunnyvale, CA, [6]University of Colorado, Denver, Greenwood Village, CO

Background: Gastrointestinal (GI) toxicity remains a major concern with NSAIDs used in the treatment of OA, RA, and pain. Proton pump inhibitors (PPI) and other gastroprotective agents are recommended to decrease NSAID-associated GI injury. Concerns exist regarding the potential for PPIs to adversely interact with antiplatelet agents as well as increase the risk of fractures. High-dose H_2 receptor antagonists provide significant benefit in decreasing NSAID-associated GI injury (Cochrane review). Most NSAID users at increased risk for GI events do not receive or adhere to gastroprotective co-therapy. HZT-501 [single-tablet combination of ibuprofen (IBU; 800 mg) and famotidine (FAM; 26.6 mg)] has been shown to significantly reduce upper GI ulcers as compared to IBU (800 mg) alone given thrice daily (REDUCE-1 and REDUCE-2).

Methods: Assessment of long term safety of HZT-501 or IBU tablets for up to 52 wks of treatment for patients with OA, RA or moderate pain. Patients who completed one of two large 24-week double-blind prospective trials of identical design (REDUCE-1 or REDUCE-2) were eligible for an additional 28 weeks of treatment; enrollment goal was at least 150 patients. Patients 40–80 yrs expected to require daily NSAID therapy ≥ 6 months with no history of ulcer complications, a negative H. pylori stool antigen test and baseline EGD showing no ulcers and <5 erosions in the upper GI tract were randomly assigned in a 2:1 ratio either to HZT-501 or IBU tablets. Randomization was stratified based on concomitant low-dose aspirin/anticoagulant therapy and prior ulcer history. Patients completing 24 weeks of blinded treatment (no ulcer development; expected to continue requiring daily NSAID therapy) were eligible to enroll into a follow-on study for an additional 28 weeks on the same double-blind treatment assignment. Crossover between treatments was not allowed. Safety data included serious adverse events (SAEs), treatment emergent adverse events (TEAEs), clinical laboratory assessments, vital signs, and physical exams.

Results: A total of 179 subjects were enrolled into the follow-on study, 132 received HZT-501 (112 completed) and 47 received ibuprofen (38 completed). The incidence of TEAEs was comparable in both groups for the overall 52-week period. The Table shows the differences for HZT-501 vs. IBU for discontinuation, serious adverse events (SAE) and TEAEs of interest over 52 wks. There were no clinically relevant differences between treatment groups in vital signs, hematology, biochemistry values or physical exams.

Table.

	REDUCE 1 & 2 Follow-on Population		
	HZT-501 (N = 132)	**IBU (N = 47)**	**p-value**
Discontinuation	15.2%	19.1%	0.505
SAEs	6.1%	6.4%	
TEAEs	68.2%	68.1%	0.988
Infections and Infestations	34.8%	36.2%	0.878
GI Disorders	26.5%	23.4%	0.703
Dyspepsia[1]	3.8%	8.5%	0.184
Cardiac Disorders	0.8%	0	

[1]Preferred term for patient reported adverse event

Conclusion: These results show the safety of long-term use of HZT-501, together with the significant decrease in upper GI ulcers, demonstrate that HZT-501 offers a potential new option for OA, RA and pain patients.

Disclosure: M. H. Schiff: Horizon Pharma, Inc., 5; **M. C. Genovese:** Horizon Pharma, Inc., 5; **A. J. Kivitz:** Horizon Pharma, Inc., 2, 5; **A. E. Bello:** Horizon Pharma, Inc., 2, 5; **J. W. Sherman:** Horizon Pharma, Inc., 3; **A. Grahn:** Horizon Pharma, Inc., 3; **M. E. Weinblatt:** Horizon Pharma, Inc., 5.

947

Modified Bent Knee Approach for Highly Accurate Injection of the Knee. Suzanne Delea[1], Wilmer L. Sibbitt[3], Philip Band, Natalia Chavez-Chiang[2], Hillary Norton[2] and Arthur D. Bankhurst[4]. [1]University of New Mexico, Albuquerque, NM, [2]University of New Mexico, [3]University of New Mexico HSC, Albuquerque, NM, [4]University of NM Med Ctr, Albuquerque, NM

Background: The extended knee lateral midpatellar portal for 1 intraarticular injection of the knee is accurate but is not practical for all patients.

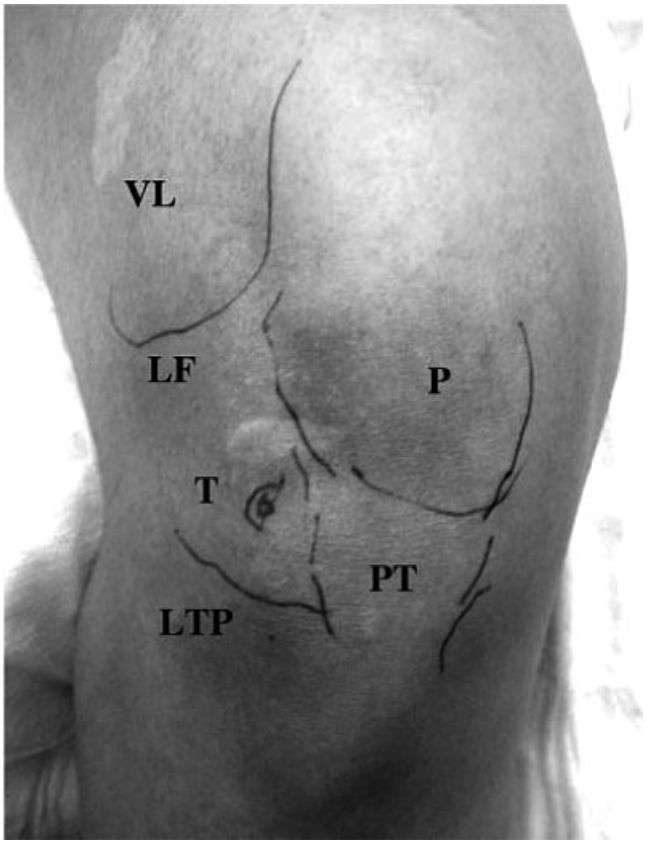
Hypothesis/Purpose: We hypothesized that a highly accurate modified anteriolateral portal where the synovial membrane of the medial femoral condyle is the target would be effective for intraarticular injection of the knee.

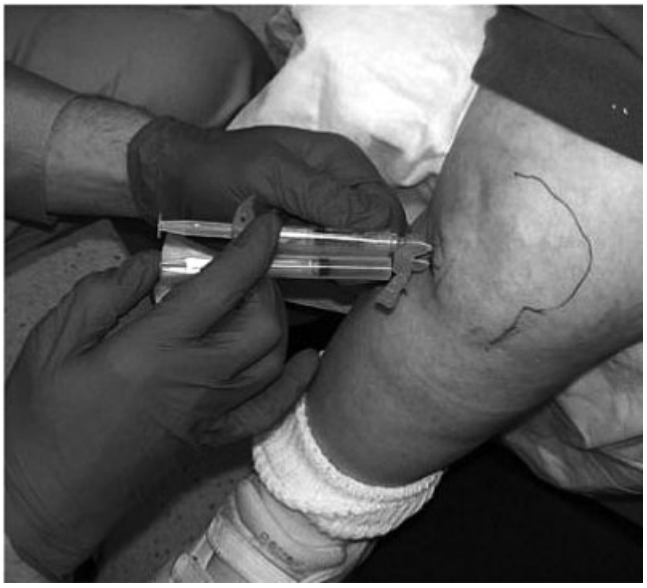
Study Design: Randomized controlled clinical trial. Level 1.

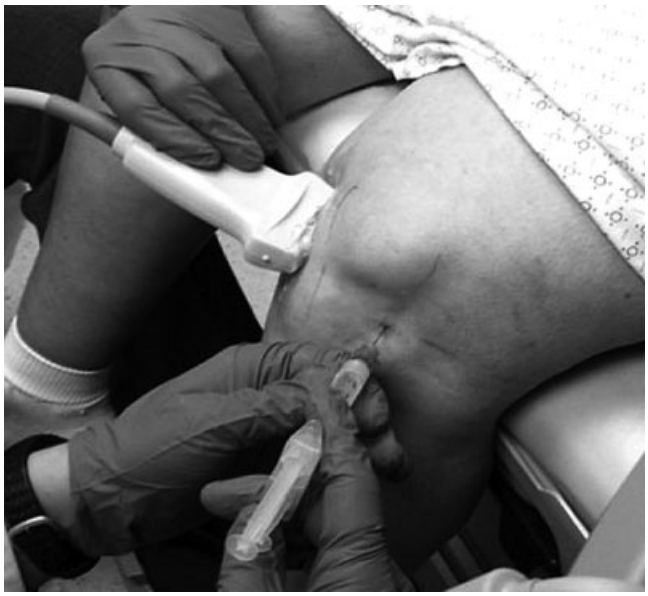
Methods: 83 subjects with "dry" non-effusive osteoarthritis of the knee were randomized to intraarticular injection using the modified anteriolateral bent knee versus the standard lateral midpatellar portal. 80 mg of triamcinolone acetonide was injected into the knee using a 2.0-in (5.1-cm) 21-gauge needle on a RPD procedure syringe (reciprocating procedure device) using the one-needle two-syringe technique. Baseline pain, procedural pain, and pain at outcome (2 weeks and 6 months) were determined with the 0–10 cm Visual Analogue Pain Score (VAS).The

accuracy of needle placement was determined by sonographic imaging with provocative testing.

Results: The lateral midpatellar and modified anteriolateral portals resulted in similar levels of procedural pain (VAS midpatellar: 4.6±3.1 cm; anteriolateral: 4.8±3.2 cm; p =0.77), pain at 2 weeks (VAS midpatellar: 2.6±2.8 cm; anteriolateral: 1.7±2.3 cm; p= 0.11), pain at 6 months (VAS midpatellar: 4.9±3.1 cm; anteriolateral: 4.8±3.2 cm; p =0.89), responders (midpatellar: 45.0%; anteriolateral: 55.8%; p=0.33), non-responders (midpatellar: 55.0%; anteriolateral: 44.2%; p =0.33), duration of therapeutic effect (midpatellar: 3.9±2.4 months; anteriolateral: 4.1±2.2 months; p=0.69), time to next procedure (midpatellar: 7.3±3.3 months; anteriolateral: 7.7±3.7 months; p=0.71), and cost per year (midpatellar: $243±110; anteriolateral: $231±111; p= 0.61). The bent knee anteriolateral portal was 97.4% accurate.







Conclusions and Clinical Relevance: The modified anteriolateral 1 bent knee portal is an effective and accurate alternative to the standard lateral midpatellar portal for intraarticular injection of the knee, and results in equivalent levels of responders, pain reduction, costs, and duration of therapeutic effect.

Disclosure: S. Delea: None; **W. L. Sibbitt:** Abbott Intravascular, Inc, 1, 9, Apple, Inc, 1, 9, Avanca Medical Devices, Inc, 1, 9, Avanca, Inc, 1, 9, Avasca Medical, Inc, 1, 9, Avasca, Inc, 1, 9, Becton Dickinson, 9, Celgene, 1, Ferring Pharmaceuticals Inc., 9, Intellig; **P. Band:** None; **N. Chavez-Chiang:** None; **H. Norton:** None; **A. D. Bankhurst:** None.

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OARSI-OMERACT Virtual Joint Replacement in Disease Modifying Osteoarthritis Drug (DMOAD) Randomized Clinical Trials (RCTs) for Knee and Hip Osteoarthritis (OA): Selection of Optimal Thresholds for Symptomatic Severity.

Rebecca L. Manno[5], Clifton O. Bingham[6], Simon Paternotte[1], Philippe Coste, Giampaolo Giacovelli[9], Lucio C. Rovati[8], Kenneth D. Brandt[7], Steven A. Mazzuca[4], Daniel O. Clegg[10], Helen Shi, Eleonora Tajana Messi[3], Arturo Lanzarotti[3] and Maxime Dougados[2]. [1]AP-HP Cochin Hospital, René Descartes University, Paris, France, [2]Hospital Cochin, Paris, France, [3]IBSA Institut Biochimique SA, [4]Indiana Univ Schl of Medicine, Indianapolis, IN, [5]Johns Hopkins University, Baltimore, MD, [6]Johns Hopkins University, Baltimore, MD, [7]Kansas Univ Medical Center, Fairway, KS, [8]Rottapharm, Monza Milan, Italy, [9]Rottapharm, [10]University of Utah Med Ctr, Salt Lake City, UT

Background: DMOAD development has been limited by few patients (pts) fulfilling xray (XR) progression criteria. Joint arthroplasty (AP) has been proposed as an optimal outcome in DMOAD RCTs; however, disparities by race, gender, socioeconomic status, access to care, surgeon preference, and health care systems have generated concerns regarding biased outcomes. Moreover, a trial using AP outcomes would require a large sample size and long duration to capture sufficient event numbers. A combined OARSI/OMERACT initiative to develop "virtual total joint replacement" (VJR) criteria for DMOAD RCTs has proposed several thresholds of sustained pain, reduced function, or XR change as AP indications. Our objective is to evaluate the prevalence of pts fulfilling different clinical/XR progresson scenarios from existing DMOAD RCTs. We evaluated the prevalence of multiple cutoffs that could potentially be used as future criteria for VJR in DMOAD RCTs.

Methods: We analyzed data from placebo arms of 8 RCTs of putative DMOADS for hip or knee OA. XR progression was defined as decrease in joint space width (JSW) by the study's smallest detectable difference (SDD) for XR Δ or 0.5mm. The proportion of pts fulfilling 9 VJR scenarios with combined pain + function scores ≥80 or 100, or [(pain ≥50 + function ≥30) OR (function ≥50 and pain ≥30)] at 2, 3, or 4 consecutive visits with/without XR progression was assessed for each trial. Effect sizes of clinical scenarios were modeled in regression analyses using XR pro-

gression as a continuous (JSW Δ) and dichotomous (cutoff 0.5mm) variable.

Results: 8 OA RCTs between 1–3 yrs duration representing 1379 pts were included. Pain was assessed by WOMAC and/or VAS and function assessed by WOMAC and/or Lequesne. Radiographic SDD was evaluated in 4 trials (range 0.20–0.50). Weighted mean baseline measures demonstrated: JSW 3.18 mm (range: 2.39–4.05), pain 37.78, function 37.97, pain+function 76.78. Among 6 knee and 2 hip studies, 248 (22%) and 132 (51%) pts respectively had XR progression by JSW Δ ≥0.5mm and 366 (37%) by JSW Δ ≥SDD. Among the 9 clinical scenarios, the highest prevalence (n=486, 36%) was in the least stringent scenario (pain+function≥80 at ≥2 visits); the fewest pts fulfilled criteria (n=101, 7%) in the most stringent scenario (pain+function≥80 at ≥4 visits). When XR progression was added, the prevalence of pts fulfilling a VJR scenario ranged from 2.16% to 12.14% for JSW Δ ≥0.5mm; 3.4% to 16.7% for JSW Δ ≥ SDD. Although individual studies demonstrated associations between a clinical scenario and XR progression, in pooled regression analyses of all RCTs there was no relationship. Using the prevalence of 9 scenarios among all 8 RCTS a sample size of 545–3532 per group would be needed to demonstrate a 30% Δ.

Conclusions: The prevalence of pts with sustained symptomatic OA of at least a moderate degree with XR progression is low. Even using the most lenient criteria to define a "VJR," large numbers of pts would be required to detect differences between groups in DMOAD RCTs. RCT heterogeneity with a range of baseline JSW, symptoms, study duration and assessments may have contributed to the lack of association between XR progression and clinical symptoms in these post hoc analyses.

Disclosure: R. L. Manno: None; **C. O. Bingham:** None; **S. Paternotte:** None; **P. Coste:** None; **G. Giacovelli:** None; **L. C. Rovati:** None; **K. D. Brandt:** None; **S. A. Mazzuca:** None; **D. O. Clegg:** None; **H. Shi:** None; **E. Tajana Messi:** None; **A. Lanzarotti:** None; **M. Dougados:** None.

949 WITHDRAWN

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Patient Global Impression of Change Results from a 1-Year Open-Label Extension Study of Tapentadol Extended Release in Patients with Chronic Osteoarthritis or Low Back Pain. Bettyanne McCann[2], Robert Lange[1], Bertil Wagner[2], Achim Steup[1], Bernd Lange[1] and Mila Etrolpolski[2]. [1]Global Development, Grünenthal GmbH, Aachen, Germany, [2]Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Raritan, NJ

Background: Tapentadol is a centrally acting analgesic with 2 mechanisms of action, μ-opioid receptor agonism and norepinephrine reuptake inhibition. The safety and tolerability of tapentadol extended release (ER) were assessed in a 1-year open-label extension study (ClinicalTrials.gov Identifier: NCT00487435); efficacy was evaluated using the patient global impression of change (PGIC).

Methods: Patients were eligible for enrollment in this study if they completed 1 of 4 phase 3 studies: two 15-week studies that evaluated the efficacy of tapentadol ER and oxycodone controlled release (CR) compared with placebo for chronic osteoarthritis knee pain (NCT00421928) or low back pain (NCT00449176), a crossover study (two 2-week periods following a 3-week titration with tapentadol immediate release) to assess dose conversion between the immediate-release and extended-release formulations of tapentadol in patients with chronic low back pain (NCT00594516), or a 1-year controlled long-term safety study of tapentadol ER and oxycodone CR in patients with chronic osteoarthritis hip or knee pain or low back pain (NCT00361504). Patients who completed 1 of the efficacy studies or the crossover study or who received oxycodone CR in the 1-year safety study were titrated to their optimal therapeutic dose of tapentadol ER (100–250 mg bid) during a titration period of up to 4 weeks; patients then continued on that optimal dose during a maintenance period of up to 48 weeks. Patients who received tapentadol ER during the 1-year safety study continued on their optimal dose determined in the parent study. Dose adjustments within the therapeutic range were permitted under the supervision of a physician throughout the current study. The PGIC, which was completed at baseline of this trial, at Weeks 24 and 48 of maintenance, and at the end of treatment, was used to assess patient's subjective changes in their overall status from baseline to endpoint. Patients indicated their perceived change by completing the statement "Since I began study treatment, my overall status is:" using a 7-point scale (1 = "very much improved," 2 = "much improved," 3 = "minimally improved," 4 = "no change," 5 = "minimally worse," 6 = "much worse," 7 = "very much worse"). Adverse events (AEs) were monitored throughout the study.

Results: The safety population included 1,154 patients, the intent-to-treat population included 1,149 patients, and PGIC data at endpoint were available for 1,059 patients. The majority (61.4% [650/1,059]) of patients reported a change in overall status at endpoint of "very much improved" or "much improved," and an additional 25.7% (272/1,059) of patients reported that their overall status was "minimally improved." The most commonly reported (>10%) TEAEs included headache (13.1% [151/1,154]), nausea (11.8% [136/1,154]), and constipation (11.1% [128/1,154]).

Conclusion: Long-term treatment with tapentadol ER (100–250 mg bid) for up to 1 year (and up to 2 years for some patients) was associated with an improvement in overall status for the majority of patients in this open-label extension study of patients with moderate to severe chronic osteoarthritis pain or low back pain.

Disclosure: B. McCann: Johnson & Johnson, 1, 3; **R. Lange:** Grünenthal GmbH, 3; **B. Wagner:** Johnson & Johnson, 1, 3; **A. Steup:** Grünenthal GmbH, 3; **B. Lange:** Grünenthal GmbH, 3; **M. Etrolpolski:** Johnson & Johnson, 1, 3.

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Analysis of the Multicenter Osteoarthritis (MOST) Study. Jasvinder Singh[1], Tuhina Neogi[2], David T. Felson[3], James Torner[7], Kristin Baker[4], Michael C. Nevitt[5], Irina Tolstykh[5] and Cora E. Lewis[6]. [1]Birmigham VA Medical Center and University of Alabama, Minneapolis, MN, [2]Boston Univ Schl of Med, Boston, MA, [3]Boston University School of Medicine, Boston, MA, [4]Boston University School of Medicine, [5]UCSF, San Francisco, CA, [6]University of Alabama, [7]University of Iowa

Objective: OA has been labeled an inflammatory disorder but studies have examined only a limited repertoire of inflammatory markers with disease and have reported inconsistent findings. We assessed whether inflammation biomarkers and those representing adipokines are associated with synovitis and knee pain in participants in a cohort study of knee OA.

Methods: A subgroup of 100 Caucasian women were included from the NIH-funded Multicenter Osteoarthritis (MOST) Study. MOST participants were age 50 to 79 years at baseline and either with symptomatic knee OA or at high risk of disease. At baseline and 30 month follow-up, subjects were queried about the presence of knee pain on most days, completed a knee-specific Western Ontario McMaster Osteoarthritis Index (WOMAC), and had weight-bearing PA and lateral knee x-rays. New knee pain was present if a subject did not have knee pain on most days at baseline but did at follow-up irrespective of x-ray OA. At 30 months, participants underwent a gadolinium contrast-enhanced MRI using a 1.5 Tesla scanner to detect synovitis, categorized as none/questionable, mild, or a lot/extensive. WORMS readings of MRI's were used to score bone marrow lesions (BML's) and size of effusion. We assessed the multivariable-adjusted association of 1 standard deviation change in each biomarker level at baseline (blood or urine) with synovitis, prevalent pain and incident pain on most days on WOMAC scale at 30 months: TNF-alpha, MCP-1, leptin, adiponectin, PAI-1, CRP, MMP3, TIMP3, ICAM-1, IGF-1, IGF-BP3, oxidized LDL, TGF-beta 1, estradiol (total), DHEA-S, sex hormone binding globulin (SHBG) and cartilage oligomeric matrix protein (COMP).

Results: Mean age (standard deviation) was 59.5 years (7.2), body mass index (BMI) was 29 (4.8) kg/m^2, 57% had no radiographic OA at baseline, 20% with unilateral OA and 23% with bilateral OA and 68% were using an pain medications at baseline. Adjusted for site, age, BMI, baseline K/L grade, BML score (>0) and effusion score (>0), the following associations were significant for presence of a lot/extensive synovitis at 30-month visit: baseline adiponectin, OR 2.6 (95% CI:1.3, 4.9) and baseline TGF-beta 1, OR 0.3 (95% CI: 0.2, 0.7).

Significant predictors of outcomes in Multivariable adjusted Odds per 1 Standard deviation increase in each biomarker

	A lot /extensive Synovitis (ref: none/mild)		Prevalent knee pain on WOMAC (ref: none)		Incident knee pain on WOMAC (ref: none)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Adiponectin	**2.6 (1.3, 4.9)**	**0.005**	1.4 (0.9, 2.4)	0.16	0.9 (0.4, 2.2)	0.84
TGF-B1	0.3 (2.0, 0.7)	**0.002**	1.2 (0.7, 2.1)	0.43	1.2 (0.5, 2.9)	0.71
TNF-alpha	1.2 (0.7, 2.1)	0.44	**1.9 (1.1, 3.2)**	**0.015**	2.4 (0.8, 6.6)	0.10
ICAM-1	1.1 (0.7, 1.8)	0.71	1.1 (0.7, 1.8)	0.57	**0.3 (0.1, 0.97)**	**0.044**

Similarly, in multivariable-adjusted analyses, the following associations were significant for any synovitis (versus none) at 30-month: baseline ICAM-1, OR 1.9 (1.1, 3.4) and baseline IGF-1, OR 1.9 (1.1, 4.1). Adjusted for all the variables above and use of pain medications, baseline TNF-alpha was significantly associated with prevalent knee pain at 30-months, OR 2.0 (1.2, 3.4) and ICAM-1 was associated with incident knee pain, OR 0.3 (0.1, 0.97).

Conclusions: In this hypothesis-generating study using a longitudinal cohort of Caucasian women, we found several biomarkers predictive of synovitis, prevalent and incident knee pain at 30-month follow-up.

Disclosure: J. Singh: None; **T. Neogi:** None; **D. T. Felson:** None; **J. Torner:** None; **K. Baker:** None; **M. C. Nevitt:** None; **I. Tolstykh:** None; **C. E. Lewis:** None.

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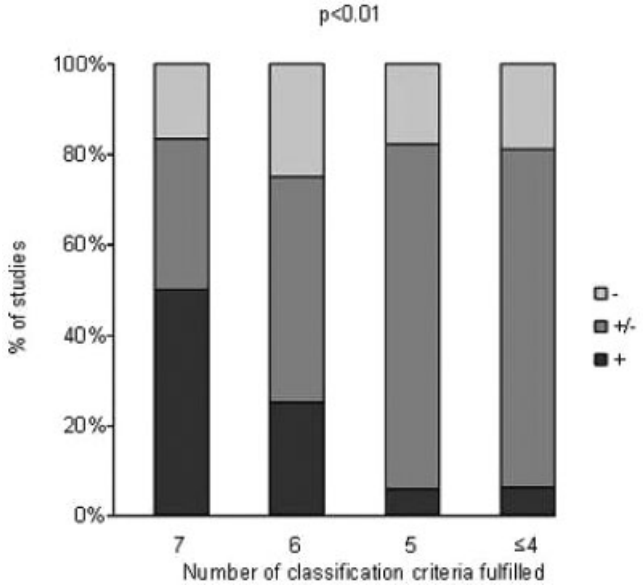
The Importance of Methodological Quality for the Association between Radiographic and Clinical Features of Hip and Knee Osteoarthritis: A Systematic Review. M. B. Kinds[2], E. P. Vignon[5], J. W. J. Bijlsma[4], M. A. Viergever[1], A. C. A. Marijnissen[4], F. P. J. G. Lafeber[4] and P. M. J. Welsing[3]. [1]Image Sciences Institute, University Medical Center Utrecht, The Netherlands, [2]Rheumatology & Clinical Immunology, Image Sciences Institute, University Medical Center Utrecht, The Netherlands, [3]Rheumatology & Clinical Immunology, Julius Center for Health Sciences & Primary Care, University Medical Center Utrecht, The Netherlands, [4]Rheumatology & Clinical Immunology, University Medical Center Utrecht, The Netherlands, [5]Rheumatology, University Hospital Lyon-Sud Pierre-Benite, France

Background: Still there is debate on the presumed association between radiographic and clinical features of osteoarthritis (OA). Inconsistency in reported associations might be caused by different definitions of clinical OA, and by different protocols and scoring methods for radiographic damage. Objective of this review was to evaluate whether there is an association between radiographic OA and clinical OA of hip and knee, accounting for the importance of disease definition, radiographic protocol, and standardized outcome measures.

Methods: A systematic literature search was performed with the keywords 'OA', 'hip', 'knee', 'radiographic', and 'clinical'. For comparison of study results, seven classification criteria for general study quality and methodological quality were developed. All studies were evaluated for an association between radiographic and clinical OA. Associations were classified as 'present' when statistically significant, as 'absent' when not statistically significant, and as 'non-evident' when not all performed comparisons were statistically significant. The influence of classification criteria on the association was investigated, by classifying both the number and the specific criteria fulfilled.

Results: The literature search resulted in 47 studies describing associations between radiographic and clinical OA. When all studies were evaluated, associations were present in 15%, absent in 19%, and non-evident in 66%. Associations were strongest in the six studies fulfilling all classification criteria; present in 50%, absent in 17%, and non-evident in 33% of studies. The frequency of studies with present associations significantly ($p<0.01$) diminished when the number of fulfilled criteria decreased.



Frequency of associations: + (association), +/− (non-evident association), and − (no association) in 6, 8, 17, and 16 studies fulfilling 7 (all), 6, 5, and ≤4 classification criteria respectively. Linear regression analysis with number of criteria as independent variable and association + vs association +/− and − as dependent variable: $p<0.01$.

Specifically the criteria for radiographic protocol, and standardized outcome measures were important. Associations were present in 35%, absent in 12%, and non-evident in 53% of the 17 studies in which the radiographic protocol was adequate. In the 30 studies not fulfilling this criterion, associations were significantly less present ($p=0.012$): associations were non-evident in 74% of studies, present in only 3%, and absent in 23% of studies. Considering standardized outcomes, associations were present in 26%, absent in 37%, and non-evident in 37% of studies when the criterion was fulfilled. When the criterion was not fulfilled, associations were significantly less present ($p=0.002$): associations were non-evident in 86%, present in only 7%, and absent in 7% of studies.

Conclusion: Radiographic OA and clinical OA were more commonly associated when studies fulfilled criteria for study quality and methodological quality. Specifically the radiographic protocol and standardized outcome measures are important for future research regarding the association between radiographic and clinical OA.

Sponsor: Dutch Arthritis Association.

Disclosure: M. B. Kinds: None; **E. P. Vignon:** None; **J. W. J. Bijlsma:** None; **M. A. Viergever:** None; **A. C. A. Marijnissen:** None; **F. P. J. G. Lafeber:** None; **P. M. J. Welsing:** None.

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Time to Onset of Gastrointestinal Adverse Events of Naproxcinod vs. Naproxen and Placebo in Patients with Osteoarthritis. Byron Cryer[2], Angel Lanas[1], Rosanna Fleming[4], Fabrizio Dolphi[3], Diana Aguirre[3] and Brigitte Duquesroix[3]. [1]Aragon Health Sciences Institute, University of Zaragoza, [2]Department of Veterans Affairs Medical Center, [3]NicOx SA, [4]NicOx, Inc

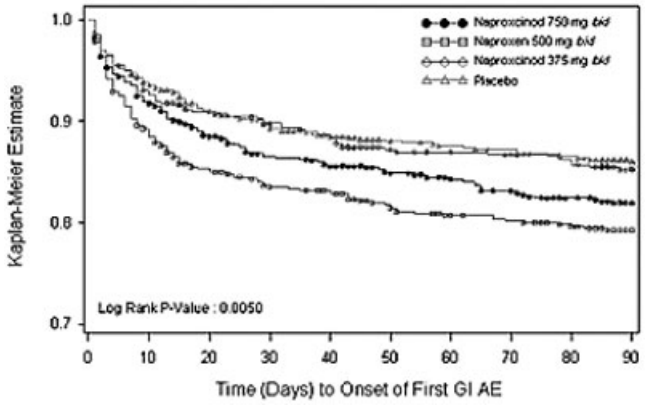
Background: Naproxcinod is a first-in-class COX-Inhibiting Nitric Oxide Donator (CINOD). Previous studies showed naproxcinod was effective compared to placebo in osteoarthritis (OA) patients.

Objectives: To evaluate the time to onset of GI adverse events (AEs) of naproxcinod 750 mg bid and naproxcinod 375 mg bid vs naproxen 500 mg bid and placebo bid in OA patients.

Methods: The safety populations were pooled from three Phase 3 OA studies (13 weeks of treatment) including two dose regimens of naproxcinod, naproxen and placebo. GI AEs and discontinuations due to GI AEs were part of a pre-planned descriptive statistical analysis. A post-hoc analysis of time to onset of GI AEs and discontinuations due to GI AEs among the different treatment groups was performed by estimating the distributions of the times to onset using Kaplan-Meier methods and comparing the distributions among the treatment groups using log rank test.

Results: A total of 2741 patients were included in the analysis: 801 on naproxcinod 750 mg, 489 on naproxcinod 375 mg, 638 on naproxen 500 mg and 813 on placebo. Demography and baseline characteristics were well balanced among groups and reflected those of the general OA population. At least one GI AE was reported by 138 (17.2%) patients on naproxcinod 750 mg bid, 69 (14.1%) on naproxcinod 375 mg bid, 128 (20.1%) on naproxen and 109 (13.4%) on placebo. Few patients discontinued due to at least one GI AE: 27 (3.4%) on naproxcinod 750 mg bid, 9 (1.8%) on naproxcinod 375 mg bid, 29 (4.5%) on naproxen and 27 (3.3%) on placebo.

Time to onset of GI AEs for the different treatment groups is presented below.



Overall, the difference among the treatment groups was significant (log Rank p-value=0.0050). Time to onset of discontinuations due to GI AEs showed a similar trend but the difference was not significant among treatment groups.

Conclusions: This analysis showed that over the 13 weeks of treatment the onset of GI AEs was less likely to have occurred for naproxcinod-treated patients than for naproxen-treated patients. A similar trend was observed for discontinuations due to GI AEs.

References:
HCT 3012-X-301, −302 up to 13 weeks of treatment, −303

Disclosure: B. Cryer: None; **A. Lanas:** None; **R. Fleming:** None; **F. Dolphi:** None; **D. Aguirre:** None; **B. Duquesroix:** None.

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Topical Diclofenac Solution (PENNSAID®) Compared with Oral Diclofenac in Osteoarthritis of the Knee: Pooled Analysis from 2 Controlled Clinical Trials. Sanford H. Roth[1] and Philip Fuller[2]. [1]Arizona Research and Education, Arthritis Research Laboratory, Arizona State University, Phoenix, AZ, [2]Covidien

Background: The use of topical nonsteroidal anti-inflammatory drug (NSAID) formulations, which produce less systemic exposure to NSAIDs compared with oral formulations, is recommended in current guidelines for the management of osteoarthritis (OA). Several randomized clinical trials have shown that topical diclofenac solution (TDiclo) with penetration enhancer dimethyl sulfoxide (DMSO) is effective and well tolerated in the treatment of OA. Results of a pooled analysis of data from 2 trials comparing the safety and efficacy of TDiclo with that of oral diclofenac (ODiclo) are presented here.

Methods: Pooled analysis was performed for two 12-week, double-blind, double-dummy, randomized, controlled, multicenter studies comparing the safety and efficacy of TDiclo with ODiclo in patients with radiologically confirmed symptomatic OA of the knee. Safety and tolerability assessments in both studies included recording of vital signs and adverse events (AEs), dermatologic evaluation of the knee, and clinical laboratory measurements. Primary efficacy variables were pain and physical function as measured by the Western Ontario and McMaster Universities Arthritis (WOMAC) Index and a patient global assessment.

Results: A total of 927 patients (randomized population) were included in pooled safety analysis, and 909 patients (intent-to-treat population) were included in the pooled efficacy analysis. AEs occurred in 312 (67.1%) of patients using TDiclo vs 298 (64.5%) of those taking ODiclo. The most common AE with TDiclo was dry skin at the application site, reported in 24.3% of patients (vs 1.9% with ODiclo; $P<.0001$). Fewer gastrointestinal-related AEs (25.2% vs 39.0%; $P<.0001$) and fewer cardiovascular AEs (1.5% vs 3.7%; $P=.037$) occurred with TDiclo compared with ODiclo. Efficacy as measured by WOMAC scales and patient global assessment was similar between treatment groups.

Conclusions: Although minor skin irritation at the application site was more common in patients using TDiclo, the incidence of gastrointestinal and cardiovascular AEs was significantly lower with TDiclo compared with ODiclo.

Disclosure: S. H. Roth: Covidien, 1, 3, 5, 8, 9, Self-employed, 1, 3, 5, 8, 9, Transdel Pharmaceuticals, 1, 3, 5, 8, 9; **P. Fuller:** Covidien, 3.

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Topical Diclofenac Solution with the Absorption Enhancer Dimethyl Sulfoxide (PENNSAID®) for the Treatment of Osteoarthritis of the Knee: Integrated Summary of Safety. Sanford H. Roth[1] and Philip Fuller[2]. [1]Arizona Research and Education, Arthritis Research Laboratory, Arizona State University, Phoenix, AZ, [2]Covidien

Background: Several randomized clinical trials have shown that topical diclofenac solution (TDiclo) with the penetration enhancer dimethyl sulfoxide (DMSO) is effective and well tolerated in the treatment of osteoarthritis (OA) of the knee. Because topical nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with less systemic exposure to the active molecule, TDiclo may present a safer treatment alternative to oral NSAIDs. To further characterize the safety and tolerability profile of TDiclo, data were analyzed across clinical studies conducted in patients with OA of the knee.

Methods: Adverse events (AEs) with TDiclo therapy were analyzed for seven phase 3 controlled trials and one open-label study conducted in patients

with primary OA of the knee. The data reflect TDiclo exposure in 911 patients treated for 4 to 12 weeks (mean duration, 49 d) in the phase 3 controlled trials and 793 patients from the open-label study. In the open-label study, 463 patients were treated for at least 6 months, and 144 patients were treated for at least 12 months.

Results: Mean age of the study participants was approximately 60 years. Of the evaluated patients, 89% were white and 64% were female. The most common AEs with TDiclo were application site reactions, including dry skin (32%), contact dermatitis characterized by skin erythema and induration (9%), contact dermatitis with vesicles (2%), and pruritus (4%). Application site reactions were the most common cause of patient withdrawal from studies. In controlled trials, gastrointestinal-related AEs occurring with TDiclo at a rate at least twice that with placebo included constipation (3% vs <1%), diarrhea (4% vs 2%), dyspepsia (8% vs 4%), nausea (4% vs 1%), flatulence (4% vs <1%), abdominal pain (6% vs 3%), and edema (3% vs 0%).

Conclusions: TDiclo offers a well-tolerated potential alternative to oral NSAID therapy in patients with OA. There was a low incidence of gastrointestinal-related AEs in patients treated with TDiclo. The most common AEs across controlled and uncontrolled clinical trials were application site reactions.

Disclosure: S. H. Roth: Covidien, 1, 3, 5, 8, 9, Self-employed, 1, 3, 5, 8, 9, Transdel Pharmaceuticals, 1, 3, 5, 8, 9; **P. Fuller:** Covidien, 3.

ACR Poster Session B
Osteoporosis and Metabolic Bone Disease: Clinical Aspects and Pathogensis
Tuesday, November 9, 2010, 9:00 AM–6:00 PM

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Adenosine A2A Antagonist ZM241385 Increases Osteoblast Differentiation and Function In Vitro. Louisa Ziglar[2] and Bruce N. Cronstein[1]. [1]New York Univ Med Ctr, New York, NY, [2]NYU Medical Center, New York, NY

Introduction: Adenosine, a potent endogenous physiological mediator, regulates a wide variety of physiological processes via interaction with one or more of four G protein-coupled receptors (A1, A2a, A2b, and A3), expressed on many cell types. Because we have reported that adenosine receptors affect bone mineral density (BMD), we determined whether adenosine, acting through one or another of these receptors, regulated the formation of osteoblasts and their function in vitro.

Methods: Murine MC3T3-E1 Osteoblast precursor cells were cultured for 12 or 21 days in alpha-MEM media with vitamin C and beta-glycerolphosphate enrichment. Adenosine receptor A1 and A2a agonist and antagonist were added individually at a concentration of 10^{-6} mg/ml. To evaluate osteoblast differentiation, alkaline phosphatase (ALP) assay activity was performed on day 12. Alizarin red activity was measured on day 21 to evaluate osteoblast function. Experiment was performed in triplicate.

Results: Our preliminary results report no significant difference in osteoblast differentiation using A1 receptor treatment and increased differentiation and function under the presence of adenosine A2A antagonist ZM241385. Alizarin red activity showed no significant difference from control in the presence of A1 receptor agonist or antagonist where the A2A antagonist showed increased activity by 71% ($p<0.001$ n=1). Cells treated with ZM241385 showed an increase in ALP activity by 53% ($p=0.19$ n=1).

Discussion: Adenosine receptors are targets for a variety of drugs, including anti-inflammatory drugs (e.g. adenosine mediates the anti-inflammatory effects of low-dose methotrexate in the treatment of Rheumatoid Arthritis). Other indications are currently under study in pre-clinical and clinical studies. Our results suggest that adenosine A2A receptors may be potential targets for the treatment of bone disease as well.

Disclosure: L. Ziglar: None; **B. N. Cronstein:** Amgen Inc., 5, Bristol-Myers Squibb, 5, Canfite Pharma, 1, 5, Combinatorx, 5, Cypress Biosciences, Inc., 5, Hoffmann-La Roche, Inc., 5, King Pharmaceuticals, 2, 5, NIH, 2, Prometheus Laboratories, 5, Regeneron Pharmaceuticals.

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Algorithm for Using a Bone Formation Marker PINP To Monitor the Response to Teriparatide (TPTD) in Patients with Glucocorticoid-Induced Osteoporosis (GIO). Nancy E. Lane[2], Kyoungah See[1], Margaret Warner[1] and John H. Krege[1]. [1]Eli Lilly, Indianapolis, IN, [2]Univ of California at Davis, Hillsborough, CA

Biochemical markers of bone turnover may provide useful information about response to a treatment. A least-significant change algorithm using the serum concentration of N-terminal type I procollagen propeptide (PINP), has been proposed to aid in the management of patients with postmenopausal osteoporosis treated with TPTD (Eastell et al. Curr Med Res Opin 2006;22: 61-6). The purpose of this post-hoc analysis was to assess this approach in GIO patients treated with teriparatide (TPTD). Patients who took at least 5 mg of prednisone or equivalent for at least 3 months were treated for up to 36 months with TPTD 20 g/day. Patients with a baseline and postbaseline (1 and 6 months) PINP were included in this analysis. Responders were defined as patients with an increase in PINP of >10 g/L (least significant change) at 1 or 6 months. At 1 month, the signal-to-noise ratio for PINP was 3.0 compared with 1.2 for bone-specific alkaline phosphatase (bone ALP), 1.4 for C-terminal telopeptide of type I collagen (CTX), 3.2 for osteocalcin (OC), and 2.0 for C-terminal type I procollagen propeptide (PICP). Of the TPTD-treated patients, 88% were responders. PINP responders had significantly greater increases in bone ALP, PICP, and OC ($p<0.03$) at 1 month, compared with nonresponders. In summary, PINP responders had greater than two-fold larger mean percentage increases from baseline in lumbar spine (LS) bone mineral density (BMD) at 12, 24, and 36 months versus non-responders. In patients with GIO, PINP had a high signal-to-noise ratio and most patients treated with teriparatide had a significant increase in PINP. Patients who had a significant increase in PINP had a significantly greater increase in BMD than the small number of patients who did not have a significant increase in PINP. The PINP findings in patients with GIO treated with TPTD in this study were similar to previously reported results in postmenopausal women with osteoporosis.

Lumber Spine BMD gain [mean ± SE (n)]**

PINP	12 months	24 months	36 months
> 10ug/L	8.2% ± 0.73 (n=70)	11.4% ± 1.00 (n=60)	13.3% ± 1.21 (n=55)
< 10 ug/L	3.6% ± 1.13 (n=10)	5.1% ± 1.37 (n= 9)	4.6% ± 3.19 (n= 7)
p-value*	0.023	0.021	0.018

*Responders vs non-responders based on Wilcoxon rank-sum test
**Values are mean percentage change from baseline in LS BMD
SE= standard error.

Disclosure: N. E. Lane: Lilly USA, LLC., 8; **K. See:** Lilly USA, LLC., 3; **M. Warner:** Lilly USA, LLC., 1, 3; **J. H. Krege:** Lilly USA, LLC., 1, 3.

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Anti-Hypertensive Therapy and Bone Mineral Density: Analysis in a Population-Based U.S. Sample. Mitsuyo Kinjo[3], Soko Setoguchi[1] and Daniel Hal Solomon[2]. [1]Brigham and Women's Hospital, [2]Brigham and Womens Hospital, Boston, MA, [3]Okinawa Chubu Hospital, Japan

Background: Several prior studies suggest that beta-blockers and anigiotensin converting enzyme inhibitors (ACE-I) may increase bone mineral density (BMD) in humans. Many studies have examined fracture risks associated with anti-hypertensive treatments. We examined BMD in subjects using beta-blockers, ACE-Is, angiotensin receptor blockers (ARBs), calcium, thiazide diuretics and calcium channel blockers (CCBs), and BMD in a representative U.S. population-based sample from the National Health and Nutrition Examination Survey 1988–1994 (NHANES III) and 1999–2004.

Methods: We identified adult subjects 20 years and older using beta blockers, ACE-Is, ARBs, thiazide diuretics, or CCBs who underwent dual energy X-ray absorptiometry scanning in NHANES. Femoral neck BMD available in NHANES III and lumbar spine BMD in NHANES1999–2004 were examined. Subjects on beta blockers, ACE-I or thiazide monotherapy were compared to CCB users in adjusted linear regression models that included known demographic, anthropometric, and medical risk factors for osteoporosis.

Results: The mean age of study subjects was 65 years old. Among subjects with BMD measured, 2,532 used these medications in NHANES III and 1,224 used them in NHANES 1999–2004. In multiple regression analyses (see Table), ACEI use was associated with higher lumbar spine BMD in both women ($P = 0.03$) and men ($P = 0.037$). Thiazide use was

associated with higher BMD at femoral neck BMD in women, although statistically not significant. Beta-blocker use was only significantly associated at the lumbar spine BMD (P = 0.027) in women. BMD did not differ between ARB and CCB users.

Table 2-1. Adjusted BMD (least square mean) among female subjects in NHANES 1999–2004 and NHANES III

	BB	P-value	ACEI	P-value	Thiazide	P-value	ARB	P-value	CCB
NHANES 1999–2004 (Female)	151		99		68		41		132
Lumbar spine BMD	1.02 (1.00, 1.05)	0.027	1.03 (1.00, 1.03)	0.03	0.98 (0.91, 1.03)	0.5	1.00 (0.94, 1.06)	0.3	0.95 (0.92, 0.97)
NHANES III (Female)	257		195		110		n/a		389
Femoral Neck BMD	0.71 (0.70, 0.71)	0.2	0.73 (0.72, 0.74)	0.3	0.74 (0.73, 0.75)	0.082			0.72 (0.71, 0.73)

*age, race, bmi, smoking, and estrogen use only for female

Table 2-2. Adjusted BMD (least square mean) among male subjects in NHANES 1999–2004 and NHANES III

	BB	P-value	ACEI	P-value	Thiazide	P-value	ARB	P-value	CCB
NHANES 1999–2004 (Male)	158		104		48		40		94
Lumbar spine BMD	1.03 (1.01, 1.05)	0.7	1.11 (1.09, 1.14)	0.037	1.08 (1.00, 1.15)	0.7	1.04 (1.00, 1.09)	0.6	1.05 (1.02, 1.07)
NHANES III (Male)	211		186		63		n/a		279
Femoral Neck BMD	0.82 (0.81, 0.83)	0.5	0.81 (0.80, 0.82)	0.6	0.83 (0.82, 0.85)	0.2			0.81 (0.80, 0.82)

Conclusions: Bone mineral density appears higher in users of ACE-I and thiazides than CCB users among adults, but a causal relationship is not clear.

Disclosure: M. Kinjo: None; **S. Setoguchi:** None; **D. H. Solomon:** None.

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Bone Density Following Long-Duration Spaceflight and Recovery. Shreyasee Amin[1], Sara Achenbach[1], Elizabeth Atkinson[1], L. Joseph Melton[1], Sundeep Khosla[1] and Jean Sibonga[2]. [1]Mayo Clinic, [2]NASA-Johnson Space Center

Background: Rapid bone loss in the weight-bearing skeleton is well recognized during microgravity exposure in long-duration spaceflight, but the implications on long-term bone health remain unclear. How bone mineral density [BMD] in US crew members serving on long-duration missions in space [US crew] compare with what would be expected had they not been exposed to microgravity, is unknown.

Methods: We therefore examined the observed changes in BMD (g/cm^2) among 28 US crew (immediately post-flight and following ~12 months recovery) relative to comparable age- and gender-expected changes derived from 348 men (age range at baseline: 22–90 yrs) and 351 women (range: 21–93 yrs) representing an age-stratified, random sample of the adult community population. BMD measurements (Hologic QDR 2000) were made at the total hip, lumbar spine, ultradistal and midshaft radius, and total body (sites also measured in US crew). Men were measured at baseline, 2, and 4 yrs; women were measured at baseline, 1, 2, and 4 yrs. Linear mixed effects models were used to predict follow-up BMD using baseline BMD, age, gender, and follow-up time, adjusting for the fact that most people were measured more than once. Models including body mass index (BMI) or lean mass were also considered. In US crew (24 men, age range at pre-flight scan: 36–53 yrs; 4 women, age: 41–53 yrs), BMD was measured pre-flight, immediately post flight and at ~12 months post-flight using Hologic QDR 2000, QDR 4500 and Discovery scanners. The majority had pre- and post-flight BMD on similar machines. Immediate post-flight BMD was performed a median of 6 (range: 3–33) days after return, with a median flight duration of 167 (range: 95–215) days. 22 men and 4 women had a scan within 6–18 months post-flight; median days from landing to ~12 months scan was 376 (range: 184–534) days.

Results: Using their age, gender, pre-flight BMD and follow-up time, post-flight BMD values for US crew were predicted based on the model developed from the community sample. The predicted and observed BMD and rates of change immediately and ~12 month post-flight for US crew are presented (see Table). Findings were similar using prediction models which included BMI or lean mass. Due to microgravity exposure, the observed immediate post-flight BMD at all sites was significantly lower than predicted. However, at ~12 months post-flight, BMD values at most sites in US crew were still lower than would be expected had they not been exposed to microgravity.

BMD Site	Mean BMD (g/cm^2) (% change in BMD per month) [95% Confidence Interval]					
	Immediate Post Flight			~12 Month Post Flight		
	Predicted	Observed	p-value	Predicted	Observed	p-value
Total Hip	1.082 (−0.00) [−0.05, 0.04]	1.012 (−0.87) [−1.04, −0.71]	<0.001	1.086 (0.01) [−0.01, 0.02]	1.062 (−0.10) [−0.15, −0.06]	<0.001
Spine	1.078 (0.12) [0.10, 0.13]	1.028 (−0.48) [−0.61, −0.34]	<0.001	1.086 (0.05) [0.05, 0.06]	1.068 (−0.03) [−0.01, 0.03]	0.004
Ultradistal Radius	0.519 (−0.02) [−0.05, −0.00]	0.511 (−0.21) [−0.34, −0.09]	0.01	0.512 (−0.07) [−0.07, −0.06]	0.517 (−0.002) [−0.07, 0.02]	0.03
Mid Shaft Radius	0.710 (0.17) [0.11, 0.23]	0.695 (−0.06) [−0.17, 0.04]	0.001	0.705 (0.06) [0.03, 0.09]	0.694 (−0.01) [−0.06, 0.04]	0.02
Total Body	1.264 (−0.05) [−0.05, −0.04]	1.240 (−0.26) [−0.37, −.0.16]	0.002	1.264 (−0.02) [−0.03, −0.02]	1.248 (−0.08) [−0.15, −0.01]	0.08

Conclusion: These findings have implications on potential long-term adverse effects to bone health of US crew serving on long-duration spaceflight missions.

Disclosure: S. Amin: None; **S. Achenbach:** None; **E. Atkinson:** None; **L. J. Melton:** None; **S. Khosla:** None; **J. Sibonga:** None.

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Bone Geometry Parameters among Black and White Women with SLE. Jimmy D. Alele[2], Diane L. Kamen[2], Kelly J. Hunt[2], Gary S. Gilkeson[1] and Rosalind Ramsey-Goldman[3]. [1]Med Univ of South Carolina, Charleston, SC, [2]Medical University of South Carolina, Charleston, SC, [3]Northwestern University, Chicago, IL

Purpose: Recent studies reported an increased prevalence of osteoporotic fractures among patients with systemic lupus erythematosus (SLE). While the prevalence of low bone mineral density (BMD) is higher among these subjects than the general population, this finding does not fully account for increased fracture rate. The purpose of this study was to determine if SLE status was associated with bone geometry parameters that predict increased skeletal fragility among black and white women.

Methods: Study subjects included 153 women who had participated in the Study of Lupus Vascular and bone Long Term Endpoints (SOLVABLE) (69% white, 31% black) and 4920 controls from the third National Health and Nutrition Examination Survey (NHANES III) (59% white, 41% black). Dual energy x-ray absorptiometry (DXA) scans from SOLVABLE (Hologic DQR-4500), and NHANES III (Hologic DQR-1000) were analyzed using the Hip Structure Analysis (HAS) program to derive BMD and bone geometry parameters (section modulus, buckling ratio, outer diameter and cross-sectional area) at the femoral neck, intertrochanter and proximal femoral shaft. Linear regression was used to examine differences (SLE vs. NHANES) in bone density and geometry in blacks and whites after adjusting for age and body mass index.

Results: NHANES participants were older than SLE subjects, and were more likely to smoke. We detected significant BMD and bone geometry differences (SLE vs. non-SLE, black and white subjects) at the intertrochanter as follows and per table below:

1) BMD (g/cm^2) was lower among both black and white SLE subjects (0.80 vs. 0.94, $p<0.0001$ and 0.82 vs. 0.86, $p<0.01$ respectively).

2) BMD reduction was associated with reductions of cross sectional area (cm^2) among black and white SLE subjects (3.76 vs. 4.61 and 4.05 vs. 4.35 respectively, $p<0.0001$), suggesting that low BMD among SLE patients was a result of reduced total bone quantity.

3) Section modulus (cm^3) was also reduced among SLE subjects in both races (3.03 vs. 3.81, $p<0.0001$ and 3.54 vs. 3.76, $p<0.01$ respectively), suggesting reductions in bending resistance among SLE patients.

4) Reductions in section modulus were accompanied by reductions in outer skeletal diameter (cm) among both black and white SLE subjects (4.98 vs. 5.20, $p<0.0001$ and 5.19 vs. 5.31, $p<0.001$, respectively), suggesting reduced subperiosteal apposition.

5) Finally, buckling ratio was increased among black patients vs. NHANES (9.49 vs. 8.58, $p<0.01$), suggesting increased tendency for local cortical buckling among black patients at this location. Similar findings were detected at the narrow neck and proximal shaft.

Table. Age and BMI-adjusted mean (95% CI) bone mineral density and bone geometry parameters stratified by race and SLE status.

	Whites		Blacks	
	NHANES (n = 2916)	SLE (n = 105)	NHANES (n = 2004)	SLE (n = 48)
Intertrochanter Region				
BMD (g/cm^2)	0.86 (0.86, 0.87)	0.82 (0.79, 0.85)*	0.94 (0.93, 0.94)	0.80 (0.75, 0.84)‡
Section Modulus (cm^3)	3.76 (3.74, 3.79)	3.54 (3.40, 3.68)*	3.81 (3.78, 3.85)	3.03 (2.81, 3.24)‡
Cross Sectional Area (cm^2)	4.35 (4.32, 4.37)	4.05 (3.91, 4.20)‡	4.61 (4.58, 4.65)	3.76 (3.55, 3.97)‡
Width (cm)	5.31 (5.30, 5.32)	5.19 (5.13, 5.26)†	5.20 (5.18, 5.22)	4.98 (4.89, 5.08)‡
Bucking Ratio	9.25 (9.17, 9.32)	9.27 (8.88, 9.66)	8.58 (8.49, 8.67)	9.49 (8.90, 10.1)*

P-values are for comparisons within racial group between NHANES participants and individuals with SLE: *, p-value < 0.01; †, p-value < 0.001; ‡, p-value < 0.0001.

Conclusion: Our study suggests that SLE is associated with BMD and bone geometry profiles that predict increased skeletal fragility among both black and white women. These skeletal differences probably result from the inflammatory nature of SLE and common therapies, especially steroids.

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Cardiovascular Disease Is Associated with Increased Bone Loss and Fracture Risk; a Systematic Review of the Association between Cardiovascular Disease and Osteoporosis. Debby den Uyl[2], Mike T. Nurmohamed[1], Lilian H. D. van Tuyl[2], Hennie G. Raterman[2] and Willem F. Lems[2]. [1]Department Rheumatology/Jan van Breemen Institute, Amsterdam, The Netherlands, [2]Department Rheumatology/VU University Medical Centre, Amsterdam, The Netherlands

Background: Both cardiovascular disease and osteoporosis are important causes of morbidity and mortality in the elderly. The co-occurrence of cardiovascular disease and osteoporosis prompted us to review the evidence of an association between cardiovascular (CV) disease and osteoporosis and potential shared common pathophysiological mechanisms.

Methods: A systemic literature search (Medline-Pubmed and Embase) was conducted to identify all clinical studies that investigated the association between cardiovascular disease and osteoporosis. Relevant studies were screened for quality according to guidelines as proposed by Dutch Cochrane Centre (1) and evidence was summarized.

Results: Seventy-one studies were included in this review. Due to a large heterogeneity in study population, design and outcome measures a formal meta-analysis was not possible. Six of the highest ranked studies (mean n=2000) showed that individuals with prevalent CV disease had higher risk for increased bone loss and fractures during follow-up compared to persons without CV disease (range of reported risk: HR 1.5; OR 2.3–3.0). The largest study (n=31936) reported an over 4 times higher risk in women and over 6 times higher risk in men. There is moderate evidence that individuals with low bone mass had higher CV mortality rates and incident CV events than subject with normal bone mass (risk rates 1.2–1.4). Although the shared common pathophysiological mechanisms are not fully elucidated, the most important factors that might explain this association appear to be age, estrogen deficiency and inflammation.

Conclusions: The current evidence indicates that individuals with prevalent CV disease are at increased risk for bone loss and subsequent fractures. Hence, evaluation of bone mass could be considered in patients with prevalent CV disease. Presently no firm conclusions can be drawn to which extent low bone mineral density might be associated with increased cardiovascular risk.

References:

1) Dutch Cochrane Centre. Available from: http://www.cochrane.nl/nl/newPage1.html

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Cholecalciferol High Dose Supplementation Should Be Preferred in Rheumatic Patients Independently to the Presence of an Autoimmune Disease. Mattia Bellan[3], Pier Paolo Sainaghi[1] and Mario Pirisi[2]. [1]Immuno-Rheumatology Outpatient Unit, DMCS, "A. Avogadro" University and IRCAD (Interdisciplinary Reseach Center of Autoimmune Diseases), Novara, Italy, [2]Immuno-Rheumatology Outpatient Unit, DMCS, "A. Avogadro" University and IRCAD (Interdisciplinary Reseach Center of Autoimmune Diseases), Novara, Italy, [3]Immuno-Rheumatology Outpatient Unit, DMCS, "A. Avogadro" University, Novara, Italy

Introduction: Hypovitaminosis D is common in rheumatic patients, but the response to different supplementation regimens in this setting has not been fully investigated. We aimed to compare two different supplementation regimens of cholecalciferol in patients with rheumatic diseases.

Methods: The clinical records of 832 consecutive adult patients attending a tertiary level immuno-rheumatology clinic from June 2007 to May 2010 were evaluated retrospectively. We included all patients diagnosed to have either an autoimmune rheumatic disease (ARD: rheumatoid arthritis, spondyloarthritis, polymyalgia rheumatica and other connective tissue diseases) or a non-autoimmune rheumatic disease (NARD: osteoarthritis, osteoporosis), who received a) a single 100.000 IU oral dose followed by a 800–1000 IU daily dose of cholecalciferol (loading treatment-LT) or b) standard oral supplementation (ST: 800–1000 IU daily), both regimens maintained for ≥6 months. We excluded patients with renal failure, primary hyperparathyroidism, liver failure and those already receiving vitamin D supplementation. Plasma 25(OH)vitamin D (VITD) concentration together with other clinical data were recorded at baseline and after 6 months of treatment; due to its non-normal distribution (test Shapiro-Wilk, $p<0.05$), a non parametric statistic analysis was chosen.

Results: The study population included 116 patients, 81 with ARD and 35 with NARD; 86 received the ST, and 32 the LT (2 of them after ST). Plasma VITD concentrations were suboptimal both in NARD (median [IQR], 27.2 [12.7–47.4] nmol/L) and ARD (30.0 [17.2–43.4]) (Mann-Whitney U test, p=ns). After receiving ST, plasma VITD increased similarly in the two groups (ARD: 56.4 [40.7–79.4], and NARD: 60.4 [48.9–75.1], p=ns), with only 27.9% [19.5–38.2 95%CI] of patients able to reach the reference value of 75 nmol/L. Among patients who received LT, VITD concentrations also increased similarly in ARD (71.6 [55.4–81.4]) and NARD (72.9 [60.4–79.4]), but a higher proportion of patients (43.8% [28.1–60.8]) reached a plasma VITD concentration ≥75 nmol/L. Indeed, plasma VITD increments from baseline were significantly higher after LT (40.2 [27.5–58.4]) than following ST (22.5 [3.7–45.9], $p<0.009$), again without differences between ARD and NARD (ST: ARD 22.7 [3.7–52.2] vs NARD 22.2 [4.2–44.7] p=ns; LT ARD 37.2 [29.5–56.7] vs NARD 46.7 [13.0–64.9] p=ns).

Conclusions: Hypovitaminosis D is common in patients with rheumatic diseases with and without autoimmune features. A LT supplementation regimen is more efficient than ST in increasing VITD plasma levels, with higher rates of VITD normalization. Finally, following Vitamin D supplementation plasma VITD normalization is achieved similarly in ARD and NARD patients.

Disclosure: M. Bellan: None; **P. P. Sainaghi:** None; **M. Pirisi:** None.

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Differences in the Observed Rate of Hip Fracture in Male and Female Patients Diagnosed with Osteoarthritis or Ankylosing Spondylitis Compared with the Expected Based on the General Population Seeking Health Care. Martin Englund[2], Jonas Franklin[3] and Ingemar F. Petersson[1]. [1]Lund University Hosp, Lund, Sweden, [2]Musculoskeletal Sciences, Department of Orthopedics, Clinical Sciences Lund, Lund University, Lund, Sweden, [3]University Hospital, Akureyri, Iceland

Background: There are conflicting reports of the association between hip osteoarthritis (OA) and hip fracture, and little is known of the association between knee OA or ankylosing spondylitis (AS) and hip fracture.

Objective: To study the rate of hip fracture in male and female OA and AS patients compared with the general population seeking health care.

Methods: Cohort design; Sweden has publicly funded health care with all in- and outpatient health care consultations registered by the patient's personal identifier. We studied residents aged ≥20 yrs of southern Sweden by 1 Jan 2004 who consulted a physician at least once the following 4 calendar years (n=761,210 of total adult population n=879,624), thus being captured with diagnostic codes in the Skane Health Care Register (SHCR). We identified all residents with an ICD-10 code given by a physician for: hip OA (M16), n=11,901, mean age 69.6 yrs, 57.1% women; knee OA (M17), n=23,866, mean age 66.3 yrs, 58.8% women; AS (M45), n=1374, mean age 53.1 yrs, 39.8% women. To obtain observed hip fracture rates we calculated the person-time for each individual, from the day of his/her first OA or AS diagnosis within the study period until the day of first hip fracture (ICD-10 codes: S72.0, S72.1, or S72.2) or until another censoring event (death, relocation, or end of study period by cross-referencing with the population register). The person-time for each subject in the general population aged ≥20 yrs seeking health care (n=761,210, the background population) started to count by his/her first diagnostic code (any ICD-10 code) in the SHCR within the period until first hip fracture or another censoring event (in an

identical fashion as for OA and AS patients). We then calculated the standardized fracture-rate ratio (SFR) by dividing the observed rate of hip fracture in OA or AS patients by their expected rate (based on the age- and gender-specific rates in the background population). Thus, a SFR >1 equals an increased rate of hip fracture and <1 equals a reduced rate of hip fracture compared with the background population. In a sensitivity analysis for estimates in OA patients, we excluded all residents (in both the OA cohort and the background population) being registered with total hip replacement within the study period.

Results: In female knee OA patients the hip fracture rate was significantly reduced by about 20%, but not in men. No significant SFRs were found for hip OA patients, neither men nor women (figure). In AS we found the SFR increased by about 70% for both men an women. However, due to the relatively rare AS diagnosis and low number of fractures observed, the 95% CIs were large and included one (the SFR for men and women combined was 1.68, 95 % CI 0.94, 2.77).

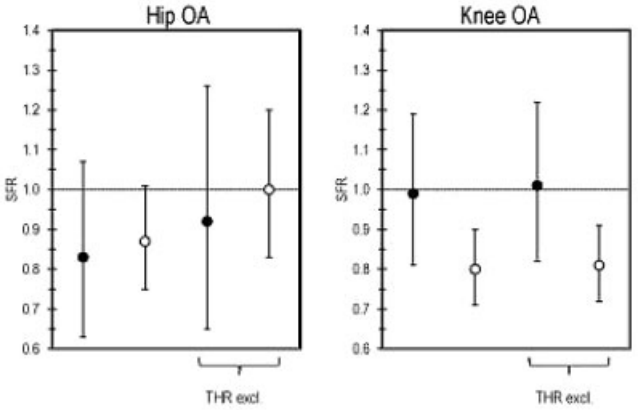

Figure. Standardized hip fracture-rate ratio (SFR) in male (●) and female (○) hip and knee OA patients. The ratio is obtained by dividing the observed fracture rate among OA patients divided by their expected rate based on the hip fracture rate in the background population. In the second set of estimates in each graph subjects with total hip replacement (THR) within the study period are excluded. Error bars are 95% confidence intervals.

Conclusion: In a comprehensive population-based dataset over 4 years, we observed a 20% decreased rate of hip fracture in female knee OA patients compared to the expected, while there was an 70% increased rate in AS patients.

Disclosure: M. Englund: None; **J. Franklin:** None; **I. F. Petersson:** None.

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Effect of Oral Ibandronate on Bone Microarchitecture in Women with Osteopenia—A Randomized Placebo-Controlled Trial. Roland Chapurlat[2], Michel Laroche[4], Thierry Thomas[1], Stéphanie Rouanet[5], Pierre D. Delmas[2] and Marie-Christine de Vernejoul[3]. [1]CHU St Etienne, Saint Etienne, France, [2]INSERM U831, Université de Lyon, Hôpital E Herriot, Lyon, France, [3]Lariboisière Hospital, Paris, France, [4]Pôle Institut Locomoteur Hôpital Purpan, Toulouse, France, [5]Roche France, Neuilly, France

Bone microarchitecture is associated with bone fragility, but little is known about the effects of osteoporosis treatments on microarchitecture. The aim of this study was to examine the effect of ibandronate on bone microarchitecture measured non invasively with peripheral high resolution quantitative computed tomography (HR-pQCT).

We have conducted a randomized placebo-controlled trial among 148 women with osteopenia. Patients received either oral 150 mg monthly ibandronate or an identical placebo, over 24 months. Bone microarchitecture was assessed at baseline, 6, 12 and 24 months, using HR-pQCT (XtremeCT, resolution 82 mm, Scanco, Switzerland) at distal radius and tibia; areal bone mineral density (aBMD) was measured with DXA at the spine, hip and radius. The primary endpoint was the trabecular bone volume (BV/TV) at 12 months at distal radius; the secondary endpoints were volumetric BMD (vBMD) at the trabecular and cortical envelopes, trabecular number (Tb.N), trabecular thickness (Tb.Th), trabecular separation (Tb.Sp) and cortical thickness (Ct.Th). The analysis was intent to treat. All the parameters were analyzed using an analysis of covariance model including baseline value as covariate.

The baseline variables did not differ between those women on ibandronate (n = 72) and those on placebo (n = 76). At 12 months, there was no significant difference in BV/TV at the radius between women on ibandronate (0.108 ± 0.025) and placebo (0.105 ± 0.029), p = 0.25. Similarly, there was no significant difference in other radius trabecular and cortical microarchitecture parameters at 12 and 24 months. In contrast, at the tibia, cortical vBMD in the ibandronate group was significantly greater than in the placebo group as soon as 6 months (810.7 ± 50.7 vs 806.9 ± 69.1, p=0.002) and also at 12 (813.1 ± 50.0 vs 807.3 ± 66.9, p<0.001) and 24 months (816.3 ± 50.3 vs 800.5 ± 68.1, p<0.001), in parallel with better Ct.Th at 6 (0,91 ± 0,22 vs 0,89 ± 0,25, p<0.001), 12 (0,91 ± 0,21 vs 0,90 ± 0,25, p=0.004) and 24 months (0,92 ± 0,22 vs 0,87 ± 0,25, p<0.001). Tibial trabecular parameters, however, remained unaltered at 6, 12 and 24 months in treated women compared with placebo. In the ibandronate group, areal BMD was significantly increased at the hip and spine at 12 and 24 months, and significantly superior to placebo only at 24 months at the radius.

We conclude that 12 months of treatment with ibandronate in women with osteopenia did not affect trabecular bone microarchitecture, but improved cortical vBMD at the tibia at 12 and 24 months, as well as Ct.Th at the tibia, possibly corresponding to decreased cortical porosity. This might be relevant regarding protection against non vertebral fracture. The tibia may be a better bone site to evaluate the effects of antiresorptive agents with HR-pQCT.

Disclosure: R. Chapurlat: Roche, 2; **M. Laroche:** Roche, 2; **T. Thomas:** Roche, 2; **S. Rouanet:** Roche, 3; **P. D. Delmas:** None; **M.-C. de Vernejoul:** Roche, 2.

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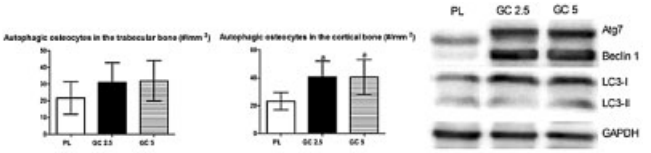
Effects of Glucocorticoid on Osteocyte Autophagy In Vivo. Wei Yao[1], Junjing Jia[1], Weiwei Dai[1], Min Guan[1], Lynda Bonewald[3] and Nancy E. Lane[2]. [1]UC Davis Medical Center, [2]Univ of California at Davis, Hillsborough, CA, [3]Univ. of Missouri at Kansas City, School of Dentistry, Dept. of Oral Biology, Kansas City, MO

Objective: We evaluated dose dependent changes in osteocyte autophagy and apoptosis at both the cancellous and cortical bone sites and serum mineral metabolism in male mice exposed to glucocorticoids (GCs).

Methods: Three month old male Swiss-Webster mice were implanted with prednisolone slow release pellets (2.5mg, 1.5mg/kg/d, or 5 mg/60, 3mg/kg/d, 60-day slow release pellets). The mice were sacrificed at day 28. Minerals and calcitrophic hormones were measured in serum by ELISA or RIA. Autophagy and apoptosis real-time RT-PCR gene pathways were assayed from the tibiae. The percentages of osteocytes undergoing apoptosis or autophagy were measured by immunohistochemistry in both the cancellous and cortical bone regions of the distal femurs.

Results: Twenty-eight days of GC exposure dose-dependently decreased serum phosphorus by about (10% and 25%), 1,25(OH)2 D (65% and 90%) and increased FGF23 (78% and 107%). There was a significant increase in the activation of autophagic RT-PCR gene pathway by an average of 50-fold at 2.5mg dose level and activation of the apoptosis RT-PCR gene pathway by an average of 30-fold at 5mg dose level. Autophagic osteocytes did not differ significantly at the trabecular region of the femurs but were increased by about 50% at the cortical region at both dose levels. Osteocyte apoptosis was not different from placebo-treated group at the trabecular bone region and increased at the cortical bone region by approximately 40% at 5mg dose level.



Conclusions: Mice exposure to GCs for 28 days resulted in significant increase in osteocyte autophagy in the cortical region at 2.5mg dose level. Osteocyte apoptosis was increased in the cortical bone region at 5mg dose level. These data suggest that GC exposure may have created a "stress" that induced osteocyte autophagy that may contribute to the deterioration of the localized matrix around the osteocytes and the death of the osteocytes, which may reduce localized bone material properties and whole bone strength that we previously reported.

Disclosure: W. Yao: None; **J. Jia:** None; **W. Dai:** None; **M. Guan:** None; **L. Bonewald:** None; **N. E. Lane:** None.

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Fracture Epidemiology among a Cohort of HIV-Infected Adults in the UK: An Epidemiologic Study. Karen Walker-Bone[1], Reshad Malik[2], Martin Fisher[2], Yvonne Gilleece[2] and Amanda Samarawickrama[2]. [1]Brighton & Sussex Medical School, Brighton, East Sussex, United Kingdom, [2]Brighton & Sussex University Hospitals NHS Trust

Background: HIV is a global pandemic. The devastating mortality associated with HIV infection has been dramatically reduced by highly-active anti-retroviral therapies (HAART). However, this has led to increasing numbers of HIV-infected patients living with comorbidities including metabolic diseases. Low bone mass and osteoporosis were implicated as consequences of HAART approximately 10 years ago but fracture data in HIV-infected populations are rare.

Methods: A well-characterised cohort of HIV-infected adults attending one UK centre for outpatient care was surveyed. Trained nurses administered a questionnaire which enquired about demographic factors, lifestyle factors, diet and exercise, exposure to glucocorticoids and other drugs affecting bone mineral and HIV factors. Exposure to HAART, stage of HIV infection and status of viral load, CD4 counts etc were collated.

Results: In total, 1050 HIV infected adults were surveyed. 859 (82%) responded. Mean age of respondents was 42.7 (range 19–77) years. 87% were Caucasian and 90% were male (predominant mode of transmission of infection: MSM). Mean duration of HIV infection was 6 years and 76% were current users of ARVs. Overall, 125 subjects (119 (15%) men and 6 women (7%)) reported 200 fractures. 65 respondents had fractured their distal forearm, 6 reported hip fractures and 2 vertebral fractures. In total, 57% of the 200 fractures occcurred under age 25 years with the peak age 7–12 years. However, 33 fractures (26%) occurred among respondetns aged >40 years and 8 (24% among those aged >50 years. The second peak of fractures occurred at the distal forearm (n=6, mean age 48.2 years) and there was 1 hip fracture (age 46 years). 15% of those who sustained a fracture at aged >40 years had been exposed to oral glucocorticoids as compared to 9% of those who had not fractured.

Conclusion: Our results suggest a traditional bimodal distribution of fracture in this population. The first peak occurs in childhood/adolescence and is maximal aged 7–12 years. However, our results suggest a second peak of fracture aged >40 years at sites with a high proportion of trabecular bone (distal forearm, hip, vertebrae). This peak is seen much earlier than in non-HIV infected adults but affects similar sites to those of traditional osteoporotic fractures. Although low bone mass has been documented widely in prevalent HIV infection, fracture has not. Our data suggest that fracture may be a consequence of low bone mass in HIV infection. If these data are replicated, HIV may become one of the most important causes of secondary osteoporosis worldwide.

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Fracture Incidence, Quality of Life and Back Pain in Women with Osteoporosis and Concomitant Glucocorticoid Use Treated with Teriparatide: 36 Month Results from the European Forsteo Observational Study (EFOS). Willem Lems[9], Bente Langdahl[6], Osten Ljunggren[7], Annabel Barrett[2], Dimitrios Karras[8], James Bernard Walsh[4], Astrid Fahrleitner-Pammer[3], Gerald Rajzbaum[5], Clare Barker[2], Franz Jakob[1] and Fernando Marin[2]. [1]Julius-Maximilians-Univ, Würzburg, Germany, [2]Lilly Research Ctr., Windlesham, UK, [3]Med Univ, Graz, Austria, [4]St James's Hosp Trinity College, Dublin, Ireland, [5]St Joseph Hosp, Paris, France, [6]Univ Hosp, århus, Denmark, [7]Univ Hosp, Uppsala, Sweden, [8]Veterans Admin Hosp, Athens, Greece, [9]VU Univ Hosp, Amsterdam, Netherlands

Aim: To describe clinical fractures (Fx), back pain and health-related quality of life (HRQoL) outcomes in postmenopausal women with osteoporosis and glucocorticoid (GC) use, treated with teriparatide (TPTD) for up to 18 mths and followed-up for a further 18 mths in EFOS.

Methods: Prospective, observational study in 8 EU countries. Data on incident clinical vertebral and non-vertebral Fxs were collected, back pain assessed using a 100mm VAS and questionnaire, HRQoL measured using EQ-5D. Changes in women with incident Fx rates over time analysed using logistic regression with repeated measures (RM). Changes from baseline in back pain VAS & EQ-VAS analysed using an RM model.

Results: Of 1581 EFOS patients with follow-up data, 294 (18.6%) were concomitantly treated with GC. At baseline, GC treated patients had a mean (SD) age of 69.9 (8.2) years and 75.1% had ≥2 Fxs after age 40. Post-TPTD follow-up data were available for 156 patients. Of these patients, 47.4% had rheumatoid arthritis at baseline, and 95.5% received antiresorptive medication after TPTD, including any bisphosphonate (61.5%). During the 36 mths study, 49 (16.7%) women sustained at least one incident Fx, compared with 159 (12.4%) in the non-GC group. There was an 89% decrease in the odds of fracture in the 30–36 mth period compared with 0–6 mths ($p<0.028$). An increase in HRQoL was seen over 18 mths of TPTD treatment ($p<0.001$) and was maintained over the 18 mth post-TPTD follow-up. At all timepoints relative to baseline there was a significant reduction in adjusted mean back pain VAS ($p<0.001$).

Table. Health-related quality of life and back pain in GC treated patients

GC treated patients n = 294	Baseline n = 294	18 mths n = 238	36 mths n = 182
EQ-SD Health State Value (median, IQR)	0.52 [−0.02, 0.69]	0.69 (0.52, 0.80)	0.69 (0.52, 0.81)
EQ-VAS mean (SD)	48.8 (22.19)	63.5 (22.14)	64.8 (24.16)
Back pain*			
	n = 291	n = 232	n = 174
Every day/almost every day	63.9%	26.3%	24.7%
	n = 276	n = 191	n = 137
Moderate/severe	90.9%	68.1%	63.5%
	n = 290	n = 232	n = 178
VAS (mm) mean [SD]	58.4 (27.38)	32.8 (26.06)	31.3 (27.62)

*in the last month

Conclusion: Postmenopausal women with severe osteoporosis receiving GCs who were prescribed TPTD in a routine setting had a significant reduction in back pain and improvement in HRQoL during 18 mths of TPTD treatment. These outcomes were maintained for at least 18 mths after TPTD discontinuation. The results should be interpreted in the context of a non-controlled observational study and the limited number of women taking GCs in this cohort.

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Fracture Risk Assessment and Osteoporosis Treatment Disparities in 4027 Japanese Patients with Rheumatoid Arthritis. Takefumi Furuya[2], Takayuki Hosoi[1], Eisuke Inoue[3], Atuo Taniguchi[3], Shigeki Momohara[3] and Hisashi Yamanaka[4]. [1]Department of Clinical Research and Development, National Center for Geriatrics and Gerontology, [2]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [3]Institute of Rheumatology, Tokyo Women's Medical University, [4]Tokyo Women's Medical University, Shinjuku-ku, Tokyo, Japan

Purpose: We previously reported that osteoporosis appeared to be undertreated in Japanese patients with rheumatoid arthritis (RA) (J Rheumatol 2007). Using clinical risk factors from the World Health Organization (WHO) Fracture Risk Assessment (FRAX) tool and recommendations from the National Osteoporosis Foundation (NOF), we evaluated fracture risk and osteoporosis treatment in a cohort of Japanese RA patients.

Methods: Among patients participating in a single-institute, prospective observational cohort study of Japanese RA patents, namely IORRA (Institute of Rheumatology Rheumatoid Arthritis), 4027 (≥40 years of age, 84% female, median age 61 yrs) responded to questions related to fracture risks in October or November 2008. The WHO-FRAX tool without bone mineral density estimated 10-year hip fracture risk and 10-year risk of a major osteoporosis fracture. Multivariable logistic regression evaluated the association between taking any osteoporosis medications and fracture risk, controlling for potential confounders.

Results: Among women (n = 3376), 100% and 82% ≥ 70 years of age (n = 700), 56% and 23% 60–69 years of age (n = 1252), 5% and 2% 50–59 years of age (n = 933), and 0% and 0% 40–49 years of age (n = 491) were identified as having a 10-year hip fracture risk ≥3% and a 10-year risk of a major osteoporosis fracture ≥20%, respectively. Among men (n = 651), 93% and 14% ≥ 70 years of age (n =176), 26% and 0.4 % 60–69 years of age (n = 233), 0% and 0% 50–59 years of age (n = 171), and 0% and 0% 40–49 years of age (n = 71) were identified as having a 10-year hip fracture risk ≥3% and a 10-year risk of a major osteoporosis fracture ≥20%, respectively. Multivariate models identified corticosteroid use (odds ratios (OR) 1.89, 95%

confidence interval (CI) 1.50–2.38), Japanese health assessment questionnaire (HAQ) scores (OR 1.75, 95% CI 1.53–2.01), daily prednisolone dose (mg/day) (OR 1.12, 95% CI 1.08–1.17), age (OR 1.06, 95% CI 1.05–1.07), body mass index (kg/m^2) (OR 0.92, 95% CI 0.89–0.94), and male gender (OR 0.25, 95% CI 0.19–0.33) as significantly associated ($p < 0.01$) with taking any osteoporosis medications. Among the patients with a 10-year hip fracture risk ≥3% or a 10-year risk of a major osteoporosis fracture ≥20% (n = 1685, 41.8%), only 50.1% (n = 844) and 36.0% (n = 607) reported taking any osteoporosis medications and taking bisphosphonates, respectively.

Conclusions: The WHO-FRAX tool identified a substantial proportion of Japanese elderly RA patients who had a high risk of hip and major osteoporosis fractures and for whom the 2008 NOF guidelines recommended treatment. A substantial gap exists between the 2008 NOF treatment guidelines based on fracture risk and osteoporosis treatment in Japanese RA patients. The FRAX tool appears useful for assessing risk and identifying high-risk persons in need of additional evaluation.

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Health Care Utilization Following a Fracture: Global Longitudinal Study of Osteoporosis in Women (GLOW). George Ioannidis[3], Jonathan D. Adachi[2], Laura Pickard[3], Roland Chapurlat[4], Kenneth G. Saag[5], Stuart L. Silverman[1], Julie Flahive[6] and Stephen Gehlbach[6]. [1]Cedars-Sinai Medical Center, University of California Los Angeles, Beverly Hills, CA, [2]McMaster University, Hamilton, ON, Canada, [3]McMaster University, [4]Universite de Lyon, [5]University of Alabama-Birmingham, Birmingham, AL, [6]University of Massachusetts

Background: The consequences of fractures are dramatic, including reduced quality of life, and increased mortality and health care costs. Given the high prevalence and negative consequences of fragility fractures resulting from osteoporosis, it is important that health care services are used efficiently to reduce the burden of fracture. However, there is a lack of data regarding the relationship among various fracture types and health care service utilization. The purpose of the study was to determine the health care utilization in women with various fracture types.

Method: The Global Longitudinal Study of Osteoporosis in Women (GLOW) is an observational, prospective study of women 55 years of age and older who were recruited from 723 primary physician practices across 10 countries (17 sites, 60 393 patients). Women were eligible to participate in GLOW if they were non-institutionalized and if they visited their practice within the past 2 years. Self-administered questionnaires were mailed (2:1 over-sampling of women ≥65) at baseline and at 12 months to all eligible patients. The current study was designed to determine the health care utilization among various fracture types using items from both the baseline and year 1 follow-up surveys. New fractures were divided into 4 categories (spine/neck, hip, wrist/hand, and upper arm/shoulder) and occurred during the first year of the study. Health care utilization included where the fracture was treated (doctor's office/clinic, hospital, rehabilitation centre or nursing home), if surgery was performed (yes/no), and the patient's length of stay (days) at the treatment facility.

Results: A total of 120, 115, 358 and 158 new fractures occurred at the spine, hip, wrist and upper arm, respectively. The mean age (SD) and number of prior fractures (%) were 72.7 (9.1 yr) and 64 (54.2%) for spine, 75.7 (9.0 yr) and 56 (50.0%) for hip, 69.6 (8.9 yr) and 138 (38.9%) for wrist, and 72.1 (9.2 yr) and 60 (39.2%) for upper arm fracture participants. The table displays healthcare utilization for participants with fractures at 1 year.

Healthcare utilization	Spine n = 120	Hip n = 115	Wrist n = 358	Upper arm n = 158
Fracture treated: n (%)				
Office/clinic	83 (74.1)	62 (57.9)	245 (71.4)	104 (70.3)
Hospital	61 (55.5)	107 (96.4)	275 (79.7)	127 (84.1)
Rehabilitation center	13 (11.7)	66 (60.0)	55 (16.8)	43 (29.9)
Nursing home	3 (2.8)	17 (16.5)	3 (0.9)	7 (4.9)
Length of stay (days): mean (SD)				
Hospital	12 (13)	11 (12)	6 (12)	9 (13)
Rehabilitation centre	17 (18)	19 (19)	10 (19)	22 (29)
Nursing home	5 (8)	28 (25)	58 (42)	18 (3)
Preformed surgery: n (%)	16 (26.7)	94 (87.9)	97 (36.9)	41 (34.5)

Conclusions: In a large practice-based international cohort study, results reveal a wide range in the use of healthcare resources depending of the fracture type, and included where the fracture was treated, the length of stay at the treatment facility, and whether surgery was performed to treat the fracture. However, treatment strategies across countries may, in part, explain the variation in resource utilization observed among fracture types. These data may aid researchers and decision makers in determining policies that will optimize health care service utilization and improve patient outcomes.

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High Adherence with Bisphosphonate Therapy in US Veterans with Rheumatoid Arthritis. J. Steuart Richards[10], Grant W. Cannon[9], Candace L. Hayden[8], Richard L. Amdur[11], Ted R. Mikuls[6], Andreas Reimold[2], Liron Caplan[3], Dannette S. Johnson[5], Pascale Schwab[7], Deana Lazaro[1], Bogdan N. Cherascu[4] and Gail S. Kerr[11]. [1]Brooklyn NY VA Medical Center, New York, NY, [2]Dallas TX VA Medical Center, Dallas, TX, [3]Denver CO VA Medical Center, Denver, CO, [4]Iowa City IA VA Medical Center, Iowa City, [5]Jackson MS VA Medical Center, Jackson, MS, [6]Omaha NE VA Medical Center, Omaha, NE, [7]Portland OR VA Medical Center, Portland, OR, [8]Salt Lake City UT VA Medical Center, Salt Lake City, UT, [9]Salt Lake City VA Medical Center, Salt Lake City, UT, [10]Washington DC VA Medical Cener, Washington, DC, [11]Washington DC VA Medical Center, Washington, DC

Background: Patients adherent with prescribed bisphosphonates have a reduction in fractures compared with noncompliant patients. Most reports on compliance with bisphosphonate therapy are for post menopausal osteoporosis with unclear relevance for other groups. We examined predictors of being prescribed a bisphosphonate, as well as predictors of patients who are adherent to therapy and remain on therapy.

Methods: Patient data from the Veterans Affairs Rheumatoid Arthritis (VARA) registry were available for analysis, and included demographics, features of disease severity and activity of rheumatoid arthritis (RA), osteoporosis, prior dual energy X-ray absorptiometry (DXA) testing, use of prednisone and site of enrollment (Dallas, TX; Denver, CO; Jackson, MS; Omaha, NE; Salt Lake City, UT and Washington, DC). Using data from the Veterans Affairs' national Pharmacy Benefits Management (PBM) database for each bisphosphonate prescription, we determined predictors of bisphosphonate adherence and persistence. The time gap between anticipated refill and actual refill of the next prescription was calculated. Treatment course duration was defined as the time from the initial prescription until the expected refill date for the bisphosphonate prescription before a 90 day gap or discontinuation. The medication possession ratio (MPR), a measure of adherence, was calculated as the proportion of treatment time that the patient had drug available. Adherence was defined as an MPR ≥ 0.80.The persistence ratio on bisphosphonate therapy (PRBT), defined as duration of prescribed therapy from the time of the initial prescription until the last expected refill date of the final prescription. Factors associated with receipt of a bisphosphonate, adherence by MPR, and persistence by PRBT were determined by multiple regression analyses.

Results: Bisphosphonates were prescribed to 573 (41.5%) of 1382 VARA subjects. These subjects were mostly males (89.9%), with a mean age of 68.7 years, (± 10.3); 82.4% were Caucasian, 12.7% African American (AA), and 3.5% Hispanic. 258 subjects (45.3%) had a DXA; 66 (11.5%) had osteoporosis and 392 (70.4%) had been prescribed prednisone. Older subjects, females, non-Caucasians, prednisone use, DXA, a higher MDHAQ score and enrollment at Washington, DC site were predictive of receiving a bisphosphonate.

The mean MPR was 0.69 ± 0.28 and only 271 (47.3%) subjects had MPR ≥ 0.80. Subjects from Omaha, NE had the highest rate of adherence (55.3%) while those from Washington, DC had the lowest (30%). MPR ≥ 0.80 was 50%, 35% and 25% for Caucasians, AA and Hispanics, respectively ($p < 0.01$). Gender, age, DXA, and use of prednisone were

not predictive of MPR. In multivariate analysis AA ethnicity was associated with low MPR.

The PRBT for bisphosphonates was 39.2 ± 31.4 months, and longer PRBT was associated with older age and enrollment at Omaha, NE; there was no association with clinical diagnosis of osteoporosis or performance of a prior DXA.

Conclusions: Adherence with bisphosphonates was greater in VARA cohort than most previous reports. Factors associated with higher adherence were Caucasian ethnicity and treatment site.

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Impact of Incident Clinical Vertebral Fractures on Back Pain Outcomes in Postmenopausal Women Who Participated in the FREEDOM Trial.

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Background: Published evidence suggests a relationship between osteoporotic fractures and back pain outcomes. Denosumab (DMAb) is a fully human monoclonal antibody that inhibits RANKL, an essential mediator of osteoclast formation, function, and survival. In the FREEDOM trial, DMAb significantly reduced the risk of fractures (Cummings et al., *N Engl J Med*. 2009;361:756). Here we evaluate the impact of incident clinical vertebral fractures on back pain outcomes, regardless of treatment group, in women who participated in the FREEDOM trial.

Methods: The FREEDOM trial randomized 7808 women aged 60–90 years with a total hip and/or lumbar spine DXA T-score < -2.5 and not < -4.0 at either site. Women were randomized to receive subcutaneous DMAb 60 mg every 6 months or placebo for a total of 36 months, in addition to daily calcium and vitamin D. Back pain and limited activity days were assessed with the Back Pain and Limited Activity Days questionnaire (BPLAD) in person at each study visit (baseline and months 6, 12, 18, 24, 30, and 36) and by telephone between study visits (months 3, 9, 15, 21, 27, and 33). The BPLAD recorded subjects' back pain, limited activity, hospitalization, and bed rest experience (yes/no); the severity of back pain (very mild, mild, moderate, severe, very severe); the number of days of back pain; and the number of days of limited activity, hospitalization, and bed rest due to back pain during the past 3 months.

Results: About 24% of women had a prevalent vertebral fracture at study entry (Placebo, N=915; DMAb N=929). Compared to women without incident fractures, a significantly higher percentage of women with incident clinical vertebral fractures reported the occurrence of back pain, limited activity, hospitalization, and bed rest (Table 1). Additionally, women with incident clinical vertebral fractures reported a significant increase in the total days of back pain, limited activity, and bed rest than women without an incident fracture (Table 1). Women with incident clinical vertebral fractures also reported an approximately 2- to 3-fold increase in the rate of all recorded back pain outcomes *after* the fracture occurrence compared with the rate *before* the fracture occurrence (Table 2).

Conclusions: Incident clinical vertebral fractures were associated with a significant increase in the occurrence, severity, and duration of back pain outcomes in the women who participated in the FREEDOM trial. Efforts to reduce the occurrence of clinical vertebral fractures may lead to improved back pain outcomes for postmenopausal women with osteoporosis.

Table 1. Back Pain and Disability Due to Back Pain Through Month 36 by Incident Vertebral Fracture Status

	With Incident Clinical Vertebral Fracture (N = 108)	Without Incident Fracture[a] (N = 6821)	*P* value[b]
Reporting back pain[c]	100% (108)	80% (5424)	<0.0001
Reporting limited activity[c]	75% (81)	37% (2498)	<0.0001
Reporting hospitalization[c]	10% (11)	1% (78)	<0.0001
Reporting bed rest[c]	41% (44)	11% (742)	<0.0001
Total days of back pain	225 (80, 420)	118 (38, 315)	0.0002
Total days of moderate, severe, or very severe back pain	161 (51, 367)	102 (30, 283)	0.0171
Total days of severe or very severe back pain	78 (30, 158)	70 (21, 157)	0.5543
Total days of limited activity due to back pain	62 (23, 111)	29 (10, 90)	0.0015
Total days of hospitalization due to back pain	10 (6, 14)	10 (5, 20)	0.7737
Total days of bed rest due back pain	14 (7, 44)	8 (3, 20)	0.0141

N = Number of subjects.
Includes only post-baseline BPLAD responses.
Data shown are presented as % (n) for binary responses and median (Q1, Q3) for continuous variables
[a]Includes subjects with no incident fractures of any type.
[b]Based on Chi-square test or Fisher's exact test, when expected cell count <5, for binary responses and Wilcoxon rank-sum test for continuous variables.
[c]Includes subjects responding yes and reporting ≥ 1 affected day for the endpoint of interest.

Table 2. Back Pain and Disability Due to Back Pain by Pre and Post Incident Clinical Vertebral Fracture

	With Incident Clinical Vertebral Fracture (N = 108)				Without Incident Fracture (N = 6821)	
	Days of Observation Before Fracture = 72454		Days of Observation After Fracture = 41127		Days of Observation[a] = 6830858	
	Total	Rate	Total	Rate	Total	Rate
Total days of moderate, severe of very severe back pain	10765	14.9	13338	32.4	899811	13.2
Total days of severe or very severe back pain	3368	4.6	4346	10.6	194899	2.9
Total days of limited activity due to back pain	2312	3.2	4247	10.3	171943	2.5
Total days of hospitalization due to back pain	57	0.1	67	0.2	1284	0.0
Total days of bad rest due to back pain	338	0.5	654	1.6	16397	0.2

N = Number of subjects. Total = Sum of days with symptom Rate = 100*(Total)/(Days of Observation)
[a]Observation period includes the entire 36-month study duration for subjects without incident fracture.

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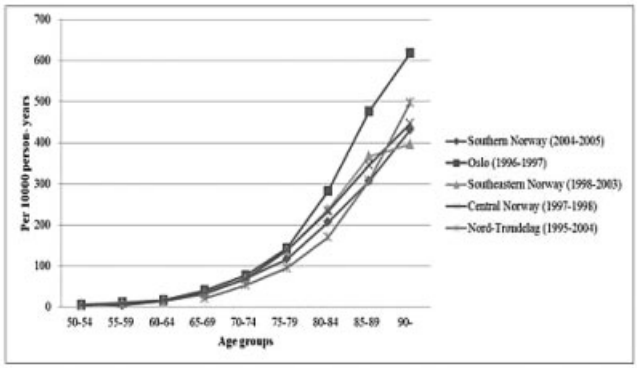
Incidence of Low Energy Hip Fracture in Southern Norway Significantly Lower Than Reported from the Capital of Norway (Oslo). Andreas Diamantopoulos[1], Gudrun Rohde[2], Irene Johnsrud[1], Inger Marie Skoie[1], Villy Johnsen[1], Marc C. Hochberg[3] and Glenn Haugeberg[1]. [1]Department of Rheumatology, Soerlandet Hospital SSHF, Kristiansand, Norway, [2]Faculty of Health and Sport, University of Agder, Kristiansand, Norway, [3]University of Maryland, Baltimore, MD

Background: Hip fractures contribute to increased morbidity and mortality in individuals above 50 years. As the average age of the population is increasing, the burden on the health care system is a growing challenge. The highest incidence of hip fracture worldwide has been reported from Oslo, the capital of Norway. During the last decades the awareness of hip fracture has increased and efforts have been undertaken to reduce fracture risk.

Aim: Our aim was to study the incidence of low energy hip fracture in individuals aged 50 years or older in southern Norway.

Methods: Patients with low energy hip fractures were recruited from the four hospitals in the two most southern counties of Norway in 2004 and 2005. Age adjusted and age specific incidence rates for men and women were calculated. We also searched for differences between seasons and between urban and rural areas. Our age adjusted incidence rates were compared with previous national and international reports.

Results: A total of 920 (261 men, 659 women) individuals aged ≥ 50 years with hip fracture were identified. The age adjusted incidence rate was 33.3 and 74.3 per 10.000 person years for men and women consecutively. Age specific incidence rates were significantly higher in women than in men but only for age groups between 70 and 90 years.Hip fracture were significantly higher in winter ($p<0.05$). No significant difference was seen between rural and urban areas.In the male cohort no major differences in age specific incidence rates was found compared with the Oslo study, however the incidence was lower in women above 80 years in our study.



*Incidence rates from Nord Trøndelag >65 years and only in women.

Fig. 1. Comparing the annual age specific incidence rates of hip fracture among individuals per 10,000 person-years in Southern Norway with previous reports from Oslo, Southeastern, central and northern Norway in women.

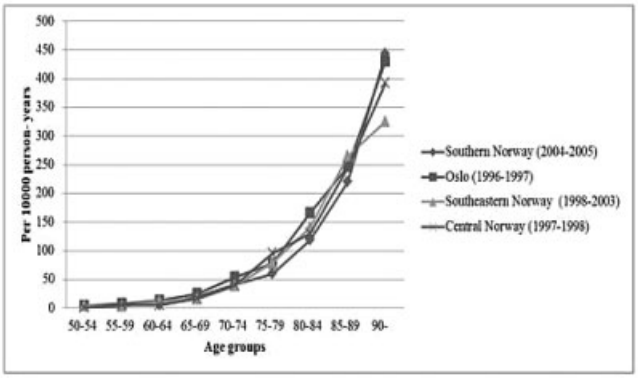


Fig. 2. Comparing the annual age specific incidence rates of hip fracture among individuals per 10,000 person-years in Southern Norway with previous reports from Oslo, Southeastern and Central Norway in men.

Our age adjusted incidence rates are the lowest reported from Norway and among the lowest reported from Scandinavia but is still among the highest in the world.

Conclusion: Age adjusted incidence rates of hip fracture in men and women in Southern Norway are the lowest reported from Norway and among the lowest in Scandinavia. The higher number of hip fractures seen in winter months may indicate that environmental factors increase the risk of hip fractures. Increased awareness and higher preventive and treatment methods are warranted both among men and women to reduce hip fracture risk.

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Increases in Macrophage Inhibitory Factor Correlate with Increases in Bone Mineral Density in Glucocorticoid-Treated Patients with RA. Jos Nicolaas Hoes[1], Marlies C. Van der Goes[2], Johannes W. G. Jacobs[2], Johannes W. J. Bijlsma[2] and Joel A. G. Van Roon[2]. [1]University Medical Center Utrecht, Department of Rheumatology & Clinical Immunology, Utrecht, The Netherlands, [2]University Medical Center Utrecht, Department of Rheumatology & Clinical Immunology

Background: Inflammation and bone metabolism are characterized by crosstalk and shared mechanisms. (1) Both glucocorticoids (GCs) and vitamin D can influence each of these mechanisms; by studying these, the process of osteoimmunity in GC-induced osteoporosis could be further unraveled. Of special interest are cytokines, such as macrophage migration inhibitory factor (MIF), IL-13 and IL-7 which could influence bone metabolism by antagonizing the effects of GCs. In addition, vitamin D might add to the anti-inflammatory effects of GCs by acting on the differentiation and/or activity of T cells that are involved in the pathogenesis of rheumatoid arthritis (RA).

Objective: To investigate the correlation of levels of inflammatory mediators and measures of bone turnover in patients with RA who were treated with GCs and to explore whether vitamin D enhances the anti-inflammatory effects of GCs.

Methods: RA patients (n=40) on oral GCs treatment received either active vitamin D (alfacalcidol) or the bisphosphonate alendronate in a double blind double placebo controlled manner for 18 months. Associations of lumbar spine bone mineral density (lBMD) and bone turnover markers procollagen type I C-propeptide (P1CP), osteocalcin, osteoprotegerin (OPG), deoxypyridinoline (dPyr), and cross-linked N-telopeptides (Ntx) with cytokines capable of antagonizing GCs (MIF, IL-13 and IL7), cytokines causing T cell differentiation (IL-6, IL-7, IL12, IL-10 and IL-23), and cytokines produced by effector T cells (Th1, IFNγ; Th2: IL4; Th17: IL17, IL22) were explored with multiple regression analyses.

Results: Treatment active vitamin D treatment did not influence cytokine levels that are associated with T cell differentiation or that are indicative of T cell activity. At baseline, higher levels of IL-6 and IL-23 ($B = -0.001$, $B = -0.00003$, $p = 0.088$, $p = 0.080$) showed a trend of association with low lBMD. Changes in T cell associated cytokines did not predict changes in lBMD or bone markers at 18 months. Alendronate significantly influenced lBMD, (2) but neither vitamin D nor alendronate treatment significantly influenced levels of cytokines antagonizing GCs. However, increases in MIF were significantly associated with increased lBMD ($B=0.055$, $p=0.039$) and decreases of deoxypyridinoline ($B=-0.012$ $p=0.037$). Other cytokines antagonizing GCs were not associated with (changes in) bone parameters, but an increase in GC dose tended to be associated with increase in MIF.

Conclusion: Our data do not provide evidence for an anti-inflammatory effect of vitamin D in RA patients on GCs. Although not influenced by vitamin D or alendronate treatment, increases in MIF, an antagonist of GCs, are associated with increases in lBMD during GC treatment.

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Low Bone Mineral Density in Depoprovera Users – An Under Recognised Health Issue. Mani Nallasivan[1] and Tim Gillott[2]. [1]Diana Princess of Wales Hospital, Northern Lincolnshire and Goole Hospitals NHS Trust, Hull, Yorkshire, United Kingdom, [2]Diana Princess of Wales Hospital, Northern Lincolnshire and Goole Hospitals NHS Trust, Grimsby, Northeast Lincolnshire, United Kingdom

Background: Women using Depo-Provera may lose bone mineral density, putting them at increased risk of osteoporosis. In November 2004, the FDA issued a black box warning which stated "Use of Depo-Provera contraceptive injection may cause you to lose calcium stored in bones". As this drug is being used by very young women; it could have serious implications on bone health in future. Oldroyd and colleagues have demonstrated significant decline in BMD in femoral neck but not in the spine, in whom median exposure of Depo-Provera was less than three years.[1] Studies show that discontinuation of Depo-Provera will allow near complete reversal of BMD loss.

Objectives: To examine the bone density in patients, who have been on Depo-Provera (medroxyprogesterone acetate) for contraception, referred for BMD estimation using dual X-ray absorptiometry (DEXA) and analyse whether the bone loss was significant enough to warrant change in the form of contraception.

Materials and Methods: We analysed 50 patients from 2008 and 2009 referrals for Bone mineral density assessment, with history of Depo-Provera use. They were asked to fill in standard questionnaire, about the risk factors, BMI, smoking, family history as well.

Their bone mineral density assessment was recorded using T and Z scores. In addition some had vertebral morphometry performed as well.

Results: Out of fifty patients, 24 were scanned in 2008 and remaining in 2009. Mean age was 28.6 years, mean duration of Depo-Provera use was 4.65 years (range 18 months to 10 years and even long term) and mean BMI-23.5. 42% were found to be osteopenic using T scores and one patient was in the osteporotic range. 56% had normal BMD. Median T score for low the BMD group was −1.14.

Few patients had other risk factors including celiac disease, long term steroid use because of Inflammatory bowel disease or liver transplantation. 3 patients had family history of osteoporosis. The T score was low in only 3 patients in femoral neck, while remaining (18/21) was low in lumbar spine.

Ten patients who have low T scores, were recommended to stop DP and two had already changed to oral pills.

Discussion: With oestrogen deficiency, the lumbar spine has a greater tendency to lose BMD because of its high trabecular bone content. Our findings are in keeping with this. This is in contrast to the finding by Oldroyd and colleagues, which reported significant reduction in femoral neck. We have recommended change in the form of contraception and to stop using DP for those who have T Scores in osteopenic/osteoporotic range. Though this is a small study, this needs further validation with wider cohort and also compare with normal age matched control.

Conclusion: Use of Depo-Provera cause reduced bone mineral density and hence needs risk assessment and appropriate advice given. Perhaps Public awareness also needs attention.

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Disclosure: M. Nallasivan: None; **T. Gillott:** None.

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National Registry of Paget Disease of Bone. Estibaliz Loza, Nuria Guañabens, Maria Jesus Garcia de Yebenes, Antonio Morales, Javier Del Pino, Antonio Torrijos, Jesus Garrido, Jesus Tornero, Jorge Malouf, Jordi Carbonell and Manuel Rodriguez. Spanish Society of Rheumatology

Objective: a) To identify and establish a national registry of patients with Paget disease of bone (PDB); b) To describe patient's demographic, clinical, environmental and familiar characteristics.

Methods: A registry-based cross-sectional study was performed. It started with a prevalence study (2006–2007) in which stratified samples throughout Spain of abdominal radiographs, of subjects aged ≥55 years, from stored consecutive digitalized films in selected hospitals were obtained. Radiographs including all lumbar vertebrae, pelvis, sacrum and femoral heads were examined for the diagnosis of PDB, according to standardized criteria. Afterwards, experts on Paget disease were invited to include patients in the registry from their clinics (apart from those identified in the prevalence study). Data were recorded following a standardized electronic form: demographics (age, sex); clinical (diagnosis date, age at the disease onset, symptoms and treatment); quality of life [EuroQol 5D, visual analog scale (VAS) of pain]; environmental factors (infections, place of birth, birth weight, number of brothers/sisters and position, measles virus infection, contacts with domestics animals, non pasteurized milk intake, home characteristics during childhood, ≥ 1 year-places of residence, work status); familiar (positive familiar history and place of birth of positive cases, number of children and their measles exposure/vaccination). A descriptive study was performed.

Results: The crude prevalence of PDB was 1% (95% Confidence Interval (CI): 0.7–1.3) in patients aged ≥55 years, and the estimated prevalence ranged from 1.1% (95%CI: 0.8–1.4) to 1.6% (95%CI: 1.1–2.1) when a reported pelvic involvement in 60–90% of PDB patients was considered. A total of 602 patients with PDB from 24 hospitals were included in the registry. We found more men (55%), with a mean age of 62 years ± 11 years. More than 80% had followed any treatment, 55% risedronate, 32% calcitonin, and almost 50% ≥2 drugs. The mean VAS pain score was 65 ± 21. The dimension which showed the worst score was anxiety/depression (64% reported moderate or severe limitations), followed by mobility (47%), and just 24% reported moderate or severe limitations in usual activities. Most of patients (99%) were born in Spain: Barcelona (11%), Ávila (10%), Toledo (7%) and Salamanca (5%). Measles infection was reported in 65%, and 80% had had contacts with animals: dogs (70%), cats (48%), and birds (38%). Non pasteurized milk intake was observed in 75% of patients and 53% were retired. A positive familiar history was registered in 14%, especially in Ávila and Salamanca, and PBD was identified in 1.5% of patient's children.

Conclusions: The National Registry of PDB includes 602 patients with PDB. Up to 14% have a positive familiar history, 80% contacts with domestic animals, and most of them had been on pharmacological treatment.

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Prevalence of Osteoporosis and Osteoporotic Fractures: A Population Based Survey Including Vertebral Fracture Assessment by Morphometry (VFA). Liana E. Euller-Ziegler[1], Christian H. Roux[1], Veronique Breuil[1], Virginie Dasilva[1], Christine Albert-Sabonnadiere[1], Christian Grisot[1], Philippe Flory[1], Yacine Allam[1], Hasna Chami[1], Gerard Ziegler[1] and Pascal Staccini[2]. [1]L'Archet Hospital, University of Nice, Nice, France, [2]Labstic Santé, University of Nice, Nice, France

Prevalence studies on osteoporosis (OP) in the general population are scarce; vertebral fractures (VF) are frequently underdiagnosed.

Objectives: To estimate the prevalence of low bone mineral density (BMD), osteoporotic fractures and risk factors in women aged 50 to 85 years.

Methods: After random selection in the national insurance system regional database (French Alpes Maritimes area), a sample of women aged 50 to 85 years, representative of the general population, was evaluated: medical and risk factors questionnaires, bone densitometry (DXA / hip, femoral neck, spine), screening for vertebral fractures (VF) by high density morphometry (VFA, Hologic QDR4500, Genant scoring by 2 independent MD). Statistical analysis was performed using χ^2, ANOVA or Kruskall-Wallis test when appropriated.

Study granted by Ministry of Health and promoted by CHU of Nice (Academic Hospital of Nice, France).

Results: 519 women were evaluated, mean age 63.4± 8.8 years, BMI 25,4± 4,9 kg/m^2, hip fracture in 1st degree relatives (15%), long term steroid treatment (9.4%), alcohol ≥ 3 units (3.7%), current smoking (2.7%), RA (0.8%), early menopause (14.6%), personal history of low energy clinical fracture after 50 years (15%), including non vertebral fractures 13.5%.

DXA demonstrated OP in 13.7% of the women (mean age 68 ± 9.4 years), osteopenia in 59% (63.8± 8.4 years).

The prevalence of VF by *VFA* was 29.7% (presence of ≥1 VF Genant stage ≥1), (18.1% with ≥1 VF Genant stage ≥2). The VF were scored Genant stage 1 (55.1%), stage 2 (39.3 %), stage 3 (5%), with a median number of 2 VF by woman (1 – 8). VF scored Genant stage ≥1 were present in women classified by DXA as having osteoporosis (24%), but also osteopenia (61%), even normal BMD (15%) (and VF scored Genant stage ≥ 2 in respectively 27.7%, 58.5%, 13.8% of the women); conversely, 52% of women classified by DXA as having osteoporosis, 30.7% osteopenia and

16.2% normal BMD had VF Genant stage ≥1 (and 36.6%, 18% & 9.1% had VF Genant stage ≥ 2).

The overall prevalence of osteoporotic fractures was *37.4%* (VF and/or non vertebral fracture), mean age 67.3 ± 8.9 years, classified by DXA as osteoporosis (20.6%), osteopenia (61.3%), normal (18%).

Correlations: T-score decrease (global status and at each site) was linked with age ($p=0.001$) and BMI ($p=0.001$); the presence of fracture was linked with age ($p<0.001$), T-score ($p<0.001$) (globally and for VF), BMI (globally). Fractures were more frequent in subjects with a personal history of prior fracture ($p<0.001$, globally and for VF), without significant link with other risk factors.

Discussion: Methological issues of prevalence studies on OP are well known. The partnership with the national insurance system allowed us to analyse a representative sample of the general population. VFA, delivering a lower dose of radiation than XRays and well accepted by our subjects, allowed easier VF detection (according to Genant stages ≥1 & ≥2) and therefore VF prevalence analysis.

Conclusion: This study brings new data emphasizing the public health dimension of osteoporosis and the high frequency of undiagnosed vertebral fractures in the general population, even in women with osteopenia or normal BMD.

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Proactively Contacting Men with Prostate Cancer Treated with Anti-Androgen Medications Improves the Evaluation and Treatment of Osteoporosis. Brian P. Oppermann[1], Thomas M. Harrington[2] and William Ayoub[3]. [1]Geisinger Medical Center, Danville, PA, [2]Geisinger Medical Center, Danville PA, [3]Geisinger Medical Group, Scenary Park PA

Purpose: Men treated with androgen deprivation therapy for prostate cancer are at higher risk for osteoporosis and osteoporotic fractures. This relationship is dose and length of therapy dependent. Despite this known association, men treated with anti-androgen therapy do not routinely receive osteoporosis screening with dual energy X-ray absorptiometry (DXA).

Methods: Using an electronic health record (EHR), in a rural tertiary health care system, we identified 64 men followed by our primary care physicians with the diagnosis of prostate cancer who have been treated with anti-androgen therapy (leuprolide acetate) for this pilot study. This EHR search identified any man who met the above criteria from 2007–2009. Of these 64 men, 61 had not undergone osteoporosis screening with DXA scanning. The other 3 men had undergone DXA and one was on bisphosphonate therapy. These three men were excluded. The remaining evaluation naïve 61 men were then contacted via letter. This letter explained reasons that they were being contacted, mainly they may be at high risk for osteoporosis given treatment with anti-androgen therapy. The letter instructed them to call to schedule a DXA scan. If no response was obtained several weeks after the mailing, patients were contacted by telephone to schedule the DXA scan. From initial contact via letter to scheduling the men for evaluation took 4 months.

Results: For the pilot study, 30 of the 61 men contacted agreed to osteoporosis screening with DXA scanning. Of these 30 DXA's, 18 (60%) were low/moderate risk and 12 (40%) were deemed high risk for fracture (osteoporotic) using the 2008 National Osteoporosis Foundation criteria. None of these 12 high risk DXA scan patients had been on bisphosphonate therapy prior to this project, with all 12 being placed on therapy after DXA results.

Conclusion: Using our EHR, we proactively captured a subset of men at high risk for osteoporosis and fracture – those with prostate cancer. As the pilot project demonstrates, a significant proportion (40%) of these patients indeed are at high risk for fracture based on DXA and none of these patients were on approved osteoporosis medications. Unfortunately we only captured 50% of the identified patients, with most refusing to be evaluated given their age or the feeling this did not apply to them. Regardless, this pilot project demonstrates that this specific group of patients is at risk for osteoporosis and there needs to be better awareness to capture these patients and obtain appropriate osteoporosis evaluation and treatment. We plan to develop best practice alerts to identify the patients, risk stratify them with DXA and hopefully prevent future morbidity, mortality and health care expenditures with appropriate medical therapy.

Disclosure: B. P. Oppermann: None; **T. M. Harrington:** None; **W. Ayoub:** None.

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Quality Assurance Study of the Use of Preventative Therapies in Glucocorticord Induced Osteoporosis (GIOP) in Early Inflammatory Arthritis (EIA): Results from the CATCH Cohort. Emily McKeown[10], Vivian P. Bykerk[5], Faye Deleon[4], J. Carter Thorne[6], Carol A. Hitchon[8], Gilles Boire[2], Boulos Haraoui[3], Diane S. Ferland[1], Ed C. Keystone[9] and Janet E. Pope[7]. [1]LaSalle, QC, Canada, [2]CHUS-Sherbrooke University, Sherbrooke, QC, Canada, [3]Institut de Rhumatologie, Montreal, QC, Canada, [4]McMaster University, Hamilton, ON, Canada, [5]Mt Sinai Hospital, Toronto, ON, Canada, [6]Southlake Regional Health Care, Newmarket, ON, Canada, [7]St Joseph Health Care London, London, ON, Canada, [8]University of Manitoba, Winnipeg, MB, Canada, [9]University of Toronto, Toronto, ON, Canada, [10]University of Western Ontario, London, ON, Canada

Background: Exposures to glucocorticoids are common in patients with inflammatory arthritis (IA) despite treatment with DMARDs. The ACR has published guidelines for the prevention and treatment of glucocorticoid induced osteoporosis (GIOP), but adherence to guidelines is variable. This study characterizes steroid use and compliance with GIOP guidelines within a large early IA cohort.

Methods: Using the Canadian Arthritis Cohort Database (CATCH), patients with IA on glucocorticoids (oral or intramuscular) were identified. Steroid exposure was defined as using oral glucocorticoids for two consecutive clinic visits (at least 90 days apart). The primary outcome was the proportion of patients receiving calcium, vitamin D and a bisphosphonate among patients treated with chronic glucocorticoids. Those with postmenopausal osteoporosis were excluded. Secondary analysis was done to determine which factors were associated with use of preventative therapies.

Results: 655 were in the CATCH database, where 311 (47%) were glucocorticoid users of whom 50% were on oral prednisone, 41% received intramuscular or intra-articular (ia) steroids and 9% both. The mean oral daily dose in prednisone users was 6 mg (SD 7.5). Chronic users (CU) compared to non-users (NU) showed that CU were older (56 vs. 50 years, $p=0.002$); similar proportion of females (68% vs. 73%) and rheumatoid factor positivity (55%, RF mean 97 IU/mL in CU vs. 57%, RF mean 171 IU/mL in NU); DAS (CRP) was 4.72, (SD1.48) in CU vs. 4.85 (SD 1.59) in NU, $p=0.50$). Less than half (45%) on chronic steroids were treated with calcium, 41% with Vitamin D, 38% with both and 18% were taking a bisphosphonate. Rates of prophylaxis were only slightly higher for users of chronic oral steroids; 54% were taking Calcium, 48% were taking Vitamin D, 45% were taking both and 23% were on a bisphosphonate. There were no significant differences in use of Calcium, Vitamin D or bisphosphonate among females compared to males (OR 0.49, 95% CI 0.20–1.18, $p = 0.11$), or among post-menopausal females compared to pre-menopausal females (OR 2.34, 95% CI 0.92–5.95, $p = 0.07$). Women with a history of hormone treatment and smokers had no significant increase in being treated (OR 1.50, 95% CI 0.49–4.62, $p = 0.48$ and OR 0.73, 95% CI 0.32–1.66, $p = 0.46$). Treatment rates were similar among patients on steroids for one year compared to those treated for at least 90 days so longer duration of steroids did not increase prophylaxis.

Conclusions: Glucocorticoid therapy is frequently used in early IA. The use of calcium, vitamin D or a bisphosphonate was low among chronic glucocorticoid users and illustrates a care gap.

Disclosure: E. McKeown: None; **V. P. Bykerk:** Amgen Inc., 2, Pfizer Inc, 2; **F. Deleon:** None; **J. C. Thorne:** None; **C. A. Hitchon:** None; **G. Boire:** Amgen Inc., 2, Pfizer Inc, 2; **B. Haraoui:** Amgen Inc., 2, Pfizer Inc, 2; **D. S. Ferland:** Amgen Inc., 2, Pfizer Inc, 2; **E. C. Keystone:** Amgen Inc., 5; **J. E. Pope:** Amgen Inc., 2, Pfizer Inc, 2.

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Relationships between Changes in Bone Mineral Density or Bone Turnover Markers and Vertebral Fractures Incidence in Patients Treated with Bazedoxifene. Olivier Bruyere[2], Johann Detilleux[3], Arkadi Chines[1] and Jean Y. Reginster[2]. [1]Pfizer, [2]University of Liege, Liege, Belgium, [3]University of Liege

Objective: To analyze the relationships between bone mineral density (BMD) or bone turnover markers (BTM) changes and vertebral fractures incidence in women treated with bazedoxifene.

Material and Methods: Post-hoc analysis from a 3-year randomized, placebo-controlled study evaluating the effect of bazedoxifene (20 or 40 mg) on fracture risk reduction. BMD was assessed at baseline and every 6 months during 3 years. Osteocalcin (OC) and C-telopeptide of type I collagen (CTX-I) were assessed at baseline, month 3, 12 and 36. Vertebral fractures were assessed with a semiquantitative visual assessment.

Results: Data was available for 5244 women of which 3476 were treated with bazedoxifene. Using logistic regression analysis and the classical Li approach, the proportion of fracture incidence explained by BMD change after 3 year of bazedoxifene treatment was 29% for the total hip and 44% for the femoral neck. The proportion of treatment explained by lumbar BMD change could not be quantified accurately because of the significant interaction between treatment and change in BMD. With the same model, the 3-month BTM changes explained between 14 and 18% of the fracture risk reduction observed with bazedoxifene. With another new statistical method using structural equation models, the proportion of fracture incidence explained by 3-year BMD change was between 29 and 43%, for total hip and femoral neck, respectively. Using the same methodology, BMD changes after one year of therapy explained between 8 and 15% of the fracture incidence observed during 3 years of treatment.

Conclusion: In women treated with bazedoxifene, changes in femoral neck or hip BMD explained up to 44% of the fracture risk reduction observed during the 3 years of follow-up. Short-term BTM changes poorly explained the fracture risk reduction observed during the 3-year treatment with bazedoxifene.

Disclosure: O. Bruyere: Wyeth Pharmaceuticals, 2; **J. Detilleux:** Wyeth Pharmaceuticals, 2; **A. Chines:** Pfizer Inc, 3; **J. Y. Reginster:** Wyeth Pharmaceuticals, 2.

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The Direct Assessment of Nonvertebral Fractures in Community Experience (DANCE) Study: 2-Year Nonvertebral Fragility Fracture Results. Stuart L. Silverman[2], Paul Miller[4], Anthony I. Sebba[1], Michael Weitz[3], Xiaohai Wan[5], Kathleen Taylor[5], Valerie Ruff[5] and Kelly D. Krohn[6]. [1]Arthritis Associates, Palm Harbor, FL, [2]Cedars-Sinai Medical Center, University of California Los Angeles, Beverly Hills, CA, [3]Center Arthritis and Rheumatology, South Miami, FL, [4]Colorado Center for Bone Research, Lakewood, CO, [5]Eli Lilly and Company and/or One of Its Subsidiaries, Indianapolis, IN, [6]Lilly USA, LLC, Indianapolis, IN

Statement of Purpose: To evaluate the occurrence of nonvertebral fragility fractures (NVFX) in subjects treated with teriparatide (TPTD) for osteoporosis (OP) for up to 24 months in a community based setting.

Methods: The DANCE study is a multi-center, prospective, observational trial designed to examine the long-term effectiveness, safety, and tolerability of TPTD. Patients judged by study physicians to be suitable for TPTD therapy received TPTD 20 μg/day for up to 24 months. The percentage of patients experiencing a new NVFX during 4 TPTD treatment duration periods (table) was calculated. The proportion of patients reporting new NVFX during longer TPTD treatment duration categories was compared to the proportion during TPTD treatment duration of 0 to 6 months using a binomial proportion test. The 0–6 months interval was chosen as the reference since Kaplan-Meier analysis of NVFX in the Fracture Prevention Trial showed that the TPTD and placebo groups appeared to begin to separate after approximately 8 months of study drug.

Results: The mean TPTD exposure was 17 (95% CI: [16.8, 17.4]) months, and the median TPTD exposure was 23 months. Overall, 115/3649 (3.15%) experienced a NVFX. The incidence of patients experiencing new NVFX during the four TPTD treatment durations was 1.43%, 0.97%, 0.72%, and 0.78%, respectively (table). The incidence of new NVFX during each TPTD treatment duration longer than 6 months was significantly lower than the incidence during TPTD treatment duration 0 to 6 months ($p<0.0001$). Compared to TPTD treatment of 0 to 6 months, NVFX incidence during treatment durations 6 to 12, 12 to 18, and 18 to 24 months was 32%, 50%, and 45% lower, respectively.

Conclusions: The results of this observational study indicate that the incidence of new NVFX decreased for patients receiving TPTD treatment for greater than 6 months.

Duration (months)	Number of patients with a new NVFX	Number of patients at risk	Incidence (%)
>0 to ≤6	52	3649	1.43 (1.04, 1.81)
>6 to ≤ 12	28	2901	0.97 (0.61, 1.32)*
>12 to ≤ 18	18	2506	0.72 (0.39, 1.05)*
>18 to ≤ 24	17	2172	0.78 (0.41, 1.15)*

*$p<0.0001$ when compared to the 0–6 months study duration period.

Disclosure: S. L. Silverman: Eli Lilly and Company, 2, 5, 8; **P. Miller:** Eli Lilly and Company, 2, 5, 8; **A. I. Sebba:** Eli Lilly and Company, 8; **M. Weitz:** Eli Lilly and Company, 5, 8, 9; **X. Wan:** Eli Lilly and Company, 3; **K. Taylor:** Eli Lilly and Company, 1, 3; **V. Ruff:** Eli Lilly and Company, 1, 3; **K. D. Krohn:** Eli Lilly and Company, 3.

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The Effects of Biologics on Bone Metabolism of Patients with Rheumatoid Arthritis. Tadashi Okano, Masahiro Tada, Shigeyuki Wakitani, Hiroaki Nakamura and Tatsuya Koike. Osaka City Univ Med School, Osaka, Japan

Background: Rheumatoid arthritis (RA) is associated with systemic bone loss, subchondral bone erosion and cartilage degradation. Biologics therapy has proven efficacious in improving both disease activity and focal bone erosions in patients with RA. We investigated the effects of biologics on bone mineral density (BMD) and biochemical markers in Japanese RA patients.

Objectives: To examine whether treatment with biologics prevents loss of BMD in patients with RA, and to study the changes in markers of bone metabolism during biologics treatment.

Methods: 123 (103 women, 20 men, 55.8±12.9 years old) patients with active RA, who were treated with biologics (Infliximab:93, Etanercept:27, Tocilizumab:3) during 1 year, were included in this study. The disease duration was 13.0±12.8 years. The BMD of the lumbar spine and total hip (DXA:QDR-4500) was measured at baseline and after at least more than one year. As bone metabolic marker, serum bone specific alkaline phosphatase;BAP and urine type I collagen cross-linked N-telopeptide;NTX was measured at baseline and after at least more than one year. 33 patients received bisphosphonates while 84 patients were under oral glucocorticoid, we also assessed these effect.

Results: After biologics treatment, the BMD of the lumbar spine did not reduced from 0.865±0.159 to 0.871±0.149 g/cm2 ($p=0.22$). Similarly, hip BMD did not reduced from 0.726±0.139 to 0.717±0.141 g/cm2 ($p=0.12$). The BMD of the hip in patients who have received glucocorticoid without bisphosphonates (n=55) showed significantly decreases from 0.755±0.136 to 0.738±0.140 g/cm2 ($p=0.03$) compared with patients not receiving glucocorticoid or receiving glucocorticoid with bisphosphonates. Moreover, the BMD of lumbar spine has increased from 0.818±0.151 to 0.838±0.150 g/cm2 ($p=0.04$) in patients who were administered with bisphosphonates (n=32). In whole patients, BAP was not significantly changed from 27.1±12.4 to 26.2±11.8 U/L ($p=0.41$), NTX was significantly decreased from 66.0±67.9 to 51.9±37.7 nmol/mmol CRE ($p<0.01$).

Conclusion: The BMD of the lumbar spine and hip did not reduced after treatment with biologics. However our data provide additional evidence, to maintain BMD, dose reduction of glucocorticoid or the introduction of bisphosphonate should be required, even if biologics are administered.

Table 1. Analysis of the effect of biologics on BMD

	Lumbar BMD			Femoral BMD		
	Baseline	Final	*P*	Baseline	Final	*P*
All patients (n =123)	0.865 ± 0.159	0.871 ± 0.149	0.22	0.726 ± 0.139	0.717 ± 0.141	0.12
G − (n = 39)	0.890 ± 0.165	0.897 ± 0.153	0.41	0.752 ± 0.155	0.751 ± 0.155	0.99
G + (n = 84)	0.854 ± 0.156	0.859 ± 0.146	0.36	0.714 ± 0.130	0.701 ± 0.132	0.06
BP − (n = 90)	0.882 ± 0.159	0.884 ± 0.147	0.85	0.755 ± 0.136	0.738 ± 0.140	0.03
BP + (n = 33)	0.818 ± 0.151	0.838 ± 0.150	0.04	0.640 ± 0.108	0.657 ± 0.127	0.23
G − B − (n = 32)	0.906 ± 0.171	0.913 ± 0.157	0.55	0.775 ± 0.158	0.768 ± 0.162	0.44
G + B − (n = 58)	0.869 ± 0.152	0.868 ± 0.141	0.8	0.745 ± 0.124	0.723 ± 0.126	0.02
G − B + (n = 7)	0.816 ± 0.115	0.827 ± 0.121	0.27	0.652 ± 0.0989	0.679 ± 0.098	0.12
G + B + (n = 26)	0.818 ± 0.161	0.841 ± 0.159	0.07	0.636 ± 0.113	0.651 ± 0.135	0.56

G: glucocorticoid, BP: bisphosphonate

Table 2. Analysis of the effect of biologics on bone markers

	BAP			NTX		
	Baseline	Final	P	Baseline	Final	P
All patients (n = 123)	27.1 ± 12.4	26.2 ± 11.8	0.41	66.0 ± 67.9	51.9 ± 37.7	0.006
G − (n = 39)	30.8 ± 16.3	27.9 ± 11.9	0.21	87.0 ± 106	58.1 ± 53.5	0.03
G + (n = 84)	25.3 ± 9.69	25.3 ± 11.8	0.99	55.7 ± 33.2	48.9 ± 26.8	0.09
BP − (n = 90)	27.4 ± 12.4	26.8 ± 12.6	0.68	74.1 ± 75.6	55.8 ± 41.3	0.001
BP + (n = 33)	26.2 ± 12.6	24.0 ± 8.91	0.24	41.0 ± 21.0	39.9 ± 19.3	0.86
G − B − (n = 32)	30.7 ± 15.8	28.5 ± 12.4	0.44	97.6 ± 119	67.3 ± 57.6	0.07
G + B − (n = 58)	25.8 ± 10.1	26.0 ± 12.8	0.9	62.1 ± 34.4	49.9 ± 28.9	0.01
G − B + (n=7)	31.2 ± 19.2	25.5 ± 10.5	0.18	50.6 ± 20.9	26.3 ± 9.64	0.03
G + B + (n=26)	24.1 ± 8.59	23.4 ± 8.46	0.73	36.8 ± 20.3	45.9 ± 19.6	0.12

G: glucocorticoid, BP: bisphosphonate

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982

The Effects of Denosumab (DMAb) on Bone Mineral Density (BMD), Fracture and Safety Outcomes by Level of Renal Function. Sophie A. Jamal[8], Peter R. Ebeling[7], Osten Ljunggren[9], Catherine Stehman-Breen[1], Steven R. Cummings[5], Michael R. McClung[4], Stefan Goemaere[3], Edward Franek[2], Yu-Ching Yang[1], Ogo I. Egbuna[1] and Paul Miller[6]. [1]Amgen Inc., Thousand Oaks, CA, [2]Central Clinical Hospital, Warsaw, Poland, [3]Ghent University Hospital, Belgium, [4]Oregon Osteoporosis Center, Portland, OR, [5]San Francisco Coordinating Center, CPMC Research Institute and University of California, San Francisco, San Francisco, CA, [6]University of Colorado Health Sciences Center, CO, [7]University of Melbourne, Melbourne, Australia, [8]University of Toronto, Toronto, ON, Canada, [9]Uppsala University Hospital, Sweden

Treatments for osteoporosis in patients with renal impairment, both common conditions in the older population are limited. DMAb is not excreted by the kidney and is a potential treatment option.

The efficacy and safety of DMAb given as a 60 mg s.c injection every 6 months for 3 years among patients in Phase 3 FREEDOM Study was evaluated. Creatinine clearance (CrCl) was estimated using the Cockcroft-Gault equation. A subgroup interaction term was used to assess differences in treatment effect by CrCl. We examined incident fracture rates, changes in BMD, serum calcium, serum creatinine and the incidence of adverse events after 36 months of follow-up in subjects receiving DMAb and placebo, stratified by level of renal function using linear regression models adjusted for multiple baseline characteristics including prevalent vertebral fractures and years since menopause.

Most (97%) women were Caucasian, the mean age was 72.3 ±5.2 years, the mean weight was 63.8 ± 10.4 kg, serum creatinine was 70.8 ± 15.3mmol/L and serum calcium was 2.44 ±0.11mmol/L. Subject disposition by level of renal function was balanced between DMAb and placebo treated subjects. 73 women had a CrCl between 15 to 29ml/min (CKD stage 4); 2817 between 30 to 59 mL//min (CKD stage 3); 4069 between 60 to 89 mL/min (CKD stage 2) and 842 had a CrCl of ≥ 90 mL/min (CKD stage 1/normal). Vertebral and non-vertebral fracture risk reduction and differences in the percent change in BMD at all sites were in favour of DMAb. The test for treatment by subgroup interaction indicated that fracture risk reduction was not statistically different by level of renal function. The difference in the mean % changes in BMD in subjects treated with DMAb compared with placebo did not differ by level of renal function. Changes in serum creatinine, serum calcium and the incidence of adverse, serious adverse and fatal events were similar between the treatment groups and did not differ by level of renal function.

DMAb reduces fracture risk and is not associated with an overall increase in adverse events among patients with impaired kidney function.

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The Serum Level of Undercarboxylated Osteocalcin (ucOC) in Patients with Rheumatoid Arthritis – A High Dose of Predonisolone Decrease the Serum Level of ucOC. Yoshitada Sakai[2], Akira Hashiramoto[4], Teppei Hashimoto[4], Yoshiko Kawasaki[4], Chihiro Tanaka[4], Shunichi Shiozawa[3] and Masahiro Kurosaka[1]. [1]Department of Orthopaedic Surgery, Kobe University Graduate School of Medicine, [2]The Center of Rheumatic Diseases, Kobe University Hospital, Kobe, Hyogo, Japan, [3]The Center of Rheumatic Diseases, Kobe University Hospital, Kobe, Japan, [4]The Center of Rheumatic Diseases, Kobe University Hospital

Purpose: Rheumatiod arthritis (RA) causes systemic osteoporosis as well as periarticular osteoporosis, and becomes one of the risk factor of osteoporotic fracture. On the other hand, several previous studies have indicated that the higher serum level of undercarboxylated osteocalcin (ucOC) could be a risk factor for osteoporotic fracture. However, the relationship between the serum level of ucOC in patients with RA and the medication of DMARDs or predonisolone (PSL) were still unknown. In this study, we have evaluated the serum level of ucOC in patients with RA, and investigated the related factors, such as medications, biochemical markers and bone mineral density.

Methods: 88 patients with RA were enrolled in this study (83 females, 5 males, average age 63 yrs). We compared the ucOC levels with other biochemical marker (Serum cross-linked N-teropeptide of type1 collagen (NTx), Bone alkaline phosphatase (BAP), Calcium (Ca), phosphorus (P) and C reactive protein (CRP)). The examination of bone mineral density was performed with lumbar spine and femoral neck using dual energy X-ray absorptiometry (DEXA). Oral medications including PSL, methotrexate (MTX) and bisphosphonate (BP) were also examined. The statistical analysis was performed using Mann-Whitney U test.

Results: The average of serum level of ucOC in all patients was 5.25±3.8(ng/ml), and then patients were categorized into high ucOC group (≥4.5ng/ml) and low ucOC group (<4.5ng/ml). The results of biochemical markers and BMD in these two groups were showed in Table1. These data showed that the patients with low serum ucOC level have low biochemical marker of bone metabolism and high dose of PSL (≥5mg/day). When compared the medications with the serum ucOC level in Table2, results indicated that medication of high dose PSL and medication of BP significantly decreased the serum ucOC level.

Conclusion: Our results clearly showed that the serum levels of ucOC were increased in higher state of bone turnover as indicated by biochemical markers, and *vice versa*, decreased when the bone turnover was ameliorated by the high dose of PSL and BP. We should carefully evaluate the risk of osteoporotic fracture of the patient with RA who has a low level of serum ucOC during medication of high PSL and/or BP.

Table 1

	Low ucOC group	High ucOC group	p-value
Age (yrs)	64.2 ± 9.8	61.3 ± 12.2	0.8116
Serum NTx	15.3 ± 5.6	19.3 ± 5.9	0.021
Serum BAP(ug/l)	15.6 ± 7.1	25.7 ± 9.5	0.0001
Serum Ca (mg/dl)	9.2 ± 0.4	9.4 ± 0.3	0.039
Serum P (mg/dl)	3.4 ± 0.5	3.6 ± 0.5	0.0622
Serum CRP (mg/dl)	1.2 ± 1.6	0.7 ± 0.9	0.6267
BMD L-Spine (g/cm3)	0.91 ± 0.2	0.81 ± 0.2	0.0175
BMD Femoral neck(g/cm3)	0.61 ± 0.1	0.57 ± 0.1	0.1369
PSL amount (mg/day)	3.7 ± 3.4	1.9 ± 2.5	0.067
MTX amount (mg/week)	4.3 ± 3.2	3.6 ± 3.4	0.4196

Table 2

Stage	Early (Stage1,2)	Progressive (Stage3,4)	p-value
ucOC(ng/ml)	6.1 ± 2.3	6.3 ± 4.5	0.8022
PSL on/off	No PSL	PSL	p-value
ucOC(ng/ml)	6.2 ± 3.4	4.5 ± 4.0	0.057
PSL dose	Low dose (<5mg/day)	High dose (≥5mg/day)	p-value
ucOC(ng/ml)	6.2 ± 4.0	3.3 ± 2.7	0.0004
MTX on/off	No MTX	MTX	p-value
ucOC(ng/ml)	5.1 ± 3.2	5.3 ± 4.2	0.966
BP on/off	No BP	BP	p-value
ucOC(ng/ml)	6.2 ± 3.8	2.4 ± 1.9	0.0001

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ACR Poster Session B
Quality Measures and Innovation in Practice Management and Care Delivery
Tuesday, November 9, 2010, 9:00 AM–6:00 PM

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"Early Arthritis: Early Act". A Community-Based Knowledge Transfer Program To Improve Ability of General Practitionner to Rapidly Detect and Refer to the Rheumatologist Patients with Early Arthritis. Bruno Fautrel[3], Patrick Froger[1], Cecile Gaujoux-Viala[2] and Eric Leutenegger. [1]Lyon, France, [2]Paris, France, [3]Pitie Salpetriere Hospital, Paris, France

Background: Several guidelines have recommended that early arthritis / early rheumatoid arthritis (EA / ERA) should be detected and rapidly referred

to a rheumatologist, ideally within the 6 weeks after symptom onset according to the French Health Authority guidelines published in 2007. However, guideline implementation and dissemination are always challenging, especially when guidelines concern both specialists and family doctors (GP).

Methods: The collaboration between rheumatologists and a continuous medical education (CME) organization enabled the development of a community-based knowledge-transfer program about the diagnosis of early arthritis, based on a few key messages: early RA diagnosis is a key prognostic factor; detection of EA patients can be based on 3 clinical signs suggestive of early RA[1]; GPs have an pivotal role to detect and refer EA patients to the specialist; remission is an achievable goal in RA.

The program was implemented over the phone among the GP community using the Academic Detailing methodology, which 3 different phases: 1) a first confraternal exchange between the training medical doctor in charge of the program and the practising GP who previously agreed to participate in the program, during which a few key messages were delivered; 2) a 2-month practise phase during which the participating GP had to identify patients for whom the national EA guidelines could applied; 3) a second confraternal exchange with the same medical trainer during which the key messages were recalled and the applicability of EA guidelines into daily practise discussed.

Results: 1,054 GP participated in phase 1 of the "Early Arthritis: Early Act" program between August 2008 and March 2009. 645 of them also participated in the practise phase and collected medical information about 1,116 EA patients. Finally, 852 GP participated to the 3rd phase, i.e., the second phone confraternal exchange. The main impact of the program on GP knowledge is presented in the table below:

Table. Impact of the "Early Arthritis: Early Act" program on GP knowledge about EA and RA

	"Early Arthritis: Act Early" Program	
% respondents	**Before**	**After**
Awareness of the 2007 national EA guidelines	48%	100%
Knowledge of the impact of RA on life expectancy	25%	100%
Awareness of the notion of window of opportunity in EA	13%	100%
Knowledge that remission is an achievable goal in RA	47%	100%
Ability to perform a squeeze test to detect patients with EA	19%	81%

Conclusion: The "Early Arthritis: Early Act" program enabled the exposition of a substantial number of GP to EA guidelines within a rather limited time frame. It was well accepted by the participating GPs: 52% acknowledged they had a definite need for such knowledge update and 85% found acceptable the time investment required by the program.

1 Emery P. et al. Ann Rheum Dis 2002;61:290.

Disclosure: B. Fautrel: None; **P. Froger:** None; **C. Gaujoux-Viala:** None; **E. Leutenegger:** None.

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A Checklist of 10 Measures, 6 from a Patient Questionnaire & 4 Physician Global Scores, Requiring <15 Seconds, To Provide Quantitative Patient History & Physical Examination Data, Analogous to Laboratory Tests, for Usual Clinical Care. Theodore Pincus[4], Yusuf Yazici[2], Martin J. Bergman[1], Tuulikki Sokka[3] and Christopher J. Swearingen[5]. [1]Arthritis and Rheumatology, Ridley Park, PA, [2]Hospital for Joint Diseases, Hastings on Hudson, NY, [3]Jyvaskyla Central Hospital, Jyvaskyla, Finland, [4]New York University Hospital for Joint Disease, Hastings-on-Hudson, NY, [5]University of Arkansas for Medical Sciences, Little Rock, AR

Purpose: To analyze a proposed checklist of 10 quantitative measures, 6 from a patient questionnaire and 4 physician global scores, compiled in less than 20 seconds, to provide quantitative patient history and physical examination (PE) data, which rheumatologists indicate are more important than laboratory tests in clinical decisions in usual care visits.

Methods: The 6 quantitative patient measures are from a self-report multidimensional health assessment questionnaire (MDHAQ) for: physical function (FN) (0–10); 21 circle 0–10 visual analog scales for pain (PN), patient global estimate (PTGL), and fatigue (FT); review of 60-symptom checklist (SX); and RAPID3, a 0–30 total of FN+PN+PTGL whcih requires 5 seconds. The 6 scores are compared on a flow sheet to scores at previous visits prior to the traditional patient encounter. The rheumatologist records 4 global estimates for: overall status (0–10), and 3 0–3 global scales for levels of inflammatory activity, joint or other organ damage, and non-inflammatory/fibromyalgia symptoms, recoded 0–10 to compare to other measures. An updated flow sheet report includes the 10 proposed checklist scores, as well as laboratory tests and medications. Mean 1st visit values for the 10 proposed checklist measures were analyzed in all 874 new patients seen at a weekly academic setting from 1996–2007 in 8 groups: rheumatoid arthritis (RA), osteoarthritis (OA), fibromyalgia (FM), systemic lupus erythematosus (SLE), gout, spondyloarthropathy (Spondy), inflammatory polyarthritis (InflPol), connective tissue disease (CTD), and "other," as well as demographic data, ESR and CRP, compared using Spearman rank order correlations.

Results: The 874 patients appear typical for rheumatic diseases (Table). ESR was >20 mm/Hr in RA, OA, SLE, Spondy, and CTD, while CRP was >10 mg/dL in RA and Spondy. Mean MDHAQ FN was highest in RA and also >3.0 in FM and Spondy. Mean PAIN was highest in FM, and >5 in Spondy, RA and InflPol; PTGL >5 in FM, RA and Spondy; FT >5 in FM, RA, SLE, InflPol, and other. Symptom scores were >20 only in FM. Mean MD global estimates were ≥5.0 in all 8 categories - mean 5.7. Estimates were >5 for inflammation in Spondy, RA, gout, InflPol, and CTD; for damage only in RA and OA; and for noninflam/fibro symptoms in FM, SLE, and other.

Quantitative demographic, laboratory tests, patient MDHAQ scores, and MD global estimates in 874 new rheumatology patients, by diagnosis, Spondy = Spondylarthropathies. InflPol = Inflammatory Polyarthritis.

	RA	OA	FM	SLE	Gout	Spondy	InflPol	CTD	Other	Total
Number of patients	174	32	196	34	12	30	152	50	194	874
Demographic and laboratory measures										
Age (years)	54.5	65.1	47.0	38.8	59.3	43.9	51.9	47.6	51.0	50.7
Disease duration (years)	8.4	6.3	5.9	9.1	9.1	11.3	4.8	6.9	5.4	6.6
Formal education (years)	13.0	15.0	13.7	13.6	13.8	14.9	14.2	13.9	13.9	13.8
% Female	71.3%	65.6%	88.7%	85.3%	16.7%	46.7%	72.9%	82.0%	71.7%	74.9%
ESR (mm/h)	29.7	22.2	16.8	28.9	11.1	26.5	16.6	22.1	18.6	21.6
CRP (mg/dL) [normal < 10]	17.5	3.9	6.1	6.7	3.6	11.5	6.1	7.9	8.6	9.9
Patient MDHAQ self-report questionnaire measures for proposed checklist										
1. Function (FN) [0–10]	3.2	2.3	3.0	1.9	1.8	3.0	2.2	2.1	2.4	2.7
2. Pain (PN) [0–10]	5.4	4.4	6.5	3.7	5.8	5.9	5.0	3.0	5.2	5.3
3. Global (PTGL) [0–10]	5.4	4.4	6.1	4.3	3.8	5.1	4.5	3.9	4.8	5.1
4. RAPID3 [0–30]	13.7	10.0	15.4	8.5	10.2	13.4	11.4	8.3	11.0	12.4
5. Fatigue (FT) [0–10]	5.7	4.2	7.3	5.4	4.1	4.5	5.3	4.8	5.0	5.7
6. Symptoms (SX) [0–60]	14.1	9.4	20.5	16.1	7.7	11.4	13.8	13.2	12.8	14.9
MD global measures fir proposed checklist										
7. MD Global [0–10]	6.3	6.3	6.3	5.0	5.0	6.3	5.3	5.3	5.6	5.7
8. Inflammation [0–10]	7.0	3.3	2.3	3.6	6.0	7.7	5.7	5.3	3.7	4.7
9. Damage [0–10]	5.0	6.0	1.7	2.3	3.0	4.3	3.0	3.3	3.0	3.3
10. Non-inflam/fibro [0–10]	4.0	3.7	9.0	6.3	2.3	4.0	4.0	3.3	5.0	5.3

Shaded: Lab: ESR>20. CRP>10. Pt measures: FN>3, PN≥5, PTGL≥5, FT≥5, RAPID3>12, SX>20. All MD measures ≥5.

Conclusion: A proposed checklist of 10 measures, 6 from a MDHAQ and 4 global MD scores, provides quantitative data from a history and PE at each encounter in the infrastructure of rheumatology care, in <20 seconds. These data provide quantitative measures to assess patient status over long periods, "treat to target" values, and may lead to improved patient outcomes.

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A Model for the Development and Implementation of a National Plan for the Optimal Management of Early Spondyloarthritis: The Esperanza Program. Milena Gobbo[1], Ruxandra Schiotis[9], Santiago Muñoz-Fernández[8], Loreto Carmona[1], Eduardo Collantes[5], Eugenio de Miguel[6], M. Jesús García-Yébenes[1], Juan Mulero[4], Raquel Almodovar[2], Cristina Fernández-Carballido[7] and José Francisco García Llorente[3]. [1]Research Unit, Sociedad Espanola de Reumatología. Madrid, Spain, [2]Rheumatology Department, Fundación Hospital de Alcorcón, Madrid, Spain, [3]Rheumatology Department, Hospital de Basurto, [4]Rheumatology Department, Hospital Puerta de Hierro Majadahonda. Madrid, Spain, [5]Rheumatology Department, Hospital Reina Sofía. Córdoba, Spain, [6]Rheumatology Department, Hospital Universitario La Paz. Madrid, Spain, [7]Rheumatology Unit, Hospital General de Elda. Elda, Spain, [8]Rheumatology Unit, Hospital Infanta Sofía. San Sebastián de los Reyes, Madrid. Spain, [9]University of Medicine and Pharmacy Iuliu Hatieganu, Cluj-Napoca, Romania

The design of a program in early spondyloarthritis (SpA) should have the following objectives: 1) to enable the establishment of early SpA units, 2) to

facilitate early diagnosis; 3) to reduce the variability in SpA; and 4) to improve the knowledge and practical skills on SpA of general practitioners (GPs) and specialists.

Methods: The Esperanza Program includes: 1) a call for the creation of 25 early SpA units with specific requirements; 2) the establishment of a managed care plan with 8 measurable indicators; 3) a web-based platform which may function as an electronic medical record (EMR), and which permits evaluation, and facilitates networking and feed-back; and 4) educational initiatives.

Results: Evaluation of the 25 implemented units covers from April 2008 until October 15th 2009. As of last evaluation, 1812 GPs were participating and 792 patients had been referred by their GPs. Indicators' values: 1) Over 90% of the patients have been attended within 30 days since their visit to PC; 2) the reliability of the referrals was 92%; 3) 53% of first visits had a duration of 30 to 60 minutes; 4) 28% of the patients had a diagnosis of SpA already in the first visit; 5) a report was issued in 25% of the medical visits; 6) 2% of the electronic reports issued were consulted by the GPs; 7) missing data in the EMR was 24%; and 8) an appropriate frequency of revisions was met in 84% of the patients. The patients attended were evenly distributed among sexes, and most of them were active workers. Their disease was active but spinal mobility and structural changes were preserved.

Conclusion: It is possible to implement a large scale program that is measurable and that helps to improve the management of early disease.

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A Pilot Study To Quantify Suffering among Patients with Rheumatoid Arthritis—A New Measure for Patient Reported Outcome (PRO). Tom Sensky[2], Rieke Alten[4], Philippe Bertin[1], Boulos Haraoui[3], Ed C. Keystone[5] and Peter C. Taylor[2]. [1]CHU Dupuytren, Limoges, France, [2]Imperial College, London, London, United Kingdom, [3]Institut de Rhumatologie de Montreal, Montreal, QC, Canada, [4]Schlosspark-Klinik UnivMed, Berlin, Germany, [5]University of Toronto, Toronto, ON, Canada

Background: The potential gravity of adverse outcomes in rheumatoid arthritis (RA) is such that there is a need for outcome measures which not only reflect this but are also meaningful to patients, the public and clinicians. Alleviation of suffering is a key goal in medicine. The **P**ictorial **R**epresentation of **I**llness and **S**elf **M**easure (PRISM) is a novel, validated, brief method of measuring suffering consistent with Cassell's seminal conceptualisation of suffering. Pilot data are reported on using PRISM to assessing suffering in RA.

Methods: The survey was conducted on a convenience sample of 245 patients with clinically diagnosed RA from specialist clinics in Berlin, Limoges, London and Montreal during their routine clinic appointments with rheumatologists.

Basic sociodemographic and clinical data were collected, and all patients were asked to complete the PRISM task. Information was collected about patients' perceptions of the causes of their suffering.

Results: PRISM took 1–4 minutes to complete, and was easy to use. Most patients understood the simple instructions. Patients were consistent in their appraisal of their suffering which was related to the perceived controllability of the symptoms of RA, and/or the intrusiveness of the illness on valued aspects of the individual's life. Suffering quantified by PRISM showed significant correlations with global disease VAS (r_s=0.36, p<0.0001) and pain VAS (r_s=0.31, p<0.0001). In logistic regression analysis, with suffering dichotomised into 'high' and 'low', global disease VAS was a significant predictor (Exp(beta)=0.97, 95% CI 0.94 to 0.99, p<0.05), but pain VAS did not contribute significantly.

Conclusions: This pilot survey has confirmed that PRISM is easy to use in different languages without need for specific training, is very acceptable to patients and clinicians, and can be readily incorporated into routine clinical practice. It measures something distinct from pain and global disease burden, but associated with these. These data support further investigation of PRISM as a novel patient-reported outcome which quantifies factors salient to each individual with respect to the impact of the illness and its treatment and is likely to incorporate a wider range of such influences than existing measures. As such, it may have utility in setting agreed therapeutic targets.

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Antibodies towards Infliximab Are Associated with Poor Infliximab Maintenance and Low Infliximab Concentrations. Emilie Ducourau[3], David Ternant[2], Denis Mulleman[3], Saloua Mammou[3], Delphine Chu Miow Lin[3], Hervé Watier[1], Gilles Paintaud[2] and Philippe Goupille[3]. [1]Universite François Rabelais de Tours, Laboratoire d'Immunologie, [2]Universite François Rabelais de Tours, Laboratoire de Pharmaco-Toxicologie, [3]Universite François Rabelais de Tours, Service de Rhumatologie

Background: Despite its benefits, infliximab is responsible for the development of antibodies against infliximab (ATI), which is associated with an increased risk of infusion reactions and a reduced response to treatment [1,2]. Herein, we studied the relationship between ATI and infliximab maintenance.

Methods: All patients initiating infliximab from December 2005 to January 2009 were followed until the end of their treatment or until January 2009. Infliximab [3] and ATI serum concentrations were measured by enzyme linked immunosorbent assays before each infusion. The patients were separated into two groups: "ATIpos" if ATI were detected at least once during the follow-up period or "ATIneg" in the other patients. The characteristics (sex, age, disease, mean disease duration, concomitant treatment with methotrexate or prednisone, infliximab dose at initiation, ESR and CRP) of the 2 groups were compared using a student's t-test or a chi-square test. Infliximab treatment maintenance in the 2 groups was studied using a survival analysis and compared with a log rang test. A P value of less than 0.05 was considered statistically significant.

Results: A total of 111 patients were studied: 17 rheumatoid arthritis (RA), 91 ankylosing spondylitis (AS), and 3 others systemic diseases. ATI were detected in 22 patients (7 RA, 14 AS and 1 other disease). Median detection of ATI was 3.5 months (0.4–26.0). Infliximab dose at initiation was lower in ATIpos patients than in ATIneg patients (4.1 mg/kg vs. 4.9 mg/kg; p = 0.005). Proportion of patient with concomitant MTX treatment was lower in ATI+ group than ATI- group but the difference did not reach significant difference (14% vs. 36% p = 0.08). Maintenance of infliximab was poorer in ATIpos group than in ATIneg group, with medians of 10 and 16 months, respectively (p = 0.05). Infliximab trough concentrations during initiation were statistically lower in ATI pos than in ATI neg (see Table).

RA	ATIpos (n=7)	ATIneg (n = 10)	p
C infliximab (mg/L)			
w2	7.7 [2.8–16.9]	27.2 [7.1–41.9]	0.002
w6	0.3 [0–6.2]	15.4 [2.7–35]	0.001
w14	0 [0–0.03]	5.4 [0–21.9]	0.01
SA	**ATIpos (n = 14)**	**ATIneg (n = 77)**	**p**
C infliximab (mg/L)			
w2	25 [4–40.7]	35.8 [14.3–57.2]	0.003
w6	11.9 [0–24.2]	29.5 [3.4–69]	<0.001
w12	1.6 [0–13.5]	15.8 [0.7–47.3]	<0.001

Except where indicated otherwise, values are the median [range]

Conclusion: In our experience, 20% of patients treated with infliximab develop ATI, often within the first 3 months of treatment. High concentrations of infliximab during initiation seem to reduce the incidence of ATI, and absence of ATI is associated with prolonged durations of infliximab treatment. This clearly argues for an early monitoring of infliximab serum concentrations.

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Bridging the Gap in Osteoporosis Care, Part I: Results of the SPOOF (Secondary Prevention of Osteoporotic Fracture) Project. Mary A. Langan, John J. Carey, Robert J. Coughlan, Catherine Armstrong, Assumpta O'Brien, Sarah McNamara, Ella Murphy and Mohamed Ballal. Galway University Hospitals, Galway, Ireland

Background: Many agents have been shown to reduce the risk of future fracture in patients presenting with osteoporotic fractures. Despite widespread availability for over a decade, studies show that most patients are not evaluated or treated for osteoporosis following such fractures. Thus effective measures to improve the evaluation and treatment of osteoporosis following fragility fracture are needed.

Purpose: To examine the effectiveness of an outpatient fracture intervention program to improve the rates of osteoporosis evaluation and treatment among fracture patients aged 50 years and older seen in orthopedics fracture clinics.

Methods: Collection and analysis of data was approved by the local Institutional Review Board. We evaluated the rate of osteoporosis evaluation, diagnosis and treatment among a cohort of patients aged 50 years and older presenting to our University Hospital Orthopaedic clinic with a fragility fracture between 2005 and 2007. Groups were either assessed as part of a fracture liaison program or exposed to usual orthopedic care with referral back to their primary care doctor following treatment. A mail and telephone survey was undertaken of 190 patients in both cohorts 2 years following their fracture clinic visit. We compared the rate of osteoporosis diagnosis and treatment between the two cohorts within 2 years of their fracture.

Results: There was a greater response rate among those in active intervention group (74% Vs 63%). The most common fracture site was wrist and forearm in both groups. Age and gender of respondents was similar between the intervention and control groups: 66 years & 92% vs 71 years & 86% respectively. Treatment rates were similar between both groups before fracture (<20%). Significantly more subjects seen by a fracture liaison coordinator received: 1) a bone density measurement (89% Vs 47%, P <0.01); 2) osteoporosis treatment with calcium and vitamin D (81% vs 33%, P<0.01); and 3) pharmacologic therapy for osteoporosis (48% Vs 27%, P<0.01).

Conclusions: A case-finding fracture liaison service improves the rate of osteoporosis diagnosis and therapy following fragility fracture in persons of 50 years and older.

Disclosure: M. A. Langan: Merck Pharmaceuticals, 9; **J. J. Carey:** Eli Lilly and Company, 2, 8, Merck Pharmaceuticals, 2, 8, Novartis Pharmaceuticals Corporation, 2, sanofi-aventis, 8; **R. J. Coughlan:** Eli Lilly and Company, 2, Merck Pharmaceuticals, 2, 8, Novartis Pharmaceuticals Corporation, 2; **C. Armstrong:** None; **A. O'Brien:** None; **S. McNamara:** None; **E. Murphy:** None; **M. Ballal:** None.

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Clues To Differentiate Non-Inflammatory from Inflammatory Symptoms in Patients with Systemic Lupus Erythematosus (SLE), Using a Multi-Dimensional Health Assessment Questionnaire (MDHAQ). Theodore Pincus[2], Isabel Castrejón[5], Jill P. Buyon[6], Chung-E. Tseng[4], Peter M. Izmirly[3], Yusuf Yazici[1] and Anca D. Askanase[3]. [1]Hospital for Joint Diseases, Hastings on Hudson, NY, [2]New York University Hospital for Joint Disease, Hastings-on-Hudson, NY, [3]NYU Hospital for Joint Diseases, New York, NY, [4]NYU Hospital for Joint Diseases, Flushing, NY, [5]NYU Hospital for Joint Diseases, [6]NYU School of Medicine, New York, NY

Purpose: To analyze whether quantitative scores on a multidimensional health assessment questionnaire (MDHAQ) provide clues to the likelihood of inflammatory versus non-inflammatory symptoms and concomitant fibromyalgia, an important challenge in clinical care, according to a global scale for non-inflammatory symptoms completed by a rheumatologist in 50 patients with SLE seen in usual care.

Methods: A cross-sectional study was performed in 50 consecutive SLE patients of one rheumatologist seen in usual care. On arrival at the clinic, patients completed a multidimensional health assessment questionnaire (MDHAQ) which includes scales for physical function (FN), 0–10 visual analog scales for pain (PN), global estimate (PTGL) and fatigue (FT), and a review of systems symptom checklist (SX). SLE patients also completed a self-report Systemic Lupus Assessment Questionnaire (SLAQ). The rheumatologist, unaware of MDHAQ and SLAQ scores, recorded a physician global estimate (MDGL) and an estimate of non-inflammatory symptoms, each scored on a 0–3 scale in 0.1 increments, as well as four SLE indices: SLEDAI-2K (SLE Disease Activity Index), BILAG (British Isles Lupus Assessment Group index), SLAM (SLE Activity Measure) with and without laboratory tests, and ECLAM (European Consensus Lupus Activity Measurement). SLE patients with scores of <0.5 on the non-inflammatory symptom scale were regarded as "low" and those with scores ≥0.5 "high" non-inflammatory symptoms; the two groups were compared using the Mann-Whitney statistic.

Results: The study included 45 women and 5 men, mean age 38.7 years, mean disease duration 7.3 years. Of the 50 patients, 16 had high and 34 low scores for non-inflammatory symptoms. Those with high scores for non-inflammatory symptoms had significantly higher scores for FN, PN, FT, PTGL, SX, SLAQ, and SLAM without laboratory tests, as well as significantly lower CRP. No significant differences were seen patients estimated as "high" and "low" scoring patients for SLEDAI, BILAG, SLAM, ECLAM, C3, C4, antiDsDNA, or ESR. Fewer than 50% of "low" patients had FN, PN, PTGL, or FT ≥2, while 100% of "high" patients had FT >2, and 94% PTGL >2. All patients with high non-inflammatory symptoms (16/16) reported more than 5 SX, compared to 15/34 (44%) "low" patients, and 12/16 (75%) "high" patients reported >10 SX, compared to 6/34 (18%) "low" patients.

Table. Differences in the mean values of the MDHAQ scores, SLAQ, SLE indices and laboratory tests between SLE patients with versus without non-inflammatory symptoms. (Mann-Whitney)

Measure/Index	SLE low *non-inflammatory symptoms* (n=34)		SLE high *non-inflammatory symptoms* (n=16)		*P*
	Mean (± SD)	Median (Range)	Mean (± SD)	Median (Range)	
Physical function	0.74 (±1.25)	0 (0–5.3)	2.7 (±2.4)	2.7 (0–6.3)	<0.01
Pain VAS	2.5 (±2.6)	1.7 (0–9)	4.8 (±2.7)	5.0 (0–9)	<0.02
Patient global	2.2 (±2.5)	1.2 (0–9.5)	5.4 (±2.2)	5.5 (1.5–9)	<0.01
Fatigue VAS	2.8 (±2.5)	2.0 (0–9)	6.3 (±2.1)	6.5 (3–10)	<0.01
# Symptoms	6.9 (±6.8)	5.0 (0–31)	16.9 (±8.2)	17.0 (6–38)	<0.001
RAPID3	5.4 (±5.9)	3.0 (0–22.8)	13.0 (±6.7)	12.4 (4.5–23)	<0.01
SLAQ-total	7.0 (±5.3)	6.5 (0–18)	16.9 (±4.5)	16.0 (10–27)	<0.001
SLEDAI	5.1 (±3.9)	4 (0–16)	4.8 (±3.6)	4.0 (0–12)	0.83
BILAG	4.2 (±4.2)	2.5 (0–15)	5.4 (±4.5)	4.0 (0–15)	0.27
ECLAM	1.9 (±1.3)	1.5 (0–4)	2.2 (±1.6)	2.0 (0–6)	0.65
SLAM	3.7 (±3.2)	3.0 (0–12)	4.2 (±2.3)	4.0 (1–10)	0.32
SLAM-no lab	1.6 (±1.6)	1.0 (0–5)	3.2 (±1.8)	3.0 (0–7)	<0.01
C3	102.1 (±32.5)	103 (43–174)	123.3 (±35.1)	110 (76–197)	0.67
C4	20.1 (±11.3)	17.5 (6–63)	21.1 (±7.7)	22 (9–32)	0.37
ESR	27.1 (±33.1)	12.5 (1–112)	11.2 (±10)	10 (1–38)	0.27
CRP	5.4 (±8.1)	3.1 (0.1–31)	0.7 (±1.3)	0.2 (0.1–5)	0.015

SD= standard deviation

Conclusion: High scores for dysfunction, pain, fatigue, global estimates, and number of symptoms are common in SLE patients with high versus low levels of non-inflammatory symptoms. SLE indices do not distinguish between patients with high versus low levels of non-inflammatory symptoms. A simple global scale to estimate non-inflammatory symptoms may be informative in therapeutic decisions, particularly if consistent with patient questionnaire patterns.

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DMARD Use in Rheumatoid Arthritis: An Analysis of HEDIS Data from 2005–2008. Gabriela Schmajuk[4], Amal Trivedi[3], Daniel Hal Solomon[2], Edward H. Yelin[7], Laura Trupin[6], Eliza F. Chakravarty[1] and Jinoos Yazdany[5]. [1]Mountain View, CA, [2]Brigham and Womens Hospital, Boston, MA, [3]Brown University, [4]Stanford University, Stanford, CA, [5]UCSF, San Francisco, CA, [6]UCSF, [7]University of California, San Francisco, CA

Background: Since 1997, all managed-care plans administered by Medicare have reported on quality of care measures from the Health Plan Employer Data and Information Set (HEDIS). In 2005, HEDIS introduced a quality indicator to assess the use of disease modifying anti-rheumatic drugs (DMARDs) among patients with rheumatoid arthritis (RA). We determined sociodemographic, community, and health-plan predictors of performance on the RA measure among Medicare managed care (MMC) enrollees and health plans.

Methods: We analyzed individual-level HEDIS data for 97,587 beneficiaries at least 65 years old with a diagnosis of RA and enrolled in MMC plans between 2005 – 2008. Low personal income was identified by the state buy-in variable in the Medicare denominator file. Zip-code-based

socioeconomic status (SES) was calculated from Census 2000 variables using the Agency for Healthcare Research and Quality SES index score. We constructed logistic regression models with generalized estimating equations to determine individual, community, and health plan predictors of individual adherence to the HEDIS RA measure. We also analyzed rates of DMARD use at the health plan level: Logistic regression was used to adjust health plan rates for case-mix. Health plans in the lowest tertile of case-mix-adjusted performance (DMARD use < 58%) were considered "low-performing," and logistic regression was used to identify predictors of low-performing plans.

Results: The mean age of eligible patients was 74.4 years; 76% were female, and 81% were Caucasian. A DMARD was dispensed to 66% of patients in 2005, rising to 71% of patients in 2008 (p for trend < 0.01). The largest difference in rate of DMARD use was based on age: patients > 85 had a 29% (95% CI (28%, 31%)) lower rate of DMARD use compared to patients 65–69 years old, even after adjusting for all other factors. Males, non-Caucasians, patients with low personal income, and those with lower zip-code-based SES were also less likely to receive a DMARD, as were patients in the Middle and South Atlantic regions (see Table).

Characteristic	N	Unadjusted Difference	Adjusted difference*
Gender			
Female	73559	referent	referent
Male	24028	−2.6	**−3.4 (−4.7, −2.1)**
Age			
65–69	27810	referent	referent
70–74	25689	−5.3	**−4.9 (−5.8, −4.0)**
75–79	21863	−10.6	**−10.4 (−11.5, −9.3)**
80–84	14119	−16.8	**−16.4 (−17.8, −14.9)**
≥85	8106	−29.9	**−29.9 (−31.4, −28.4)**
Race			
White	80125	referent	referent
Black	10579	−7.3	**−4.0 (−5.6, −2.4)**
Other	6883	−6.0	**−4.6 (−6.5, −2.8)**
Personal income			
Not low	84518	referent	referent
Low	13069	−9.5	**−6.8 (−6.8, −5.1)**
Zip-code-based SES			
Quintile 1 (low)	20600	−7.0	**−4.7 (−6.6, −2.8)**
Quintile 2	20091	−6.5	**−4.4 (−5.9, −2.8)**
Quintile 3	19106	−3.9	**−2.1 (−3.7, −0.6)**
Quintile 4	18816	−2.1	**−1.7 (−3.0, −0.4)**
Quintile 5 (high)	18974	referent	referent
Geographic division			
New England	4320	−0.5	0.3 (−3.9, 4.5)
Middle Atlantic	18458	−8.5	**−9.6 (−14.0, −5.1)**
East North Central Midwest	7941	1.8	0.0 (−4.1, 4.2)
West North Central Midwest	5840	3.7	1.5 (−3.8, 6.9)
South Atlantic	16437	−15.6	**−15.2 (−26.1, −4.3)**
East South Central	3829	−5.7	−8.2 (−16.6, 0.1)
West South Central	6858	−5.5	**−6.6 (−10.8, −2.4)**
Mountain	9846	0.2	−0.3 (−4.8, 4.3)
Pacific	24058	referent	referent
Health professional shortage area			
No shortage	14626	referent	referent
Shortage	82896	−5.4	**−3.5 (−5.2, −1.7)**

* adjusted for all listed variables in addition to calendar year.

DMARD use varied widely by health plan (ranging from 13% to 91%). Health plans that opened their health maintenance organization operation later than 1999 were more likely to be low-performing plans, even after adjusting for case-mix and other health plan characteristics.

Conclusions: One third of Medicare managed care beneficiaries with a diagnosis of RA are not receiving a DMARD. Differences in rates of DMARD use exist based on demographics, socioeconomic status, geographic location, and health plan. Quality improvement initiatives should focus on increasing the performance rates among groups and health plans with lower DMARD use and regions with lagging adherence.

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Does Asymptomatic Hyperuricemia Treatment Improve Health? A Decision-Analytic Evaluation. Roopa Akkineni[2], Alexandra Lee[2], Katherine Miller[2], Anna Tosteson[2] and Daniel A. Albert[1]. [1]Dartmouth-Hitchcock Med Ctr, Lebanon, NH, [2]The Dartmouth Institute

Purpose: Recent studies have suggested that elevated uric acid levels are associated with an increase in coronary and cerebrovascular disease. Treatment for asymptomatic hyperuricemia with uric acid lowering drugs, such as Allopurinol, may reduce cardiovascular events. However, some patients have experienced adverse drug reactions while treated with Allopurinol. A decision analysis was designed to identify the optimal treatment strategy for patients with asymptomatic hyperuricemia.

Methods: A Markov state-transition model was constructed to assess the occurrence of cardiovascular events and life expectancy in patients undergoing urate-lowering treatment with Allopurinol, compared with watchful waiting. The model was built for a hypothetical 50-year old asymptomatic hyperuricemic male patient. Probabilities were derived from current literature. Developments of gout or uric acid stones as well as cardiovascular events were modeled. Sensitivity analyses were conducted for drug effectiveness and probability of adverse drug reaction.

Results: In the base–case analysis, the two treatment options had a similar occurrence of vascular events and life expectancy. However, watchful waiting was associated with a slightly greater gain in quality adjusted life years (QALYs) than treatment with Allopurinol (10.61 QALYs versus 10.58 QALYs). A sensitivity analysis was conducted on drug effectiveness, drug protection from cardiovascular events, the probability of adverse drug event, and death from adverse drug reaction. When the probability of having an adverse drug reaction increased, watchful waiting was always favored. The results were similar for probability of death from adverse drug reaction. By contrast, when the effectiveness of drug therapy varied, treatment with Allopurinol was the optimal choice for effectiveness rates over 69.2%. The maximum gain in QALYs assuming 100% effectiveness of Allopurinol therapy was approximately 0.35 QALYs.

Conclusions: Watchful waiting was preferred for patients with asymptomatic hyperuricemia at the base rate of 21% effectiveness of Allopurinol; however, the number of QALYs gained with watchful waiting was small compared to treatment with Allopurinol. At 100% effectiveness, treatment with Allopurinol was the preferred strategy with a gain of 0.35 QALYs, which in magnitude is similar to statin therapy with 0.25 QALYs gained.

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Early Experience with the American College of Rheumatology (ACR) Rheumatology Clinical Registry (RCR). Salahuddin Kazi[2], Elizabeth A. Tindall[3], Kristen McNiff[1] and Itara Barnes[1]. [1]American College of Rheumatology, Atlanta, GA, [2]Arthritis Consultation Center, Dallas, TX, [3]Oregon Health and Science University, West Linn, OR

Background: The RCR was launched by the ACR to provide members with an infrastructure for quality reporting related to rheumatoid arthritis, gout, osteoarthritis, osteoporosis, and drug safety. This abstract describes the initial uptake of the RCR, and initial findings related to functional status, DMARD use, TB screening, prognosis, and disease activity assessment for RA patients in rheumatology practice.

Methods: Rheumatology providers and/or designated practice staff conduct retrospective medical records abstraction, for a sample of patients seen by the rheumatologist. Reporters submitted data via a secure, web-based registry system. The analytic specifications for RA measures include adults (≥18 years of age) with a diagnosis with RA receiving treatment by the reporting rheumatology provider. Additional components of each measure are listed in Table 1.

Results: 240 rheumatology providers in 125 practices submitted data on 7,806 patients with RA (mean submission/rheumatologist = 31) from July 1, 2009 to January 31, 2010. Reporting providers practice in sites ranging from solo practitioner offices to large academic medical centers.

Table 1. Concordance with RA Measures Assessed through the RCR (6/09-1/10)

	Total applicable cases	% Concordant
Functional status assessment performed at least once within 12 months, and documented using a standardized descriptive or numeric scale, standardized questionnaire, or notation of assessment of the impact of RA on patient activities of daily living	6131	79%
Patient prescribed, dispensed, or administered at least one ambulatory prescription for a DMARD within 12 months	7260	93%
Documentation of TB screening performed and results interpreted within 6 months prior to receiving first course DMARD	1714	92%
Assessment and classification of disease prognosis at least once within 12 months	Good 4051 Poor 2042 Not assessed 1667	Good 52% Poor 26% Not assessed 22%
Disease activity assessed at least once within 12 months, using a standardized descriptive or numeric scale or composite index, and classified as low, moderate or high	High 929 Moderate 2205 Low 3157	High 15% Moderate 35% Low 50%

Conclusions: Rheumatologists across the country used the RCR in 2009 to report quality data. Establishing RCR as a mechanism for CMS PQRI reporting especially incentivized use and enhanced participation (consistent with the ACR goal that RCR provide maximal benefit from data submission).

Ongoing data collection and analysis will help reveal the clinical significance of the data and monitor improvement over time.

Next steps planned for the RCR include continually enhance the quality of data collected, analytic reports, and EHR-enabled reporting.

RCR provides an opportunity for rheumatology providers to facilitate practice improvement, contribute to collaborative improvement projects, and contribute to national data, led by their professional society.

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Evaluating Adherence to Quality Indicators in Prevention of Glucocorticoid Induced Osteoporosis in Patients at the Veterans Affairs in Lexington. Magdalena Winiarska[1], Joseph Conigliaro[2], Heather Bush[2], Lucia Hardi[1], Elnaz N Tabrizi[1] and Leslie J. Crofford[3]. [1]Univ of Kentucky, Lexington, KY, [2]Univ of Kentucky, [3]Univ of KY, Lexington, KY

Background: Osteoporosis is a systemic skeletal disease characterized by low bone mass, microarchitectural deterioration of bone tissue, and a consequent increase in bone fragility and susceptibility to fractures. Glucocorticoids are widely used agents for many inflammatory diseases. Glucocorticoid-induced osteoporosis (GIOP) is the most common type of secondary osteoporosis ultimately leading to fractures in up to 50% of patients. Despite steadily increasing evidence of effective preventive therapies among patients initiating long term glucocorticoid therapy, prevention of GIOP is often neglected, with a low level of awareness among primary and specialist physicians. The specific aim of this study was to evaluate adherence to known recommendations on prevention of GIOP. The long term goal of this study is to improve quality of care among patients treated with glucocorticoids.

Methods: A retrospective computer-generated chart review of electronic health records from the Veterans Affairs Medical Center in Lexington, Kentucky identified 453 patients treated with prednisone 7.5 mg daily or its equivalent for at least six months between October 2004 and October 2009. Using this population we extracted following data: age, race, body mass index, bone density testing, dose of glucocorticoid therapy, bone loss prevention medication use including calcium, vitamin D, bisphosphonate, calcitonin, hormone replacement therapy, testosterone replacement therapy, steroid prescribing practitioner's speciality and diagnosis for which glucocorticoids were prescribed.

Results: The average age of the patients was 68 years (SD = 11.7). Of the 453 patients, 430 were males and 420 were Caucasian. Bone mineral density testing was performed on 128 (28.3%). Of 430 male patients, 69 (15.2%) had testosterone levels checked. Of 22 patients with low testosterone, 8 were on testosterone replacement therapy. Calcium and vitamin D was given to 210 (48.8%) patients and bisphosphonates to 147 (32.5%) of patients; 184 (40.6%) were not on any prescribed pharmacologic therapy to prevent GIOP. Primary care providers wrote 233 (51.5%) of the total prescriptions for glucocorticoids followed by 67 (15%) rheumatologists and 52 (11.5%) pulmonologists. The most common diagnosis for which the patients were prescribed prednisone were chronic obstructive pulmonary disease (n=69) and rheumatoid arthritis (n=49).

Conclusions: GIOP is a common but still relatively neglected problem. Although it is not possible to define an absolute standard of care, the overall adherence to guidelines for prevention of GIOP in our study was low. This study identifies areas amenable to targeted educational efforts that will improve care of patients requiring glucocorticoid treatment.

Disclosure: M. Winiarska: None; **J. Conigliaro:** None; **H. Bush:** None; **L. Hardi:** None; **E. N Tabrizi:** None; **L. J. Crofford:** None.

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Formal Joint Counts Are Performed at More Than 50% of Visits of Patients with Rheumatoid Arthritis in Usual Care outside of Clinical Research, by 64% of European Rheumatologists in 2010 Compared to 44% in 2003. Theodore Pincus[2], Ed C. Keystone[4], Marc de Longueville[3] and Sophie Costello[1]. [1]Costello Medical Consulting, [2]New York University Hospital for Joint Disease, Hastings-on-Hudson, NY, [3]UCB Pharma, [4]University of Toronto, Toronto, ON, Canada

Purpose: To analyze responses of European rheumatologists concerning the likelihood of performing of a formal swollen and tender joint count in 2010, and compare results to a similar estimate in 2003.

Methods: About 300 rheumatologists attended a meeting in March 2010 sponsored by a pharmaceutical company. Most had participated in clinical trials of patients with RA. Keypads were available for instant recording of responses. A query was presented: "In patients with RA seen in usual care outside of clinical trials and other clinical research, how often do you perform a formal tender and swollen joint count?" Response options were 0, 1–24, 25–49, 50–74%, 75–99%, and 100% of the time. Results were instantly totaled. Results at this 2010 meeting were compared with results obtained from European rheumatologists in a similar study performed at a similar meeting in 2003 (Pincus T, Segurado OG. *Ann Rheum Dis.* 2006;65:820–2).

Results: Overall, 143 responses were recorded in 2010 for the joint count; only 4% of rheumatologists responded that they "never" performed a formal joint count, 13% at 1–24% of visits, 19% at 25–49%, 16% at 50–74%, 23% at 75–99% of visits, and 25% "always." Each of the 4 countries with more than 5 responding rheumatologists – United Kingdom, Germany, Spain, and Italy – included at least one respondent in 4 of the 6 categories. Results of a similar survey of 500 European rheumatologists in 2003 were 13% "never", 32% at 1–24% of visits, 11% at 25–49%, 14% at 50–74%, 16% at 75–99% of visits, and 14% "always." Overall, 64% of European rheumatologists in 2010 reported that they performed formal joint counts at ≥50% of visits, compared to 44% in 2003.

Question for rheumatologists: For RA patients under your care (when not required for clinical trials or reimbursement), how often do you perform:

Measure	Year	Never	1–24%	25–49%	50–74%	75–99%	Always
Formal joint count	2003	13%	32%	11%	14%	16%	14%
Formal joint count	2010	4%	13%	19%	16%	23%	25%
Formal joint count	2003		56%			44%	
Formal joint count	2010		36%			64%	

Conclusion: An increase in the likelihood of performing a formal joint count among physicians in treatment of patients with RA was reported in 2010 compared to 2003. Nonetheless, one-third of rheumatologists indicated that a formal joint count was performed at fewer than 50% of visits. Further educational efforts for rheumatologists might emphasize greater use of formal joint counts in standard clinical care.

Disclosure: T. Pincus: UCB, Inc., 5; **E. C. Keystone:** None; **M. de Longueville:** UCB, Inc., 3; **S. Costello:** Costello Medical Consulting, 4, UCB, Inc., 5.

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Frequency of PAP Smears among Lupus Patients—A Patient Report Survey. Eileen J. Lydon and H. Michael Belmont. NYUHJD, New York, NY

Purpose: In our practice 2 patients (pts) with systemic lupus erythematosus (SLE) who received intravenous (IV) cyclophosphamide (CYC) for lupus nephritis developed anal cancer (ca). Both had a history of human papilloma virus (HPV) & presented with bright red blood per rectum (BRBPR). HPV is responsible for almost all cervical & 90% of anal ca. Studies suggest that women with SLE are at greater risk of developing cervical dysplasia & ca than the general population. It is unknown whether this is attributable to immunosuppressive exposure or baseline defective immunity to HPV. Furthermore, immunocompromised pts & women with a history of cervical ca (or high-grade cervical lesions) are among high risk groups for the development of anal ca. Appropriate screening and knowledge of cervical & anal ca is imperative for SLE pts.

Methodology: We developed a patient report survey (PRS) to assess knowledge & educate our pts regarding cervical & anal ca. From May-June 2010 we surveyed pts at Bellevue & NYUHJD lupus clinics as well as private practice. Both genders were included & questions consisted of HPV awareness, HPV/SLE/ca risk, frequency of cervical & anal pap smears, & HPV vaccine. Education and recommendations were also provided.

Results: 75 pts participated; 69 F, 6 M; Age mean = 48; AA 24, H 32, C 6, A 11; Sexually active 39/75(52%); Unaware of HPV 40/75(53%); Ever told had HPV 11/75(15%); Smoked cigarettes 7/75(9%); Unaware of SLE/HPV/ca risk 67/75(89%); Unaware of utility for cervical PAP 20/69(29%); No GYN 15/69(22%); Greater than 1 year since last cervical PAP 19/69(28%) & 6/19(32%) never had; Abnormal cervical PAP 14/63(22%); Unaware of anal ca risk 64/75 (85%); Had anal pap smear 0/75(0%); Unaware of HPV vaccine 41/75(55%); Had vaccine 3/75(4%). Almost half the cohort were unaware of HPV & a strikingly high number unaware of SLE, HPV & ca risk. The few smokers were encouraged to quit. Many needed to be counseled about the importance of yearly cervical screening & more frequently if abnormal. A few never had cervical PAP smears & were encouraged to make an appointment. The majority of pts lacked knowledge regarding risks of anal ca & screening tools such as anal pap smears. Finally, most were unaware of the HPV vaccine & only a few eligible pts had yet to receive it.

Conclusion: The RPS allowed for assessment of knowledge and the ability to provide education to help decrease the development of cervical and anal ca. Our immunocompromised pts should undergo appropriate screening. Yearly PAP smears with HPV testing can help identify high risk (HR) types of HPV early in the disease. The SLE pts exposed to immunosuppressants also need to receive annual screenings. In addition, eligible pts should be educated about the HPV vaccine which prevents up to 70% of HR HPV. Also, as we experienced, pts exposed to CYC with HPV who develop BRBPR need prompt evaluation. Furthermore, anal ca screening should be considered for our high risk pts even though there are currently no standardized guidelines. Finally, education about these malignancies will help ensure that our pts are screened appropriately & increase awareness to report associated symptoms.

Disclosure: E. J. Lydon: None; **H. M. Belmont:** None.

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Impact of a Screening Protocol with Added Thoracic CT and Quantiferon on Prophylactic Treatment of Latent Tuberculosis in Anti-TNFa Candidate Patients. Nathalie Saidenberg-Kermanac'h[3], Luca Semerano[4], Jean-Marc Naccache[1], Michel Brauner[2], Géraldine Falgarone[4], Dominique Dumont-Fischer[4], Xavier Guillot[4] and Marie-Christophe Boissier[4]. [1]Department of Pneumology, Avicenne Hospital (AP-HP), Bobigny, France, [2]Department of Radiology, Avicenne Hospital (AP-HP), Bobigny, France, [3]Department of Rheumatology, Avicenne Hospital (AP-HP), Bobigny, Bobigny, France, [4]Department of Rheumatology, Avicenne Hospital (AP-HP), Bobigny, France, EA4222, Paris-13 University, France

Background: Screening for latent tuberculosis (LTBI) is current clinical practice before anti-TNFa treatment given the risk of disease reactivation with this class of therapeutics. The current screening protocol for LTBI in France (Sc1) comprises the parallel performance of chest X-ray, TST and anamnesis for LTBI risk factors.

A higher disease prevalence reduces the negative predictive value of a given screening test (i.e. increases the number of false negatives), and, additionally, patients under immunomodulating treatments can be falsely negative to tuberculin skin test (TST). In our hospital, which serves the district with the highest incidence of tuberculosis in France, we had a case of LTBI reactivation under anti-TNFa treatment, in a patient who hadn't been treated for LTBI due to negativity of Sc1.

For these reasons, taking into account the 2006 recommendations of the French Health Authority (HAS), and in accord with local TB experts, it was decided to screen all candidate patients to anti-TNF treatment with a screening protocol (Sc2) where QuantiFERON and chest CT were added to current screening tests for LTBI. The aim of the study was to evaluate the impact of this screening protocol (Sc2) on the prescription of LTBI treatment.

Methods: 96 consecutive patients candidate to anti-TNFa treatment for rheumatoid diseases underwent a screening protocol for LTBI comprising chest x-ray, TST (performed using Mantoux method), anamnesis for LTBI risk factors, a chest CT scan and blood QuantiFERON TB Gold IT (Cellestis) test. All medical records were discussed with a radiologist and a pulmonologist, leading to the final therapeutic decision of treating or not for LTBI before anti-TNF treatment. The ROC curve of sensitivity and specificity of Sc1 and Sc2 were compared, with the final therapeutic decision considered as the gold standard.

Results: among the 96 patients there were 39 positive TST, 12 positive quantiFERON, 10 chest X-rays and 8 CT scans suggestive of LTBI respectively. The sensitivity and specificity and ROC AUC of Sc1 were 88,9%, 93,5% and 0,912 [95% CI 0,843–0,961] respectively. For Sc2 they were 100%, 93,5% and 0.967 [95% CI 0,907–0,993]. The difference between the two ROC curves was not significant (p=0,096) at an a-error of 0,05 and a b-error of 0,2. 48 patients were finally treated with Sc2 vs. 43 that would have been treated with Sc1.

Conclusion: In a population at high prevalence of LTBI a screening protocol before anti-TNFa treatment implying the parallel performance of TST, chest x-ray, quantiFERON and chest CT scan lead to treat more patients than the screening protocol currently adopted in France. This difference was not statistically significant in a study with 80% power.

Disclosure: N. Saidenberg-Kermanac'h: None; **L. Semerano:** None; **J.-M. Naccache:** None; **M. Brauner:** None; **G. Falgarone:** None; **D. Dumont-Fischer:** None; **X. Guillot:** None; **M.-C. Boissier:** None.

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Implementation of an Electronic Interface for Medical Record Documentation in an Academic Pediatric Rheumatology Outpatient Clinic. Jennifer M. P. Woo[2], Miriam F. Parsa[2], Gil Amarilyo[2], Nasim Afsarmanesh[1], Kerry T. Gallagher[2], Ornella J. Rullo[2] and Deborah K. McCurdy[2]. [1]Division of Internal Medicine and Neurosurgery-Medicine; Hospital Medicine and Neurosurgical Clinical Quality Programs, UCLA, Los Angeles, CA, [2]Division of Pediatric Rheumatology, UCLA, Los Angeles, CA

Background: Health information technology (HIT) has gained importance in clinical practice in an effort to improve clinic efficiency and to minimize medical and communication errors resulting from handwritten notes. Our healthcare center utilizes an electronic medical record (EMR) system that requires outpatient clinic physicians to document patient visits on paper clinical notes (PCN) and send them outside the department to be uploaded. This process generates a lag period, ranging from 2 to 14 days when PCN are inaccessible via network computer. In response, we have designed, created, and implemented an EMR interface or electronic note (EMRI) that mimics the paper template, allowing the physician use a portable tablet computer in the exam room to directly upload their findings to an established clinical document system (CDS) and the EMR. We are assessing patient perception of the use of an EMRI in clinic and evaluating its effects on the workflow of the pediatric rheumatology outpatient clinics.

Methods: Our EMRI is a Microsoft Excel form and includes measures to verify medication dosing based on body surface area and weight, to maximize billing criteria, and to facilitate retrieval of clinical data for future research. Patients or their parents were asked, via paper survey, to anonymously assess the quality of care and their perception of EMRI use in clinic; we will continue these observations until our EMRI is fully integrated into clinical practice. Clinic efficiency was evaluated by monitoring the length of time physicians spent with each patient, the additional time dedicated to charting following the patient visit, and the time required for the clinical notes to be uploaded to the EMR.

Results: With the implementation of our EMRI, we have reduced the average time required to upload clinical documents by 6 days and increased the average percentage of notes uploaded within 48 hours of the patient visit by 75% ($p < 0.0001$). Currently, 93% of patients/parents

surveyed (n = 25) were receptive to the use of a clinical EMRI and 75% believed that an EMRI would benefit the patient's quality of care. There was no significant difference in perceived satisfaction in visit length or quality of care between visits documented with EMRI compared with those documented using PCN. On average, rheumatologists spent 38 minutes with each patient when using PCN, comprising about 40% of the clinic visit. Patients generally spent the majority of the remaining 60% of their visit waiting to be roomed or to be seen by the rheumatologists. These PCN times will be compared with EMRI times to assess improvement in clinic workflow.

Conclusions: Patients and their parents have indicated receptiveness to EMRI use in clinic and believe that it would benefit patient care. The implementation of an EMRI can improve clinic efficiency and minimize errors resulting from handwritten notes in an academic outpatient rheumatology practice without compromising patient perception of quality of care.

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Inpatient HiROC (High Risk Osteoporosis Clinic): Improving Osteoporosis Care Post Fracture. Gwynne L. Maloney-Saxon[2], Thomas P. Olenginski[3], Cynthia K. Matzko[2], Haiyan Sun[1], Karen Mackiewicz[4] and Eric D. Newman[2]. [1]Center for Health Research, Danville, PA, [2]Geisinger Medical Center, Danville, PA, [3]Geisinger Medical Center, Danville, PA, [4]Geisinger Medical Center, Davnille, PA

Purpose: Ineffective care pathways and process flows hinder post fracture care. To enhance the care of high risk osteoporosis patients across our health system, the rheumatology department created HiROC (High Risk Osteoporosis Clinic). Success was achieved by partnering with fellow stakeholders (orthopedists, hospitalists) to provide comprehensive post fracture care to this high risk group.

Method: HiROC utilizes rheumatology physician experts, clinical nurse specialists, electronic tools, and redesigned care processes in an efficient manner to provide comprehensive osteoporotic care to patients after fracture. HiROC has both inpatient and outpatient components. Inpatient HiROC involves an auto-consult to the Inpatient HiROC Team on all patients admitted with a low-impact fracture. Patients are logged into a task management database. Vitamin D testing and supplementation is initiated. At 6 weeks post-fracture, all Inpatient HiROC patients are contacted to re-assess their status. They are then seen in Outpatient HiROC, or their treating physician is contacted and given a consultative osteoporosis management plan, if they decline outpatient HiROC followup. We report on the first 200 Inpatient HiROC patients, including baseline demographics, risk assessment, treatment, and financial performance. High risk for future fracture was assessed by fracture type (vertebral or hip) and/or DXA results.

Results: Inpatient HiROC admission fracture types included hip (50.5%), vertebral (13.0%), other (38.0%). Mean Vitamin D level at time of consultation was 23.9 ± 11.7 ng/mL and increased to 46.3 ± 21.9 ng/mL at HiROC return. All 200 patients reached their 6 week assessment point with 48 % of patients transitioning to Outpatient HiROC, 26 % returning to a non-system primary physician, 13% to an in-system primary care physician (PCP), 1.5% were lost to follow up, and 11.5 % were deceased. Significantly more high risk patients received treatment in the Outpatient HiROC group (83%) than the in-system PCP group (25%), ($p<.0001$). Financial evaluation demonstrated the program to be self supporting, sustainable, and scalable.

Conclusion: By combining inpatient and outpatient components, organized task management, and electronic tools, the HiROC program demonstrates significant treatment success. Quality of care was greatest when an Inpatient HiROC visit was paired with an Outpatient HiROC visit. We are exploring ways to increase this connectivity by expanding Outpatient HiROC site availability and increasing patient motivation. HiROC is effective, self-sustainable, scalable, and may serve as a model for other groups to improve osteoporosis care for the patients they serve.

Disclosure: G. L. Maloney-Saxon: None; **T. P. Olenginski:** None; **C. K. Matzko:** None; **H. Sun:** None; **K. Mackiewicz:** None; **E. D. Newman:** None.

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Lipid and C-Reactive Protein Screening Thresholds and CVD Risk in a Community Lupus Cohort. Christie M. Bartels[4], Kevin Buhr[5], Jerry Goldberg[2], Carolyn Bell[3] and Robert Greenlee[1]. [1]Marshfield Clinic Research Foundation, [2]Marshfield Clinic Rheumatology, [3]Univ of Wisconsin School of Medicine and Public Health, Dept of Medicine, Rheumatology, [4]Univ of Wisconsin School of Medicine and Public Health, Dept of Medicine, Rheumatology, Madison, WI, [5]University of Wisconsin Department of Biostatistics

Background/Purpose: Systemic Lupus Erythematosus (SLE) is an independent cardiovascular (CVD) risk factor without clear guidelines informing cholesterol screening intervals or treatment thresholds. In non-lupus populations, the JUPITER trial demonstrated that highly sensitive CRP (hsCRP) elevation, as an indication for statin treatment, reduced CVD risk. We sought to examine current thresholds for lipid screening, CRP testing, and statin treatment in a community-based lupus cohort, as well as hazards for CVD events relative to these thresholds.

Methods: This retrospective cohort study examined all patients with incident SLE diagnosed between 1991–2008 in a regional medical care system capturing >90% of all regional health care encounters. "Definite lupus" cases were verified by the 1997 revised 1982 ACR SLE criteria. CVD events including myocardial infarction, stroke, or heart failure hospitalization were MD verified by record review. Screening and risk thresholds examined include (a) ever receiving US Preventive Task Force (USPTF) recommended standard adult lipid screening (b) identification of LDL> 130 mg/dl or >100mg/dl or (c) CRP>1 mg/dl (normal <1, analogous to hsCRP<10). Medical history of documented hyperlipidemia diagnosis or ever receiving statins was also examined. Comparison between SLE cases without and with CVD new events (n= 22 events) used Wilcoxon and Chi-Square tests and hazard ratios.

Results: Among 71 incident lupus cases followed for a mean of 9 years (mean age 52, 82% female) only 60% of females and 85% of males ever received lipid screening (Table). Among those tested, 43–72% had LDL elevation at >130 mg/dl and >100 respectively. Only 20% of all SLE patients ever received a hyperlipidemia diagnosis, and only 15% (n=11) ever received statin treatment. CRP was more commonly tested and showed less of a gender gap than cholesterol testing. CRP elevations were seen in 49% of patients. Ever or current CRP elevations reflected higher hazards of CVD events than formal hyperlipidemia diagnosis or LDL elevation.

Lipid and CRP Screening and Predicted Hazards of CVD Events Among 71 Patients with SLE

	Total SLE n = 71	%	Female n = 58	%	HR* CV Event	95% CI	p
Lipid Screen Ever	46/71	65%	35/58	60%			
LDL>130	20/46	43%	15/35	43%	0.99	[0.35, 2.74]	0.98
LDL>100	33/46	72%	24/35	69%	0.52	[0.19, 1.47]	0.22
Diagnosed Hyperlipidemia	9/71	20%	6/58	17%	2.96	[1.08, 8.15]	0.04
CRP Ever	53/71	75%	42/58	72%			
CRP>1 Ever	26/53	49%	19/42	45%	3.31	[1.17, 9.33]	0.02
CRP>1 Current	16/53	30%	11/42	26%	4.33	[1.68, 11.2]	<0.01

* Hazard ratios calculated at each level of risk among screened patients relative to event status.

Conclusions: While possible thresholds for lipid screening and treatment vary widely in the lupus literature, these findings demonstrate a clear gap in adherence to USPTF recommended lipid screening in this community based cohort of lupus patients. Women were more likely to lack lipid screening. Regardless of gender, more patients ever had CRP screening, and associated hazards of CRP elevation in this population exceeded those with hyperlipidemia. In this observational study CRP monitoring was not controlled and may reflect indication bias, however, a prior report showed low rates of serious SLE disease in this cohort. Sample size limited meaningful adjustment. Future work is needed to close gaps in standard USPTF recommended lipid screening in community lupus patients, and to determine the role of CRP and hsCRP for informing CVD risk management.

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Measuring the Impact of Patient Educational Materials about Medications in Meeting Patient Needs: Development and Validation of the Medication Education Impact Questionnaire (MeiQ). Sabina Ciciriello[3], Rachelle Buchbinder[1], Ian Wicks[4] and Richard H. Osborne[2]. [1]Cabrini Medical Center, Malvern, Australia, [2]Deakin University, Melbourne, Australia, [3]Royal Melbourne Hospital, Melbourne, Victoria, Australia, [4]Royal Melbourne Hospital, Melbourne, Australia

Background: Patient education is essential for patients to participate in decision-making and self-management. Evaluation of new educational interventions should incorporate outcomes that are relevant to patients as well as healthcare professionals. At present there are no measures that adequately evaluate the impact of education in meeting patient needs. The objectives of this study were to: (i) To determine the perceived needs of patients when starting a new medication; (ii) to develop a questionnaire assessing the impact of education about medications in meeting patient needs, facilitating shared decision-making and self-management and (iii) to validate this questionnaire within the target population.

Methods: Patients perceived needs when starting a new medication were explored in concept mapping workshops with patients (N=24). Quantitative and qualitative analyses were used to identify and define distinct areas of need (constructs). 130 questions were drafted to capture these needs and administered to 653 patients taking various medications for their rheumatic conditions. Exploratory and confirmatory factor analyses (CFA) were undertaken to create a robust questionnaire. A refined set of 29 questions divided into 6 scales, each measuring a patient need, were administered to 876 patients and a further CFA validation step was undertaken. To assess test-retest reliability, 200 respondents were sent a second copy of the MeiQ two weeks later (response rate of 90%).

Results: Four key independent areas of need were identified for patients starting a new medication: The need for quality information; the ability to participate in decision-making; coming to terms with their diagnosis and treatment; and the ability to self-manage. Statistical analyses revealed that some of the subheadings within the constructs worked best as separate scales: self-management as 3 scales measuring role & responsibility, capacity and support to self-manage. Decision-making as 2 scales: active communication and informed decision-making. All questions within the scales were strongly congruent with their underlying construct. No items had substantial associations with other constructs (cross-loadings), and CFA fit indices supported the hypothesized factor model. The refined MeiQ consisted of 29 questions across 6 scales; Perception of information quality, Ability to communicate with health professionals, Coming to terms with diagnosis and treatment, Self-management role and responsibility, Self-management capacity, and Self-management support. The final scales were found to be valid, reliable (Cronbach alpha $\geq$ 0.7) and stable over time (ICC 0.68 to 0.87).

Conclusions: The MeiQ was developed using advanced psychometric processes and found to be a robust, multidimensional questionnaire which incorporates the patient's perspective. The MeiQ is generic and can therefore be used to evaluate education about any medication. It is likely to fill an important gap in the evaluation of educational interventions about medications.

Disclosure: S. Ciciriello: None; **R. Buchbinder:** None; **I. Wicks:** None; **R. H. Osborne:** None.

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Multispecialty Unit for Infusion Therapy: Patient, Nursing and Provider Satisfaction. Barbara E. Ostrov, Kristine Reynolds and Lisabeth V. Scalzi. Penn State Hershey, Hershey, PA

Background: Current treatment of many complex diseases includes infusion therapy. In recent years, individuals with autoimmune diseases have been increasingly treated in infusion centers (Pat Pref Adherence 2009:3 335), second only to the long term tradition of infusion therapy for hematology-oncology (HO) patients. Patients with rheumatologic diseases may have reservations about being treated in a unit for "cancer" patients. Additionally, due to long term experience, infusion nurses may be more at ease caring for HO patients than individuals with RA, for example. Education about the different needs of non-HO patients is lacking for infusion nurses (J Infusion Nurs 2008;31:350). Therefore, in 2009, when building a new Cancer Institute, we considered moving non-hematology-oncology (non-HO) patients into a separate infusion unit. We assessed patient versus provider and staff satisfaction with the multispecialty combined unit to determine whether a separate infusion unit should be recommended.

Methods: A 7-question Likert scale survey about satisfaction with the infusion unit was collected over 2 weeks from 3 groups: infusion nurses, non-HO physicians and non-HO patients. The tool was designed to assess differences in patient satisfaction and perceived patient satisfaction by staff with our multispecialty infusion unit. Reliability of the tool was measured using Cronbach's alpha. Mean sums for all questions were calculated for individuals within their groups and analyzed using a one-way ANOVA. A post-hoc analysis was examined to determine which groups were similar.

Results: Surveys were completed by 13 nurses, 52 non-HO patients and 18 non-HO physicians. Missing responses resulted in a total of 49 patients, 12 nurses, and 14 physicians. The tool was reliable, with good internal consistency (Cronbach's alpha=0.92). The overall mean of the 7 items in the instrument was 28.1 $\pm$ 6.8. Patients had higher satisfaction than perceived by providers and nurses across all of the items, as evidenced by higher total mean score: patients 31.3 $\pm$ 4.8, nurses 22.1 $\pm$ 6.8, physicians 21.9 $\pm$ 4.8. These results demonstrated significant intergroup differences ($p<0.001$) shown in the figure.

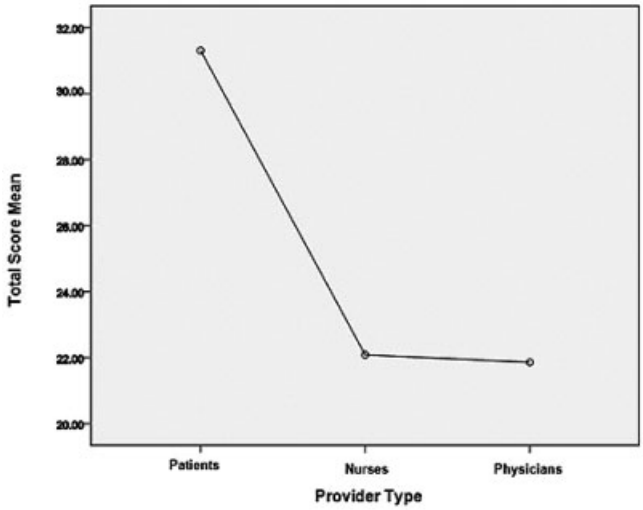

Figure 1. Mean infusion satisfaction scores by provider type.

The post-hoc analysis demonstrated that patients were significantly different from nurses and doctors ($p<0.001$), but nurses and doctors were not different from one another ($p=0.9$).

Conclusions: Physicians and nurses were more concerned than were patients about non-HO infusion therapy in a multispecialty but primarily cancer infusion center. Based on this survey, a combined multispecialty infusion center is acceptable to patients. Improved understanding of patient preferences were demonstrated to providers and nurses by this assessment. A follow-up survey is planned.

Disclosure: B. E. Ostrov: None; **K. Reynolds:** None; **L. V. Scalzi:** None.

1003

Rheumatoid Arthritis (RA) Disease Activity Assessment and Treatment Decisions in Rheumatology Practice. J. Timothy Harrington[6], Leslie R. Harrold[4], George Reed[5], Hong Chang[3], Joel M. Kremer[2] and Jeffrey D. Greenberg[1]. [1]Millburn, NJ, [2]The Center for Rheumatology, Albany, NY, [3]Tufts Medical School, [4]UMass Medical Schl, Worcester, MA, [5]UMass Medical Schl, [6]University of Wisconsin, Madison, WI

Background: Disease Activity Scores (DASs) for RA include a variety of patient, physician, and laboratory derived data. DASs have been used in clinical trials, but seldom in rheumatology practice in the United States. Treatment is guided instead by a variably determined Physician Global Assessment (PhGA). We have studied the PhGA and other DASs using the CORRONA registry (the Consortium of Rheumatology Researchers of North America, Inc).

Objectives: 1. To compare the correlations between the PhGA and the Clinical Disease Activity Index (CDAI), Disease Activity Score 28 joint (DAS28), Global Assessment Score (GAS), and the Patient Global Assessment (PtGA). 2. To evaluate treatment changes in relation to the PhGA and PtGA.

Methods: RA patients enrolled from 6/2001 to 11/2008 were included in this study if they had 2 visit reports within 3–6 months indicating no treatment changes during that interval, and if all data required to calculate each DAS

were reported, including the 0 – 100 visual analogue PhGA, PtGA, and patient global pain scores, swollen and tender 28 joint counts, ESR, and mHAQ. Correlation coefficients were computed for the PhGA versus the PtGA and the 3 composite measures. Both the PhGA and PtGA were stratified by disease activity as controlled [0–10], mild [11–40], moderate [41–80], and high [81–100]. Agreement or disagreement between the PhGA and PtGA in terms of controlled to mild disease activity (≤40) or moderate to high disease activity (>40) were determined, as were the proportions of patients in each group whose non-biologic or biologic DMARDs were changed at their second visit or during the following 6 months.

Results: The 2456 CORRONA-enrolled RA patients who met the study inclusion criteria had a mean age was 62 (SD = 13), and most were female (76%) with established disease (mean disease duration of 12.0 years). The majority had low to moderate disease activity (mean PhGA=15.1, PtGA = 25.7, CDAI=9.3, DAS28=3.1 and GAS=10.5). After adjusting for clustering of physicians, the correlation coefficients versus the PhGA were, CDAI=0.774, DAS28=0.629, GAS=0.644, and PtGA=0.445. There was slight correlation between the PhGA and PtGA (kappa=0.20). Table 1 shows agreement between the PhGA and PtGA in 1859 patients (76%) of whom 125 (7%) had moderate to high disease activity. DMARD initiation or dose escalation occurred in only 32% of the latter patients.

Conclusions: 1. The variable correlations between the PhGA and other disease activity measures and the level of discordance between the PhGA and PtGA reflect the complexities of using DASs in clinical practice. 2. Their adoption will also require better understanding of the weak relationships observed between treatment changes and both the PhGA and PtGA, especially for those patients with moderate or high disease activity.

Table 1. Agreement/Disagreement Between the Physician and Patient Global Assessments and Treatment Changes Related to These Assessments

	Agreement		Disagreement	
	Controlled to mild disease N=1734	Moderate to high disease N=125	MD > pt* N=54	Pt > MD** N=543
DMARD initiation (N, %)	128 (7%)	28 (22%)	11 (20%)	78 (14%)
DMARD dose increases (N, %)	206 (12%)	13 (10%)	7 (13%)	72 (13%)

*Physician states moderate to high disease activity but patient reports controlled or mild disease ** Patient reports moderate to high disease activity but physician states controlled or mild disease

Disclosure: J. T. Harrington: Corrona, 5; **L. R. Harrold:** Corrona, 5; **G. Reed:** Corrona, 5; **H. Chang:** Corrona, 5; **J. M. Kremer:** Corrona, 9; **J. D. Greenberg:** Corrona, 5.

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Scleroderma QuERI: Reduced Utility of Echocardiography in Pulmonary Hypertension Screening in the Community. James R. Seibold[6], Amparo Casanova[1], Mary Tan[1], Daniel E. Furst[5], Nicholas Hill[4], Vallerie V. McLaughlin[7], Richard M. Silver[3], Virginia D. Steen[2] and Anatoly Langer[1]. [1]Canadian Heart Research Centre, [2]Georgetown University Medical Center, Washington, DC, [3]Medical University of South Carolina, Charleston, SC, [4]Tufts Medical Center, [5]University of California Los Angeles Medical School, Los Angeles, CA, [6]University of Connecticut Health Center, Farmington, CT, [7]University of Michigan

Objective: Strategies are needed for early recognition of pulmonary arterial hypertension (PAH) in patients with systemic sclerosis (SSc, scleroderma). Current modalities include history and physical exam information, pulmonary function testing, biomarkers of myocardial stress (NTproBNP) and echocardiography with Doppler for estimate of right ventricular systolic pressure. None are fully validated and few measures have been made of a potential "care gap" between specialty centers and primary care settings.

Methods: Physicians (27 US rheumatologists including 22 community practice settings) enrolled 207 scleroderma patients (known or newly diagnosed) and provided data on a recommended panel of diagnostic tests. The QuERI methodology prompts by computerized feedback for completeness of testing and use of appropriate follow up testing, e.g. right heart catheterization (RHC). We report results on the use of echocardiography (echo).

Results: Data are reported as median, 25th and 75th percentile. Patients enrolled were 57 years old (49, 66), 90% female. There were a total of 193 patients (93%) that had at least one echo done during the study, however, only 86 (45%) of these had an RVSP value recorded and only 108 (56%) had the presence of TR jet mentioned. Estimated RVSP value was greater than the a priori threshold of 40 mmHg in 24 patients (12%) and of these 6 had RHC, 9 had only echo repeated and 9 had neither. During the follow up period, mortality/hospitalization rate was 29% among those with RVSP >40 vs 5% in those with RVSP reported <40 vs 19% in those in whom RVSP was not reported (p =0.008).

Conclusions: Echocardiography with Doppler is a robust tool for screening for pulmonary hypertension in a research setting and in specialized programs. However, these data derived from community practices suggest that RVSP and or tricuspid jet velocity measures are inconsistently reported. This is in spite of these tests being utilized as part of a funded research project focused on PAH. Interdisciplinary teamwork and education between rheumatologists and cardiologists continues to require attention Better understanding and stricter adherence to published guidelines could advance quality of care of these high-risk patients.

Disclosure: J. R. Seibold: Actelion Pharmaceuticals US, 2, 5, Gilead Sciences, Inc., 2, 5, Pfizer Inc, 2, 5, United Therapeutics, 2, 5; **A. Casanova:** None; **M. Tan:** None; **D. E. Furst:** None; **N. Hill:** None; **V. V. McLaughlin:** Actelion Pharmaceuticals US, 2, 5, 8, Bayer, 5, Gilead Sciences, Inc., 2, 5, 8, Novartis Pharmaceuticals Corporation, 2, United Therapeutics, 2, 5, 8; **R. M. Silver:** None; **V. D. Steen:** None; **A. Langer:** Actelion Pharmaceuticals US, 2.

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Secondary Fracture Prevention in Home Health Care: Initial Results from a Group Randomized Trial. Meredith L. Kilgore[2], Jeffrey R. Curtis[4], Ryan C. Outman[5], Julie Locher[1], Jeroan Allison[3] and Kenneth G. Saag[5]. [1]Univ of Alabama at Birmingham, Birmingham, AL, [2]Univ of Alabama at Birmingham, [3]Univ of Massachusetts, Worcester, MA, [4]University of Alabama-Birmingham, Birmingham, AL, [5]University of Alabama-Birmingham, Birmingham, AL

Statement of Purpose: To develop and evaluate a multimodal intervention to increase rates of osteoporosis treatment in high risk patients receiving home health services.

Methods: We developed and tested an intervention to improve the rates of treatment, particularly use of prescription osteoporosis drugs, among patient with a history of fracture receiving home health services. The intervention included an educational component for nurses, a computerized care plan that prompted the nurse to initiate specific actions related to osteoporosis management, easy reference materials for physicians, prepared order sheets to facilitate osteoporosis drug prescription, and patient education materials focused on osteoporosis, fracture risks, fracture prevention, and medication adherence. Field offices (n=24) of a home health agency operating throughout Alabama were randomized to receive the intervention or serve as controls. The primary outcome measure was the rate of osteoporosis medications prescribed among patients with a fracture history. A t-Test of proportions was used to assess difference between groups

Summary of Results: We found an absolute difference of 3.9% (NS) between the treatment and control group in post-intervention osteoporosis care. The figure shows the monthly distribution of treatment rates by office before and after the intervention.

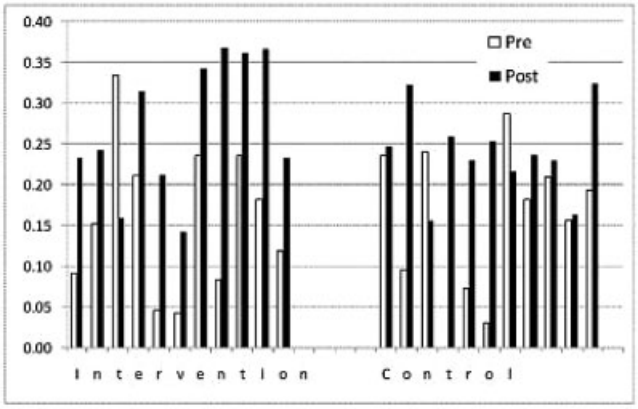

Figure 1. Pre- & post-intervention osteoporosis medication prescription rates in intervention and control groups.

While all but one of the treatment offices showed an improvement, overall rates were low, and the corresponding rates in the control arm improved as well.

A secondary analysis tested whether treatment rates increased when the nursing care plan was activated. In this case the difference was 15.3% (p < 0.0001).

Conclusions: Preliminary results do not demonstrate significant efficacy of the intervention overall, but suggest that improvements in processes of care could have significant effects on appropriate osteoporosis care delivery. Future studies should examine the impact of reinforcement of the nursing in-service training with audit and feedback to field offices on their relative performance rates, particularly with respect to activating the nursing care plan.

Disclosure: M. L. Kilgore: None; **J. R. Curtis:** Eli Lilly and Company, 2, 8, Merck Pharmaceuticals, 2, 5, Novartis Pharmaceuticals Corporation, 2, 8, Proctor and Gamble, 2, 5; **R. C. Outman:** None; **J. Locher:** None; **J. Allison:** None; **K. G. Saag:** Amgen Inc., 2, 5, 8, Eli Lilly and Company, 2, 5, GlaxoSmithKline, 2, Merck Pharmaceuticals, 2, 5, Novartis Pharmaceuticals Corporation, 2, 5, 8, Proctor and Gamble, 5, Roche, 2.

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Self-Scheduling of DXA Scans To Improve Osteoporosis Screening in Women. Amy H. Warriner[2], Ryan C. Outman[5], Kenneth G. Saag[5], Sarah L. Morgan[1], Elizabeth Kitchin[3] and Jeffrey R. Curtis[4]. [1]U of Alabama in Birm, Birmingham, AL, [2]Univ of Alabama at Birmingham, [3]Univ of Alabama at Birmingham, Birmingham, AL, [4]University of Alabama-Birmingham, Birmingham, AL, [5]University of Alabama-Birmingham, Birmingham, AL

Purpose: U.S. guidelines recommend bone density screening with central dual energy x-ray absorptiometry (DXA) in all women 65 years or older. However, less than one-third of eligible U.S. women undergo DXA testing. The main barrier in achieving greater rates of osteoporosis screening is identifying a systematic, effective and generalizable way for healthcare providers and patients to schedule and receive DXA results.

Methods: We conducted a group randomized, controlled trial involving 39 primary care physicians at the University of Alabama at Birmingham. Women 65 years or older with no identifiable DXA scan in the past 4 years cared for by these physicians were identified using administrative billing data (n=5122). Randomization was performed in two waves, each forming a cohort. In each of the two cohorts, 30 patients per physician were randomized to the intervention (sent mailed materials twice), the remainder of each physician's patients comprised the control group (received no mailing). The intervention included a patient brochure regarding osteoporosis and fracture risk and a letter providing patients the opportunity to self-schedule a DXA. Results from the two cohorts were similar and pooled for analysis. Stratified results compared receipt of DXA among women receiving primary care proximate to the site where the DXA scanner was located (62% of study population) vs. a more distant location which required additional travel to the DXA scanner.

Results: Of 5122 identified women meeting inclusion criteria, 978 women were randomized to the intervention group and 4,144 to the control group. A total of 19.5% of women in the intervention group scheduled and received a DXA, compared to 6.3% women receiving DXA in the control group (Risk Difference for DXA receipt 13.2%, 95% CI 10.8 16.0).

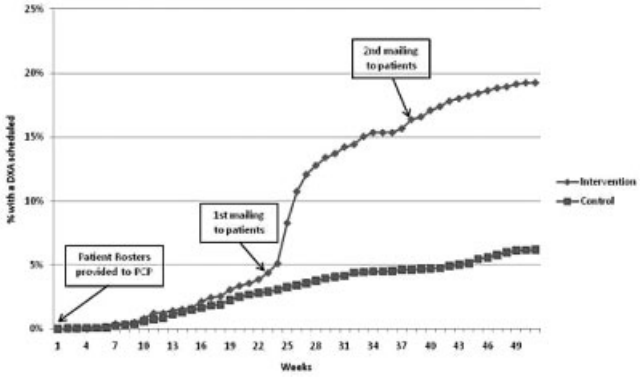

Figure. Scheduling of DXA scans in control and intervention.

Receipt of DXA in main clinic patients compared to patients from satellite clinics was greater in the main clinic patients for both the intervention group (22.7% vs. 13.4%, respectively; RR 0.59, 95% CI 0.43 0.80) and the control group (7.6% vs. 4.3%, RR 0.57, 95% CI 0.43 0.74).

Conclusions: DXA scan scheduling and receipt was improved significantly through the use of a simple mailed osteoporosis brochure and the availability for patients to self-schedule their own scans. This modality may be an effective component of a multi-faceted quality improvement program to increase rates of osteoporosis screening.

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Spanning Generations: Appointment Reminder Preferences among Outpatient Rheumatology Patients. Carl Gauthier[3], William E. Davis[2] and Robert J. Quinet[1]. [1]Ochsner Med Ctr-New Orleans, New Orleans, LA, [2]Ochsner Med-Ctr-New Orleans, New Orleans, LA, [3]Ochsner Med-Ctr-New Orleans, Hammond, LA

Background: Up to 21% of patients miss their outpatient clinic appointments. Forgetfulness is a major reason for non-attendance, and studies have shown that appointment reminders increase attendance rates. Text/Short Message Service (SMS) technology has been a promising modality in the deliverance of appointment reminders in primary care and subspecialty clinics. Sociologic studies have reported differences in technology usage among generational ages. While studies focusing of the appointment reminder preferences of patients in outpatient rheumatology clinics are limited, they have suggested that age may be a determinant of preferred reminder modality. No studies performed in the United States have been published. The goal of the present study is to determine appointment reminder preferences among outpatients in a United States rheumatology clinic and ascertain whether these preferences vary by generational age.

Methods: Between December 2009 and April 2010 an anonymous, self-directed questionnaire was intermittently administered to all rheumatology outpatients attending our clinic. Included in this survey were questions concerning age, current opinions regarding the usefulness of appointment reminders, access to technology, and preferences regarding method and timing of appointment reminders. Patients were divided into generational age groups as follows: Generation Y (18–28 years), Generation X (29–49 years), Baby Boomers (50–67 years), Silent Generation (68–85 years), and GI Generation (≥ 86 years). Overall group preferences, as well as preferences by generational age, were analyzed.

Results: A total of 637 surveys were included in the final analysis. The patients surveyed ranged in age from 18 to 94 years, with a mean age of 58 years. Baby Boomers comprised the largest percentage of the patient population (46%), followed by Generation X (25%), and the Silent Generation (24%). Over 99% of patients viewed appointment reminders as a good idea. Overall, the preferred method of reminder was a phone call (52%), followed by standard mail (24%). SMS was the least preferred modality (4%). There was a significant difference in the mean ages between reminder groups ($P < 0.0001$). Generation Y was more likely to prefer SMS reminders ($P < 0.0001$) and this was the preferred method of reminder in that age group. The mean age of those preferring SMS reminders was 39 years, which was significantly younger than any other reminder group. Overall, the preferred time frame in which to receive reminders was 1–2 days (46%), followed closely by 3–4 days (26%). Only 12% of patients surveyed wished to be reminded about their outpatient appointments ≥ 8 days in advance. Preferred time frame did not vary between age groups. Patient who preferred letter reminders were more likely to desire advanced notice ($P < 0.0001$).

Conclusions: Improved attendance rates in rheumatology clinics would be beneficial given the requirement for disease and medication monitoring. Patients value appointment reminders. Phone call reminders are preferred in all generational age groups except Generation Y. The preference of new modalities such as SMS varies with age and is limited to the younger patients of Generation Y.

Disclosure: C. Gauthier: None; **W. E. Davis:** None; **R. J. Quinet:** None.

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Survey of Teen Transition Needs among Pediatric Rheumatologists in the United States and Canada: Barriers, Services and Opportunities. Tova Ronis[3], Stacy P. Ardoin[2], Patience H. White[1] and Peter Chira[3]. [1]Arthritis Foundation, Bethesda, MD, [2]Ohio State University, Columbus, OH, [3]Stanford University, Palo Alto, CA

Purpose: To assess teen transition needs, barriers and opportunities among pediatric rheumatology providers

Methods: Using surveymonkey, we queried all Childhood Arthritis and Rheumatology Research Alliance (CARRA) members about teen transition care including needs, barriers and opportunities for transition program development. We compared our results to the American Academy of Pediatrics (AAP) 2008 survey on transitional care.

Results: 158/291 (54%) providers responded. Top two major stated barriers to transition are fragmented adult medical care and lack of sufficient time to provide services (Table 1).

Table 1. Barriers Affecting the Provision of Transition Support Services in Pediatric Rheumatology Practices

Barriers	Major Barrier	Somewhat a barrier
Pediatric staff lack sufficient time to provide transition services	40.3%	42.4%
Fragmentation of primary and specialty care in adult care	39.2%	44.8%
Adolescents/parents/physicians have developed an effective bond that is hard to break	32.6%	59.7%
Adolescents' lack of knowledge about their own condition and/or skills to self-advocate at physician visits	31.3%	61.8%
Pediatric staff lack skills in transition planning	28.7%	51.7%
Lack of knowledge about or linkages to community resources that support older adolescents/young adults	27.0%	61.0%
Lack of available adult specialists to care for older adolescents/young adults with special needs	26.4%	47.9%
Lack of insurance reimbursement for transition services	25.4%	38.7%
Lack of available family physicians and internal medicine physicians to care for older adolescents/young adults with special needs	24.5%	44.8%

As a part of routine transition care services, respondents help with finding an adult rheumatologist (70%), discuss confidentiality and consent before 18 (49%), assist with medical summary (51%), provide educational packets (42%), create an individualized transition plan (21%), utilize an assessment of transition readiness (30%), and 2/3 discuss patient's educational and vocational plans. Compared with AAP survey participants, pediatric rheumatologists are similar or more proficient in many transition practices, except for creating a medical summary and referring to a primary care provider.

Useful resources for the transition process include brochures and pamphlets (91%); open ended discussions during visits (91%); and having a portable personal health/medical record (82%). 78% use open ended discussions already, but use of phone calls (56%) and emails (43%) directly with teens is less frequent. Providers do not want to communicate via texting (58%) or social networking (49%).

Outcomes ranked as very important in defining a successful transition are survival (76%), seeing an adult rheumatologist within 6 months of the final pediatric rheumatology visit (66%), and maintaining insurance coverage (57%).

Discussion: Pediatric rheumatologists report many barriers to transition care, revealing unmet needs in improving teen self-efficacy, and assuring adequate provider time, education and reimbursement for transition planning. Technology offers some potential solutions including portable personal health records and health information access via hospital/health insurance portals. From the provider perspective, assessment of long term transition outcome is focused on quantitative measures rather than qualitative items as provider/patient satisfaction or patient quality of life.

Conclusion: Pediatric rheumatologists report the same concerns about providing transition care as general pediatricians. Opportunities include creating a standardized transition protocol to be followed by CARRA members, incorporating technology to facilitate the process such as developing personal health records, educational programs, and tracking long term outcomes after transfer of care.

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1009

Testing Patient Knowledge about Methotrexate: Development and Validation of the Methotrexate in Rheumatoid Arthritis Knowledge Test (MiRAK). Sabina Ciciriello[3], Ian Wicks[4], Richard H. Osborne[2] and Rachelle Buchbinder[1]. [1]Cabrini Medical Center, Malvern, Australia, [2]Deakin University, Melbourne, Australia, [3]Royal Melbourne Hospital, Melbourne, Victoria, Australia, [4]Royal Melbourne Hospital, Melbourne, Australia

Background: The study describes the development and validation of the MiRAK, a new tool designed to specifically measure patient knowledge about methotrexate (MTX) treatment for RA. MTX is an effective treatment for RA and is the cornerstone of modern RA treatment. However it is not without risks and patients need to understand complex information in order to make an informed decision about starting MTX and to take it safely. In planning a randomized controlled trial to assess the effectiveness of a new multimedia patient education program about MTX and RA we found no suitable outcome tool designed to measure patient knowledge about MTX.

Methods: The knowledge tested by the MiRAK was guided by a literature review and consultation with rheumatologists (N=15) as well as concept mapping workshops with RA patients (N=24) exploring their information needs when starting MTX. To ensure face validity, draft items of the MiRAK were tested with both patients and rheumatologists. The draft questionnaire was administered to 317 RA patients treated with MTX (response rate 53%). The data was analyzed using item response theory with a Rasch model. To assess test-retest reliability, 146 respondents were sent a second copy of the MiRAK two weeks later (response rate 90%).

Results: 60 candidate questions were generated, with True/False/Don't Know response options, to test a wide range of knowledge about MTX. Rasch analyses revealed that the MiRAK was unidimensional allowing the questions to be summated into a single knowledge score. Scores ranged from 8–57 correct responses out of 60 (mean (SD) 35.78 (7.7)). Scale fit indices revealed that the observed responses fit well with the Rasch model indicating sound measurement properties. The MiRAK questions covered all levels of underlying knowledge in the sample population. The MiRAK had excellent internal consistency (Cronbach's alpha 0.84) and test-retest reliability (ICC 0.89).

Conclusions: Advanced psychometric analyses were used to generate the MiRAK and provide strong evidence for its validity and reliability. Further work is underway to evaluate its sensitivity to change. The MiRAK may be useful as an outcome measure in both clinical trials of interventions designed to educate patients about MTX, and in routine care to assess patient knowledge of MTX prior to commencement of treatment.

Disclosure: S. Ciciriello: None; **I. Wicks:** None; **R. H. Osborne:** None; **R. Buchbinder:** None.

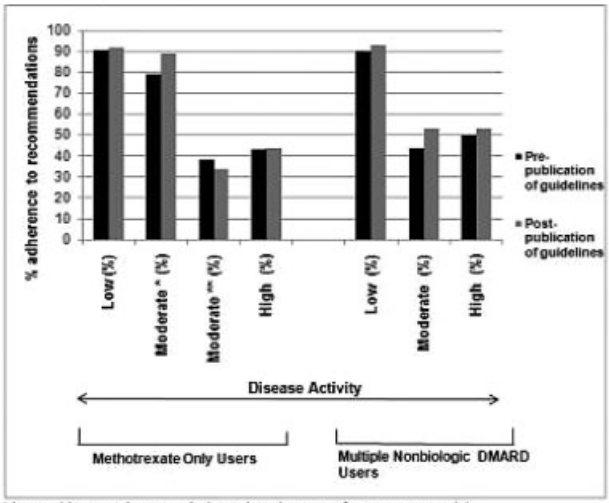
1010

The Impact of the ACR Treatment Recommendations on Physician Prescribing in a U.S. Cohort of Rheumatoid Arthritis Patients. Leslie R. Harrold[3], Jeffrey D. Greenberg[1], Jeffrey R. Curtis[5], Daniel E. Furst[6], Mary Jane Bentley[4], Ying Shan[4], George Reed[2] and J. Timothy Harrington[7]. [1]Millburn, NJ, [2]george.reed@umassmed.edu, [3]UMass Medical Schl, Worcester, MA, [4]Umass Medical School, [5]University of Alabama - Brimingham, Birmingham, AL, [6]University of California Los Angeles Medical School, Los Angeles, CA, [7]University of Wisconsin, Madison, WI

Purpose: To examine changes in prescribing patterns in relation to publication of the American College of Rheumatology (ACR) Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Anti-Rheumatic Drugs (DMARDs) in Rheumatoid Arthritis (RA). Specifically we examined nonbiologic and biologic DMARD use based on disease activity in order to evaluate the impact of the ACR recommendations on medication patterns.

Methods: We identified biologic naïve RA patients cared for by US rheumatologists participating in the CORRONA registry with visits prior to and/or at least 6 months after publication of the ACR recommendations on 6/15/08 (time period: 2/02–6/08 vs. 12/08–12/09). Initiation or dose escalation of biologic and nonbiologic DMARDs in response to active disease (using the CDAI) was assessed in comparison to the ACR recommendations. The population was divided into two mutually exclusive cohorts: 1) methotrexate (MTX) only users; and 2) multiple nonbiologic DMARD users. The proportion of patients with treatment regimens compliant with the ACR recommendations before and after publication was compared in the two cohorts stratified by disease activity using regression models adjusting for clustering of physician and geographic region.

Results: In MTX only users, 91–95% of those with low disease activity and 79–89% of those with moderate disease activity and good prognosis were receiving nonbiologic DMARDs, consistent with the recommendations. Among those with moderate disease activity and poor prognosis, 20–23% had their MTX dose increased and/or initiated another nonbiologic DMARD and 14–15% initiated a biologic, resulting in 34–38% of patients receiving care consistent with the recommendations. Similarly, among those with high disease activity, 24–26% had their MTX dose increased and/or were initiated on a non-biologic DMARD and 18–19% initiated a biologic (43–44% receiving care consistent with the guidelines). In the multiple nonbiologic DMARD users with moderate activity, 44–53% received care consistent with the recommendations (30% had initiation and/or dose escalation of their nonbiologic DMARD therapy and 14–21% initiated a biologic). Among those with high disease activity 50–53% received care consistent with the recommendations (30% with initiation and/or dose escalation of their nonbiologic DMARD therapy and 9–22% initiated on a biologic). In adjusted analyses there were no significant differences in prescribing pratices after publication of the treatment recommendations.



*those with a good prognosis (meaning absence of a poor prognosis)
**those with a poor prognosis (mHAQ >0.5, presence of rheumatoid nodules, erosive changes on x-ray, rheumatoid factor positive and secondary Sjogren's

Figure 1. Proportion of patients adherent to the ACR Recommendations stratified by disease activity and drug use.

Conclusions: Only approximately 40 to 50% of RA patients in the CORRONA US registry with high disease activity or moderate disease activity with a poor prognosis received care consistent with the current ACR treatment recommendations within 6 to 18 months after their release. In addition, publication of the recommendations did not appear to change prescribing patterns.

Disclosure: L. R. Harrold: Corrona, 5; **J. D. Greenberg:** Corrona, 9, Genentech and Biogen IDEC Inc, 5, Roche, 5, UCB, Inc., 5; **J. R. Curtis:** Amgen Inc., 2, Centocor, Inc., 2, 5, Corrona, 2, 5, Roche, 2, 5, UCB, Inc., 5; **D. E. Furst:** Abbott Immunology Pharmaceuticals, 5, Abbott Laboratories, 2, 8, Actelion Pharmaceuticals US, 2, 5, 8, Amgen Inc., 2, 5, Biogen Idec, 5, Bristol-Myers Squibb, 2, 5, Centocor Ortho Biotech Inc., 5, Corrona, 3, Genentech and Biogen; **M. J. Bentley:** None; **Y. Shan:** None; **G. Reed:** Corrona, 5; **J. T. Harrington:** Corrona, 5.

1011

The Preliminary Testing of a Core Set To Monitor SLE Patients in Routine Clinical Practice. Marta Mosca[6], Chiara Tani[6], Federico Quaglierini[6], Katia Goehner[5], Joao Matos Costa[2], Oskar Psenak[3], Magdalena Szmyrka-Kaczmarek[7], Jan Sznajd[4], Nuntana Kasitanon[1] and Stefano Bombardieri[6]. [1]Chiang Mai, University, Thailand, [2]Hospital de Santarem, Portugal, [3]Saltzbugr University, Austria, [4]University Hospital, Krakow, Poland, [5]University Hospital, Zurich, Switzerland, [6]University of Pisa, Italy, [7]Wroclaw University, Poland

Introduction: Systemic lupus erythematosus (SLE) is a complex disease; patient assessment in clinical practice mainly relies upon the experience of the treating physician and thus is subject to great variability. Unexplained variability may affect health care and lead to poor outcomes and complicates comparisons among practices. Recently "EULAR Recommendations for monitoring SLE patients in clinical practice and in observational studies" have been published. In addition a core set of minimal assessments to evaluate SLE patients in clinical practice was developed. The strength of this core set is represented by the fact that it was developed by combining available evidence and expert opinion, it includes only feasible variables and can be easily done in routine clinical practice.

Aim of the Study: Aim of the present study was to preliminary test the feasibility of this core set in routine clinical practice and to develop a computerized data base to collect patient's data.

Methods: Seven centres (Austria, Italy, 2 Poland, Portugal, Switzerland, Thailand) participated to the study and were asked to collect data of at least 5 consecutive SLE patients during routine assessment.

Results: Sixty-five patients were enrolled (55 Caucasians and 10 Asians; F: 64; M: 1; mean age 41 years), on average 10 minutes were required to fill the chart of the core set, although the time required appeared related with the type of organ involvement.

Disease activity using validated indices was calculated in all patients in routine clinical practice (ECLAM (15 patients): mean 2, SLEDAI (50 patients): mean 5), while the SLICC/ACR damage index (mean value 1) and the quality of life were evaluated only in 49% of patients. With respect to the adherence to recommendations, interestingly, this preliminary analysis showed that 86% of patients treated with immunosuppressive drugs had been assessed for the presence of chronic HBV and HCV infections and only 38% for tuberculosis. In addition, 15% of patients had never been assessed for osteoporosis or for lipid profile.

Following this preliminary testing, and based on the participants comments and suggestions, a Web based data base has been developed to collect data on SLE patients using the core set chart and including the ECLAM and SELENA- SLEDAI and the SLICC/ACR damage index. Recorded data can be downloaded and used for additional statistical analysis.

Conclusions: These preliminary data show that the use of a standardized core set in routine clinical practice is feasible and could represent a tool to reduce variability in data collection and to increase adherence to recommendations in clinical practice and therefore could lead to improvement of quality of care and of data travelling.

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1012

The Use of Electronic Health Record To Improve Tuberculosis Screening in Pediatric Rheumatology Patients Receiving Biologic Response Modifiers. David W. Moser[4], Elaine Haddix[5], Mary Beth Burns[5], James Brown[3], Anna Carmela P. Sagcal-Gironella[4], Thomas A. Griffin[1], Hermine Brunner[2] and Esi M. Morgan DeWitt[6]. [1]Childrens Hospital Med Ctr, Cincinnati, OH, [2]Cincinnati Child Hosp Med Ctr, Cincinnati, OH, [3]Cincinnati Children's Hospital, [4]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [5]Cincinnati Children's Hospital Medical Center, [6]Cincinnati Children's Hospital, Cincinnati, OH

Purpose: Activation of latent tuberculosis (TB) has been associated with tumor necrosis factor inhibitor (TNFi) use. As a result, screening with tuberculin skin testing (TST) is recommended prior to initiating treatment with biologic response modifiers (BRMs). However, compliance with this recommendation is imperfect. The electronic health record (EHR) can be leveraged to measure and improve compliance. We conducted a quality improvement (QI) project using the EHR and other interventions to increase the proportion of patients with Juvenile Idiopathic Arthritis (JIA) screened for TB prior to the start of BRMs.

Method: During January 2010 to May 2010 we conducted a QI initiative employing "Plan, Do, Study, Act" (PDSA) cycle improvement ramps. Baseline data from March 2008 to December 2009 was obtained by querying the EHR for all patients who initiated a BRM, the date of TST placement, and whether a result was reported. During the project's first three months, we developed non-EHR based interventions which included: Introduction of a log to track patients who had a TST placed, development of a patient instruction sheet and TST results card, and initiation of reminder phone calls 40–48 hours after TST placement. Rheumatology providers completed a weekly survey of new BRM starts to ensure that no eligible patients were missed. At the end of the third project month, the intervention was modified to include an EHR based best practice alert (BPA) instructing physicians to confirm the placement of a TST each time a BRM is ordered. An EHR BPA is a pop-up box programmed into the EHR with a reminder and an order that

satisfies the alert. The outcome measure was the proportion of patients who received a TST with documentation of results within 180 days of BRM start.

Results: Our baseline data spanned a period of 21 months. There were 247 eligible patients identified; of these, 65 (26.3%) had both a TST placed and resulted. During the 3 month period of non-EHR based interventions, 30 eligible patients were identified, 60.0% of which had both a TST placed and resulted. After the EHR BPA was activated 9 patients were identified in six weeks, 8 (88.9%) of which had TSTs ordered and resulted. A t-test comparing non-EHR based interventions to baseline was significant at $p<.001$. A t-test comparing the EHR BPA phase to the non-EHR phase generated a $p=0.225$.

Conclusion: We observed a statistically significant improvement in the proportion of patients with JIA screened for TB prior to the start of BRMs compared to baseline during the non-EHR portion of our QI project. Further improvements were seen once the EHR BPA was activated. Additional time and patients will be required to determine if the improvement with the EHR BPA intervention reaches conventional levels of statistical significance. We conclude that the use of EHR in conjunction with non-EHR based interventions may be an effective tool to improve the proportion of JIA patients screened for TB prior to the start of BRMs.

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1013

Treating Rheumatoid Arthritis to Target: Multinational Recommendations Assessment Questionnaire. Boulos Haraoui[13], Josef S. Smolen[18], Daniel Aletaha[21], Ferdinand C. Breedveld[4], Maarten de Wit[25], Maxime Dougados[8], Paul Emery[2], Allan Gibofsky[9], Desiree M. Van Der Heijde[19], Gerd R. Burmester[3], Mario Cardiel-Rios[7], Catalin Codreanu[1], Patrick Durez[23], Joao Eurico Fonseca[11], Winfried B. Graninger[20], Verdat Hamuryudan[12], Maria Jose Jannaut-Pena, Jochen Kalden[14], Tore K. Kvien[5], Ieda Laurindo[6], Carlomaurizio Montecucco[16], Jose A. Pereira Da Silva[24], Guyla Poor[22], Pedro Ivan Santos Moreno[10], Ewa Stanislawska-Biernat[15], Tsutomu Takeuchi[17] and the Treat to Target Taskforce. [1]Center of Rheumatic Diseases, Bucharest, Romania, [2]Chapel Allerton Hospital, Leeds, United Kingdom, [3]Charite-University Medicine, Berlin, Germany, [4]Dept. of Rheumatology, Leiden University, Medical Centre, Leiden, The Netherlands, [5]Diakonhjemmet Hospital, Oslo, Norway, [6]Division of Rheumatology, University of Sao Paolo, Brazil, [7]Facultad de Ciencias Medicas y Bioplogicas Dr. Ignacio Chavez UMSNH, Morelia, Michoacan, Mexico, [8]Hospital Cochin, Paris, France, [9]Hospital for Special Surgery, New York, NY, [10]Hospital Militar Central, Bogota, Colombia, [11]Hospital Santa Maria, Lisboa, Portugal, [12]Instanbul University, Cerrahpasa Medical School, Istanbul, Turkey, [13]Institut de Rhumatologie, Montreal, QC, Canada, [14]Institute for Clinical Immunology, Erlangen, Germany, [15]Institute of Rheumatology, Warszawa, Poland, [16]IRCCS Policlinico S Matteo, Pavia, Italy, [17]Keio University, Toyko, Japan, [18]Krankenhaus Lainz, Vienna, Austria, [19]Leiden University Medical Center, Meerssen, The Netherlands, [20]Medical University of Graz, Graz, Austria, [21]Medical University of Vienna, Vienna, Austria, [22]National Institute of Rheumatology and Physiotherapy, Budapest, Hungary, [23]Universite Catholique de Louvain, Brussels, Belgium, [24]University of Coimbra, Protuga, Algés, Portugal, [25]VU Medical Centre, Department of Medical Humanities, Amsterdam, The Netherlands

Purpose: An international survey was conducted to measure the level of agreement and application of the 10 recommendations developed by the Treat to Target initiative (Smolen JS, et al. *Ann Rheum Dis*. 2010), aimed at defining therapeutic goals and achieving optimal outcomes for rheumatoid arthritis (RA).

Methods: A10-point Likert items scale (1 = fully disagree, 10 = fully agree) measured the level of agreement with each of 10 recommendations. A 4-point Likert items scale (1 = never, 2 = not very often, 3 = very often, 4 = always) assessed the degree to which each recommendation was being applied in current daily practice. If responders answered "never" or "not very often", they were asked whether they would change their practice according to the particular recommendation.

Results: 1568 physicians, representing 33 countries, participated. Practices in University hospitals, general hospitals, and private clinics were well represented, with 37%, 31%, and 21% of respondents, respectively. Years in practice ranged from 0 to 52 years (mean 18+/−10.72. Both agreement with and application of the recommendations were high. Recommendations #1 ("The primary target for treatment of RA should be a state of clinical remission") and #10 ("The patient has to be appropriately informed about the treatment target and the strategy planned to reach this target under the supervision of the rheumatologist") received the highest agreement scores of 9.156 and 9.272, respectively. Recommendations #5 ("Measures of disease activity must be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently [such as every 3 to 6 months] for patients in sustained low disease activity or remission") and #3 ("While remission should be a clear target, based on available evidence low disease activity may be an acceptable alternative therapeutic goal, particularly in established long-standing disease") received the lowest agreement scores, 8.445 and 8.515, respectively, although these are still very high. In regard to application of recommendations in daily practice, the majority of responses were "always" and "very often". However, recommendation #5 also received the highest number of "never" or "not very often" responses (12.43%). Of the participants who were currently not applying these recommendations in clinical practice, many (36.27% to 68.18% depending on the recommendation) were willing to change practice according to the recommendations. However, 38.92% of participants not applying recommendation #5 indicated they would not change their practice.

Conclusion: The results of this survey demonstrated great support of "Treating RA to Target" recommendations amongst the international rheumatology community. Since these recommendations are based on evidence and consensus, additional efforts may be needed to encourage their application also amongst clinicians who are hesitant to change their practice.

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Disclosure: B. Haraoui: Abbott Laboratories, 2; **J. S. Smolen:** Abbott Laboratories, 2; **D. Aletaha:** Abbott Laboratories, 2; **F. C. Breedveld:** Abbott Laboratories, 2; **M. de Wit:** Abbott Laboratories, 2; **M. Dougados:** Abbott Laboratories, 2; **P. Emery:** Abbott Laboratories, 2; **A. Gibofsky:** Abbott Laboratories, 2; **D. M. Van Der Heijde:** Abbott Laboratories, 2; **G. R. Burmester:** Abbott Laboratories, 2; **M. Cardiel-Rios:** Abbott Laboratories, 2; **C. Codreanu:** Abbott Laboratories, 2; **P. Durez:** Abbott Laboratories, 2; **J. E. Fonseca:** Abbott Laboratories, 2; **W. B. Graninger:** Abbott Laboratories, 2; **V. Hamuryudan:** Abbott Laboratories, 2; **M. J. Jannaut-Pena:** Abbott Laboratories, 2; **J. Kalden:** Abbott Laboratories, 2; **T. K. Kvien:** Abbott Laboratories, 2; **I. Laurindo:** Abbott Laboratories, 2; **C. Montecucco:** Abbott Laboratories, 2; **J. A. Pereira Da Silva:** Abbott Laboratories, 2; **G. Poor:** Abbott Laboratories, 2; **P. I. Santos Moreno:** Abbott Laboratories, 2; **E. Stanislawska-Biernat:** Abbott Laboratories, 2; **T. Takeuchi:** Abbott Laboratories, 2; **Treat to Target Taskforce:** Abbott Laboratories, 2.

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Using an Electronic Data Capture System To Measure Outcomes in Patients on Biologic DMARD Therapy: The Rheumatology Health Tracker (RHT). Sita A. Narayanan[1], Jeffrey R. Lisse[2], Alexis A. Alvarez[4], Catherine Lo, Rafael G. Grau[3], Eric P. Gall[2] and Oscar Furet[4]. [1]Univ of Arizona, Tucson, AZ, [2]Univ of AZ Arthritis Ctr, Tucson, AZ, [3]Univ of AZ Arthritis Ctr, Indianapolis, IN, [4]Univ of AZ Arthritis Ctr

Background: Patient outcomes are increasingly important to track the response to disease modifying drugs (DMARD) over time. The Rheumatology Health Tracker (RHT) is an electronic capture system that tracks the outcomes in patients with rheumatoid arthritis on different biologic DMARDS over time in a real world setting, and can be important in detecting outcomes. This report evaluated outcome measures for a patient population undergoing biologic DMARD therapy after a second year of analyzing RHT use in an academic rheumatology clinic.

Methods: Patients with rheumatoid arthritis were already participating in an observational study using a web based electronic capture system. After informed consent, at each visit they were asked to record the following outcome parameters: Involved Joint Count (IJC), Short Form 12 (SF-12), Health Assessment Questionnaire (HAQ), and Visual Analog Scale of their overall disease activity (VAS), demographic information, and information on health care utilization. Practitioners then filled out a Tender Joint Count (TJC), Swollen Joint Count (SJC), and a visual analog scale. These outcomes were analyzed after a year and found to be statistically and clinically stable. A second annual analysis was performed on the same biologics with inclusion of newly consented patients resulting in a larger sample size.

Results: There were 155 patients enrolled in the study who were on biologic DMARDs. Overall HAQ was 0.824, SJC was 5.062, TJC was 6.662, SF-12 was 35.302, and VAS was 24.175. Initial baseline HAQ scores for the different biologics was 0.5547 for etanercept (n=41), 0.9184 for infliximab (n=39), 0.642 for adalimumab (n=41), 0.99 for rituximab (n=20), and 1.18 for abatacept (n=14). The change in HAQ score between the initial visit and the first follow up visit was +0.175 for etanercept, −0.088 for rituximab, −0.218 for infliximab, +0.121 for adalimumab, and −0.151 for abatacept. SF12 scores all increased however infliximab, rituximab, and abatacept showed the most improvement in patient-perceived health status.

Conclusions: Electronic medical records offer a means to record outcome parameters in patients on biologic DMARDs in a clinic outpatient setting over time. This reflects the use of different biologics in our practice. This second

annual analysis showed the utility of using this system over time to record patient and physician reported outcomes.This allows long-term monitoring of patients on biologic DMARDs with the RHT, and gives physicians the opportunity to adjust treatment accordingly. It is an accessible, reproducible electronic information source that can be accessed by multiple practitioners to assess and treat their patients over time.

Disclosure: S. A. Narayanan: None; **J. R. Lisse:** Centocor, Inc., 2; **A. A. Alvarez:** None; **C. Lo:** None; **R. G. Grau:** None; **E. P. Gall:** None; **O. Furet:** None.

ACR Poster Session B
Rheumatoid Arthritis - Clinical Aspects: Clinical Features, Disease Risk Factors, Bone in RA, CVD II
Tuesday, November 9, 2010, 9:00 AM–6:00 PM

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Anti-Cyclic Citrullinated Peptide Antibodies in Rheumatoid Arthritis Patients with Lymphoma. Eva Baecklund[10], Karin Ekström Smedby[3], Carin Backlin[5], Johan Rönnelid[2], Erik Åhlin[2], Rene Toes[6], Johan Askling[4], Ephraim Hochberg[1], Mandakolathur Murali[7], Lars Klareskog[8], Tom Huizinga[9], Fred Hochberg[1] and Jonathan Kay[11]. [1]Cancer Center, Massachusetts General Hospital, Boston, [2]Clinical Immunology, Uppsala University, [3]Epidemiology Unit, Karolinska Institutet at Karolinska University Hospital, Stockholm, [4]Epidemiology, Rheumatology, Karolinska Institutet at Karolinska University Hospital, Stockholm, [5]Genetics and Pathology, Uppsala University, [6]Immunology, Leiden University Medical Center, [7]Immunology, Massachusetts General Hospital, Boston, [8]Karolinska University Hospital, Stockholm, Sweden, [9]Rheumatology, Leiden University Medical Center, [10]Rheumatology, Medical Sciences, Uppsala University, Uppsala, Sweden, [11]UMass Memorial Medical Center, Worcester, MA

Background: The risk for lymphoma and, in particular, diffuse large B-cell lymphoma (DLBCL), is increased in patients with rheumatoid arthritis (RA). No biomarkers for the development of lymphoma in patients with RA have been identified.

Objective: To investigate if anti-CCP antibody levels and subclasses are associated with occurrence of lymphoma in patients with RA.

Methods: We identified 37 index patients with RA and subsequent lymphoma from two population-based Swedish case-control studies, one of lymphoma (the SCALE study, 1999–2002) and the other of RA (the EIRA study, 1996–2006). To each index RA-lymphoma case, three pairs of control subjects were matched based upon age at diagnosis of RA or lymphoma (± 5 years) and lymphoma subtype. Controls consisted of 73 patients with RA (EIRA), 73 patients with lymphoma only (SCALE), and 74 individuals with neither disorder (EIRA). Blood samples were collected from all subjects at either diagnosis of lymphoma (SCALE) or of RA (EIRA). The self-reported RA diagnosis (SCALE) was validated in medical records. Blood samples from all 257 study subjects were analyzed for anti-CCP IgG (ELISA, Eurodiagnostica) and ACPA-isotypes: anti-CCP IgG1–4, IgA, and IgM (Leiden). Anti-CCP IgG levels ≥25 U/ml were defined as positive. The chi^2 and Wilcoxon rank sum tests were used for statistical analysis.

Results: Similar proportions of patients with RA only (65%) and of patients with RA-lymphoma (65%) had positive anti-CCP IgG levels, as did lymphoma cases (1.4%) and population controls (3%). Similar results were obtained for all anti-CCP subclasses. The median level of anti-CCP IgG in index patients with RA- lymphoma (306 U/ml; min 1- max 5033) was higher than in non-lymphoma RA patients (140 U/ml; min 0-max 5706), but the difference was not statistically significant ($p=0.25$).

The most common lymphoma subtype among the index cases was DLBCL (37%). The median anti-CCP IgG was numerically higher in RA patients with DLBCL (495 U/ml; min 1-max 5033) compared to patients with RA and other non-Hodgkin lymphoma subtypes (175 U/ml; min 1-max 3626), ($p=0.87$).

Conclusion: This population-based study with carefully matched controls does not support an association between IgG anti-CCP antibody positivity or levels or ACPA subclasses (IgG, IgG1–4, M or A) and lymphoma occurrence in RA. Further studies are needed to identify other potential biomarkers of lymphoma occurrence in RA.

Disclosure: E. Baecklund: None; **K. Ekström Smedby:** None; **C. Backlin:** None; **J. Rönnelid:** None; **E. Åhlin:** None; **R. Toes:** None; **J. Askling:** None; **E. Hochberg:** None; **M. Murali:** None; **L. Klareskog:** None; **T. Huizinga:** None; **F. Hochberg:** None; **J. Kay:** None.

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Assessment of Cardiovascular Risk in Rheumatoid Arthritis. Impact of the New EULAR Recommendations. Montserrat Robustillo, Carmen Gomez-Vaquero, Javier Narváez, Jesus Rodriguez-Moreno, Paula Estrada, Laura López-Vives and Joan M. Nolla. Rheumatology Service. Hospital Universitari de Bellvitge

Introduction: Rheumatoid arthritis (RA) is a systemic inflammatory disease that is associated with an increased cardiovascular risk and a greater number of ischemic events than the general population.

Objectives: To evaluate the cardiovascular risk and frequency of ischemic events in a group of patients diagnosed with RA.

Material and Methods: We have included, consecutively, two hundred patients with rheumatoid arthritis diagnosed according to 1987 criteria of American College of Rheumatology (ACR), which are monitored regularly in the outpatient clinic of a tertiary care university hospital. We have reviewed retrospectively both the physical and the informatised medical record in the hospital and primary care and have gathered the following variables: a) age, sex, weight and height, b) duration of RA, c) parameters of activity of the disease, d) rheumatoid factor and anti-CCP, e) cardiovascular risk factors (smoking history, hypertension, hyperlipidemia, diabetes mellitus) and f) vascular ischemic events registered to date. From the age, sex, smoking history, arterial blood pressure levels and serum total cholesterol, we calculated the SCORE cardiovascular risk index (low-risk model). We calculated the SCORE cardiovascular risk index and we multiplied the result by 1.5 in patients who fulfilled the last EULAR recommendations (modified SCORE). The data were collected in an Access 2003 database and analyzed with the statistical software SPSS. Statistical significance was set at $p < 0.05$.

Results: The mean age of patients was 60 ± 12 years. 76% were women. The mean duration of RA was 12 ± 10 years. 82% were rheumatoid factor positive and 77%, positive anti-CCP. According to the DAS28, 51% of patients had a low activity, 39% moderate and 10% high. With regard to cardiovascular risk factors: 30% of patients were smokers or former smokers, 41% were diagnosed with hypertension, 52% were dyslipidemic and 12% had diabetes (2%, treated with insulin). The medium SCORE index (modified according to EULAR criteria) was 2.7 ± 2.9%, the change was indicated in 59% of patients. The cardiovascular risk calculated by SCORE correlated with classical vascular risk factors (age, male gender, smoking, hypertension and diabetes) and C-reactive protein. The modified SCORE is correlated also with positive RF and positive anti-CCP.

With regard to ischemic events, nine patients had had one or more: coronary (2 angina pectoris and 5 acute myocardial infarctions) or neurologic (two transient ischemic attacks and three strokes). Patients who had presented an ischemic event had higher age and higher modified SCORE than the other patients and they were more frequently male and smokers in a statistically significant way.

Conclusions: In patients with RA in our series, the incidence of cardiovascular risk factors and ischemic events is significant and is related to classical cardiovascular risk factors and C-reactive protein.

Disclosure: M. Robustillo: None; **C. Gomez-Vaquero:** None; **J. Narváez:** None; **J. Rodriguez-Moreno:** None; **P. Estrada:** None; **L. López-Vives:** None; **J. M. Nolla:** None.

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Association between Serum Osteoprotegerin Levels and Carotid Atherosclerotic Plaque in Patients with Rheumatoid Arthritis. Yu Asanuma, Yuki Shimada and Toshihide Mimura. Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University

Background: Osteoprotegerin (OPG), a regulator in bone resorption, is implicated in pathogenesis of rheumatoid arthritis (RA) and atherosclerosis. The expression of OPG is detected in human atherosclerotic

plaque. OPG concentrations are elevated in patients with coronary artery disease and associated with severity of disease and increased cardiovascular mortality in general population. The purpose of this study is to determine the relationship of serum OPG levels, traditional coronary risk factors and RA-related factors to carotid atherosclerotic plaque in patients with RA.

Methods: Ninety-six patients with RA were studied (84.4% female, age 60±10(SD) years). Serum OPG levels were measured by ELISA. All patients underwent carotid ultrasonography. The relationship between the patients' clinical characteristics and the presence or absence of carotid atherosclerotic plaque was examined. Spearman correlation analyses and Mann-Whitney tests were used to define the association between OPG levels and other variables. Logistic regression was used to assess association among OPG, cardiovascular risk factors, markers of inflammation and carotid plaque.

Results: OPG concentrations were significantly higher in patients with plaque than those without plaque (median: 1374 vs. 868 pg/ml, $P<0.001$). The prevalence of carotid plaque increased across OPG quartiles (p trend=0.005). Older age and higher levels of CRP or MMP-3 were more common in RA patients with plaque. Significant difference was not found in sex, disease duration, blood pressure, BMI, smoking, LDL cholesterol, DAS28, modified Sharp score and daily dose of prednisolone between RA patients with and without plaque. Serum OPG levels were correlated with CRP after adjusting for age and sex ($P=0.009$). After adjusting for age, sex and CRP, increased levels of OPG were associated with carotid plaque in patients with RA ($P=0.024$), however the association was not found between other risk factors for atherosclerosis, markers of inflammation or disease activity and presence of carotid plaque.

Conclusions: Patients with RA, a group that is known to have accelerated coronary atherosclerosis, also have increased concentrations of OPG, a mediator linked to coronary artery disease in other populations. OPG concentrations are independently associated with carotid plaque. Increased OPG levels would be a useful biomarker for atherosclerosis in patients with RA.

Disclosure: Y. Asanuma: None; **Y. Shimada:** None; **T. Mimura:** None.

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Body Composition Trends in Patients with Rheumatoid Arthritis: Associations with Disease Characteristics and Inflammatory Markers. Henry R. Kramer[1], Joan M. Bathon[1] and Jon T. Giles[2]. [1]Division of Rheumatology, Johns Hopkins University, Baltimore, MD, [2]Johns Hopkins Univ, Baltimore, MD

Background: Recent evidence suggests that patients with rheumatoid arthritis (RA) have altered body composition (BC) relative to non-RA patients. However, while it is hypothesized that systemic inflammation and the RA disease process play a major role in the development of these alterations, these associations have not been thoroughly evaluated.

Methods: Using a longitudinal study design, BC was evaluated by total body dual-energy x-ray absorptiometry (DXA) in 152 patients enrolled in the Evaluation of Subclinical Cardiovascular Disease and Predictors of Events in Rheumatoid Arthritis (ESCAPE-RA) study. DXA was performed at visits 1 and 3. DXA-derived measures included total body fat mass (TFM), fat mass index (FMI; kg/m^2 of height), total body lean mass (TLM), and fat-free mass index (FFMI; kg/m^2). Associations of RA characteristics with yearly rates of change in BC measures were explored using multivariate linear regression, adjusting for baseline BC and pertinent sociodemographic and lifestyle characteristics identified from univariate models.

Results: Of the 152 patients, mean age was 63 years, 64% were women, and 88% were Caucasian. Median RA disease duration at baseline was 12 years, 75% of patients were seropositive by RF or CCP, and median DAS28-CRP was 3.1. Median follow-up time was 3.2 years. As expected, significant gender differences in BC were detected, with men having significantly greater TLM than women and women having greater TFM than men. However, the rates of change were similar by gender, with a median gain of 0.31kg/year for TFM and a median loss 0.27kg/year for TLM. FMI increased at a median rate of 0.16kg/m^2·year, and FFMI decreased at a median rate of 0.43kg/m^2·year. Yearly change in FMI was negatively correlated with depression score ($p=0.044$) and cumulative CRP ($p=0.038$). Compared to seronegative patients, those with RF or CCP had a significantly lower adjusted yearly change in FMI (Figure 1A). Patients with higher baseline Sharp scores demonstrated a higher adjusted yearly change in FFMI compared to those with lower scores (Figure 1B).

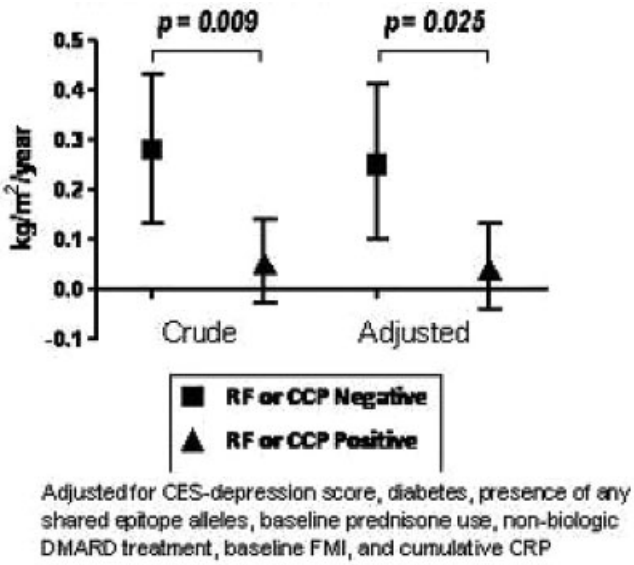

Figure 1A. Crude and adjusted average yearly change in FMI according to RF or anti-CCP status.

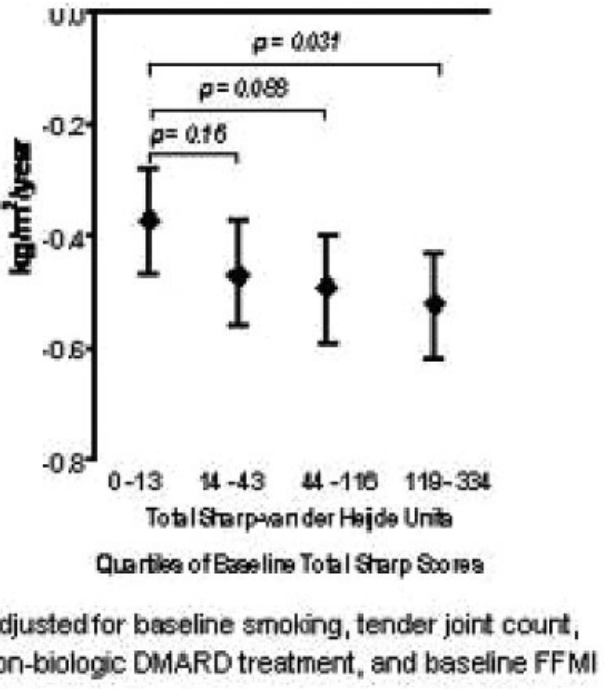

Figure 1B. Adjusted average yearly change in FFMI stratified by quartiles of baseline total Sharp scores.

Conclusions: In RA patients, yearly changes in BC were similar in both men and women, and patients with greater disease burden by radiograph experienced a higher rate of loss of lean mass. Interestingly, in our study population with a median of 12 years of disease, patients with RF or CCP did not experience the same yearly increases in fat mass compared to seronegative patients. These data suggest that factors associated with RA severity may promote low body mass, a state associated with all-cause and cardiovascular mortality, by both accelerating loss of lean mass and limiting the gain of fat associated with normal aging.

Disclosure: H. R. Kramer: None; **J. M. Bathon:** None; **J. T. Giles:** None.

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Cardiovascular Risk Estimates in Rheumatoid Arthritis in the Netherlands. Inger L. Meek[3], Harald E. Vonkeman[2] and Mart A. F. J. van de Laar[1]. [1]Enschede, The The Netherlands, [2]Enschede, The Netherlands, [3]Rheumatology Centre Twente, University Twente & Medisch Spectrum Twente, Enschede, The Netherlands

Background: Over the past decades many reports have shown a relationship between rheumatic disease and cardiovascular morbidity and mortality. This relationship may be due to clustering of risk factors or a feature of the chronic inflammatory processes. In recent years both these factors have received special attention as part of general healthcare and development of potent anti-inflammatory agents and goal directed antirheumatic therapy respectively. Therefore new data concerning cardiovascular risks in modern rheumatologic practice are needed.

Objective: To assess the prevalence of traditional cardiovascular risk factors in current daily clinical rheumatoid arthritis (RA) outpatient care compared to the general population.

Methods: A cohort containing all consecutive patients attending a large rheumatology outpatient department in The Netherlands was cross-sectionally examined for prevalent cardiovascular risk factors. Data were collected between May and December 2009, and included demographics, lifestyle, body mass index (BMI), blood pressure, laboratory tests, rheumatologic diagnosis and disease activity, use of medication and medical history. Parameters of cardiovascular risk in RA patients were compared with data from the general population from the same region. Also, the SCORE 10-year risk estimate for the development of fatal cardiovascular events (developed for the use in daily clinical practice as described previously, a risk estimation above 10% or above 5% with one additional risk factor being regarded an indication for primary cardiovascular risk intervention[1]) was calculated for each RA patient.

Results: Cardiovascular risk profiles were measured in 334 RA patients (mean age 60 years, 72% women, mean disease duration 88 months, 70% being in remission according to DAS28 or expert opinion, 8,7% having previously documented atherosclerotic cardiovascular disease). In RA patients we found significantly more hypertension (67 vs. 43% in men and 59 vs. 41% in women), higher mean BMI in women (27,7 vs. 26,4) and lower mean values of total cholesterol (5,0 vs. 5,79 mmol/L in men and 5,3 vs. 6,09 mmol/L in women) and total/HDL cholesterol ratio (4,2 vs. 5,1 mmol/L in men and 3,5 vs. 4,6 mmol/L in women) compared to the general population. In RA patients the calculated mean SCORE 10-year risk for fatal cardiovascular events was 8,3% in men and 4,5% in women; 73% and 52% having a SCORE risk calculation above 5% and one additional risk factor, respectively.

Conclusions: When compared to the general population this cohort of RA patients, treated according to the current standard of goal directed therapy aiming at remission or low disease activity, shows reassuring results regarding traditional cardiovascular risk factors, with even surprisingly favourable serum cholesterol profiles. Possible advantageous effects of effective antirheumatic therapy on serum lipid profiles and the consequences of our findings on cardiovascular event rates need further investigation.

References:

1. Conroy RM, Pyörälä K, Fitzgerald AP, et al. Estimation of ten year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24(11): 987–1003.

Disclosure: I. L. Meek: None; **H. E. Vonkeman:** None; **M. A. F. J. van de Laar:** None.

1020

Circulating Immune Complexes in Patients with Severe Extra-Articular Rheumatoid Arthritis Induce Tumour Necrosis Factor Production by Peripheral Blood Mononuclear Cells. Carl Turesson[1], Linda Mathsson[3], Lennart Jacobsson[1], Gunnar Sturfelt[2] and Johan Rönnelid[3]. [1]Skåne University Hospital, Malmö, Sweden, [2]Skåne University Hospital, Lund, Sweden, [3]Uppsala University Hospital, Uppsala, Sweden

Objective: A subset of patients with rheumatoid arthritis (RA) develop severe extra-articular disease manifestations. Autoantibodies and immune complexes (IC) have been implicated in the pathogenesis, but their role in systemic inflammation in RA remains to be defined. Our aim was to study circulating IC and their influence on cytokine production by peripheral blood mononuclear cells (PBMC) in patients with active, severe extra-articular RA (ExRA) compared to RA controls with no extra-articular manifestations.

Methods: Thirty-five consecutive patients with RA and severe ExRA manifestations according to predefined criteria (pericarditis, pleuritis, major cutaneous vasculitis, Felty's syndrome, glomerulonephritis, vasculitis related neuropathy, scleritis, episcleritis, retinal vasculitis or major organ vasculitis involving other organs) were studied. Seventy controls with RA but no ExRA manifestations, individually matched for age, sex and disease duration, served as the comparison group. Blood was drawn directly after ExRA was diagnosed and before any new treatment was started, and samples were stored at –70°C until investigated. IC prepared as serum polyethylene glycol (PEG) precipitates were added to serum-free PBMC cultures and tumour necrosis factor (TNF) levels were measured after 20 hours using ELISA. Circulating C1q-binding IC and anti-CCP antibodies were determined using ELISA. RF was detected using nephelometry.

Results: Circulating IC levels were higher among patients with ExRA compared to RA controls [median 8.52 μgEq/mL; interquartile range (IQR) 3.63–24.27 vs median 4.51 μgEq/mL; IQR 1.81–10.45 ($p=0.005$)]. TNF induction from PBMC was greater after adding serum PEG precipitates from ExRA patients [mean 17.7 pg/mL; standard deviation (SD) 12.1 vs mean 12.9; SD 7.6; for RA controls ($p=0.02$)], and levels of C1q-binding IC correlated with IC-induced levels of TNF among ExRA patients ($r=0.40$; $p=0.02$) as well as among RA controls ($r=0.35$; $p=0.004$). There was a strong association between circulating IC levels and RF among patients with ExRA ($r=0.62$; $p<0.001$), in particular in the subset with major cutaneous vasculitis ($n=9$; $r=0.76$; $p=0.03$). Anti-CCP antibodies did not correlate with circulating IC levels in patients with ExRA.

Conclusion: Patients with severe ExRA manifestations were characterized by high levels of circulating IC, and IC from ExRA patients were stronger inducers of TNF production from PBMC compared to IC from RA controls. These results suggest that circulating IC enhance RF production and systemic inflammation in severe ExRA.

Disclosure: C. Turesson: None; **L. Mathsson:** None; **L. Jacobsson:** None; **G. Sturfelt:** None; **J. Rönnelid:** None.

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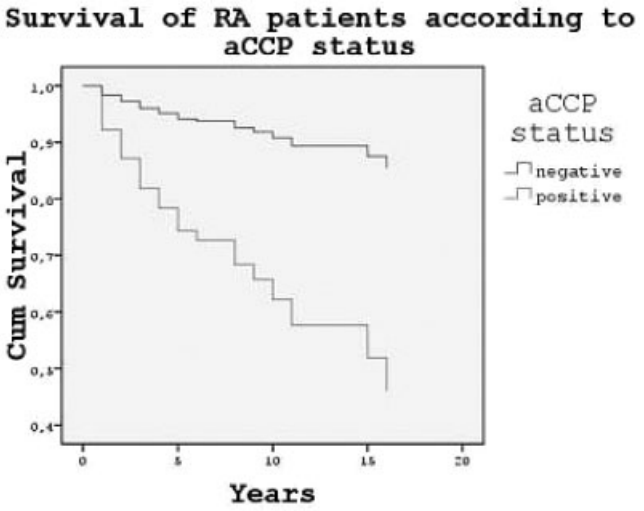
Clinical and Laboratory Risk Factors of Cardiovascular Disease (CVD) in a Cohort of Greek Patients with Early Rheumatoid Arthritis (RA). Nikolaos Papadopoulos[3], Georgios Tsiaousis[2], Marios Katsounaros[1], Dimitrios Baltzis[3] and Vasiliki Galanopoulou[3]. [1]B' Internal Medicine Clinic, Papanikolaou General Hospital, Thessaloniki, Greece, [2]Cardiologist, Kastoria, Greece, [3]Rheumatology Unit, Papageorgiou General Hospital, Thessaloniki, Thessaloniki, Greece

Background: Previous studies have shown that RA patients are at increased risk of developing cardiovascular disease.

Aim of the Study: To investigate the contribution of various clinical and laboratory risk factors to the development of CVD in a cohort of Greek patients with early RA.

Patients and Methods: From January 2000 until June 2009, one hundred and ninty seven patients with early RA and without a prior history of CVD, were first diagnosed and subsequently followed-up, every three months at the rheumatology unit of our hospital.Demographic, clinical, laboratory and therapeutic parameters were evaluated during every follow-up. At the end of the study, patients were divided, according to the development or not of CVD, which included accute myocardial infarction, diagnosis of a stable coronary artery disease, ischaemic cerebral vascular disease and thrombosis of a large vessel.

Results: At the end of the study 37 patients (18.27%) had suffert a CVD event. Univariate analysis revealed that late onset of RA ($p<0.0005$), male sex ($p<0.008$), high mean CRP and ESR ($p<0.008$ and 0.017 respectively), presence of extra-articular manifestations ($p<0.05$) and positivity of anti-CCP autoantibodies and RF($p<0.0005$ and 0.05 respectively), were in a statistically significant manner associated with the development of CVD. Concerning co-morbidities, the presence of hypertension ($p<0.0005$) and dyslipidaemia ($p<0.0005$) were also associated with CVD. A logistic regression model showed that anti-CCP positivity, age at RA onset, presence of extra-articular manifestations and history of hypertension and dyslipidaemia were independent risk factors of CVD. Cox regression analysis demonstrated that anti-CCP positivity significantly influenced the time of first CVD occurence (Figure 1).



Conclusion: Patients with early RA, positive to anti-CCP autoantibodies, who display extra-articular manifestations and a history of hypertension and dyslipidaemia are at higher risk of developing CVD.

Disclosure: N. Papadopoulos: None; **G. Tsiaousis:** None; **M. Katsounaros:** None; **D. Baltzis:** None; **V. Galanopoulou:** None.

1022

Computed Tomographic Densitometry (CTD) for the Evaluation of Interstitial Lung Fibrosis in Rheumatoid Arthritis (RA). Dimitrios A. Pappas[3], Jon T. Giles[4], Geoffrey Connors[2], Noah Lechtzin[2], Joan M. Bathon[3] and Sonye Danoff[1]. [1]Division of Pulmonary and Critical Care, Johns Hopkins University, Baltimore, MD, [2]Division of Pulmonary and Critical Care, Johns Hopkins University, [3]Division of Rheumatology, Johns Hopkins University, Baltimore, MD, [4]Johns Hopkins Univ, Baltimore, MD

Background: Pulmonary disease is a major source of morbidity and mortality in RA patients. Current diagnostic modalities lack sensitivity and are highly dependent on observer experience. We compared the reliability of expert visual CT scan evaluation ("Visual evaluation") of interstitial lung fibrosis, with CT densitometry (CTD), an automated modality for determining the density of pulmonary parenchymal tissue, and the association of both methods with the presence of respiratory symptoms, pulmonary function test (PFT) abnormalities, impaired quality of life (QOL) and fatigue.

Methods: RA patients were evaluated with chest CT, PFT, respiratory questionnaires, fatigue (FACIT-F) and QOL (SF-36) instruments. Fibrosis by CTD was measured as the percentage of voxels with attenuation between −640 and – 250 Hounsfield units (HU). A single expert radiologist evaluated the same CT scans for the presence of fibrosis. A subset of scans was blindly read twice by the same reader who was not aware of any patient characteristics.

Intra-operator/observer reproducibility was evaluated by means of percent agreement. Univariate analyses were applied to evaluate the relationship of visual and CTD measurements with the presence of respiratory symptoms and PFT abnormalities.

For multivariable analysis, the SF36 physical function scale and the FACIT –F subscale were used as outcomes and were handled as binary variables (lower quartile vs. upper quartiles). Independent variables were selected based on biologic plausibility. Final logistic regression models were built using forward and backward stepwise selection of variables.

Results: Among the 192 patients who underwent CTD, fibrosis affecting ≥10% of lung parenchyma was observed in 39 (20%). Fibrosis of ≥7.5% of parenchyma was observed in 79 (41%). Among the 176 scans with visual evaluation, 57 (32%) were read as having fibrosis. The intraoperator percent agreement for CTD fibrosis was 100% while the intraobserver agreement for visual evaluation was only 65%.

In univariate analysis, the presence of ≥10% fibrosis by CTD was associated with impaired diffusion capacity with or without coexistent restriction (Odds Ratio (OR): 2.6, 95% CI:1.1–6.1), breathlessness while walking on level ground (OR: 3.1, 95% CI: 1.2–8.1) or breathlessness while walking 100 yards (OR: 3.9, 95% CI: 1.3 –11.5). Visual evaluation was associated with the presence of impaired diffusion capacity with or without coexistent restriction (OR: 3.4, 95% CI: 1.5–8.0), but not with the presence of respiratory symptoms.

Multivariate logistic regression analysis revealed that the presence of ≥ 10% fibrosis by CTD was associated with a worse SF36 physical function scale (OR: 5.2, 95% CI: 1.9–14.1). The presence of ≥ 7.5% CTD fibrosis was associated with a worse FACIT-F score (OR: 2.5, 95% CI: 1.1– 5.3). No similar association was detected between visual evaluation and outcomes of interest.

Conclusions: In RA, visual evaluation of lung CT for evaluation of fibrosis has inferior reliability than evaluation with CT densitometry. The later is associated with the presence of respiratory symptoms, worse quality of life and fatigue.

Disclosure: D. A. Pappas: Corrona, 5, 9; **J. T. Giles:** None; **G. Connors:** None; **N. Lechtzin:** None; **J. M. Bathon:** None; **S. Danoff:** None.

1023

Cystatin C, Renal Function and Atherosclerosis in Rheumatoid Arthritis. Ratchaya Lertnawapan[2], Aihua Bian[2], Yong Hee Rho[2], Vivian Kawai[2], Paolo Raggi[1], Annette Oeser[2], Joseph Solus[2], Tebeb Gebretsadik[2], Ayumi Shintani[2] and Charles Michael Stein[2]. [1]Emory University, Atlanta, GA, [2]Vanderbilt University, Nashville, Nashville, TN

Purpose: Cystatin C, a novel marker of renal function, is a more accurate measure of glomerular filtration rate (GFR) than serum creatinine. Cystatin C is a cysteine protease inhibitor and its serum concentrations are associated with inflammation, insulin resistance, and cardiovascular risk. Patients with rheumatoid arthritis (RA) frequently have inflammation, insulin resistance, subclinical renal dysfunction and premature atherosclerosis. We examined the hypothesis that cystatin C is increased in RA, and associated with inflammation, insulin resistance and coronary artery atherosclerosis.

Methods: We measured serum cystatin C, creatinine, C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) concentrations in serum samples from 167 patients with RA and 91 control subjects without inflammatory rheumatic disease. Coronary calcium score, homeostasis model assessment (HOMA) index, Modified Diet in Renal Disease formula-estimated GFR (MDRD-eGFR) and clinical parameters including RA disease activity (DAS28) were also measured. We compared cystatin C concentrations in patients with RA and controls using a multivariable regression analysis that adjusted for demographic variables and renal function (MDRD-eGFR). In patients with RA we assessed the relationship between cystatin C and measures of inflammation, Framingham risk score (FRS) and coronary-artery calcium score (CACS) using Spearman correlation and multivariable regression.

Results: Concentrations of cystatin C were significantly higher in patients with RA (median (IQR): 1.16 (0.99–1.35) mg/L) than controls (1.01 (0.90–1.19) mg/L), (adjusted $P<0.001$). Serum creatinine concentrations ($P=0.62$) and MDRD-eGFR ($P=0.53$) did not differ significantly among RA and control groups. In patients with RA, cystatin C concentrations were significantly positively correlated with creatinine ($rho=0.43$, $P<0.001$) and significantly inversely correlated with MDRD-eGFR ($rho=-0.43$, $P<0.001$). In RA cystatin C was positively correlated with ESR ($rho=0.26$, $P<0.001$), CRP ($rho=0.20$, $P=0.01$), DAS28 ($rho=0.19$, $P=0.006$), FRS ($rho=0.44$, $P<0.001$) and TNF-α ($rho=0.20$, $P=0.01$), but not with IL-6, or HOMA (both $P>0.05$) (Table). After adjustment for age, race and sex, only associations with ESR, CRP, DAS28 and FRS retained statistical significance. Cystatin C also correlated with CACS ($P<0.001$) in RA but this was not significant after adjustment for age, race, sex and FRS ($P=0.67$).

Conclusions: Cystatin C concentrations are higher in patients with RA than compared to subjects without RA; this may reflect undetected subclinical renal dysfunction and inflammation. Cystatin C provides information regarding the risk of atherosclerosis in RA, but this is not independent of the information provided by conventional cardiovascular risk factors.

Table. Relationship between Cystatin C and Cardiovascular Risk Factors, Inflammation and Coronary Calcium Score in RA

Factor	Rho** (ρ)	Cystatin C Unadjusted p-value	Adjusted p-value*
Age	0.44	<0.001	–
Homocysteine	0.49	<0.001	<0.001
HOMA index	0.09	0.261	0.15
Framingham score	0.44	<0.001	0.05
DAS28	0.19	0.013	0.006
ESR	0.26	0.001	<0.001
CRP	0.20	0.01	0.009
TNF-α	0.20	0.011	0.11
IL-6	0.10	0.185	0.322
Coronary calcium score	0.32	<0.001	0.674

*Adjusted p-values are all adjusted for age, race and sex, except for coronary calcium score that is additionally adjusted for Framingham risk score. Multivariable linear regression was used in Adjusted p-value.
**Univariate Spearman correlation coefficient (n=167)
HOMA Index=Homeostasis Model Assessment Index; DAS28=Disease Activity Score 28-joint assessment; ESR=Erythrocyte Sediment Rate; CRP=C-Reactive Protein; TNF-α=Tumor Necrosis Factor-α; IL-6=Interleukin-6

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Depressive Symptoms and Perceived Communication around Shared Decision Making among Patients with Rheumatoid Arthritis. Jennifer L. Barton[1], Laura Trupin[2], Mary E. Margaretten[1], Laura J. Julian[5], Jonathan D. Graf[1], John Imboden[2], Edward H. Yelin[4] and Dean Schillinger[3]. [1]UCSF, San Francisco, CA, [2]UCSF, [3]UCSF, Center for Vulnerable Populations at San Francisco General Hospital, [4]University of California, San Francisco, CA, [5]University of California San Francisco, San Francisco, CA

Background: Due to the high cost and potential toxicity of therapies for rheumatoid arthritis (RA), shared decision making is central to patient safety and quality of care. While depressive symptoms have been associated with poor clinician-patient communication in diabetes and coronary heart disease, this has not been studied in RA. We sought to examine whether depressive symptoms influence clinician-patient communication around shared decision making among RA patients.

Methods: Data were derived from a cohort of adults with diagnostically confirmed RA seen at two university-affiliated clinics. Subjects completed a structured telephone survey in English, Spanish, or Chinese, that included the Interpersonal Processes of Care Survey (IPC), a validated patient-reported measure. The IPC decision-making subscale is based on the mean score for two items, "How often did you and your doctors work out a treatment together?" and "If there were treatment choices, how often did doctors ask if you would like to help decide your treatment?" (range: 1 "never" to 5 "always"). Mean scores <4 (corresponding to never/rarely/sometimes) were categorized as poor communication. The Patient-Health Questionnaire-9 (PHQ-9) was administered in-person in the patient's preferred language to determine depression symptom severity. PHQ-9 was categorized using three severity classifications: none-minimal (0–4), mild (5–9), and moderate to severe ($\geq$ 10). Multivariate logistic regression was used to evaluate the independent association of depressive symptoms with poor communication, adjusted for demographic and disease characteristics, and trust in physician.

Results: The 227 subjects were 84% female with a mean age of 55 $\pm$ 14 years and mean disease duration of 11 $\pm$ 11 years; 143 (63%) spoke English, 52 (23%) Spanish, and 32 (14%) Cantonese. Fifty-five (24%) had moderate to severe depressive symptoms on the PHQ-9 and 70 (31%) reported poor communication on the decision-making subscale. Results from the multivariate model suggest that moderate to severe depressive symptoms were independently associated with poor communication (AOR = 3.8, 95% CI 1.4–10.7) (Table).

Table. Predictors of Poor Doctor-Patient Communication Around Shared Decision Making Among 227 Patients with RA

	Age-adjusted OR (95% CI)	p-value	MV adjusted* OR (95% CI)	p-value
Depressive symptoms (ref. PHQ-9† <5)				
Mild (PHQ-9 5–9)	1.5 (0.7–2.9)	0.27	2.3 (0.9–6.1)	0.082
Moderate to severe (PHQ-9 ≥10)	2.2 (1.1–4.4)	0.03	3.8 (1.4–10.7)	0.011
Age, per 10 years	1.2 (1.0–1.5)	0.103	1.6 (1.2–2.2)	0.003
Language (ref. English)				
Spanish	5.7 (2.7–11.9)	<0.001	5.6 (1.7–18.3)	0.004
Cantonese	5.9 (2.6–13.6)	<0.001	7.4 (2.0–26.9)	0.002
Less than high school education	2.8 (1.5–5.3)	0.001	0.6 (0.2–1.7)	0.34
Disease severity				
Disease duration	1.0 (0.9–1.0)	0.09	1.0 (0.9–1.0)	0.45
Health Assessment Questionnaire (HAQ)	1.3 (0.9–2.0)	0.15	0.8 (0.5–1.4)	0.5
Suboptimal Trust in Physician	1.3 (0.7–2.6)	0.46	2.7 (1.1–6.4)	0.03

† PHQ-9=Patient Health Questionnaire-9 *Multivariate model adjusts for age, gender, language, education, along with variables shown in the table.

Conclusions: Among patients with RA, we found that moderate to severe depressive symptoms were independently associated with poor doctor-patient communication around shared decision making. While older age and suboptimal trust in physician have been associated with poorer communication in prior studies, depression status has not been observed as a correlate of shared decision making in RA. This study highlights the need for interventions to improve shared decision making in rheumatology practices, especially for those RA patients at greatest risk of poor communication.

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Differences in the Autonomic Reactivity Pattern upon Various Stressors in Patients with Rheumatoid Arthritis. Olga Malysheva[2], Petra Baum[2], Anke Voitzsch[1] and Christoph G. O. Baerwald[2]. [1]University Hopital, Leipzig, Germany, [2]University Hospital, Leipzig, Germany

Background: Stress is recognized as an important risk factor in the pathogenesis of rheumatoid arthritis (RA). However, it is still incompletely understood how the autonomic nervous system and the immune system interact in patients with RA.

Methods: To characterize the stress pattern in 90 RA patients the autonomic response upon various stressors the heart rate variability (HRV) test (ProSciCard III, Version 2.2a, Medi-Syst GmbH, Germany) was performed and compared to 30 osteoarthritis (OA) patients exhibiting equal distribution of age and gender. Standardized stress tests included mental arithmetic tasks to induce mental stress (MST), Ewing test, deep breathing test (DBT) and Valsalva maneuver (VM). HRV measures including frequency domain analysis (employing rapid processing of a 5 minute ECG rhythm strip) yielding measures of parasympathetic and sympathetic activity as well as the total power (TP) of autonomic nervous system influence on various parameters: high frequency (HF), low frequency (LF), and very low frequency (VLF) index of heart rate variability, variation coefficient (VC), and square root of the mean of the squares of successive R-R interval differences (RMSSD).

Results: At base line patients with RA were characterized by a combination of reduced TP as well as decreased parasympathetic activity compared to OA patients (TP: 4.79 $\pm$ 0.5 Hz vs. 10.5 $\pm$ 3.6 Hz; HF 1.47 $\pm$ 0.18 Hz vs. 4.6 $\pm$ 1.5 Hz, respectively, $p < 0.01$). Stress tests revealed a disturbed sympathetic activity in RA patients compared to OA patients in the MST (LF HRV: 1.69 $\pm$ 0.21 Hz vs. 3.05 $\pm$ 1.0 Hz, and LF/HF HRV: 1.1 $\pm$ 0.09 vs. 1.34 $\pm$ 0.06, $p < 0.05$, respectively) as well as in the DBT (RMSSD: 34.7 $\pm$ 2.16 ms vs. 46.5 $\pm$ 4.2 ms, and VC: 7.02 $\pm$ 0.4 vs. 9.46 $\pm$ 0.43, $p<0.05$, respectively). Comparing low disease activity RA patients (DAS $\leq$ 2.3, LDA) to RA patients with high disease activity (DAS $>$ 3.2, HDA) demonstrated a significant improvement in the sympathetic activity of LDA patients at base line (LF/HF HRV: 1.36 $\pm$ 0.1 Hz vs 0,87 $\pm$ 0.02 Hz, $p<0.01$) as well as in various stress tests (MST, Ewing test, VM). Furthermore, in RA patients with HDA the DBT showed a disturbed sympathetic activity compared to LDA RA patients (VC: 6.2 $\pm$ 0.2 vs 8.1 $\pm$ 0.3, $p<0.01$). Stratifying the patients for therapy revealed an increase of the parasympathetic tone at base line, as well in various stress tests (DBT, Ewing test), for RA patients under anti-TNF medication compared to methotrexate mono-

therapy (at base line RMSSD: 30.7 ± 1.8 ms vs. 26.1 ± 0.6 ms, LF/HF 0.88 ± 0.02 vs. 1.1 ± 0.02, respectively, $p<0.05$).

Conclusions: To study autonomic nervous system reactivity in RA patients a panel of standardized stress tests is mandatory. Our findings demonstrate that in RA patients the autonomic response to minor stress is characterized by a reduced sympathetic activity which is associated with disease activity. Therapeutic interventions leading to low disease activity in RA patients, e.g. anti-TNF therapy may modify the stress reactivity. Further studies are warranted to determine the role of the autonomic nervous system in the disease process of RA and the modulation of neuro-immune interactions by various medications.

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Disease Specific Cardiovascular Risk Factors in Patients with Rheumatic Diseases. Stefan Kleinert[2], Margret Breunig[1], Hans Peter T. Tony[3], Martin Feuchtenberger[4], Stefanie Bouma[1], Angermann E. Christiane[1], Georg Ertl[1] and Stefan Stoerk[1]. [1]Department of Cardiology, Med. Klinik 1, University of Wuerzburg, [2]Rheumatology / Clinical Immunology, Med. Klinik 2, University of Wuerzburg, Wuerzburg, Germany, [3]Rheumatology / Clinical Immunology, Med. Klinik 2, University of Wuerzburg, Wuerzburg, Germany, [4]Rheumatology/Clinical Immunology, Med. Klinik 2, University of Wuerzburg

Introduction: The increased cardiovascular risk in patients with rheumatic diseases (RD) may be attributed to traditional cardiovascular (CV) as well as to RD-specific risk factors. We aimed to identify RD-specific correlates of CV risk in patients with RD.

Methods: 628 consecutive patients attending the rheumatology outpatient department of the University Hospital were assessed regarding CV risk factors by structured history taking, questionnaires, ECG and laboratory measurements including natriuretic peptides (NT-proBNP). Screening for increased risk of CV disease was regarded positive (RISK+) if any of the following was present: European CV Risk Score (EURO-Score) ≥3% or NTproBNP >200 pg/ml or any pathological ECG pattern.

Results: Patients had rheumatoid arthritis (RA, n=333), spondylarthropathies (SpA, n=124), connective tissue diseases (CTD, n=145) and no RD (Control, n=73). For details of patients' characteristics see table 1 and 2.

	% female	Mean Age (years)	Disease Duration (years)	NSAR+	Steroids+	DMARD+	Biologic+
RA (1)	79	55	8.7	42%	66%	83%	20%
SpA (2)	37	44	9.3	55%	14%	49%	29%
CTD (3)	86	49	9.2	15%	49%	47%	1%
Control (4)	73	48	–	27%	13%	3%	0%

"+" indicates use of substance class

	DM	pAVK	Stroke	FamHx	Hypert	HLP	Smoker	ESC ≥ 3	ECG	BNP >200	RISK +
RA	15%	12%	2%	42%	38%	47	19%	32%	14%	18%	43%
SpA	10%	12%	1%	465%	24%	39%	33%	17%	16%	5%	32%
CTD	6%	16%	3%	49%	35%	40%	19%	18%	14%	17%	34%
Con	4%	12%	3%	61%	18%	32%	23%	22%	18%	14%	34%

DM=Diabetes mellitus, pAVK=peripheral artery disease, stroke=history of stroke, FamHx = family history of myocardial infarction, Hypert=Arterial Hypertension, HLP=Hyperlipoproteinemia, Smoker (ex)=current smoker, ESC=EURO-Score, ECG=Electrocardiogram, BNP=NTproBNP > 200 pg/ml, RISK+=at least one risk factor positive i.e. EURO-Score ≥3% or NTproBNP > 200 pg/ml or pathological ECG.

Logistic regression (dependent variable RISK+) was performed within the 4 groups using rheumatoid factor, disease duration, sex, haemoglobin, GFR, CRP, LDL-cholesterol, BSG, usage of NSAR, Steroids, DMARDs, or Biologicals, as well as DAS28 in RA. Odds ratio and 95% CI are reported. Positive correlates of RISK+ were **in the RA group:** use of DMARD 4.1 (1.49–11.30; p=0.006), disease duration 1.05 per year (1.01–1.09, p=0.011), LDL-cholesterol 1.01 per g/dl (1.00–1.03, p=0.017), and CRP 1.27 per mg/dl (1.00–1.61; p=0.048); negative correlates were: male sex 0.16 (0.07–0.39; p<0.001) and renal function (GFR per ml/min/kg 0.98 (0.96–0.99; p=0.007)).

In the SpA group a high CRP 2.25 per mg/dl (1.23–4.10, p=0.008) and haemoglobin 2.20 per g/dl (1.16–4.17, p=0.015) were associated with a worse risk profile.

Screening results in *patients with connective tissue diseases* were more likely to be positive in patients using DMARDs (3.73, 1.25–11.19, p=0.019) and less likely if patients were male (0.18, 0.04–0.85, p=0.031) and if renal function was good (GFR per ml/min/kg (0.96, 0.94–0.99, p=0.002)). In the *control group* male sex (0.17, 0.001–0.25; p=0.003) was associated with a reduced and ESR per mm (1.19, 1.003–1.42; p=0.003) with an increased risk profile.

Conclusion: In different rheumatic conditions disease-specific risk factors indicating an increased cardiovascular risk could be identified, justifying further cardiologic diagnostics and closer long-term follow-up.

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Do Men and Women Cope Differently with Disease Impact of Rheumatoid Arthritis, and If So, Why? Matthias Englbrecht[2], Laure Gossec[1], Anita DeLongis[3], Tore K. Kvien[4], Marieke Scholte-Voshaar[6], Tuulikki Sokka[5] and Schett Georg[2]. [1]APHP, Rheumatology B Department, Paris Descartes University, Medicine Faculty, Paris, France, [2]Department of Internal Medicine 3, University of Erlangen-Nuremberg, Erlangen, Germany, [3]Department of Psychology, University of British Columbia, Vancouver, Canada, [4]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [5]Jyvaskyla Central Hospital, Jyvaskyla, Finland, [6]Rheumatology, VU University Medical Center and Jan van Breemen Institute, Amsterdam, Netherlands.

Background: Coping with impact of disease is recognized as essential by RA patients(1). However, the knowledge of promising strategies to handle RA is still very limited and gender differences in coping have only been scarcely investigated. We therefore checked the use of a previously introduced 18-item questionnaire(2) during the validation process of the RAID-questionnaire(1).

Objectives: First, to investigate the usage of coping strategies among men and women. Secondly, to find reasons for eventually occurring differences.

Methods: We analyzed the data of 433 RA patients from 12 countries stemming from the RAID study database(1) and providing complete information on all coping items. Before the start of the validation process, two numeric rating scales asking for the extent of coping effectiveness and helplessness were added to the original coping questionnaire(2). First, we evaluated to which extent men and women are using cognitive reframing, pushing through the pain, emotional expression and active problem solving – the coping scales previously derived(2) from the questionnaire. We then addressed the question whether there are gender differences with respect to coping effectiveness and perceived helplessness. Finally, we set these results into relation to other common outcome variables measuring disease activity and health status.

Results & Conclusion: Men (N=99) and women (N=334) had longstanding (mean disease duration, men: 10.27±9.77yrs; women: 13.47±10.24yrs) and active (mean DAS28, men: 3.45±1.72; women 4.3±1.54) RA. Women made significantly more use of coping strategies when compared to men and showed a strong trend towards higher levels of perceived helplessness whereas coping effectiveness was not different.

Table 1. Descriptive data of coping scales and comparison of gender differences

	Mean ± SD (sample)	Mean ± SD (stratified for gender)		p Value	Significance test
Pushing Through The Pain*	1.90 ± 0.78	Male	1.79 ± 0.80	0.11	t-test
		Female	1.93 ± 0.77		
Active Problem Solving*	1.66 ± 0.87	Male	1.51 ± 0.86	0.04	t-test
		Female	1.72 ± 0.87		
Cognitive Reframing*	1.73 ± 0.79	Male	1.57 ± 0.79	0.03	t-test
		Female	1.78 ± 0.78		
Emotional Expression†	1.43 ± 0.74	Male	1.30 ± 0.74	0.04	t-test
		Female	1.47 ± 0.73		
Helplessness†	4.00 ± 2.75	Male	3.54 ± 2.60	0.06	t-test
		Female	4.13 ± 2.78		
Coping Effectiveness†	5.65 ± 2.22	Male	5.64 ± 2.19	0.94	t-test
		Female	5.66 ± 2.23		

*Scale ranging from 0–3 †Scale ranging from 0–10

We set these results into relation to measures of disease activity and found significantly elevated levels of the patient's and physicians evaluation of general health (VAS), the tender joint count 28, the HAQ-DI and accordingly

the DAS28 in female patients (all $p < 0.01$). Hence, female RA patients seem to have both, a higher disease activity and worse physical functioning. Therefore, they might be urged to cope more frequently with impact of disease, while tending to feel more helpless at the same time.

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Effects of HMG-CoA Reductase Inhibitor on Progression of Carotid Intima-Media Thickness and Arterial Stiffness in Rheumatoid Arthritis – A Randomized Controlled Trial. Lai-Shan Tam[3], Edmund K. Li[2], Qing Shang[3], Brian Tomlinson[3], Vivian W. Lee[3], Kenneth K. Lee[3], Martin Li[3], Woon-Pang Kuan[1], Tena K. Li[3], Lorraine Tseung[3], Gabriel Yip[3], Ben Freedman[4] and Cheuk-Man Yu[3]. [1]Hospital Selayang, Malaysia, [2]The Chinese University of Hong Kong, Hong Kong, China, [3]The Chinese University of Hong Kong, [4]University of Sydney

Objectives: To ascertain the efficacy and safety of rosuvastatin in the prevention of subclinical atherosclerosis and arterial stiffness markers in patients with rheumatoid arthritis (RA)

Methods: Fifty RA patients with stable disease activity (DAS<5.1 for at least 3 months) were randomized in a double-blind placebo-controlled trial to receive 10mg rosuvastatin (n=24) or placebo (n=26). Patients were prospectively followed every 3 monthly for 12 months. Intima-media thickness (IMT), augmentation index (AIx) and subendocardial variabilty ratio (SEVR) were measured at baseline, 6 and 12 months.

Results: Three out of 24 (12.5%) subjects in the rosuvastatin arm did not complete the study because of adverse event (n=1) and major flare (DAS> 5.1) requiring escalation of DMARDs (n=2), while 5/26 (19.2%) subjects had major flare requiring escalation of DMARDs in the placebo arm (p=0.704). Rosuvastatin resulted in statistically significant reductions of total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), apolipoprotien B (Apo B) and urate levels vs placebo. After 1 year, rosuvastatin treatment resulted in a mean (±SE) percent change of LDL-C: −35.8 ± 5.0 compared to placebo: 16.8 ± 10.5 ($p<0.001$). Comparing the changes within each group, significant reduction in the TC, HDL-C, LDL-C, Apo B, fibrinogen and urate levels were observed at 6 and 12 months compared with baseline in the rosuvastatin group.

Table 1. Changes in cardiovascular risk factors

		Baseline	6 months	12 months	p-value†
TC, mmol/L	Rosuvastatin	4.6 ± 0.8	3.3 ± 0.6*	3.3 ± 0.9*	<0.001
	Placebo	4.9 ± 0.9	4.9 ± 1.0	5.1 ± 1.0	
HDL-C, mmol/L	Rosuvastatin	1.7 ± 0.5	1.5 ± 0.4#	1.6 ± 0.4#	0.557
	Placebo	1.6 ± 0.4	1.6 ± 0.4	1.6 ± 0.5	
LDL-C, mmol/L	Rosuvastatin	2.5 ± 0.7	1.4 ± 0.5*	1.6 ± 0.8*	<0.001
	Placebo	2.7 ± 0.9	2.8 ± 1.0	3.0 ± 1.0#	
TG, mmol/L	Rosuvastatin	0.9 (0.7–1.1)	0.9 (0.6–1.1)	0.8 (0.6–1.2)	0.353
	Placebo	1.1 (0.8–1.7)	1.2 (0.8–1.7)	1.2 (0.9–1.6)	
Apo A1, mg/dL	Rosuvastatin	137 ± 42	149 ± 30	144 ± 31	0.804
	Placebo	144 ± 28	153 ± 35	142 ± 35	
Apo B, mg/dL	Rosuvastatin	87 ± 30	63 ± 21*	61 ± 29*	<0.001
	Placebo	95 ± 32	97 ± 39	98 ± 28	
Fibrinogen, g/L	Rosuvastatin	4.1 ± 0.7	3.8 ± 0.7#	3.8 ± 0.7#	0.468
	Placebo	3.9 ± 0.5	3.8 ± 0.7	3.7 ± 0.9	
Urate, mmol/L	Rosuvastatin	0.29 ± 0.10	0.26 ± 0.09#	0.26 ± 0.09#	0.01
	Placebo	0.30 ± 0.09	0.30 ± 0.09	0.31 ± 0.09	
Creatinine, μmol/L	Rosuvastatin	65.6 ± 15.7	65.4 ± 14.7	64.4 ± 13.5	0.205
	Placebo	65.9 ± 12.1	65.7 ± 11.9	66.8 ± 13.4	
BMI, kg/m2	Rosuvastatin	23.6 ± 3.1	23.9 ± 3.3	23.9 ± 3.4	0.952
	Placebo	22.7 ± 4.0	22.9 ± 4.1	22.9 ± 4.0	
SBP, mmHg	Rosuvastatin	130 ± 16	127 ± 17	130 ± 18	0.656
	Placebo	124 ± 15	125 ± 16	126 ± 17	
DBP, mmHg	Rosuvastatin	78 ± 9	80 ± 11	79 ± 11	0.671
	Placebo	78 ± 10	78 ± 10	78 ± 11	

Data are expressed as mean ± SD or median (interquartile range) unless specified otherwise. TC=total cholesterol, HDL-C=high density lipoprotein-cholesterol, LDL-C = low density lipoprotein-cholesterol, Apo A1=apolipoprotein A1, Apo B = apolipoprotein B, BMI=body mass index, SBP=systolic blood pressure, DBP = diastolic blood pressure. † General linear model with repeated measures. *p<0.01, #p < 0.05 compared with baseline using paired-t test.

The treatment group did not have a significant effect on the changes of the inflammatory markers. Nonetheless, a significant improvement in the DAS (2.7 ± 0.8 at baseline to 2.4 ± 1.0 at 1 year, $p<0.05$) and reduction of fibrinogen level (4.1 ± 0.7g/L at baseline to 3.8 ± 0.7g/L at 1 year, $p<0.05$) was observed compared with baseline in the rosuvastatin group.

Table 2. Changes in disease activity indexes and markers of inflammation.

		Baseline	6 months	12 months	p-value†
EMS, mins	Rosuvastatin	5 (0–30)	6 (0–60)	2 (0–30)	0.229
	Placebo	23 (0–60)	5 (0–38)	0 (0–30)∞	
Pain, VAS 0–10	Rosuvastatin	4.8 ± 2.3	5.0 ± 2.2	4.7 ± 2.3	0.453
	Placebo	4.1 ± 2.0	4.2 ± 1.6	4.1 ± 2.4	
Patient global, VAS 0–10	Rosuvastatin	4.4 ± 1.9	5.3 ± 2.2*	5.0 ± 2.5	0.684
	Placebo	4.3 ± 2.1	4.5 ± 2.1	4.5 ± 2.3	
Physician global, VAS 0–10	Rosuvastatin	1.3 (1.0–2.9)	1.5 (0.5–2.4)	1.0 (0–2.0)	0.843
	Placebo	3.0 (1.3–4.0)	2.0 (0.8–3.0)	1.8 (0.8–3.0)^	
Tender joints	Rosuvastatin	2.0 (1.0–5.0)	2.0 (0–3.0)	1.5 (0–3.0)	0.586
	Placebo	2.0 (0–7.0)	2.5 (0–5.0)	2.0 (0–4.3)	
Swollen joints	Rosuvastatin	1.0 (0–2.0)	1.0 (0–1.8)	0 (0–1.8)	0.676
	Placebo	1.5 (0–4.0)	1.0 (0–2.3)	0 (0–2.3)∞	
HAQ	Rosuvastatin	0.69 (0.50–1.13)	0.94 (0.41–1.38)	0.81 (0.50–1.47)	0.739
	Placebo	0.69 (0.13–1.28)	1.0 (0.22–1.38)	0.63 (0.13–1.38)	
ESR, mm/hr	Rosuvastatin	20 (14–45)	18 (13–47)	23 (13–49)	0.525
	Placebo	22 (11–40)	22 (8–46)	21 (6–45)	
CRP, mg/L	Rosuvastatin	2.9 (1.4–11.0)	3.0 (1.0–7.9)	3.1 (0.9–13.3)	0.705
	Placebo	5.8 (2.6–14.2)	3.7 (2.3–13.7)	4.4 (1.2–12.3)	
DAS28-CRP	Rosuvastatin	2.7 ± 0.8	2.5 ± 0.9*	2.4 ± 1.0*	0.459
	Placebo	2.8 ± 1.0	2.8 ± 1.0	2.6 ± 1.0	
WCC, $\times 10^9$/L	Rosuvastatin	6.2 (5.1–7.3)	5.5 (4.7–7.1)	6.7 (5.3–8.0)	0.140
	Placebo	6.5 (5.4–7.8)	6.6 (4.9–7.7)	6.8 (5.1–7.7)	

Data are expressed as mean ± SD or median (interquartile range) unless specified otherwise. EMS=duration of early morning stiffness, VAS=visual analog scale, HAQ=health assessment questionnaire, ESR=erythrocyte sedimentation rate, CRP=C-reactive protein, DAS28-CRP=28 joint disease activity score, WCC=white cell count. † General linear model with repeated measures. *p<0.05, #p<0.005 compared with baseline using paired-t tests. ^p<0.005, ∞p<0.05 using Friedman test.

The treatment group had a significant increase in the changes of the SEVR, but no significant effect was observed in the changes of IMT and AIx.

Table 3. Changes in intima-media thickness, augmentation index and subendocardial variability ratio.

		Baseline	6 months	12 months	p-value†
Mean IMT, mm	Rosuvastatin	0.90 ± 0.14	0.94 ± 0.14*	0.91 ± 0.14	0.877
	Placebo	0.92 ± 0.18	0.96 ± 0.18*	0.93 ± 0.16	
Maximum IMT, mm	Rosuvastatin	1.08 ± 0.20	1.08 ± 0.21	1.06 ± 0.20	0.386
	Placebo	1.11 ± 0.30	1.17 ± 0.30*	1.13 ± 0.25	
AIx @ 75, %	Rosuvastatin	32.5 ± 9.5	28.9 ± 10.0	31.3 ± 8.5	0.269
	Placebo	29.4 ± 8.8	30.6 ± 10.5	30.9 ± 10.4	
SEVR, %	Rosuvastatin	157 ± 28	148 ± 26*	163 ± 33	0.023
	Placebo	143 ± 18	144 ± 24	143 ± 26	

Data are expressed as mean ± SD. IMT=intima-media thickness, AIx @ 75 = augmentation index standardized to a heart rate of 75 b.p.m., SEVR=subendocardial variability ratio. † General linear model with repeated measures. *p<0.05 compared with baseline using paired-t tests.

Conclusions: Our data suggest that rosuvastatin has modest anti-inflammatory effect in RA patients with low disease activity in terms of reduction in DAS score and fibrinogen level. Rosuvastastin may also improve subendocardial perfusion and lower urate level. Future large scale randomized controlled trial will be required to ascertain whether statins can prevent progression of atherosclerosis in RA.

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Elevated Prevalence of Hypothyroidism in Female Inflammatory Arthritis Patients in Primary Care Amplifies the Prevalence of Cardiovascular Disease. Hennie G. Raterman[2], Mark M. J. Nielen[1], Mike J. L. Peters[2], Robert A. Verheij[1], Francois G. Schellevis[1] and Michael T. Nurmohamed[2]. [1]Netherlands Institute for Health Services Research (NIVEL), Utrecht, The Netherlands, [2]VU University Medical Center, Amsterdam, The Netherlands

Objectives: Inflammatory arthritis is an emerging risk factor for cardiovascular disease (CVD). Hypothyroidism is another CVD risk factor and appears related to inflammatory arthritis, best exemplified in secondary care arthritis patients. The aim of this study was, first, to compare the prevalence of hypothyroidism in inflammatory arthritis patients and a background population and, second, to study the association of hypothyroidism and cardiovascular disease (CVD) in subjects with and without inflammatory arthritis registered in primary care.

Methods: Data was used from the Netherlands Information Network of General Practice (LINH), which was retrieved from electronical medical records kept by a representative Dutch sample of 96 general practices with 360000 registered patients in 2006. Prevalences of hypothyroidism were calculated for subjects with and without inflammatory arthritis. Logistic multilevel multivariate regression analyses were used to study associations of hypothyroidism and CVD in inflammatory arthritis.

Results: Overall, the prevalence of hypothyroidism was 5.0 per 100 patients in inflammatory arthritis and 2.4 per 100 patients in control subjects ($p < 0.0005$). The prevalence of hypothyroidism in female arthritis patients was 6.5% compared to 3.9% in female control subjects ($p < 0.0005$). In female subjects the prevalence of CVD (14.3%) was significantly higher in hypothyroid inflammatory arthritis patients when compared to inflammatory arthritis patients (5.9%), hypothyroids (4.3%) and control subjects (2.1%) (see table 1, model 1). These results attenuated, but remained significant after adjustment for age, hypertension, dyslipidemia and diabetes (see table 1, model 2).

	Model 1* OR (95% C.I.)	Model 2† OR (95% C.I.)
Controls (n=84655)	1.0	1.0
Hypothyroidism (n=3471)	1.94 (1.63–2.31)	1.19 (0.99–1.43)
Inflammatory arthritis (n=910)	2.44 (1.83–3.24)	1.48 (1.10–2.00)
Hypothyroidism & inflammatory arthritis (n=63)	6.38 (3.10–13.12)	3.72 (1.74–7.95)

*Logistic multilevel multivariance regression analysis with CVD as outcome variable; crude analysis. †Adjustment for age, hypertension, hypercholesterolemia and diabetes only slightly changed associations

Conclusion: In primary care the prevalence of hypothyroidism is elevated in female inflammatory arthritis patients and is associated with an amplified CVD prevalence independent of traditional cardiovascular risk factors. Therefore, clinicians must be more aware of coexistence of other autoimmune disease like hypothyroidism, as our results indicate a synergistic effect of hypothyroidism and inflammatory arthritis patients for cardiovascular disease.

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Elevations in ApoC-III Containing Apolipoprotein Complexes Predict Coronary Atherosclerosis Progression in Rheumatoid Arthritis Patients. Joan M. Bathon[3], Michael Centola[4], Jon T. Giles[2], Nicholas Knowlton[5], Joshua Wages[5], Adam J. Payne[5], Guy Cavet[1] and Petar Alaupovic[5]. [1]Crescendo Biosciences, Inc., South San Francisco, CA, [2]Johns Hopkins Univ, Baltimore, MD, [3]Johns Hopkins Univ Ste, Baltimore, MD, [4]Oklahoma Med Research Foundation, Oklahoma City, OK, [5]Oklahoma Medical Research Foundation, Oklahoma City, OK

Purpose: Higher rates of cardiovascular (CV) associated events and mortality in rheumatoid arthritis (RA) cannot be accounted for with conventional lipid measures. However, alterations in the equilibrium among apolipoprotein complexes that traffic plasma lipids may have atherogenic consequences in RA.

Method: Apolipoprotein complexes were measured at baseline in RA patients participating in the Evaluation of Subclinical Cardiovascular Disease and Predictors of Events in Rheumatoid Arthritis (ESCAPE RA) study by precipitation and immunoturbidimetric analysis. Coronary artery calcium (CAC), a measure of coronary atherosclerosis, was assessed by cardiac computed tomography (CT) at two timepoints spanning approximately 3.5 years. Patients with a change in CAC ≥1 were designated as progressors, and patients with no change or improvement in CAC were designated as nonprogressors. Univariate comparisons were made using t-tests. To model all the ApoC-III containing complexes together, we combined them using a Principal Component Analysis (PCA). Multivariate analyses were performed using logistic regression.

Results: Baseline DAS 28 and ethnicity did not differ significantly between the groups ($p=0.53$ & $p=0.419$ respectively). However, gender and age distributions were significantly different between the groups, ($p=0.011$ & $p=0.009$, respectively). Of the 152 participants who had CAC measurements at two time points, 89 (59%) were progressors and 63 (41%) nonprogressors. Of the 12 apolipoprotein complexes measured, baseline mean values of 7 were statistically significantly higher in the progressors, compared to nonprogressors (see fig. 1). Interestingly, in contrast to the complexes not associated with progression, these 7 complexes all contain ApoC-III, which is predominantly a triglyceride carrier. All 7 complexes, when combined via PCA, were statistically associated with progression, both in crude analyses (OR 1.86; $p=0.003$) and after adjusting for Framingham Risk Score, age, and gender (OR 1.83; $p=0.016$).

Conclusion: Associations between ApoC-III plasma levels and CVD progression were more pronounced in RA patients than outcome associations of conventionally assessed lipoproteins (i.e. LDL-, HDL-cholesterol). Elevated plasma levels of apolipoprotein complexes containing ApoC-III particles were strongly predictive of progression of coronary atherosclerosis in RA. Elevation of these triglyceride rich particles is caused by defects in plasma triglyceride transport and metabolism, which may contribute to accelerated atherosclerosis in RA. These findings provide a means of developing a standardized assay to identify high risk CVD in RA patients and a potential therapeutic target for intervention.

Marker	Mean (SD) Nonprogressors	Mean (SD) Progression	P-Value
Triglycerides	105.57 (54.82)	146.07 (99.10)	0.002
VLDL	21.11 (10.96)	27.75 (14.32)	0.002
Apo B	93.22 (15.33)	100.65 (15.87)	0.004
LPA-II:B:C:D:E	14.65 (6.43)	17.37 (7.92)	0.021
LpB:C+LpB:C:E	8.3 (4.41)	10.28 (4.09)	0.006
ApoC-III	8.97 (2.99)	10.38 (4.17)	0.019
ApoC-III Heparin Precipitated	2.57 (1.02)	3.1 (1.60)	0.015
Framingham	0.05 (0.07)	0.09 (0.07)	0.002
ApoA1	145.34 (20.27)	140.88 (22.73)	0.206
Cholesterol	191.16 (40.23)	200 (39.89)	0.18
Age	57.13 (8.09)	60.7 (8.25)	0.009
Gender Female*	75% (0.44)	53% (0.50)	0.011

T-test - Nonprogressors (n=63, ΔCAC≤0), Progressors (n=89, ΔCAC>0) *Chi-squared Test

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Factors Associated with Upper and Lower Gastrointestinal Perforation in a Cohort of Patients with Rheumatoid Arthritis. Jeffrey R. Curtis[5], Angel Lanas[4], Winifred Werther[2], Ani John[2], David A. Johnson[1] and Kathy L. Schulman[3]. [1]Eastern Virginia Medical School, Norfolk, VA, [2]Genentech, a Member of the Roche Group, South San Francisco, CA, [3]Outcomes Research Solutions, Inc. Bolton, MA, [4]Universidad de Zaragoza, Zaragoza, Spain, [5]University of Alabama at Birmingham, Birmingham, AL

Purpose: To evaluate the incidence of upper and lower gastrointestinal (GI) perforation and to identify associated risk factors in a cohort of patients (pts) with rheumatoid arthritis (RA).

Methods: In this retrospective, claims-based study (January 2001-June 2009), pts aged >18 were selected from the MarketScan® databases if they had at least 2 diagnoses of RA (ICD 9 CM 714.0, 714.3), between 30 and 365 days apart, and at least 1 year of continuous enrollment (defining "baseline period") prior to the beginning of follow-up time. Pts were excluded if they had a baseline history of hospitalized GI perforation or any GI malignancy. A validated algorithm for identifying hospitalized GI perforation in claims data was used to identify the first upper GI (UGI) and first lower GI (LGI) perforation. Pts were followed up until the date of GI perforation, database disenrollment, or study end. The GI perforation rate was reported in years of observed person time (PY). A Cox proportional hazards model was used to estimate the relative risk of GI perforation in the first 12 months of follow-up as a function of baseline demographics (age, gender, region, population density), comorbidities (Charlson Comorbidity Index), and use of RA and GI medications during the baseline period. These medications included NSAIDs, corticosteroids, biologic agents, methotrexate (MTX), and other DMARDs.

Results: The study population included 143,433 RA patients (mean age [SD], 57.7 [14.1]; 74.8% female) with mean (SD) follow-up of 2.9 (1.9) years. Hospitalization with GI perforation occurred in 0.5% of pts (n=696), with 6.6% of patients dying during admission. At baseline, pts with GI perforation were older (57.6 vs. 62.0 years; $p<.0001$) than pts without perforation and had lower RA severity scores ($p=.01$) and higher Charlson Comorbidity scores ($p<.01$). Overall, the GI perforation rate per 1000 PY was 1.73 (95% CI, 1.61–1.86), with the majority of events concentrated in the LGI: 1.44 (1.32–1.55) vs. UGI 0.30 (0.24–0.35). The unadjusted GI perforation rate per 1000 PY was higher in pts aged ≥65 years (2.3), with exposure

to corticosteroids without accompanying NSAID (2.2), among pts with a pre-period history GI disturbance (3.4), specifically, diverticulitis (19.3), diverticulosis without diverticulitis (6.7), unspecified noninfectious gastroenteritis/colitis (4.9), esophageal or GI hemorrhage (4.2), ulcer (3.8), Crohn's disease (3.7), and ulcerative colitis (2.1). The adjusted relative risk of GI perforation associated with demographic and RA-related medications during the first year of follow-up is presented in the Table.

Conclusions: GI perforation is a rare but serious condition impacting patients with RA, most frequently in the LGI tract. The short-term risk of GI perforation increases with age and is highest among patients with a history of diverticulitis, diverticulosis, and exposure to corticosteroids and NSAIDs.

Table. Adjusted Relative Risk of GI Perforation by Significant (p<.05) Risk Factor

Baseline Parameter	Hazard Ratio	95% Confidence Limits	
		Lower	Upper
Age			
Age <40		Referent	
Age 40 to 64	2.60	1.21	5.58
Age 65 and older	3.55	1.63	7.76
Exposure to NSAIDS & corticosteroids			
No exposure to either NSAIDS or corticosteroids		Referent	
Exposure to NSAID, no corticosteroid	1.77	1.13	2.79
Exposure to corticosteroid, no NSAID	2.23	1.45	3.45
Exposure to both NSAID & corticosteroid	1.71	1.11	2.63
Exposure to MTX vs. no exposure to MTX	0.75	0.57	0.99
Diverticulosis without diverticulitis	4.26	1.73	10.45
Diverticulitis	15.47	8.57	27.93

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Fatigue in Inflammatory Arthritis: Clinical Characteristics, and Contributory Factors Following 6-Months of Anti-TNF Therapy. Patricia Minnock[1], Barry Bresnihan[3], Gabrielle McKee[2], Oliver FitzGerald[3] and Douglas Veale[3]. [1]Rheumatology Rehabilitation, Our Lady's Hospice and Care Services, Dublin, Ireland, [2]School of Nursing & Midwifery, Trinity College, Dublin, Ireland, [3]St Vincent's University Hospital, Dublin, Ireland

Background: The unique contribution of fatigue to the assessment of patients with inflammatory arthritis has been demonstrated. The aim of this study was to elucidate the clinical characteristics of, and contributory factors to, fatigue in patients with inflammatory arthritis prescribed anti-TNF therapy.

Methods: Patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA) commencing anti-TNF therapy underwent standard clinical assessment of disease activity and fatigue at baseline, 3-months and 6-months. Fatigue was measured using the multidimensional assessment of fatigue scales (MAF), validated for use in RA. The MAF comprises 16 questions concerning the quality, degree, distress, impact and timing of fatigue, compiled to give a final score of 1–50; a low score corresponds to a low level of fatigue. The clinical characteristics of, and the relationship between fatigue and 6 core outcome measures was evaluated.

Results: One-hundred thirty seven patients were evaluated (RA, 93; PsA, 44). Mean age (SD) years, and disease duration at inclusion were 52 (13), 12 (11), respectively. Both fatigue and the core outcome measures demonstrated a significant improvement over the 3-timepoints. Mean (SD) MAF levels were 27.5 (11.1) at baseline, 18.07 (12.1) at 3-months and 19.04 (11.8) at 6-months ($p<0.001$). Mean (SD) SJC were 7.6 (6.2) at baseline, 2.2 (3.1) at 3-months, and 1.6 (2.6) at 6-months ($p<0.001$). Mean (SD) TJC were 9.4 (7.8) at baseline, 2.9 (4.5) at 3-months and 2.6 (5.1) at 6-months ($p<0.000$). Mean (SD) Pain were 5.4 (2.1) at baseline, 3.5 (2.3) at 3-months and 3.5 (2.0) at 6-months ($p<0.000$). Mean (SD) GH were 5.9 (2.2) at baseline, 3.7 (2.4) at 3-months and 3.8 (2.1) at 6-months ($p<0.000$). Mean (SD) HAQ were 2.5 (1.0) at baseline, 0.78 (0.80) at 3-months and 0.75 (0.66) at 6-months ($p<0.003$). Mean (SD) CRP were 20.6 (25.4) at baseline, 71.0 (7.8) at 3-months and 8.8 (15.3) at 6-months ($p<0.000$). Tests were significant at the 0.01 level (2-tailed). Fatigue was moderately correlated with Pain 0.423 (0.578), (0.482); GH 0.425 (0.578), (0.500) and HAQ 0.470, (0.345), (0.344) ($p<0.001$) at baseline, at 3-months, and at 6-months, respectively. The strongest correlation found between fatigue and SJC (0.358) and TJC (0.409) were at 3-months only. All correlations were significant at the 0.01 level. The only variable that made a significant contribution to explanation of fatigue at 6-months was GH ($R^2=35\%$), $F=0.65$; $p=0.000$; Beta=0.345). At 6-months the relative independent variance in fatigue was 17%, greater than most of all the core clinical measures: HAQ 17%, SJC 16%, TJC 15%, CRP 14%, Pain 10%, GH, 10%.

Conclusion: Fatigue provides unique information in the assessment of outcome for patients with inflammatory arthritis which warrants further in-depth examination.

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Favorable Changes in the Lipid Profile in the First Year of Early Arthritis. Karin Britsemmer[1], Dirkjan van Schaardenburg[1], Willem F. Lems[2] and Michael T. Nurmohamed[1]. [1]Jan van Breemen Institute Amsterdam, [2]VU University Medical Center Amsterdam

Background: Several studies provided evidence for excess cardiovascular (CV) morbidity and mortality in rheumatoid arthritis (RA). The inflammatory process and traditional CV risk factors, e.g. dyslipidemia, are considered as the two major contributors to this excess CV disease. Recent studies suggested that abnormal levels of apolipoprotein A (ApoA-I) and apolipoprotein B (ApoB), and particularly the ApoB/ApoA ratio, is at least comparable with the total cholesterol:HDL-cholesterol ratio as predictor of CV morbidity. In this study we investigated the conventional lipid profile and levels of ApoA-I and ApoB in untreated patients with early arthritis and the effect of anti-rheumatic treatment on these levels after six and 12 months.

Methods: Patients from the Amsterdam Early Arthritis Cohort (EAC) with a disease duration of <2 years, at least 2 swollen joint and no prior DMARD treatment were studied. Patients with osteoarthritis, crystal arthropathy, connective tissue diseases and infectious arthritis were excluded. Lipid levels, inflammation markers and disease activity score (DAS28) were evaluated at baseline and after six and 12 months.

Summary of Results: The study population comprised 155 patients (mean age 53 [14], 72% female, median symptom duration 1.8 [IQR 1.1–3.7] months, median swollen and tender joint count 5 [3–10] and 7 [5–10], respectively, mean DAS-28 4.9 [1.4]). DMARDs were prescribed in 100% and 96% at 6 and 12 months, respectively. Biologic treatment was given in 2% and 32% at 6 and 12 months, respectively. Table 1 summarizes the mean lipid levels, disease activity markers and acute phase reactants at baseline and after 6 and 12 months. Total cholesterol, ApoA-I levels, LDL- and HDL-cholesterol increased significantly after 6 and 12 months of treatment. Since the changes were larger in HDL cholesterol and ApoA-I, this resulted in a decreased and more favorable total cholesterol:HDL ratio and ApoB:ApoA-I ratio. During the 12 months follow-up decreasing levels of CRP and DAS-28 were significantly associated with increasing levels of total cholesterol, ApoA-I and HDL-cholesterol and decreasing total cholesterol:HDL ratio and ApoB:ApoA-I ratio's.

Table 1. Lipid profile of 155 patients at baseline and after 6 and 12 months

	Baseline	*6 months (n=89)**	*12 months (n=45)***
Disease activity markers			
CRP, mg/L	8 (IQR 2–20)	2 (IQR 1–5)	2 (IQR 1–4.5)
DAS-28	4.9 ± 1.4	2.7 ± 1.2	2.9 ± 1.2
Lipid levels			
Total cholesterol, mmoles/L	5.07 ± 1.06	5.56 ± 1.07	5.59 ± 1.09
Apo A-I, gm/L	1.53 ± 0.31	1.70 ± 0.31	1.65 ± 0.32
Apo B, gm/L	0.84 ± 0.22	0.84 ± 0.21	0.82 ± 0.20
LDL, mmoles/L	3.06 ± 0.91	3.30 ± 0.93	3.35 ± 0.94
HDL, mmoles/L	1.27 (IQR 1.05–1.63)	1.49 (IQR 1.29–1.85)	1.57 ± 0.39
Total Cholesterol: HDL ratio	4.02 ± 1.32	3.66 ± 1.03	3.72 ± 0.97
Apo B:Apo A-I ratio	0.55 ± 0.17	0.50 ± 0.15	0.51 ± 0.16

* $p<0.007$ except for Apo B ** $p<0.03$

Conclusion: This is one of the first studies demonstrating that patients with early arthritis have favorable changes in the lipid profile after six and 12 months of treatment that ultimately may lower their CV risk. These changes in lipid profile, including the total cholesterol:HDL and ApoB:ApoA-I ratio, are significantly associated with decreasing levels of CRP and DAS-28.

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Free Fatty Acids Are Associated with Insulin Resistance but Not Coronary Artery Atherosclerosis in Rheumatoid Arthritis. Michelle J. Ormseth[2], Larry Swift[4], Sergio Fazio[4], MacRae F. Linton[4], Cecilia P. Chung[3], Paolo Raggi[1], Young-Hee Rho[2], Joseph Solus[4], Annette M. Oeser[5], Aihua Bian[4], Tebeb Gebretsadik[4], Ayumi Shintani[4] and C. Michael Stein[4]. [1]Emory University, [2]Vanderbilt University, Nashville, TN, [3]Vanderbilt University, Baltimore, MD, [4]Vanderbilt University, [5]VUMC 23rd Ave South Pierce, Nashville, TN

Background: Free fatty acids (FFA) affect insulin signaling and are implicated in the pathogenesis of insulin resistance and atherosclerosis. Inflammatory cytokines such as interleukin-6 (IL-6) increase lipolysis and thus FFA concentrations. Patients with rheumatoid arthritis (RA) have increased atherosclerosis that is associated with insulin resistance and higher IL-6 concentrations. Thus, a unifying mechanism underlying accelerated atherosclerosis in RA may be that increased IL-6 concentrations are associated with increased FFA concentrations resulting in insulin resistance and atherosclerosis.

Methods: Clinical variables, concentrations of non-esterified FFA and inflammatory cytokines, homeostasis model assessment for insulin resistance (HOMA), and coronary artery calcium (CAC) were measured in 166 patients with RA and 92 controls. We compared FFA concentrations in RA and controls using Wilcoxon rank sum tests and a multivariable linear regression that adjusted for age, race, sex and BMI. Among RA patients, we assessed the relationship between FFA and inflammatory cytokines, HOMA, and CAC scores using Spearman correlation and multivariable regression analysis.

Results: Patients with RA and controls were of similar age, race, sex and BMI. HOMA was significantly higher in RA (median [IQR]: 2.34 units [1.16–4.27]) than controls (0.83 units [0.54–1.79], $p<0.001$), as was CAC score (2.7 units [0.0–150.4] and 0.0 units [0.0–18.7], $p=0.016$). Triglyceride concentrations were similar ($p=0.18$), but LDL cholesterol was lower in RA than controls (111.0 mg/dL [88.0–135.0] and 122.0 mg/dL [104.0–145.0]) ($p=0.016$). FFA concentrations did not differ significantly in RA and controls (0.56 mmol/L [0.38–0.75] and 0.56 mmol/L [0.45–0.70], $p=0.75$). In RA, FFA concentration was positively correlated with CRP (rho=0.25, $p=0.001$), BMI (rho=0.16, $p=0.046$), HOMA (rho=0.20, $p=0.011$), triglycerides (rho=0.15, $p=0.048$), insulin (rho=0.18, $p=0.024$) and Framingham risk score (FRS) (rho=0.22, $p=0.005$); FFA were not correlated with IL-6 ($p=0.48$), TNF-α ($p=0.29$) or CAC score ($p=0.62$). After adjustment for age, race, sex and BMI, FFA remained associated with HOMA ($p=0.011$), insulin ($p=0.023$), CRP ($p=0.009$), triglycerides ($p=0.004$) and FRS ($p=0.048$).

Conclusions: FFA concentrations do not differ significantly in patients with RA and controls. In patients with RA, FFA concentrations are correlated with obesity, insulin resistance, CRP concentrations and FRS, but not with IL-6, TNF-α and CAC score. FFA may contribute to insulin resistance, but do not provide a mechanistic link between inflammation, insulin resistance and coronary atherosclerosis in RA.

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Gene-Environment Interaction Determines Interstitial Lung Disease in Rheumatoid Arthritis. Jose Felix Restrepo[2], Inmaculada del Rincon[4], Ricardo Zuniga[3], Samvel Pogosian[4] and Agustin Escalante[1]. [1]Univ of Texas HSC San Antonio, San Antonio, TX, [2]Univ of Texas HSC, San Antonio, San Antonio, TX, [3]University of Texas HSC, San Antonio, TX, [4]UTHSCSA, San Antonio, TX

Background: Interstitial lung disease (ILD) is a progressive fibrotic process of unknown cause that may affect rheumatoid arthritis (RA) patients. We examined the role of gene-environment interaction as a determinant of the presence of ILD in RA patients.

Method: We performed a cross sectional study of prevalence and factors associated with ILD in a cohort of RA patients. ILD was diagnosed using chest X-ray, CT scan, MRI, or lung biopsy. Patients with ILD were compared to RA patients without ILD or other pulmonary diseases. We used the following independent variables: age, gender, rheumatoid factor (RF), disease duration, DAS 28, ESR, smoking status, SF36 general health, global assessment of disease severity and activity, Steinbrocker functional class, modified HAQ, current or past use of metothrexate and current use of prednisone. HLA-DRB1 shared epitope (SE) was assessed using sequence-specific DNA primers. We used t-test for continuous variables; chi square and odds ratio (OR) for categorical variables and logistic regression for multivariable analyses, adjusting for confounders.

Results: The sample included 779 RA patients. Sixty nine of them (8.8%) had ILD. We compared them to the 563 patients without pulmonary disease. We excluded 147 patients who had other pulmonary conditions. Significant differences between the two groups included (mean in ILD vs non-ILD patients): age 60.2 vs 52.9 ($p<0.0001$), age of RA onset: 47.5 vs 42.7 ($p<0.004$), SF36 general health: 68 vs 62 ($p<0.01$), ESR: 58 vs 39 ($p<0.0001$),DAS28: 5.96 vs 5.37 ($p<0.002$), modified HAQ 2.04 vs 1.87 ($p<0.05$), diseases severity: 3.76 vs 2.77 ($p< 0.0004$)and Steinbroker functional capacity 2.40 vs 2.06 ($p<0.001$). For categorical variables, ILD was associated with nodules, OR (95% CI) = 1.85 (1.05, 3.2; $p<0.001$); rheumatoid factor,OR = 3.15 (1.32,9.10, $p<0.006$); male gender, OR = 3.33 (1.93, 5.7, $p<0.000001$), current prednisone, OR = 2.02 (95% CI, 1.17–3.5), smoking OR = 2.19 (1.23,4.04, and the SE, OR = 1.98 (0.99, 4.32). In multivariate analysis, male gender, OR = 3.08 (1.74, 5.44), RF, OR = 2.58 (1.04, 6.39), prednisone,OR = 1.77 (1.007–3.13); DAS28, OR 1.42 (1.17, 1.73) showed significant, independent association with ILD.

We tested the SE for interaction with smoking using product terms in logistic regression. Smoking was strongly associated with ILD in the presence, but not in the absence of the SE. (Table)

Shared Epitope	Smoking OR for ILD (95% CI)	p value
Negative	0.54 (0.15–1.9)	0.152
Positive	2.19 (1.1–4.5)	0.033

Conclusion: ILD is frequent in RA, and is associated with aging, male gender, nodules, active disease, positive RF and current use of prednisone. The SE was necessary for smoking to be associated with ILD, providing an example of gene-environment interaction. Further research should focus on the use of variables associated with ILD for early identification of patients at risk for ILD. Mechanistic research into the SE x smoking interaction would be of great interest.

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Glucocorticoid Use Is Not Associated with an Increased Risk of Cerebrovascular Accidents in Patients with Rheumatoid Arthritis. A Population-Based Study. Antonio Avina-Zubieta[1], Michal Abrahamowicz[2], Hyon K. Choi[4], M. Mushfiqur Rahman[1], Marie-Pierre Sylvestre[3], John Esdaile[1] and Diane V. Lacaille[1]. [1]Arthritis Res Centre of Canada, Vancouver, BC, Canada, [2]Department of Epidemiology and Biostatistics, McGill University, Montreal, QC, Canada, [3]Samuel Lunenfeld Research Institute, [4]Univ of British Columbia, Vancouver, BC, Canada

Purpose: While it has been shown that RA patients treated with glucocorticoids (GC) have an increased risk of coronary artery disease, the data available for cerebrovascular accidents (CVA) are scarce and controversial. We examined the effect of GC on risk of CVA in patients with rheumatoid arthritis (RA).

Methods: Using population-based administrative health data we assembled a cohort of 7,051 incident RA cases with disease onset between 1997 and 2001 with no history of CVA and no GC use prior to RA onset. Follow-up was until 2006. GC exposure was evaluated using four time dependent variables updated monthly: GC use, mean daily dose, total cumulative dose and total cumulative duration of use. CVA outcomes included acute thrombotic and hemorrhagic strokes, but not transient ischemic attacks, and were ascertained using ICD-9 codes (431, 434 and 436) from hospitalization and vital statistics data. To control for confounding by indication, wherein GC would be given to cases with more severe disease and/or less adverse cardiovascular profiles, we calculated propensity scores to control for the observed differences between GC users and non-users. We performed Cox-regression models to estimate the relative risk (RR) for CVA, adjusting for demographics, cardiovascular risk factors, RA characteristics, propensity scores and time-dependent prescription medications (methotrexate, Cox-2 inhibitors and other non-steroidal anti-inflammatory drugs).

Results: The mean age of the cohort was 56 yrs (57 and 54 for GC users and non users respectively) and 66% were females (70% and 64% for GC users and non-users respectively). Over a mean of 6 years of follow-up

(43,354 person-years), we identified 178 incident CVA cases (61 were fatal cases). The unadjusted stroke incidence rate was 4.1 per 1000 person-year in the RA cohort, 3.7 during GC exposure and 2.6 during non GC exposure. The directionality of the point estimates suggests a small non-significant effect in all adjusted models. The simplest time-dependent model that ignores dose and duration of exposure showed that GC use [yes/no] was not significantly associated with CVA (HR = 1.40, 95% CI; 0.83 – 2.37). Similarly, the model that accounts for current mean daily dose showed that current dose was not significantly associated with CVA (HR=1.01, 95% CI; 0.99 –1.04, for each mg increase in the current mean daily dose). In addition, cumulative duration of of use and total past cumulative dose were not significantly associated with CVA (RR = 1.01, 95% CI; 0.99 – 1.02 per month of use, and RR= 1.001, 95% CI; 1.000 – 1.002 per each gram accumulated in the past respectively).

Conclusions: This large population-based study indicates that GC use is not significantly associated with an increased risk of CVA in cases with RA. Our results may have important implications for people with RA and their treating physicians, when weighting the risks and benefits of using GC to treat RA.

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Heptavalent Conjugate Pneumococcal Vaccine (Prevenarâ) Elicits Similar Antibody Responses as 23-Valent Polysaccharide Vaccine (PPV) in Adult Patients with Established Arthritis. Meliha C. Kapetanovic[1], Carmen Roseman[2], Göran Jönsson[1], Lennart Truedsson[3], Tore Saxne[1] and Pierre Geborek[1]. [1]Dept of Clinical Sciences Lund, Section of Infectious Diseases, Lund University, Lund, Sweden, [2]Dept of Clinical Sciences Lund, Section of Rheumatology, Lund University, Lund, Sweden, [3]Dept of Laboratory Medicine, Section of Microbiology, Immunology and Glycobiology, Lund University, Lund, Sweden

Background: The immunogenicity of 23-valent polysaccharide vaccine (PPV) is debated. Heptavalent conjugate pneumococcal vaccine (Prevenarâ) has been shown to elicit better immune responses compared to PPV in children and healthy adults. Corresponding data in patients with inflammatory rheumatic diseases receiving immunosuppressive treatments is lacking.

Aim: To study immune response after vaccination with A) Prevenarâ in immunosuppressed patients with rheumatoid arthritis (RA) and patients with spondylarthropathy including psoriatic arthritis (SpA) not receiving immunosuppressive treatment compared to B) immunosuppressed RA patients and healthy controls vaccinated with PPV.

Patients and Methods: In total, 254 patients with RA on methotrexate alone, TNF-blockers as monotherapy or methotrexate +TNF blockers and 86 patients with SpA not treated with immunosuppressive drugs received a single dose (0.5 ml) of Prevenarâ. Altogether, 149 patients with RA receiving corresponding immunosuppressive treatments and 47 healthy controls were vaccinated with 0.5 ml of a single lot of PPV, as previously reported (ref). Levels of serotype specific IgG to 23 F and 6B were measured prior to vaccination and 4–6 weeks after vaccination using standard ELISA. Pre- and postvaccination antibody levels for each serotype and immune response (IR), defined as ratio between post- and prevaccination antibody levels, were compared between the groups. Differences in IR were analysed using univariate analysis of variance (ANCOVA) adjusted for age, gender, prevaccination antibody levels, and concomitant methotrexate /prednisolone treatment when appropriate.

Results: Pneumococcal vaccination resulted in significant increase in post-vaccination antibody levels in all groups compared to baseline levels for both serotypes. RA patients vaccinated with Prevenarâ gained in general similar postvaccination antibody levels and IR as those receiving PPV (Table1). SpA patients had better IR for serotype 23F compared to healthy controls who received PPV vaccine. Among Prevenarâ vaccinated RA patients, IR was similar in the respective treatment modalities as those receiving PPV.

Conclusion: Pneumococcal vaccination using conjugate vaccine elicits similar immune response as 23-valent polysaccharide vaccine in patients with established RA receiving immunosuppressive treatments. Pneumoccal conjugate vaccine did not give better immune response in general but may be better for some serotype.

Table 1. Demographic characteristics and immunization response (IR) for serotype 23 F and 6B in different groups vaccinated with Prevenarâor 23-valent polysaccharide vaccine (PPV).

	Prevenar		PPV	
	RA patients (N=254)	Spondylarthropathy patients (N=86)	RA patients (N=149)	Healthy controls (N=47)
Age (years) (mean)	60 (13)	52 (12)	55 (13)	36 (12)
Female (%)	80%	45%	72%	75%
Disease duration at vaccination (years)	16 (12)	12 (12)	16 (11)	–
Immunization response (IR) for 23F (median; min-max)	1.99 (0.51–740)	4.96 (0.17–120)*	2.02 (0.25–67)	2.28 (0.18–91)
Immunization response (IR) for 6B (median; min-max)	1.38 (0.38–100)	2.1 (0.24–129)	2.13 (0.8–280)	2.22 (0.40–75)

* p=0.005 between SpA and healthy controls (univariate analysis of variance; ANCOVA, adjusted for age, sex and prevaccination antibody levels)

Ref. Kapetanovic et al. *Rheumatology 2006; 45:110–116*

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Higher Prevalence of Coexisting Papillary Thyroid Cancer as Well as Autoimmune Thyroid Diseases in Patients with Rheumatoid Arthritis. Yeon-Ah Lee[3], Sang-Hoon Lee[1], Ran Song[2], Kyoung Min Son, Hyung-In Yang and Seung-Jae Hong[4]. [1]Seoul, Korea, Republic of, [2]Korea, Republic of, [3]Division of Rheumatology, Department of Internal Medicine, School of Medicine, KyungHee University, Seoul, Korea, Republic of, [4]Division of Rheumatology, Department of Internal Medicine, School of Medicine, KyungHee University

Background & Objectives: Although the exact pathophysiologic mechanisms of autoimmune diseases in various organs remain unclear, an accumulation of autoimmune diseases in individual patients has been observed. It has been well documented that rheumatoid arthritis (RA) is the most common autoimmune disease coexisting with autoimmune thyroid diseases(ATD) such as Graves' disease or Hashimoto's thyroiditis. However, few studies have been performed to investigate the incidence of thyroid cancers and nodules in RA patients. The goal of our study was to investigate the prevalence of concurrent thyroid diseases (ATD, thyroid nodules and thyroid cancers) in patients with RA compared to the control group involving age and sex matched subjects.

Methods: A case-control study was done in 110 RA patients and 101 osteoarthritis (OA) patients. We screened consecutive patients by thyroid ultrasonography (USG), regardless of the presence of palpable nodules. Patients with nodule(s) of 7 mm or greater were evaluated by fine-needle aspiration (FNA). Serum T3, free T4, thyroid stimulating hormone (TSH), anti-thyroglobulin antibodies (anti-TG), and anti-peroxidase antibodies (anti-TPO) were measured.

Results: The mean age was 55.2 ± 8.9 years in the RA patient group and 56.6 ± 8.5 years in the OA group. Thyroid nodule(s) were detected in 47.3% (52/110) among 110 RA patients, and in 56.4% (57/101) among 101 OA patients by USG. Among patients with thyroid nodule(s), 59 patients had nodule(s) of 7 mm or greater in size and 54 cases of them (92.0%) underwent FNA. Seven cases of thyroid cancer were histologically confirmed and all of them were papillary type. Six cases of 7 papillary thyroid cancers were RA patients. So, the cancer prevalence of sonographically detected thyroid nodules was at least 11.5 % (6/52) in RA patients and this was higher than in OA patients (11.5% vs 1.8%, P=0.052). Most of thyroid cancers(5/7) had a solid and hypoechoic pattern in USG. The positivity of anti-TG was significantly higher in RA (6% vs 0%, P=0.039) and the prevalence of ATD tended to be higher in RA patients than in controls (14.7% vs. 7.8%), although the difference was not statistically significant. Concurrent ATD comprised Hashimoto's thyroiditis (7 in RA, 4 in OA), and Grave's diseases (4 in RA). The most common thyroid dysfunction observed in both groups was subclinical hypothyroidism (9 in RA, 5 in OA). Other types of thyroid dysfunctions included overt hypothyroidism (3 in RA, 4 in OA), hyperthyroidism (4 in RA), and sick euthyroid disease (2 in RA).

Conclusions: In this study, concurrent thyroid diseases were relatively common in patients with RA and more interestingly, papillary thyroid cancers were detected dominantly in RA patients. Therefore, an extended diagnostic screening for accumulating thyroid diseases, especially Graves's disease and thyroid cancer, seems reasonable in patients with RA.

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Hospital-Based Surgical Procedures and the Risk of Perioperative Cardiovascular Events: A Comparison Study of Rheumatoid Arthritis and Diabetes Mellitus Using the National Inpatient Sample of the Healthcare Cost and Utilization Project. Ali Yazdanyar[2], Mary C. Wasko[3], Kevin L. Kraemer[3] and Michael M. Ward[1]. [1]National Institute of Arthritis and Musculoskeletal and Skin Diseases, [2]St Luke's Hospital, Bethlehem, PA, [3]University of Pittsburgh

Background: The association of rheumatoid arthritis with increased atherosclerotic burden has led some to equate the cardiovascular risk of rheumatoid arthritis (RA) with that of diabetes mellitus (DM). We compared the risk of perioperative cardiovascular outcomes among patients with RA, DM, both conditions, and neither.

Methods: This is a cross-sectional analysis of the National Inpatient Sample of the HealthCare Utilization Projects using data from years 1998 to 2002. We abstracted the diagnoses of RA, DM, potential confounding comorbidities and the principal surgical procedure using *International Classification of Diseases*, ninth revision codes. The principal surgical procedure was categorized into Low, Intermediate, and High risk according to established guidelines. The study endpoint was a composite cardiovascular outcome including an acute myocardial infarction, acute stroke, non-ST elevation MI, and/or congestive heart failure with pulmonary edema. Logistic regression accounting for survey design provided the adjusted magnitude of association between the covariates and the study endpoint.

Results: The total weighted frequency of hospitalizations with Low, Intermediate, and High risk principal procedures was 1 003 904, 6 011 950, and 277 010, respectively. The weighted frequency for individuals with RA without DM was 7 831, 92 005, and 1 767 for Low, Intermediate, and High risk surgical procedures, respectively. The weighted frequency of composite cardiovascular events in Low, Intermediate, and High surgical risk levels were 9 542, 38 542, and 31 772, respectively. The proportion of composite cardiovascular events was higher in DM as compared to RA patients for Low (1.63% vs. 0.81%), Intermediate (1.03% vs. 0.44%), and High (18.53% vs. 6.61%) risk surgical procedures. Relative to individuals without RA or DM, the adjusted odds of composite cardiovascular event in patients with RA without DM was 0.73 (95% confidence interval [CI]: 0.41, 1.30), 0.68 (95% CI: 0.54, 0.85), and 0.76 (95% CI: 0.47,1.22) for Low, Intermediate, and High risk surgical procedures, respectively. Relative to individuals without RA or DM, diabetics without RA undergoing a Low, Intermediate, and High risk surgical procedures had an adjusted odds of composite cardiovascular endpoint of 1.30 (95% CI: 1.16,1.45), 1.23(95% CI: 1.15,1.32), and 1.67(95% CI: 1.53,1.83), respectively.

Table. Odds of In-hospital Composite Cardiovascular Event by Risk Category of Principal Procedure

	Surgical Risk Category		
	Low OR (95% CI)	**Intermediate OR (95% CI)**	**High OR (95% CI)**
Characteristics			
Non-RA, Non-DM	1.00	1.00	1.00
RA, Non-DM	0.73 (0.41,1.30)	0.68 (0.54,0.85)	0.76 (0.47,1.22)
Non-RA, DM	1.30 (1.16,1.45)	1.23 (1.15,1.32)	1.67 (1.53,1.83)
RA, DM	1.48 (0.59,3.70)	0.91 (0.50,1.64)	0.84 (0.34,2.05)
Age, y			
18–50	1.00	1.00	1.00
50–75	2.61 (2.11,3.24)	12.53 (10.23,15.36)	3.10 (2.69,3.57)
>75	4.41 (3.45,5.63)	33.46 (27.54,40.66)	4.34 (3.74,5.03)
Gender			
Female	0.74 (0.66,0.82)	0.88 (0.84,0.92)	0.65 (0.61,0.70)
Comorbidities			
HTN	1.08 (0.97,1.19)	0.65 (0.61,0.69)	0.55 (0.50,0.61)
CHF	2.49 (2.20,2.83)	5.49 (5.16,5.85)	2.17 (2.00,2.35)
VHD	2.79 (2.16,3.59)	2.55 (2.22,2.94)	0.47 (0.41,0.54)
CKD	1.66 (1.21,2.28)	1.67 (1.36,2.06)	0.69 (0.53,0.89)
Admission Type			
Elective	0.24 (0.20,0.30)	0.45 (0.42,0.48)	0.15 (0.14,0.17)

Abbreviations: n, represents number; OR, Adjusted Odds Ratio; CI, Confidence internal; y, years; %, percent; SE, Lineared Standard Error; RA, rheumatoid arthritis; DM, diabetes mellitus; HTN, hypertension; CHF, congestive heart failure; VHD, valvular heart disease; CKD, chronic kidney disease. * Model adjusting for confounding covariates of age, gender, type of admission, and comorbidities including hypertension, congestive heart failure, valvular heart diseases, and chronic kidney disease.

Conclusions: Rheumatoid arthritis was not an independent predictor of perioperative cardiovascular events. In contrast, diabetes mellitus was associated with increased odds of cardiovascular outcomes across all surgical risk levels.

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Hypogonadism in Males with Rheumatoid Arthritis. Dannette S. Johnson and Robert W. McMurray. G.V. (Sonny) Montgomery VA and University of Mississippi Medical Center, Jackson, MS

Background: The pituitary-gonadal axis has significant immunoregulatory effects on autoimmune diseases and a role in the pathogenesis or modulation of rheumatoid arthritis (RA) has been suggested. We investigated the role of sex hormones on disease activity of male RA patients.

Methods: Levels of testosterone (T) and prolactin (PRL) were examined in male patients with a diagnosis of RA (n=67) from a Jackson subpopulation of the Veterans Affairs Rheumatoid Arthritis (VARA) registry. Serum T and PRL were determined by RIA in a blinded fashion and the correlation with disease activity and severity calculated.

Results: Patients had the following demographics (age=68.3 yrs (range 40–91 yrs), disease duration =14.5 yrs (range 1.7–32.5 yrs), RF positive =79%, CCP positive = 70%, mean DAS 28 = 3.2 ± 1.4). Although mean PRL levels were within normal limits with 5 patients being hypoprolactinemic and 3 with high PRL, hypogonadal patients had significantly higher prolactin levels (mean=8.02 ng/ml vs. 5.55 ng/ml, p=0.39) than patients with normal T. Mean T levels were 302 ± 121 ng/dl and there was no relationship to age or DAS28. A surprisingly high number (n=24; 36%) of male RA patients in this study were hypogonadal (T < 250 ng/dl) which was associated with higher BMI (p=0.001). There was no statistical relationship between low serum total testosterone and age, disease activity and severity, and corticosteroid or narcotic use. However, patients with hypogonadism had a trend toward higher CRP (mg/l) (mean= 14.96) that was >40% higher than those patients with normal T levels (CRP 8.95; p=0.08).

Table. Characteristics of male patients with RA.

	Low Testosterone (T < 250 ng/dl)	**Normal Testosterone (T ≥ 250 ng/dl)**	**P-value**
Testosterone (ng/dl)	183.5 ± 50	368.7 ± 94	
Prolactin (ng/ml)	8.02 ± 8	5.55 ± 2	0.039
Age	69.8 ± 10	67.5 ± 9	0.17
BMI	30.4 ± 6	26.1 ± 5	0.003
RF (+)	79%	79%	0.76
ACCP (+)	71%	70%	0.85
CRP (mg/l)	14.96 ± 24	8.95 ± 11	0.08
DAS28	3.3 ± 1.3	3.1 ± 1.4	0.28
Erosion on hand X-ray	58.3%	56.7%	0.95
Nodules	58.3%	44.2%	0.39

Conclusion: There was a high prevalence of hypogonadism in our male RA population. Hypogonadal men had higher prolactin levels and BMI and a trend toward higher CRP levels. These findings suggest hypogonadal men may fare worse overall and consideration should be given to screening testosterone in older men with RA.

Disclosure: D. S. Johnson: None; **R. W. McMurray:** None.

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Il-17 as a Novel Predictor of Vascular Damage in Rheumatoid Arthritis. Wendy Marder[2], Shokoufeh Khalatbari[3], James D. Myles[3], Rita P. Hench[2], Susan Lustig[1], Robert D. Brook[1] and Mariana J. Kaplan[2]. [1]Division of Cardiology, University of Michigan, [2]Division of Rheumatology, University of Michigan, Ann Arbor, MI, [3]Michigan Institute for Clinical and Health Research, Ann Arbor, MI

Background: The enhanced risk of premature cardiovascular risk is well recognized in patients with inflammatory diseases such as rheumatoid arthritis (RA). In addition to overt atherosclerosis, a significant proportion of RA patients have subclinical vascular disease, manifested as impaired endothelial function and increased arterial stiffness. While pro-inflammatory cytokines, particularly TNF-α, have been linked to the development of atherosclerosis and endothelial dysfunction in RA, the roles of other proinflammatory mediators such as IL-17 have not been systematically assessed. We analyzed candidate variables that could determine conduit and microvascular endothelial function and arterial compliance in a cohort of RA patients with low Framingham risk factors and overall low disease activity.

Methods: RA patients with stable disease and stable therapy for at least 3 months underwent flow-mediated dilatation (FMD) of the brachial artery, assessment of arterial compliance with SphygmoCor, and endothelium -dependent microvascular function with the Endo-PAT2000 device. Circulating biomarkers of CV damage were quantified by ELISA (ICAM-1, VCAM-1, MCP-1 and IL-17). Insulin resistance was quantified by HOMA2 and RA disease activity was quantified by DAS-28 score. Analysis was performed on 57 patients who were stratified into 2 subsets: 31 patients were on biologic therapy (with or without DMARDS) at the start of the study, and 26 patients were not on biologic therapy (with or without DMARD) at the start of the study. The RA group as a whole was also analyzed.

Results: Microvascular function for the overall group of RA patients negatively correlated with ESR (-0.40, $p=0.003$) and VCAM-1 (-0.40, $p=0.003$). In the group of patients on biologics, IL-17 was the factor that most strongly showed a negative association with microvascular endothelial function. Indeed, there was a significant negative correlation of serum IL-17 with reactive hyperemia pulse amplitude tonometry (-0.39, $p=0.03$), which persisted in multivariate regression analysis adjusting for known confounders. In contrast, arterial stiffness, which was assessed by aortic pulse wave velocity (PWV), was associated primarily with traditional CV risk factors. PWV significantly correlated with age and systolic blood pressure in the biologic-treated patients, the non-biologic treated patients, and the group as a whole (age: 0.53, $p=.004$, 0.63, $p=0.001$, 0.61, $p<.001$; SBP: 0.47, $p=.01$, 0.53, $p=0.01$, 0.54, $p<.001$ respectively). Higher levels of rheumatoid factor negatively correlated with microvascular and conduit endothelial function among patients on biologics (-0.40, $p=0.03$, -0.43, $p=0.02$ respectively), and conduit function among the group as a whole (-0.29, $p=0.04$).

Conclusion: The factors that are associated with alterations in microvascular function in RA patients differ from those that are associated with large vessel arterial stiffness, and are primarily related to the inflammatory milieu rather than to traditional risk factors. This study suggests that IL-17 may play a significant role in the development of microvascular dysfunction in RA, potentially leading to premature vascular damage.

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Incidence of Progressive Interstitial Pneumonia in Patients with Rheumatoid Arthritis. Yuko Takahashi, Hiroyuki Yamashita, Yo Ueda, Yuji Yoshida, Hiroshi Kaneko and Akio Mimori. Division of Rheumatic Diseases, National Center for Global Health and Medicine, Shinjyuku-ku, Tokyo, Japan

Objective: Rheumatoid arthritis (RA) often involves interstitial pneumonia (IP), and chronic IP is common in RA patients in the course of their disease. However, few reports have examined the incidence of progressive RA-IP needing steroid therapy. This study estimated the incidence based on our hospital records.

Methods: We used our complete database containing all 550 RA patients registered from 1990 to 2010; we obtained the number of inpatients that received steroid therapy for RA-IP during this period and the total observation years for each outpatient during the same period. As most registered RA patients are followed in our hospital, and not by family physicians, and they are almost always admitted to our hospital when they need hospitalization including treatment for pulmonary complications, the method met our purpose. Patients with IP that developed outside our observation of the RA, *i.e.*, patients referred because of IP, were excluded from the study.

Results and Discussion: During the 21-year study period, 127 cases of RA were treated for pulmonary complications accompanied by an interstitial shadow on a chest x-ray. Of these, 113 cases were excluded from the study for the following reasons: 59 cases of pulmonary infection and existing chronic IP or exacerbation of chronic IP due to infection; 10 cases of drug-induced pneumonia, including four of methotrexate-induced pneumonia; and 44 patients referred because of pulmonary complications, including infection, drug-induced pneumonia, and RA-IP. Of these last 44 cases, nine had progressive IP, which was a clue to diagnosing their RA. After excluding these 113 cases, the remaining 14 cases (14 patients) had progressive RA-IP during our observation and were treated successfully with steroid therapy. Of these, diagnoses based mainly on radiological findings indicated that four had nonspecific interstitial pneumonia (NSIP) and 10 cases had organizing pneumonia (OP, formerly called bronchiolitis obliterans with organizing pneumonia (BOOP)). From the total observation period of 3833 person-years, the calculated incidence of progressive RA-IP was 0.37%/year (14/3833).

Before this study, we estimated the incidence as 0.30–0.39%/year (8/2031–2635) based on our hospital records up to 2005, which included some ambiguity because of dropped-out patients. This study gave a similar incidence using additional patients enrolled up to 2010 and more precise information on the observation periods of the outpatients. Our RA patients had rarely been treated with biologics before 2005, whereas 38% of the patients had received at least one biologics therapy up until the present. Therefore, the incidence of progressive RA-IP may not be influenced by differences in antirheumatic therapy.

Conclusion: The incidence of progressive interstitial pneumonia caused by rheumatoid arthritis was calculated as 0.37%/year (14/3833).

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Infertility in Women with RA and Pregnancy Loss in Women with SLE Contribute to Smaller Than Desired Family Size. Megan E. B. Clowse[3], Eliza F. Chakravarty[1], Karen H. Costenbader[2], Christine D. Chambers[5] and Kaleb D. Michaud[4]. [1]Mountain View, CA, [2]Brigham & Women, Boston, MA, [3]Duke Univ Med, Durham, NC, [4]Univ of Nebraska Med Ctr, Omaha, NE, [5]University of California, San Diego

Purpose: Past studies have suggested that women with RA and SLE have diminished fecundity. We sought to understand the role of underlying RA or SLE upon family size.

Methods: A comprehensive reproductive history questionnaire was mailed to women diagnosed by a physician with RA (n=870) or SLE (n=237) participating in a US longitudinal observational study of rheumatic diseases. By disease, participants were divided into 2 main groups: those who had finished having children prior to diagnosis and those still interested in further children at the time of diagnosis. This second group was divided into 2 subgroups: those who had the same number of children that they wanted and those who had fewer children than they originally wanted. Comparisons were made by disease between the finished and not finished groups, as well as the women who had the same or fewer children than they wanted. Statistical analyses were performed using t tests and Fisher's exact tests in STATA.

Results: The response cohort consisted of 578 RA patients (66% response rate) and 114 SLE patients (48% response rate). Over 60% of women had finished childbearing at the time of diagnosis; these women were approximately 20 years older than women still interested in childbearing (see Tables 1 & 2). More than half of the women not finished with childbearing at the time of diagnosis ended up with a smaller family than they wanted.

Women who reported that they had fewer children than they desired had, on average, 1 less child than either women who had their children despite disease or had completed their family prior to diagnosis. For women with RA, those with fewer than desired children had significantly fewer pregnancies (2.2 vs. 3.2, $p < 0.01$) and a 1.5-fold higher rate of reported infertility compared to women with all of the children they desired. In contrast, women with SLE who had fewer children had a similar number of pregnancies but a 3-fold higher rate of miscarriage than those who completed their family despite SLE.

Concern about her ability to care for a child was the most common reason cited for limited childbearing (47%), followed by the risks of medications to a baby (38%) and physician guidance to avoid pregnancy (17%).

Conclusion: Young women diagnosed with RA and SLE are likely to have fewer biologic children than they wanted. Patient choice to avoid pregnancy may play a part, but much of this difference appears to be due to infertility in women with RA and pregnancy loss in women with SLE.

Table 1. Results from women with Rheumatoid Arthritis

	Not finished having children at time of diagnosis		Finished having children at time of diagnosis
	Fewer than desired children	Expected number of children	
Number of women (%)	120 (21%)	95 (16%)	363 (63%)
Mean age at diagnosis (SD)	26.9 (11)	25.8 (13)	45.6 (11)**
Mean current age (SD)	49.4 (11)	56.3 (14)*	62.2 (10)**
Number of pregnancies (SD)	2.2 (1.5)	3.2 (1.7)*	3.1 (1.5)**
Number of children (SD)	1.6 (1.0)	2.7 (1.5)*	2.6 (1.3)**
Number of miscarriages (SD)	0.5 (1.2)	0.5 (1.0)	0.5 (0.9)
Number reporting Infertility (%)	50 (42%)	27 (28%)*	65 (18%)**

* $p < 0.01$ for comparison between women who had fewer and the same number of children that they wanted. **$p < 0.01$ for comparison between women who had and had not finished having children at time of diagnosis.

Table 2. Results from women with Systemic Lupus Erythematosus

	Not finished having children at time of diagnosis		Finished having children at time of diagnosis
	Fewer than desired children	Expected number of children	
Number of women (%)	29 (25%)	16 (14%)	69 (61%)
Mean age at diagnosis (SD)	25.4 (12)	28.7 (13)	41.9 (11)**
Mean current age (SD)	52.0 (11)	50.4 (15)	55.4 (10)
Number of pregnancies (SD)	2.9 (1.8)	3.1 (1.0)	3.3 (1.7)
Number of children (SD)	1.6 (1.2)	2.7 (0.8)*	2.6 (1.3)**
Number of miscarriages (SD)	0.9 (1.6)	0.3 (0.5)	0.7 (1.2)
Number reporting Infertility (%)	5 (17%)	4 (25%)	9 (13%)

*$p < 0.01$ for comparison between women who had fewer and the same number of children that they wanted. **$p < 0.01$ for comparison between women who had and had not finished having children at time of diagnosis.

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1044

Interstitial Lung Disease in Rheumatoid Arthritis: Effect on Physical Function, Disability, Mental Health and Survival over a 10-Year Period. Inmaculada Del Rincon[2], Jose Felix Restrepo[3], Mrisa Sahai[2], Daniel F. Battafarano[1], L. Ricardo Zuniga-Montes[2] and Agustin Escalante[2]. [1]Brooke Army Medical Ctr, San Antonio, TX, [2]UTHSCSA, San Antonio, TX, [3]UTHSCSA, Bogota, Colombia

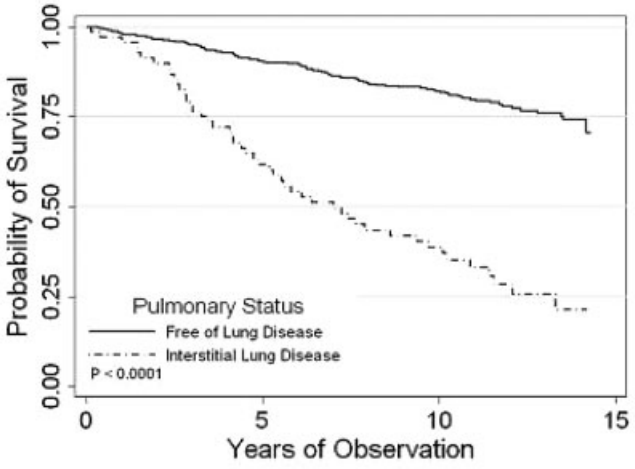
Introduction: Interstitial lung disease (ILD) is a serious complication of rheumatoid arthritis (RA), for which there are few therapeutic options. Moreover, information about how ILD affects the outcome of RA patients is limited. We examined the effect of ILD on physical function, disability, mental health and survival in a cohort of RA patients.

Patients and Methods: We studied patients with RA from rheumatology clinics. At the time of recruitment and yearly thereafter, medical records were reviewed thoroughly. ILD was diagnosed clinically using X-rays, CT scans, MRIs or biopsies of the lungs. At each yearly study visit, we performed tender, swollen and deformed joint counts, and measured the erythrocyte sedimentation rate (ESR). Patients also completed the SF36 questionnaire, the Center for Epidemiological Studies Depression (CESD) scale, timed tests of walking velocity over 50-feet and shirt button fastening, and a test of grip strength. We followed patients until they died, reached a censoring date, or were lost to follow-up. We compared outcome between patients with and without ILD using generalized estimating equations (GEE), adjusting for age, gender, follow-up time, the joint counts and ESR. To study the influence of ILD on survival, we plotted Kaplan Meier curves and used Cox proportional hazards to adjust for potential confounders.

Results: We studied 779 RA patients. Sixty nine of them (8.8%) had ILD, 147 (18.9%) had other pulmonary diagnoses, and 563 patients were free of lung diseases. Mean (95% CI) of the outcome measures in patients with ILD and patients free of lung disease, adjusted for demographics, joint findings and ESR are shown in the table.

	Velocity (ft/min)	Buttons/ minute	Grip (lbs)	Physical Function (SF36)	CESD
ILD	178 (162, 194)	7 (6, 8)	13 (11, 14)	55 (51, 58)	15 (14, 16)
No Lung Dz.	204 (199, 209)	8 (7, 8)	15 (14, 16)	60 (59, 61)	16 (14, 18)
P-value	0.002	0.03	0.02	0.006	0.3

Median observation time was 10.3 years per patient. Among ILD patients, 48 deaths occurred in 482 patient-years (9.9 deaths per 100); in patients free of lung disease, 113 deaths occurred in 5,444 person-years (2.1 per 100), hazard ratio 4.92 (3.51, 6.92). Mortality remained elevated in ILD patients, HR 3.14 (2.04, 4.85), even after adjusting for age, sex, joint findings and ESR.



Conclusion: We have provided detailed estimates of the influence of ILD on multiple aspects of RA outcome. ILD had a significant, independent negative impact on the physical function, disability and survival of patients with RA, but not on measures of mental health. A better understanding of the causes and pathogenesis of ILD in RA is needed to find ways to prevent and treat this complication.

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1045

Lower Extremity Ulcers in Rheumatoid Arthritis. David M. DeMaria[2], Christopher E. Attinger[1] and Victoria K. Shanmugam[2]. [1]Center for Wound Healing, Georgetown University Medical Center, Washington, DC, [2]Division of Rheumatology, Immunology and Allergy, Georgetown University Medical Center, Washington, DC

Lower extremity ulcers are a known complication of rheumatoid arthritis (RA). They are associated with longstanding uncontrolled RA. However, their prevalence has not been assessed since the advent of more effective biologic and non-biologic disease modifying anti-rheumatic therapies (DMARDs). The purpose of this study was to establish the prevalence of lower extremity ulcers in a modern day consecutive cohort of RA patients, and to report the features associated with ulcer development.

Methods: Consecutive patients evaluated in the Georgetown University Hospital Division of Rheumatology between June 2007 and June 2010 and fulfilling the ACR criteria for rheumatoid arthritis were identified using an ICD-9 diagnosis code search of the electronic medical record (Centricity, GE). Charts were reviewed for the presence of lower extremity ulcers during the study period. Demographic characteristics, rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) positivity, presence of comorbidities including venous and arterial disease, presence of other vasculitic manifestations of RA such as neuropathy and nodulosis, complement levels, inflammatory markers, biopsy findings and prothrombotic screen were noted.

Results: In the three years of this study 366 RA patients were evaluated, and 16 had active leg ulcers, giving a prevalence of 4.37%. Patients with ulcers were predominantly female (81.25%) and 56.25% were African American. All patients had erosive disease, and 62.5 % were RF or CCP positive. Ulcers were bilateral in 43.75%. The mean age at first ulcer was 64.81 $\pm$3.533 years. In 3 patients RA had previously been undiagnosed. In the remaining 13 patients the mean duration of RA at the time of ulcer development was 25.92 $\pm$ 4.944 years. In 37.5% of patients, the joint disease was in remission at the time of ulcer development. However at the initial visit mean ESR was elevated at 56.63 $\pm$ 7.591mm/hr, mean CRP was 5.928 $\pm$ 1.561 mg/dL and DAS-28 score was 3.836 $\pm$ 0.5460 suggesting ongoing inflammation. All patients had normal complement levels and negative SSA and B antibodies. Biopsy specimens were available in 12 cases. Only 3 had clear evidence of vasculitis, the biopsy was inconclusive in 5, 3 patients had gangrene and one had cholesterol emboli. Size of the initial ulcer ranged from 0.01 to 800 cm2. None of the patients in this study had significant titers of antiphospholipid antibodies, and the frequency of genetic prothrombotic states was similar to that reported in the general population. The mean duration of follow-up was 22.6 months but only 31.25% of ulcers were healed at the last follow-up visit. Due to the small sample size we were unable to

show a significant association between ulcer healing and use of biologic or non-biologic DMARDs.

Conclusions: Even in the era of biologic and non-biologic DMARD therapy, the prevalence of lower extremity ulcers in RA is 4.37%. We found healing rates of only 31.25% in 22.6 months of follow-up. Larger studies are warranted to evaluate the role of small vessel vasculitis in chronic wounds and to investigate the role of aggressive immune suppression even when the joint disease is in remission.

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1046

Lower Prevalence and Severity of "Vulnerable" Coronary Plaque in a-TNF-Exposed Asymptomatic Patients with Rheumatoid Arthritis (RA). George A. Karpouzas[1], Naser Ahmadi[2], Tae-Young Choi[2], Fereshteh Hajsadeghi[2], Silvia Munoz[2] and Mathew Budoff[2]. [1]Harbor-UCLA, Long Beach, CA, [2]Harbor-UCLA

Background: Tumor necrosis factor-a inhibitors (TNFi) have been recently reported to decrease the risk of myocardial infarction (MI) in patients (pts) with RA. The exact mechanisms, however, as well as the effects on coronary plaque quantity and composition are largely unknown. We prospectively evaluated the presence, total burden, and differences in the quality of coronary plaque in asymptomatic RA pts treated with TNFi vs. DMARDs alone.

Methods: We report on the first 74 of 150 recruited pts from a single center. Pt characteristics, including traditional risk factors and treatments are shown in table 1. Pts underwent 64+ slice cardiac Computed Tomography Angiography (CTA); this non-invasive modality includes an initial non-contrast phase assessing coronary calcium, followed by a contrast scan that detects plaque with equal accuracy to conventional angiography, and is superior in the assessment of non-calcified, lipid-rich, non-obstructive or "vulnerable" plaque. Individual coronary trees were evaluated for plaque volume and composition by standard methods (American Heart Association). Non-parametric tests were used for data analysis; regression models for plaque prevalence ratios (PR) and relative risk for plaque burden in TNFi vs. DMARD treated pts, adjusted for conventional risk factors were constructed.

Results: TNFi treated individuals had significantly longer disease duration (table 1). Despite that, they had significantly lower extent and severity of total plaque compared to DMARD treated pts; they exhibited lower numbers of affected coronary segments ($p=0.009$) and less total plaque burden score ($p=0.03$). More importantly, they displayed lower prevalence and severity of "vulnerable" plaque; TNFi exposed pts had significantly fewer segments harboring NC/ mixed plaque ($p=0.01$) and significantly lower NC/ mixed plaque burden score ($p=0.04$). TNFi treated pts had 76% less risk for the presence of "vulnerable" plaque ($p=0.006$) and 16% lower burden of NC/ mixed plaque risk vs. DMARD treated pts, adjusted for age, sex and Framingham RF ($p=0.03$).

n	DMARDs=27	TNFi=47	p-value
Age (yrs)	53 ± 12	53 ± 10	0.9
Gender (% female)	85	91	0.5
Disease duration (yrs)	7 ± 5.6	12 ± 7.6	*0.0004*
Diabetes (%)	11	9	0.6
Hypertension (%)	48	43	0.7
Smoking (%)	19	25	0.5
Family history of CAD (%)	4	4	0.9
Statin therapy (%)	41	35	0.6
DAS28-3v-ESR	2.8 ± 0.8	3.3 ± 1.1	0.1
ESR (mm/hr)	25.3 ± 18.5	26 ± 16.3	0.8
CRP (mg/dl)	0.7 ± 1.1	1 ± 1.7	0.4
Time on TNFi (months)	NA	51.8 ± 25.9	–
n (%) with plaque	17 (63)	28 (60)	0.7
n (%) total evaluated segments	108 (100)	188 (100)	–
n (%) diseased segments	34 (31.5)	33 (17.6)	*0.009*
Non-calcified/mixed calcified	27 (25)	24 (12.8)	*0.01*
	7 (6.5)	9 (4.8)	0.6
Total plaque burden score	3.9 ± 3.2	2.3 ± 3.3	*0.03*
Non-calcified/mixed calcified	3.6 ± 3.2	2.1 ± 2.8	*0.04*
	2.2 ± 3.1	3 ± 2.6	0.2
Prevalence Ratio for any plaque	1 (ref)	0.83 (CI:0.4–2.6)	0.67
non-calcified/mixed calcified	1 (ref)	0.24 (CI:0.09–0.6)	*0.006*
	1 (ref)	1.28 (CI:0.7–2.04)	0.49
Relative Risk-total burden score*	1 (ref)	0.85 (CI:0.74–0.99)	*0.03*
Non-calcified/mixed calcified	1 (ref)	0.84 (CI:0.09–0.6)	*0.03*
	1 (ref)	1.37 (CI:0.8–1.6)	0.38

*relative risk regression analysis: per standard deviation increase in burden score

Conclusion: TNFi-exposed asymptomatic RA pts have significantly lower prevalence and severity of total, but more importantly, "vulnerable" coronary plaque compared to DMARD treated pts, despite significantly longer disease duration. These findings insinuate additional favorable effects of TNFi on plaque homeostasis and stabilization and may reflect less future cardivascular morbidity.

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1047

Measuring Therapeutic Adherence in Rheumatoid Arthritis (RA) Using a Medication Event Monitoring System (MEMS®). Christian A. Waimann, Maria F. Marengo, Sofia de Achaval, Vanessa L. Cox, Araceli Garcia Gonzalez, Marsha N. Richardson and Maria E. Suarez-Almazor. The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Treatment adherence is an important aspect in RA. Multiple methods of measuring adherence have been proposed, with electronic monitoring considered one of the most accurate measures. The objective of our study was to electronically quantify adherence to oral disease modifying antirheumatic drugs (DMARDs) and prednisone in patients with RA.

Methods: This study was part of a 2– year prospective cohort of 201 patients from 2 publicly-funded county hospitals, in which 110 patients agreed to have their RA drug therapies electronically monitored with MEMS® caps (AARDEX). These are medication bottle caps with a microchip that records the time and date of bottle openings. Adherence to daily medications was determined as the percentage of days with correct number of doses taken. Adherence to weekly methotrexate (MTX) was determined as the percentage of doses taken within an interval of 7 ± 1.75 days. We also estimated percentage of prescribed doses taken (not considering dosing interval). MEMS® data was downloaded with each refill. Patient outcomes were assessed at baseline, 3, 6, 12, 18 and 24 months including functional status, Disease Activity Index 28 (DAS28), SF-12, Medical Outcome Study social support (MOS), Center for Epidemiologic Studies Depression Scale 10 items (CDES-10) and sociodemographic variables. 91% of the patients completed 2 years follow-up; for the remainder we used the last observation for analysis. The statistical analysis was carried out using SAS.

Summary of Results: 86% were female, 67% Hispanic, and 21% African-American; mean age was 49y(±11), disease duration 7y(±5), DAS28 4.1(±1.4),MHAQ 1.8(±0.5); 47% received monotherapy, 39% two DMARDs, 12% three DMARDs and 56% biologics (not oral, therefore not electronically monitored). Adherence of 5 drugs was electronically monitored (table). Adherence for doses taken on schedule (day/wk) was 59% for DMARDs and 61% all drugs. Only 21(20%) of patients had an average adherence ≥ 80%. At 2 years, these patients showed better patient self-reported disease activity and pain by VAS ($p<0.029$; $p<0.008$). No differences were observed for DAS28. Percent prescribed doses taken was greater than % days or weeks with correct doses taken, especially for MTX, suggesting lack of adherence with appropriate prescribed intervals. Patients with self-reported worse global status by visual analogue scale (VAS), and those with better mental health by SF12 MCS were statistically more likely to be adherent ($p<0.03$; $p<0.003$). Patients living alone, and those separated or widowed were less adherent ($p<0.008$; $p<0.003$). Social support (MOS) showed a borderline positive correlation ($r=0.18$, $p<0.06$).

Drug	N	Mean dose	Total days monitored	% prescribed doses taken on schedule	% prescribed doses taken
Methotrexate	69	16 mg/week	479 (±244)	56.1 (±24)	121.8 (±78)
Leflunomide	36	17 mg/day	389 (±266)	69.1 (±18)	80.7 (±17)
Hydroxychloroquine	31	243 mg/day	494 (±256)	58.5 (±22)	75.8 (±21)
Sulfasalazine	6	891 mg/day	394 (±344)	50.5 (±27)	73.0 (±28)
Prednisone	58	6 mg/day	437 (±274)	65.1 (±20)	79.1 (±30)
Average DMARDs	101	–	–	59.1 (±22)	101.1 (±65)
Average all drugs	110	–	–	61.1 (±21)	94.1 (±43)

Conclusion: On average, RA patients showed 61% correct medication intake, with only 1 in 5 taking oral therapies as prescribed at least 80% of the times. Long-term cohort studies should evaluate the impact of non-adherence on RA outcomes.

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1048

Polyautoimmunity and Autoimmune Aggregation in Rheumatoid Arthritis. Adriana Rojas-Villarraga[1], Ricardo A. Cifuentes[3], Diana Botello-Corzo[3], Antonio Iglesias-Gamarra[4], Ruben D. Mantilla[5] and Juan-Manuel Anaya[2]. [1]Center for Autoimmune Diseases Research (CREA), Universidad del Rosario, [2]CREA, Universidad del Rosario, Bogota, Colombia, [3]CREA, Universidad del Rosario, [4]Rheumatology Unit, Universidad Nacional, [5]Riesgo de Fractura-CAYRE IPS

Objectives: Characterization of the extent to which particular combinations of autoimmune diseases occur in excess of what could be expected as a result of chance may offer new insights into possible common pathophysiological mechanisms. The goal of this study was to investigate the spectrum of polyautoimmunity [i.e. autoimmune diseases (Ads) co-occurring within patients], familial autoimmunity (i.e. diverse Ads co-occurring within families) and aggregation in patients with rheumatoid arthritis (RA).

Methods: This was a cross-sectional study in which 304 consecutive patients with RA (ACR criteria) and their nuclear families were included. The history of 23 Ads was investigated. A multivariate logistic regression analysis was performed in a search for risk factors that were significantly associated with the presence of polyautoimmunity. Aggregation (λ_R) was obtained by the ratio between the prevalence of Ads in relatives and the current prevalence of Ads in the general population.

Results: There were 98 (32.3%) patients presenting with at least one other AD. A total of 116 Ads were observed in patients of which the most frequent were autoimmune thyroid disease (AITD), Sjögren's syndrome (SS) and antiphospholipid syndrome (APS), registered in 64 (21.1%), 36 (11.8%) and 8 (2.6%) cases respectively. Of the patients with polyautoimmunity, 16 (16.3%) presented with multiple autoimmune syndrome (i.e., two or more Ads in addition to RA). Female gender (AOR: 2.8, 95%CI:1.22–6.31), cardiovascular disease (AOR: 2.2, 95%CI: 1.17–3.94) and the presence of antinuclear antibodies (AOR: 2.0, 95%CI: 1.08–3.84) were risk factors for polyautoimmunity. Seventy-three families (24%) had at least one first degree relative (FDR) with an AD. Of the 571 FDR in these 73 families, 145 (25%) had one or more AD. The most frequent Ads registered in FDR were AITD (9.5%), RA (4%) and systemic lupus erythematosus (1.4%), with a λ_R of 3.5, 8 and 7 respectively.

Conclusion: Polyautoimmunity and familial autoimmunity are frequent in RA and influenced by clinical and immunological features. These findings support the hypothesis that clinically different autoimmune phenotypes might share common susceptibility variants.

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1049

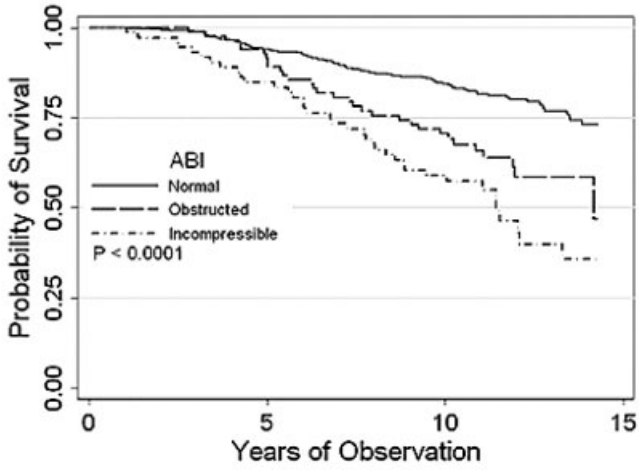
Prediction of 10-Year Cardiovascular and All-Cause Mortality in Rheumatoid Arthritis Using the Ankle-Brachial Index. Carlos Ramirez[3], Agustin Escalante[2], Mrisa Sahai[3], Daniel F. Battafarano[1], Samvel Pogosian[3] and Inmaculada Del Rincon[2]. [1]Brooke Army Medical Ctr, San Antonio, TX, [2]UTHSCSA, San Antonio, TX, [3]UTHSCSA

Introduction: The ankle-brachial index (ABI) is a non-invasive test of lower limb arterial function that can be readily performed at the bedside. It provides information about arterial flow obstruction and also about arterial wall rigidity. The ABI is frequently abnormal in rheumatoid arthritis (RA) patients. However, this is not often recognized, and its clinical significance is underappreciated. We examined the association between the ABI and 10-year cardiovascular (CV) and all-cause mortality in an RA cohort.

Methods: We studied a cohort of RA patients recruited from private and public rheumatology clinics. We measured the ABI as the systolic pressure of the lower limb arteries divided by that of the brachial arteries. A normal ABI varies from 0.91 to 1.3; while ABI $\leq$ 0.9 is considered obstructed, and ABI $>$ 1.3 is incompressible. Vital status of patients was updated annually. All reports of death were confirmed by death certificate. CV deaths were defined by any mention of a CV condition in the death certificate. We plotted Kaplan-Meier survival curves, and used Cox proportional hazards regression to adjust for potential confounders.

Results: We measured the ABI in 644 RA patients, among whom it was normal in 489 (76%), obstructed in 83 (13%) and incompressible in 72 (11%). Observation time from enrollment until death or last follow-up was 6,498 patient years (a median of 10.4 years per patient). During this time, 160 deaths occurred, for a mortality rate of 2.5 per 100 patient-years (95% CI 2.1, 2.9). Of these deaths, 90 were due to CV causes, for a CV mortality rate of 1.5 per 100 patient-years (1.2, 1.9). CV mortality rates per 100 patient years among patients with a normal ABI was 1.1 (0.8, 1.4); among patients with obstructed ABI mortality was 2.1 (1.3, 3.5), hazard ratio (HR) 2.0 (1.1. 3.6); and in patients with incompressible ABI CV mortality was 5.5 (3.1, 6.7), HR 4.4 (2.7, 7.2). Multivariable adjustment for demographic variables, measures of RA activity and damage and CV risk factors, attenuated the association of mortality with arterial obstruction, but did not efface that with incompressible lower limb arteries. The Figure shows a Kaplan-Meier plot of the all-cause survival function according to ABI.

Conclusion: Incompressibility of the peripheral arteries in RA patients is associated with increased CV and all-cause mortality. The ABI, a non-invasive test performed at the bedside with readily available equipment, is a potentially useful method to stratify mortality risk in RA.



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Prevalence and Predictors of Pain in Rheumatoid Arthritis Patients in DAS28 Remission. Yvonne C. Lee[1], Jing Cui[3], Bing Lu[2], Michelle Frits[3], Christine K. Iannaccone[3], Nancy A. Shadick[4], Michael E. Weinblatt[4] and Daniel Hal Solomon[4]. [1]Brigham & Womens Hospital, Boston, MA, [2]Brigham and Women's Hospital, Foxboro, MA, [3]Brigham and Women's Hospital, Boston, MA, [4]Brigham and Womens Hospital, Boston, MA

Background: Physicians often presume that inflammation is the stimulus for pain in rheumatoid arthritis (RA), but many patients have pain despite well-controlled disease. We assessed the prevalence of pain in RA patients in remission according to Disease Activity Score (DAS28) and examined the associations between baseline characteristics and ongoing pain despite remission.

Methods: One hundred and sixty-four RA patients in DAS28 remission (DAS28 $<$ 2.6) completed questionnaires and underwent physical examination, blood work and hand radiographs at baseline and one year. Pain severity was assessed using the pain score from the Multi-Dimensional Health Assessment Questionnaire (MDHAQ). The association between baseline clinical predictors and clinical pain severity at one-year was assessed using multivariable linear regression.

Results: Twenty-eight patients (18.7%) in DAS28 remission had an MDHAQ pain score $\geq$ 40 at baseline. Thirty-five (22.0%) had an MDHAQ pain score $\geq$ 40 at one year. In unadjusted analyses, baseline MDHAQ pain score, MDHAQ sleep score, MDHAQ fatigue score, Arthritis Self Efficacy score and smoking were significantly associated with MDHAQ pain score at one year. Baseline Sharp score, C-reactive protein level (CRP) and DAS28 were not significantly associated with MDHAQ pain score at one year. In multivariable linear regression analyses adjusted for age and gender, baseline MDHAQ pain ($P <$ 0.0001) and MDHAQ fatigue ($P = 0.002$) remained significantly associated with one-year MDHAQ pain score (see table).

Table. Association between baseline MDHAQ pain severity and baseline MDHAQ fatigue levels and MDHAQ pain at one year among rheumatoid arthritis patients in DAS28 remission (N = 164).

Clinical Factors	Mean One-Year MDHAQ Pain Score (95% CI)	*P**
Age		**0.04**
< 50	27.8 (21.8,33.9)	
50–59	30.8 (24.4,37.2)	
≥ 60	21.7 (16.1,27.3)	
Gender		0.18
Female	23.9 (20.7,27.2)	
Male	29.6 (21.8,37.4)	
Baseline MDHAQ pain (0–100)		**<0.0001**
< 10	16.6 (10.7,22.6)	
19–29	22.4 (16.7,28.2)	
> 30	41.2 (33.7,48.7)	
Fatigue (0–100)		**0.002**
< 20	19.0 (12.4,25.5)	
20–49	26.3 (19.7,32.9)	
≥ 50	35.0 (29.1,40.9)	

*P-values from multiple linear regression, adjusted for age and gender.

Conclusion: Despite being in DAS28 remission, many RA patients still experience pain. In this cohort, RA-associated factors (e.g., Sharp scores, CRP and DAS28) were not significantly associated with pain severity at one year, but baseline pain severity and fatigue were strongly associated with pain severity at one year. These findings suggest that physicians should consider non-inflammatory etiologies of pain, such as a central sensitivity/symptom intensification syndrome, when evaluating pain in RA patients in remission.

Disclosure: Y. C. Lee: Merck Pharmaceuticals, 1, Novartis Pharmaceuticals Corporation, 1; **J. Cui:** Biogen Idec, 2, Crescendo Bioscience, Inc., 2; **B. Lu:** Biogen Idec, 2, Crescendo Bioscience, Inc., 2; **M. Frits:** Biogen Idec, 2, Crescendo Bioscience, Inc., 2; **C. K. Iannaccone:** Biogen Idec, 2, Crescendo Bioscience, Inc., 2; **N. A. Shadick:** Amgen Inc., 2, Biogen Idec, 2, Crescendo Biosciences, 2; **M. E. Weinblatt:** Biogen Idec, 5, Crescendo Biosciences, 5; **D. H. Solomon:** Abbott Laboratories, 2, Amgen Inc., 2, Bristol-Myers Squibb, 9.

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Rheumatoid Arthritis Patients in Clinical Remission Manifest Persistent Joint Inflammation on Histology and Imaging. Allen P. Anandarajah[1], Ralf G. Thiele[2], Johnny Monu[4], Gwy-Suk Seo[3], Aqiba Bokhari[3] and Christopher T. Ritchlin[5]. [1]Univ of Rochester Med Ctr, Rochester, NY, [2]University of Rochester, Rochester, NY, [3]University of Rochester, [4]University of Rochester Med Ctr, [5]University of Rochester Medical Center, Rochester, NY

Background: Disease remission in rheumatoid arthritis (RA) has been defined clinically as the absence of evidence of disease activity. Several studies have shown, however, that patients in remission have persistent synovitis on ultrasound (US) and Magnetic Resonance Imaging (MRI). A central question is whether abnormal imaging findings in remission represent active joint inflammation.

Objective: To examine if patients in American College of Rheumatology (ACR) remission have persistent inflammation on histological analysis of synovial tissues and abnormal findings on ultrasound (US) and/ or magnetic resonance imaging (MRI),.

Methods: 13 synovial (joints) specimens were obtained from 12 RA patients in clinical remission as defined by the revised ACR criteria. Synovial specimens were obtained during surgical procedures on knee (5), hip (2), elbow (1), wrist (3), shoulder (1) and thumb (1). Histological specimens were scored for hyperplasia of synovial lining and synovial stroma, inflammation, lymphoid follicles and vascularity on a scale of 0–4 (absent, minimal, mild, moderate and severe) and a total score calculated by adding the individual scores (0–20). The total scores were classified as minimal (0–5), mild (6–10), moderate (11–15) or severe (16–20) disease activity. Nine of 13 joints also had US and/or MRI done prior to surgery. US was assessed for effusion, tenosynovitis, synovitis on grey scale and Doppler signal. MRIs were evaluated for bone marrow edema (BME), synovial proliferation, effusion and erosion. The biopsy specimens were scored by a pathologist and the imaging studies scored by 2 radiologists and a rheumatologist who were blinded to other results.

Results: The 12 patients comprised 10 females and 2 males with median disease duration of 2 years (range 1–20). Four of 12 patients were on anti-TNF therapy, 5 on methotrexate (MTX) alone, 3 on MTX and hydroxychloroquine (HCQ) and 1 on HCQ and sulfasalazine. The median histology score for the 13 specimens was 12 (moderate disease activity). Three specimens had severe, 6 moderate, 2 mild and 2 minimal disease activity on histology. Thickening of the synovial lining and stroma was seen in all patients. Inflammatory tissue was comprised mainly of lymphoplasmacytic cells in all specimens and neutrophils were noted in 6. Vascularity was also noted in all specimens (median score of 3). Interestingly, the 3 of 4 specimens with minimal and mild disease were subjects on anti-TNF therapy while the other was on methotrexate. Synovitis on US (grey scale)was seen in all 9 joints. Doppler signal was present in 5 of 6, effusion in 7 of 9 and tenosynovitis in 2 of 3 joints examined. All 4 joints that had MR images revealed synovitis, erosion and BME and one was also with effusion

Conclusion: Despite clinical remission, histology and imaging studies documented a persistently active disease state that may benefit from more aggressive therapy. Anti-TNF therapy may be more effective at suppression of disease activity than traditional DMARDs. Future studies will determine if this state is associated with disease progression.

Disclosure: A. P. Anandarajah: Abbott Immunology Pharmaceuticals, 8, Amgen Inc., 8, Pfizer Inc, 8, UCB, Inc., 8; **R. G. Thiele:** Abbott Immunology Pharmaceuticals, 8, Amgen Inc., 8, Pfizer Inc, 8; **J. Monu:** None; **G.-S. Seo:** None; **A. Bokhari:** None; **C. T. Ritchlin:** None.

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Rheumatoid Arthritis Patients Receive Less Frequent Acute Reperfusion and Secondary Prevention after Myocardial Infarction. Sharon Van Doornum[4], Caroline Brand[3], Vijaya Sundararajan[1], Andrew Ajani[3] and Ian Wicks[2]. [1]Monash University, [2]Royal Melbourne Hospital, Melbourne, Australia, [3]Royal Melbourne Hospital, [4]University of Melbourne, Victoria, Australia

Introduction: The 30-day case fatality rate after acute myocardial infarction (MI) for rheumatoid arthritis (RA) patients is twice that of the general population.[1] This study compared the frequency and timeliness of early reperfusion therapy and treatment with secondary prevention medications after acute MI in RA patients and controls.

Methods: We performed a structured medical chart review of RA patients and matched controls who had been admitted with acute MI to one of three hospitals in Victoria, Australia between 1995 and 2005. The administration and timing of acute reperfusion therapy and in-hospital treatment with secondary prevention medications was compared between the two groups. Acute reperfusion was defined as thrombolysis or percutaneous coronary intervention (PCI) within 12 hours of first symptom of MI.

Results: The medical charts of 90 RA patients and 90 matched controls were reviewed. Demographic details, cardiovascular risk factors and other co-morbidities of the RA and control patients are shown in Table 1.

Table 1. Demographic and clinical features of the RA and control patients acute MI

	RA (n = 90)	Controls (n = 90)
Female, n (%)	55 (61)	55 (61)
Age in years, mean (SD)	71 (10)	71 (10)
RA disease duration in years, mean (SD)	20 (13)	–
No. of DMARDs, mean (SD)	1.4 (1.1)	–
Taking NSAID at time of MI, n (%)	21 (23)	6 (7)*
Pre-existing co-morbidities:		
Ischemic heart disease, n (%)	31 (34)	33 (37)
Prior MI, n (%)	10 (11)	11 (12)
Non-cardiac vascular disease, n (%)	26 (29)	14 (15)*
IDDM, n (%)	3 (3)	1 (1)
NIDDM, n (%)	22 (24)	27 (30)
Hypertension, n (%)	52 (58)	56 (62)
Hypercholesterolaemia, n (%)	22 (24)	38 (42)*
Current smoker, n (%)	14 (15)	16 (18)
Congestive cardiac failure, n (%)	15 (17)	11 (12)
Chronic lung disease, n (%)	28 (31)	16 (18)
Chronic renal impairment, n (%)	15 (17)	8 (9)

*$p < 0.05$

Table 2 shows the treatment received by the RA and control patients after acute MI. The RA patients were significantly less likely to receive acute reperfusion compared with the controls (16% vs 37%: OR 0.27 (95% CI

0.10–0.64)), and this difference persisted after adjusting for type of MI, clinical setting of MI and prior MI (OR 0.2, 95% CI 0.05–0.6).

Table 2. Treatment received by RA and control patients following MI

	RA (n = 90)		Controls (n = 90)			
	n	%	n	%	Unadjusted OR§ (95% CI)	Adjusted OR¶ (95% CI)
Acute reperfusion*	14	16	33	37	**0.27 (0.10–0.64)**	**0.21 (0.07–0.62)**
Thrombolysis	8	9	22	24	**0.30 (0.10–0.77)**	**0.33 (0.11–0.96)**
PCI	10	11	30	33	**0.20 (0.06–0.53)**	**0.23 (0.09–0.63)**
PCA	39	43	52	58	**0.41 (0.16–0.92)**	0.54 (0.23–1.25)
CABGS	11	12	17	19	0.57 (0.21–1.46)	0.67 (0.27–1.65)

§McNemar's chi-squared test; ¶Conditional logistic regression, adjusting for type of MI (STEMI or NSTEMI), presence of prior MI and clinical setting of MI; PCI percutaneous coronary intervention (angioplasty ± insertion of stent); PCA percutaneous coronary angiography; CABGS coronary artery bypass graft surgery.

Urgent reperfusion is not necessarily indicated in all cases of MI, however in the event of STEMI early thrombolysis or PCI is considered the standard of care. Of the total study cohort, 29 of the RA patients and 39 of the controls were diagnosed with STEMI. Acute reperfusion was administered in 48% of the RA-STEMI patients versus 74% of the control-STEMI patients (p=0.027).

Table 3 shows the number of RA and control patients who received treatment with selected secondary prevention medications after MI. The RA patients received less frequent in-hospital treatment with beta blockers (71% vs 83%: OR 0.42 (95% CI 0.18–0.96)) and lipid-lowering agents (40% vs 70%: OR 0.21 (95% CI 0.09–0.46)).

Table 3. In-hospital treatment with secondary prevention medications received by RA and control patients following myocardial infarction

	RA (n = 90)		Controls (n = 90)		
	n	%	n	%	OR§ (95% CI)
Aspirin	85	94	89	99	0.20 (0.02–1.71)
Beta Blockers	64	71	75	83	**0.42 (0.18–0.96)**
ACE Inhibitors	61	68	57	63	1.18 (0.67–2.08)
Lipid-lowering agents	36	40	63	70	**0.21 (0.09–0.46)**

§McNemar's chi-squared test; PCI percutaneous coronary intervention; PCA percutaneous coronary angiography; CABGS coronary artery bypass graft Surgery

Conclusions: RA patients who experience acute MI receive acute reperfusion and secondary prevention medications less frequently than controls. This may contribute to higher case fatality rates after MI in RA patients.

1. Van Doornum S et al. Arthritis Rheum 2006;54(7):2061–8

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Risk Factors for Coronary Heart Diseases in Japanese Patients with Rheumatoid Arthritis: From a Large Observational Study, IORRA.

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Background: The incidence and mortality of coronary heart diseases (CHD) are lower among Japanese in comparison to individuals in Western countries based on population-based cohort study. However, we reported that the incidence of CHD was higher in Japanese RA patients compared to Japanese population, as previously indicated in Western countries.

Objectives: To investigate the risk factors of CHD in Japanese patients with RA, using a large cohort of RA patients.

Methods: Among 8,699 RA patients enrolled in an observational cohort study in our institute, IORRA (Institute of Rheumatology Rheumatoid Arthritis) study from October 2000 to October 2008, 8,387 RA patients without a history of CHD were selected as this study cohort (Female 82.5%, mean age 55.3 years, mean RA duration 7.5 years). All patients were of Japanese origin. The occurrence of first-ever CHD (myocardial infarction or angina pectoris) events were collected by the biannual patient self-reports and all cases were confirmed by their medical records. BMI and smoking status, and factors in relation to RA including disease activity (DAS28) and Japanese HAQ (J-HAQ) were collected. The multivariate adjusted hazard ratio (HR) for CHD events was calculated according to these factors using Cox proportional hazards model in order to identify the risks associated with CHD events in Japanese RA patients.

Results: During the observation period (38,297 person-years, the mean follow-up period 4.6 years), 34 first-ever CHD events (myocardial infarction: 16, angina pectoris: 18) in men, and 52 first-ever CHD events (myocardial infarction: 18, angina pectoris: 34) in women were observed. The age-adjusted incidence rates (per 100,000 person-years) of all CHD events were 238.5 and 92.1, and those of myocardial infarction were 134.8 and 35.5, and those of angina pectoris were 103.7 and 56.7 in men and women, respectively. DAS28 and Japanese HAQ (J-HAQ) scores at study entry were 4.3 and 0.96 in the CHD group, 4.0 and 0.77 in the non-CHD group, respectively. Cox proportional hazards after adjusting for age, gender and RA disease duration, confirmed that hypertension (HR: 2.7 [95%CI: 1.7–4.4]), hypercholesterolemia (HR: 2.6 [1.7–4.1]), current smoking (HR: 2.4 [1.3–4.4]) and DAS28 (HR: 1.2 [1.0–1.4]) were significant factors associated with CVD events.

Conclusion: Disease activity assessed by DAS28 is a risk for the excess incidence of CHD in Japanese RA patients, however traditional risk factors for CHD such as hypertension, hypercholesterolemia and smoking were more significant risk factors for CHD. These data suggest that not only controlling the RA disease activity but also managing the co-morbid diseases is important for the improvement of long-term prognosis of RA patients.

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Risk of Acute Coronary Syndromes in Relation to TNF-Inhibition in Early Rheumatoid Arthritis.

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Background: The risk of ischemic cardiovascular disease (CVD) is increased in rheumatoid arthritis (RA) also in the early course of the disease. In established RA, myocardial infarction (MI) risks have been linked to response to anti-TNF-alpha therapies (anti-TNF).

Objectives: To study the risk of acute coronary syndromes (ACS) in patients with RA during the first years of disease in relation to treatment with, and response to, TNF-inhibitor treatment.

Methods: All patients with early RA (disease duration <12 months) diagnosed 1995–2007, was identified from the Swedish RA Register (n=8,746). Data on disease activity, laboratory variables and pharmacological treatment was extracted from the register. Through linkage with the National Patient Register and the Cause of Death Register, co-morbidity and hospitalisation with ACS (ICD-10: I20-I21) were identified. Hazard ratios (HR) comparing the risk of incident ACS among patients exposed or not to anti-TNF were estimated using a propensity-score adjusted Cox proportional hazards regression among patients (n=6,000) included 1999 or later, excluding patients with previous ischemic or congestive heart disease. The relationship between response to anti-TNF and risk for an ACS in the cohort was further analysed by conditional logistic regression using a nested case-control design; 24 cases with ACS (unstable angina or MI) after start of anti-TNF were identified, and 81 matched controls were randomly selected. Patient records were reviewed for ACS validation, disease activity, pharmacological treatment, co-morbidity, CVD risk factors and extra-articular disease. No significant differences between cases and controls were noted at start of anti-TNF regarding inflammatory activity, RA therapy, RF-positivity, or extra-articular disease. There was a tendency of more prevalent CVD among cases (37% vs.16 %, p=0.07).

Results: In the cohort, 1,271 of the 6,000 patients were exposed to anti-TNF during a follow-up time of 21,677 person-years at risk (pyar) with 4,231 anti-TNF-exposed pyar. The incidence of ACS was 9.1/1000 pyar (n incident ACS=198). HR for ACS associated with anti-TNF after stratification for age, sex and year of entry in the cohort was 0.96 (95%CI 0.61–1.49), and after further adjustment for the propensity score HR was 0.81(95%CI 0.52–1.24). In the nested case-control study EULAR response (good or

moderate) at 3 and 6 months after initiation of anti-TNF therapy was achieved in 51% (cases 65 %, controls 47 %, n.s.) and 67% (cases 79 %, controls 64 %, n.s.), of the patients respectively. Comparing cases to controls, a good or moderate EULAR response at 3 or 6 months was not associated with risk of ACS, OR 1.65 (0.54–5.05) and 1.48 (0.32–6.88) respectively, adjusted for disease activity before treatment start. Furthermore, no significant associations between response and risk of ACS were observed after adjustment for previous CVD.

Conclusion: In this study of patients with early RA, treatment with, or response to, anti-TNF could not be linked to any decrease in the risk of acute coronary events. Whether this is due to factors specific for this cohort or if TNF-inhibition have limited protective abilities is not possible to conclude.

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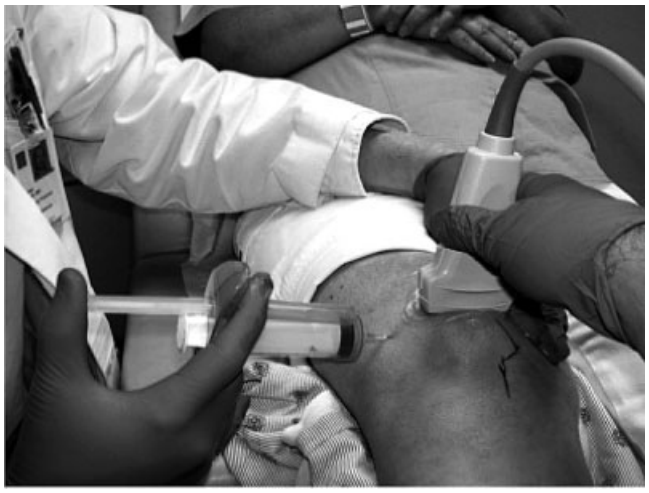
Sonographic Guidance and the Injection of the Rheumatoid Joint. Courtney R. Johnson[4], Natalia Chavez Chiang[1], Suzanne Delea[1], Hilliary Norton, Wilmer L. Sibbitt[2] and Arthur D. Bankhurst[3]. [1]Albuquerque, NM, [2]University of New Mexico HSC, Albuquerque, NM, [3]University of NM Med Ctr, Albuquerque, NM, [4]UNM Carrie Tingley Hospital, Albuquerque, NM

Objective: The present randomized controlled study addressed whether sonographic needle guidance affected the outcomes of intraarticular injection of the rheumatoid joint.

Methods: 400 rheumatoid joints were randomized to injection by conventional palpation-guided anatomic injection, sonographic image-guided injection enhanced with a one-handed RPD (the reciprocating procedure device) syringe, or the RPD alone. A one needle, two-syringe technique was used. After intraarticular placement and synovial space dilation were confirmed by sonography, a syringe exchange was performed, and triamcinolone acetonide was injected with the second syringe through the indwelling intraarticular needle. Baseline pain, procedural pain, pain at outcome (2 weeks and 6 months), responders, therapeutic duration, reinjection rates, total cost, and cost per responder were determined.



Results: Relative to conventional palpation-guided methods, sonographic guidance for injection of the rheumatoid joint resulted in 45% reduction in procedural pain ($p<0.001$), a 19% reduction in pain scores at outcome, a 20% increase in therapeutic duration, and a 23% increase in time to next injection. The RPD syringe alone was also beneficial with results midway between the conventional syringe and tsonographic guidance using the RPD syringe.

Conclusions: Sonographic needle guidance can improve the performance, clinical outcomes, and cost-effectiveness of intraarticular injections of the rheumatoid joint.

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Statin Discontinuation and Risk of Acute Myocardial Infarction in Rheumatoid Arthritis: A Population-Based Study. Mary A. De Vera[1], Hyon K. Choi[5], Michal Abrahamowicz[3], Jacek Kopec[1], Maria Victoria Goycochea-Robles[4] and Diane V. Lacaille[2]. [1]Arthritis Research Centre of Canada, Vancouver, BC, Canada, [2]Arthritis Research Ctr Canada, Vancouver, BC, Canada, [3]McGill University, Montreal, QC, Canada, [4]Research Unit of Clinical Epidemiology, Hospital Regional 1 IMSS, Mexico City, Mexico, [5]Univ of British Columbia, Vancouver, BC, Canada

Purpose: Screening for cardiovascular risk factors and treating hyperlipidemia with statins are recommended to reduce the significantly increased cardiovascular risk in individuals with rheumatoid arthritis (RA). However, poor compliance with statins may limit their therapeutic benefit. Our objective was to evaluate the impact of statin discontinuation on risk of acute myocardial infarction (AMI) among RA patients.

Methods: We conducted a retrospective longitudinal study of a population-based cohort of RA patients with incident statin use followed from May 1996 to March 2006 with administrative health data. Primary exposure was statin discontinuation for ≥3 months at any time during follow-up; primary outcome was combined hospitalized AMI and fatal AMI events occurring outside of hospitals. To evaluate the impact of statin discontinuation on AMI risk, we used Cox's proportional hazards analysis and modeled statin discontinuation as a time-varying exposure variable, updated monthly. Covariates included: age, gender, comorbidities (prior AMI, cerebrovascular accident, angina, use of diabetes, hypertension, and congestive heart failure medications), and use of medications known to influence cardiac risk (hormone replacement therapy, anticoagulants), assessed at baseline. As well, proxy measures of RA severity (use of RA medications [DMARDs, glucocorticosteroids, NSAIDs, methotrexate] and rate of RA-related medical visits) were included as time-dependent covariates.

Results: The cohort of incident statin users with RA comprised 4,102 individuals with mean age of 66 years and 60% female. Atorvastatin was the most commonly initiated statin in 48% of patients, followed by simvastatin and pravastatin, initiated in 22% and 12% of patients, respectively. Overall, 1,833 (45%) individuals in the cohort met the study definition for statin discontinuation. Over 15,669 person-years of follow-up, we identified 264 AMI events. Statin discontinuation was associated with a 67% increased risk of AMI (adjusted hazard ratio: 1.67; 95% CI: 1.24–2.25). Other significant predictors of increased AMI risk included older age, male sex, prior AMI, use of diabetes, hypertension and congestive heart failure medications, as well as current glucocorticosteroid use, and cumulative rate of RA-related medical visits measured as time-dependent covariates. In subgroup analyses, the association between statin discontinuation and AMI was not modified by timing of first statin prescription, prior AMI status, sex, and age (p-values for interactions: >0.17).

Conclusion: These population-based data indicate that RA patients who discontinue statins have an increased risk of AMI. To our knowledge, this is the first study to document the impact of statin discontinuation on cardiovascular outcomes in individuals with RA. Given the recent emphasis on the management of cardiovascular risk factors in RA, our findings have implications for the care of people with RA. Not only is it important to assess cardiovascular risk and initiate recommended statin therapy in patients, it is also essential to monitor and ensure patient compliance to the prescribed therapy regimen.

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Stroke in Rheumatoid Arthritis: (When) Is There an Increased Risk? Marie E. Holmqvist[1], Lennart T. H. Jacobsson[3], Lars Alfredsson[1] and Johan Askling[2]. [1]Karolinska Institutet, [2]Karolinska University Hospital, [3]Malmö University Hospital

We recently showed that the risk of ischemic heart disease, known to be elevated in established RA, increases rapidly after RA onset (1). Data on risk of cerebrovascular disease are conflicting and risks in relation to RA disease duration are lacking. Few have assessed the risk of ischemic and hemorrhagic stroke separately or stratified on serostatus.

Objective: To assess the risk of stroke in patients recently diagnosed with RA with short symptom duration at diagnosis, as a function of time since diagnosis, and stratified on serostatus.

Methods: From the Swedish RA register, ongoing since 1995, we

identified 7,176 patients with recently diagnosed RA (<18 months of symptoms at inclusion). As a comparator cohort, 5 individuals from the general population were selected for each RA patient, matched on age, sex, calendar year, residential area and marital status (n=35,171). Information on all hospitalizations listing stroke was retrieved from the nationwide Swedish Hospital Discharge Register (through 2006). We assessed stroke overall, as well as ischemic and hemorrhagic stroke separately. One individual could contribute first events to both subgroup outcomes, as well as to the overall outcome. Start of follow-up was date of RA diagnosis in RA patients. Comparators were given the same start date as their matched RA patient. Incidence rates were calculated. Relative risks (RR) and 95% confidence intervals (CI) of stroke after RA-diagnosis were estimated using Cox proportional hazards regression.

Results: Mean age at start of follow-up was 57 years. 70% were women. Follow-up amounted to 31,318 person-years in the RA cohort and 153,180 person-years in the general population cohort. Median follow-up was 3.9 years (range 12 years) in both cohorts. 2.6% of all patients with RA and of all comparators had any cerebrovascular event during follow up (incidence rate 6/1000 person-years in both cohorts) which corresponded to an overall RR of 1.0 (95% CI 0.9, 1.2). The incidence rates of ischemic (4.8/1000 person-years in RA and 4.1 in comparators) and hemorrhagic stroke (0.9/1000 person-years in RA and 1.2 in comparators) were similar in both cohorts, corresponding to RRs of 1.1 (95% CI 0.9, 1.3) and 0.7 (95% CI 0.5, 1.1) respectively. During this time-frame, no increased risk of stroke was observed, neither overall nor by stroke subtype nor time since RA-diagnosis. When stratified by serostatus no heterogeneities were detected (data not shown).

	<1 year since RA diagnosis	1–4 years since RA diagnosis	5–12 years since RA diagnosis
Cerebrovascular event	1.1 (0.7,1.5)	0.9 (0.8,1.2)	1.2 (0.9,1.6)
	34/154	96/489	60/255
Ischemic stroke*	1.3 (0.9,2.0)	1.0 (0.8,1.3)	1.1 (0.8,1.6)
	29/102	80/352	44/190
Hemorrhagic stroke*	0.3 (0.1,1.2)	0.6 (0.4,1.2)	1.4 (0.7,2.7)
	2/34	15/113	13/44

*The sum of ischemic and hemorrhagic strokes does not equal cerebrovascular events since some of the cerebrovascular events cannot be classified as neither ischemic nor hemorrhagic. *Cox proportional hazards model adjusted for age at diagnosis, sex, residential area, calendar year of inclusion, and marital status.

Conclusion: In contrast to the rapid increase in IHD risk, the risk of stroke, ischemic or hemorrhagic, is not elevated in RA within 12 years of RA duration. Stratification by serostatus did not alter these results. This does, however, not preclude an increased risk of stroke in RA patients with longer disease duration but may point to distinct aetiologies behind IHD and stroke in early RA.

References:
1. Gunnarsson M. *et al*. Ann Rheum Dis 2009;68(Suppl3):78

Disclosure: M. E. Holmqvist: None; **L. T. H. Jacobsson:** None; **L. Alfredsson:** None; **J. Askling:** None.

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Subclinical Atherosclerosis in Patients with Rheumatoid Arthritis Is Associated with Decreased Activity of Lecithin Cholesterol Acyl: Transferase, a High Density Lipoprotein (HDL)-Associated Protein Involved in Reverse Cholesterol Transport. Christina Charles-Schoeman[2], Yuen Yin Lee[3], Sogol Amjadi[3], John D. FitzGerald[4], Veena K. Ranganath[2], Mihaela Taylor[3], Maureen A. McMahon[2], Harold E. Paulus[1] and Srinivasa T. Reddy[3]. [1]Encino, CA, [2]UCLA School of Medicine, Los Angeles, CA, [3]UCLA School of Medicine, [4]UCLA School of Medicine Rehabilitation, Los Angeles, CA

Purpose: Patients with rheumatoid arthritis (RA) have increased cardiovascular (CV) risk which is not explained by traditional CV risk factors. Lecithin cholesterol acyl:transferase (LCAT) is an HDL-associated protein which promotes reverse cholesterol transport from cells and has been shown to protect low density lipoproteins (LDL) from oxidative modification. We previously reported that LCAT activity is decreased in RA patients compared to healthy controls, and that decreased LCAT activity is associated with abnormal anti-oxidant function of HDL. The aim of the current work was to determine whether decreased LCAT activity is associated with subclinical atherosclerosis in RA.

Methods: Carotid artery ultrasound was performed in 110 patients with rheumatoid arthritis and fasting blood was collected for lipoprotein analyses. LCAT activity was measured in patient plasma as the change in ratio of the intact to hydrolyzed LCAT monomer substrate (470/390 nm of emission intensity) over time. Lipoprotein cholesterol levels were measured by standard methods and traditional cardiovascular risk factors, medication use, and RA disease characteristics were assessed for all patients.

Results: Carotid plaque was identified in 49% of the RA patients studied. LCAT activity was significantly lower in patients with plaque compared to patients without plaque (See table). After multivariate analysis, LCAT activity (OR 0.002, p=0.009), age (OR 1.1, p<0.0001), and gender (OR 9.0, p=0.005) were significantly associated with plaque in RA patients.

Group	LCAT Activity	Age (yrs)	F (%)	HSCRP (mg/L)	DAS28	HDL-C (mg/dL)	LDL-C (mg/dL)	HTN (% yes)	BMI (lb/in2)	HAQ-DI
Plaque n = 54	0.219 ± 0.038*	61 ± 11*	78*	7.3 ± 16.9	4.4 ± 1.9	62 ± 19	106 ± 32	59*	27.4 ± 6.6	0.95 ± 0.77
No Plaque n = 56	0.237 ± 0.043	49 ± 11	93	7.1 ± 14.1	4.7 ± 1.7	59 ± 15	104 ± 37	23	27.7 ± 7.8	1.05 ± 0.88

F = Female; HTN = hypertension; DAS28 = Disease activity score with 28 joint count; HAQ - DI = health assessment questionnaire disability index; *p value < 0.05.

Conclusions: Decreased LCAT activity is significantly associated with subclinical atherosclerosis in patients with rheumatoid arthritis. This data suggest that abnormalities in the reverse cholesterol transport pathway may contribute to the increased cardiovascular disease in RA. Further investigation of abnormalities in lipoprotein function including LCAT activity may be warranted as potential biomarkers and mechanisms for increased atherosclerotic risk in RA.

Disclosure: C. Charles-Schoeman: Amgen Inc., 2; **Y. Y. Lee:** None; **S. Amjadi:** None; **J. D. FitzGerald:** None; **V. K. Ranganath:** None; **M. Taylor:** None; **M. A. McMahon:** None; **H. E. Paulus:** Abbott Immunology Pharmaceuticals, 2, Amgen Inc., 2; **S. T. Reddy:** Bruin Pharma, 9.

1059

Symptomatic Heart Failure, NT-proBNP Levels, and Diastolic Dysfunction in RA-Patients with and without Anti-TNFa Therapy. A Prospective Consecutive Cohort Study. Michael Gottwald[1], Denio Ridjab[2], Stephanie Glocke[1], Kathrin Behring[1], Robert Lange[3], Christian Butter[1] and Michael Zaenker[1]. [1]EFKH and Heart Center Brandenburg, Bernau, Germany, [2]EFKH and Heart Center Brandenburg, Bernau, Germany, [3]Hospitalverbund and Rheumazentrum Nord-Brandenburg

Background: Incidence of HF is 2-fold higher for patients with RA compared to general population. Independent association of RA with diastolic dysfunction and increased NT-proBNP levels has been demonstrated. The chronic elaboration of inflammatory cytokines like TNFa is likely substantial contributor to myocardial dysfunction. However, there are still conflicting results of clinical trials whether TNFa inhibition does promote or prevent heart failure in RA patients.

Objective: To determine the rate of symptomatic heart failure, increased NT-proBNP and diastolic dysfunction among RA-patients with and without TNFa-inhibition.

Methods: In this prospective study all RA-patients were consecutively included, who showed up in a 3 months period for follow up. Inclusion criteria were written consent, and diagnosis of RA, fulfilling ACR-criteria. All patients were interviewed using a standardized questionnaire to asess cardiovascular (cv) risk factors, cv disease, and symptoms of heart failure. Clinical signs were evaluated based upon Framingham criteria. Laboratory tests included NT-proBNP levels for all patients. Technical investigations included chest x-ray, ECG, spirometry, and echocardiography.

Results: 133 patients with RA, 68% female, mean (SD) age 60.3 (±13.6) years, median disease duration 8.0 years, median DAS28 2.7, median HAQ 1.25 were included. 57% reported any dyspnoea, 42% dyspnoea according to NYHA-class II, 9% NYHA-III, 4% NYHA-IV, 50% reported any edema, whereas raised NT-proBNP levels >220 ng/ml were found in only 29% of patients. Diastolic dysfunction was found in 13.7 %, systolic dysfunction in 1.9%. Cardiovascular risc factors were hypertension in 52%, hypercholesterolemia in 24%, current smoker in 23%, diabetes in 17% of patients. Previous diseases included TIA/stroke in 4%, peripheral artery disease in 9%, CAD in 22%, MI in 8%. N=48 (36%) had anti-TNFa therapy, 64% other treatment with DMARDs, abatacept, or rituximab. Comparing the subgroups with and without anti-TNFa therapy no significant differences were found for mean age, DAS28, HAQ, ESR, CRP, rate of increased NT-proBNP (68.7 vs. 70.6 %), mean NT-proBNP (244 vs. 263 ng/ml, rate of dyspnoea (54.2 vs. 58.8%), rate of NYHA II (41.6 vs. 42.3%), NYHA III (10.4 vs. 8.2 %), NYHA IV (2.0 vs. 4.7 %), diastolic dysfuntion (14.6 vs. 12.5%). The patients with anti-TNFa therapy had longer disease duration (14.5 vs. 6.0 years, p<0.001), worse HAQ (1.5 vs. 1.0, p=0.044), higher rate of hypercholesterolemia (33.3 vs.

18.8 % p=0.033) but no significantly different rates of hypertension (58.3 vs. 48.2%), diabetes (22.9 vs. 14.1%), apoplex/TIA (0 vs. 6%), MI (6 vs. 9%). Both subgroups had comparable hospital admission rates and treatment with β-blockers, diuretics, ACE-I/ARB, and statines. In multivariate analysis age>60y (OR 8.5 (1.2–58.6) p=0.03) and NT-proBNP>220 (OR 30.3 (4.2–215.6) p<0.001) were independent risc factors for diastolic dysfunction.

Conclusion: There is high rate of heart failure in our RA-cohort, increasing with age. However, the patients with anti-TNFa therapy did not show higer rates of dyspnoea, raised NT-proBNP, or diastolic dysfunction than the patients with other treatment.

Disclosure: M. Gottwald: None; **D. Ridjab:** None; **S. Glocke:** None; **K. Behring:** None; **R. Lange:** None; **C. Butter:** None; **M. Zaenker:** Abbott Immunology Pharmaceuticals, 2.

1060

The Clinical Features of 13 Women with Microchimerism in Rheumatoid Nodules. Christopher J. Atkins[4], William F. N. Chan[1], David Naismith[6], Nicholas van der Westhuizen[6], Janet Woo[3], Valerie Cortez[5] and J. Lee Nelson[2]. [1]Fred Hutchinson Cancer Research Center, [2]Fred Hutchinson Cancer Research Center and University of Washington, [3]University of British Columbia, [4]University of Victoria, Victoria, BC, Canada, [5]University of Washington, [6]Vancouver Island Health Authority

Introduction: Non-caseating granulomatous nodules in the setting of an inflammatory symmetrical polyarthritis have a high degree of diagnostic specificity for rheumatoid arthritis (RA). The pathogenesis of the rheumatoid nodule (RN) is unknown, although its growth over pressure points suggests a role for trauma. An increase in microchimerism (Mc) has been reported in the blood of RA patients, therefore we reasoned that microtrauma triggers an allogenic response to michrochimeric cells in the formation of the RN.

Purpose: To investigate Mc in RNs from women by testing for male DNA.

Methods: 1. DNA extraction from 19 nodules collected from 15 female patients followed by quantitative PCR on the Y-chromosome specific sequence *DYS14*; 2. Review of clinical features of women whose RNs contained male DNA, including treatment with methotrexate and anti-TNF biologics, both of which have been associated with RN formation; 3. Comparison of the concentration of Mc in RN, expressed as genome equivalents (gEq) of male-specific *DYS14* DNA per 100,000 cells, to serum concentration of anti-cyclic citrullinated peptide (CCP) antibodies.

Results: Fourteen nodules from 13 patients were positive for Mc. Mean age of RA onset was 43 years (range 26–64). The most common source of male DNA in a woman is prior birth of a son. Eight of 13 patients had given birth to sons, seven with sons born before (mean time from birth 19 years; range 0–38) and one after RA onset. Blood transfusion is an alternative potential source of Mc. The patient whose son was born after RA onset had received blood transfusions 1 and 4 years before disease onset. Mc can also originate from a miscarriage. The 5 patients without sons but positive for Mc had no history of miscarriage or transfusion. Two had daughters and one received gamma globulin 2 years before disease onset.

All patients presented with a symmetrical inflammatory polyarthritis. Eleven of 13 patients had erosions on X-ray. Twelve patients received methotrexate, all of whom developed RN after therapy, with 6 patients following the addition of a biologic. Two developed accelerated RN formation with methotrexate, one after the addition of infliximab. Eleven of 13 patients tested positive for rheumatoid factor. Twelve of 13 patients had a concentration of anti-CCP that is above the reference range (0–5 U/ml), with 7 patients >100 U/ml. Eight patients with a concentration of anti-CCP >50 U/ml (range 58 to >100) had a Mc concentration of <1 gEq (range 0.08–0.78). In contrast, 4 of 5 patients with a concentration of anti-CCP <50 U/ml (range 3–34) had a Mc concentration of >1 gEq (range 1.57–7.51).

Conclusions: The clinical features of 13 women with RA whose nodules contained male DNA were typical of those usually associated with severe disease. In 7 patients, the nodules appeared several years after the birth of their male offspring, suggesting a fetal origin for the foreign DNA. Unrecognized miscarriage, induced abortion, or transfer of cells from an older male sibling are potential sources of male DNA in the 5 women who did not have sons, known miscarriages, or transfusions. Patients with the highest Mc concentrations had the lowest anti-CCP concentrations, suggesting an inverse relationship.

Disclosure: C. J. Atkins: None; **W. F. N. Chan:** None; **D. Naismith:** None; **N. van der Westhuizen:** None; **J. Woo:** None; **V. Cortez:** None; **J. L. Nelson:** None.

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The Clinical Implication of Anti-Cyclic Citrullinated Peptide Antibody in Late Onset Rheumatoid Arthritis. Se Jin Jung[3], Yoon Kang[3], You-Jung Ha[3], Kwang-Hoon Lee[3], Sang Won Lee[3], Min-Chan Park[1], Soo Kon Lee[2] and Yong-Beom Park. [1]Gangnam Severance Hospital, Seoul, Korea, Republic of, [2]Yonsei Univ College of Med, Seoul, Korea, Republic of, [3]Yonsei Univ College of Med

Background: Late onset rheumatoid arthritis (LORA), onset of which is over 60 years old, has clinical features that are different from those of younger onset rheumatoid arthritis (YORA). While anti-cyclic citrullinated peptide antibody (anti-CCP) is known to be more disease-specific in RA, clinical implications of anti-CCP in LORA have not been reported to date.

Purpose: To investigate the association of anti-CCP and its titer with markers reflecting disease-activity of RA.

Methods: We retrospectively investigated medical records of 238 patients with RA, who visited Severance Hospital between January 2005 and May 2009. All patients were divided into two groups according to the age of 60 when they were diagnosed with RA (LORA (N=61) and YORA (N=177)). Rheumatic factor (RF) and anti-CCP were analyzed, and disease activity score (DAS) 28 at diagnosis was assessed at their first visit. Initial as well as accumulated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were measured. Accumulated levels were obtained using the area under curve (AUC) during the first year after diagnosis. Patients having anti-CCP were evenly distributed in three groups according to the range of the titer of anti-CCP (low (>5), moderate (5~135) and high (>270) titer groups).

Results: The mean ages of patients with LORA and YORA were 67.1 ± 6.0 and 43.7 ± 10.5 years old, respectively. There were no significant differences in joint involvement, symptom duration, clinical manifestations, positivity of RF or anti-CCP, and medications between the two groups. However, patients with LORA had higher DAS28, anti-CCP titer and accumulated ESR and CRP levels than those with YORA. The titer of anti-CCP was well correlated with initial and accumulated levels of ESR in patients with LORA (r=0.416 and r=0.432, p<0.05), but not with patients with YORA.

Conclusions: In patients with LORA, but not with YORA, the titer of anti-CCP was significantly correlated with initial and accumulated levels of ESR, suggesting that initial titer of anti-CCP might be used as a value to predict the extent of inflammation during the first year after diagnosis in LORA patients.

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1062

The Effect of Calcium and Vitamin D Supplementation on the Incidence of Rheumatoid Arthritis in the Women's Health Initiative Randomized Study. Marius Racovan[10], Brian Walitt[10], Christopher Collins[10], Mary Pettinger[2], Christine Parks[4], James Shikany[6], Jean Wactawski-Wende[8], JoAnn E. Manson[1], Larry Moreland[9], Nicole Wright[7], Rebecca Jackson[5] and Barbara V. Howard[3]. [1]Brigham and Women's Hospital, Harvard Medical School, [2]Fred Hutchinson Cancer Research Center, [3]MedStar Research Institute, [4]National Institute of Enviromental Health Sciences, [5]Ohio State University, [6]University of Alabama, [7]University of Arizona, [8]University of Buffalo, [9]University of Pittsburgh, [10]Washington Hospital Center

Objective: To determine if calcium and vitamin D supplementation reduces the incidence of rheumatoid arthritis (RA).

Methods: 32,435 postmenopausal women enrolled in the WHI calcium plus vitamin D (CaD) randomized controlled trial were included in a study with primary endpoints of hip fracture or colorectal cancer. The participants were assigned in a randomized, double-blind manner to either daily 1000 mg of calcium carbonate plus 400 IU of vitamin D_3 or placebo. In a post-hoc analysis, a previously validated method was used to identify RA cases using participant self-report plus concomitant use of disease modifying anti-rheumatic drugs (DMARDs). Cox proportional hazards ratios and Kaplan-Meier curves were used to compare the incidence of RA in the treatment versus the placebo groups. Covariates, such as age, hormone therapy, smoking, duration of breastfeeding and geographic location, were considered in the model.

Results: 163 new RA cases were identified over 6 years. No significant differences were observed between the two groups in terms of demographics or non-experimental vitamin D intake (total vitamin D supplementation [p = 0.96], multivitamin intake [p = 0.07] and sun exposure [p= 0.85]). There was no difference between the two groups in RA incidence (p=0.82, Figure 1). Stratification of the results by age, regional solar irradiance and total vitamin D intake and adjustments for covariates such as smoking, hormone therapy, longer duration of breastfeeding did not alter the results.

Conclusions: Calcium and vitamin D intake as a dietary supplement did not have a statistically significant effect on the incidence of RA in the WHI randomized CaD trial. These results suggest that calcium and low dose vitamin D replacement had no effect on the development of RA in post-menopausal women. Further research is needed to assess the effect of supplementation with higher doses of vitamin D on the incidence of RA.

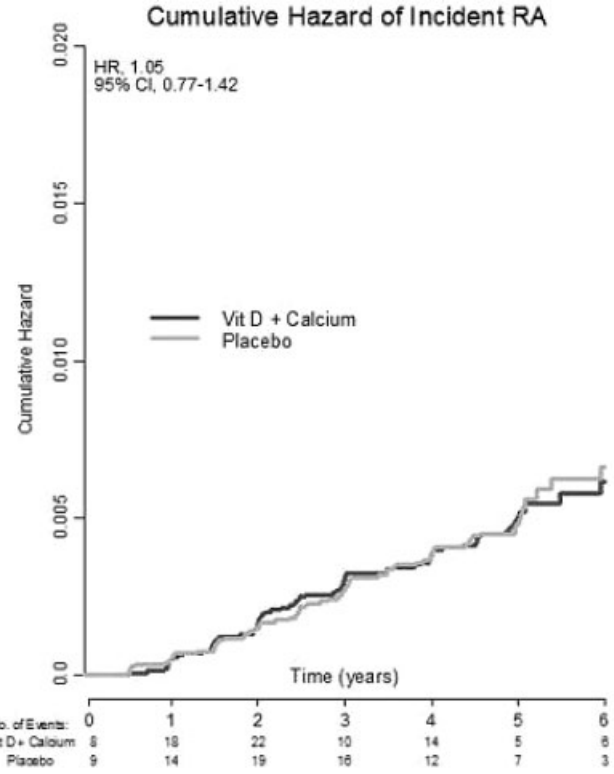

Figure 1. Cumulative hazard of incident RA.

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The Impact of Rheumatoid Arthritis (RA) on Women: Focus on Pain, Productivity and Relationships. Vibeke Strand[2], Paul Emery[1], Scott Fleming[4] and Catherine Griffin[3]. [1]Chapel Allerton Hospital, Leeds, United Kingdom, [2]Division of Immunology and Rheumatology, Stanford University School of Medicine, Palo Alto, CA, [3]Echo Research, London, UK, [4]UCB, Slough, UK

Background: It is widely recognized that daily life-burdens associated with RA, including functional impairment, pain, inability to participate in desired family, social and leisure activities and reduced productivity at work and within the home, have a profound impact on the overall health-related quality of life (HRQoL) of RA patients. However, this impact on daily life in women, as well as on relationships and overall well-being, has not been well characterized.

Objective: To explore the impact of RA on women's daily lives and relationships.

Methods: Women with RA from 7 countries (USA, Canada, UK, France, Germany, Italy, and Spain) were recruited by an online research panel to complete an internet survey regarding how their lifestyle has been affected by RA. Eligible women were aged 25–65 years with a formal diagnosis ≥6 months; screening criteria were established to exclude those without a diagnosis of RA and/or who did not satisfy the age criteria. Respondents were queried regarding the physical, emotional and social impacts of RA on their lives. Mean responses to each question were computed for the overall patient population.

Results: 27,459 women were recruited via an online research panel. Of these, a total of 1958 women with RA (USA, UK, Germany, and Spain 300 patients each; Canada, 155; France, 301; Italy, 302) completed the survey between July 30 and August 31, 2009. No major regional differences were observed in any outcome measured. Mean age was 46 years, 75% had RA diagnosed >1 year and 69% self-reported moderate to severe disease. Among the 75% of respondents who were currently taking pain-relief medications, a high proportion still reported experiencing daily pain (72%). The majority of respondents felt they had to conceal pain (68%). Furthermore, 67% of respondents agreed/strongly agreed that they constantly look for new ideas to address pain, and nearly 9 out of 10 mentioned pain in discussions with their physicians. Another key finding of the survey was the negative impact of RA on productivity at work. Of those employed (n=1108), 71% reported they were less productive at work because of RA, 23% had to stop work altogether, and 17% had to switch to part-time employment. Respondents reported that the emotional impact of RA is high: many have feelings of detachment and isolation from their friends and family due to their condition; 26% felt isolated, and 32% that RA had affected their closest relationships for the worse. RA was also reported to negatively affect the most intimate aspects of patients' lifestyles, with 4 of 10 single women agreeing that RA makes it more challenging to find a partner, and 22% divorced/separated respondents indicating that RA had at least some role in their decision to separate.

Conclusions: Pain is a paramount issue for women with RA; the majority experience pain despite taking pain relief medication. In all countries evaluated, respondents indicated that RA had a negative impact on employment and caused them to feel isolated, negatively affecting intimate relationships. Optimization of treatment strategies to reduce pain, increase productivity, and manage the social aspects of the disease is thus needed.

Disclosure: V. Strand: Abbott Immunology Pharmaceuticals, 5, Alder, 5, Amgen Inc., 5, AstraZeneca, 5, Biogen Idec, 5, Canfite Pharma, 5, CBio, 5, Centocor, Inc., 5, Chelsea, 5, Crescendo, 5, Cypress Biosciences, Inc., 5, Euro-Diagnostica Inc., 5, Fibroge; **P. Emery:** UCB, Inc., 2, 5; **S. Fleming:** Antisoma, 1, UCB, Inc., 1, 3; **C. Griffin:** UCB, Inc., 2.

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There Are No Differences in Lipids between RA Patients and Their Siblings, Despite Higher Incidence of CHD in RA. Namita Kumar, Nicola J. Marshall, David J. Walker and Philip N. Platt. University Hospital of North Durham

Introduction: The interest in coronary heart disease (CHD) and cardiovascular risk remains high in our patients with inflammatory arthritis and especially Rheumatoid Arthritis (RA). The exact cause of the increased risk is still unclear with contradictory data regards the role of lipids and their response to treatment.

We looked at a cohort of RA patients and their siblings to assess this further.

Method: A population of RA patients and their same sex siblings were studied in Newcastle-upon-Tyne, UK. This population were matched for age and sex. Diagnosis of CHD and a number of risk factors were assessed and compared. Diabetics were excluded.

Results: Data from 79 pairs were available, Female:male ratio was 67: 12. There was a twofold increase in the amount of diagnosed CHD in the index cases compared to the siblings (Mann-Whitney test, (p less than 0.0001). There was a significant increase in CRP and ESR (p less than 0.0004) in the index cases and increased BMI in the siblings. Current and previous smoking status between the 2 groups was similar. There was no difference in the use of statins and other lipid lowering drugs between the 2 groups.

Linear regression showed no association between CRP, cholesterol: HDL, LDL apolipoprotein A or B and the incidence of CHD in our patients with RA. There was also no correlation with CRP and any of the lipids shown in Table 1.

N = 79 pairs	RA	Sibling	P-value
Age	61.9 (9.2)	59.4 (10.8))	*ns*
Diagnosed CHD	16 (20%)	9 (11%)	*<0.0001*
CRP mg/l median (range)	11 (3.232)	3 (0.21)	*<0.001*
BMI (kg/m^2) (mean SD)	25.7 (5.6)	27.3 (5.1)	x*0.016*
Cholesterol mmol/l (mean, SD)	5.5 (1.1)	5.9 (1.2)	*ns*
Triglycerides mmol/l	1.5 (0.6, 3.8)	1.3 (0.4, 4.1)	*ns*
HDL-cholesterol mmol/l	1.5 (0.4)	1.6 (0.4)	*ns*
Cholesterol: HDL mmol/l	3.8 (1.0)	3.9 (1.0)	*ns*
LDL mmol/l (mean, SD)	3.3 (1.0)	3.6 (1.1)	*ns*
Apolipoprotein A1 (mean, SD)	1.45 (0.3)	1.5 (0.3)	*ns*
Apolipoprotein B (mean, SD)	0.99 (0.25)	1.01 (0.3)	*ns*

In those pairs who had no CHD there was still no difference in cholesterol, triglycerides, cholesterol: HDL and apolipoprotein A and B levels, all of which were in the normal range.

Conclusion: RA patients have higher CHD than same sex siblings when matched for age, sex, diabetes and smoking status. They have lower BMIs and higher inflammatory markers. This data suggest that lipids within this RA population were not a major component of risk.

Disclosure: N. Kumar: None; **N. J. Marshall:** None; **D. J. Walker:** None; **P. N. Platt:** None.

1065

Thigh Fat and Muscle in Rheumatoid Arthritis: Associations with Disease Features and Physical Functioning. Henry R. Kramer[1], Kevin R. Fontaine[1], Joan M. Bathon[1] and Jon T. Giles[2]. [1]Division of Rheumatology, Johns Hopkins University, Baltimore, MD, [2]Johns Hopkins Univ, Baltimore, MD

Background: Body fat is increased and lean mass decreased, on average, in rheumatoid arthritis (RA) patients. However, no studies have explored longitudinal predictors of thigh fat and muscle composition, an important anatomic site for physical functioning.

Methods: Participants in ESCAPE RA, a prospective cohort study of cardiovascular disease in RA, underwent mid-femur computed tomography (CT) scanning at study visit 3, occurring 3.2 ± 0.3 years from baseline. The associations of baseline and cumulative demographic, lifestyle, and RA disease and treatment characteristics with thigh fat area (TFA), thigh muscle area (TMA), and thigh muscle density (TMD) were explored using multivariate linear regression (MVLR). MVLR was also used to model associations of TFA, TMA, and TMD with disability, assessed using HAQ and with the components and summary score of the Short Physical Performance Battery (SPPB).

Results: A total of 152 RA patients (64% female; 88% Caucasian; mean age=63 years; median baseline RA duration=12 years, median DAS28 at visit 3=3.1) were scanned. Among RA characteristics, longer RA duration, higher tender joint count, higher cumulative IL-6, and current prednisone use were significantly associated with lower TMA, even after adjusting for demographics, smoking, physical activity, depression, and thyroid disease. RA characteristics accounted for 24% of the explainable variability in TMA. These same RA characteristics were also significantly associated with TMD, and accounted for 45% of the explainable variability. For TFA, longer RA duration and higher FACIT fatigue scores were significantly associated with higher TFA, and current prednisone use was associated with 28cm^2 lower TFA compared to non-use (p=0.001); however, cumulative prednisone dose was not associated with TFA. RA characteristics accounted for 28% of the explainable variability in TFA. Biologic and non-biologic DMARD treatment was not significantly associated with thigh composition. Lower TMD and higher TFA (but not TMA) were significantly associated with higher HAQ scores, after adjusting for exercise, DAS28, Sharp score, and FACIT score. These six characteristics accounted for 59% of the explainable variability. RA patients with the lowest SPPB scores had significantly lower TMA and TMD compared to those with the highest scores (Figure). TFA was not significantly associated with SPPB score.

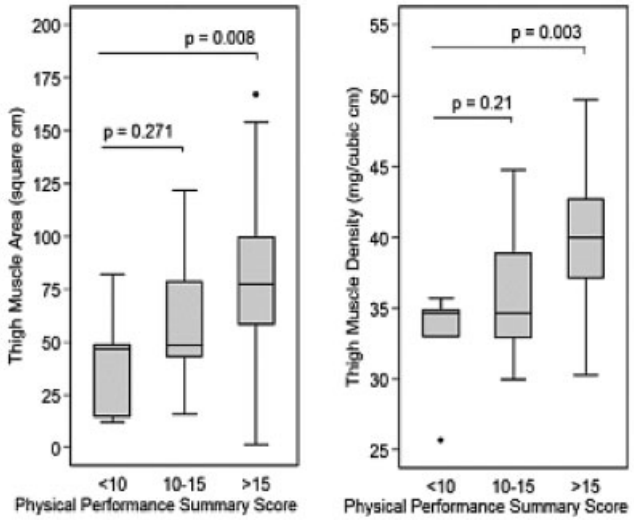

Figure. Thigh muscle area and density according to short physical performance battery summary score.

Conclusions: These findings suggest that: 1) the origins of altered muscle bulk and quality, and changes in fat distribution, are likely multifactorial in RA patients, with contributions from inflammation, joint damage, fatigue, and treatments (i.e. glucocorticoids) and 2) abnormal fat and muscle composition, in particular muscle quality, contribute substantially to physical functioning.

Disclosure: H. R. Kramer: None; **K. R. Fontaine:** None; **J. M. Bathon:** None; **J. T. Giles:** None.

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TNF Inhibitors and the Risk of Fracture in Rheumatoid Arthritis. Daniel Hal Solomon[3], Seo Young Kim[1], Jun Liu[2], Claire Canning[2] and Sebastian Schneeweiss[2]. [1]Brigham and Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital, [3]Brigham and Womens Hospital, Boston, MA

Background: Prior studies suggest an increased risk of fracture with RA. Potential causes include the underlying inflammation of RA as well as use of glucocorticoids. Several prior investigations demonstrate an improvement in bone mineral density associated with use of TNF inhibitors (TNFi). However, there are no studies comparing the risk of fracture related to different DMARDs in patients diagnosed with RA.

Methods: Our study cohort was drawn from two data sources—a population-based cohort from a Canadian province and a large US commercial insurance plan. Patients with at least 2 diagnoses of RA were eligible for the study cohort at the time of a DMARD addition or switch. DMARD additions or switches were categorized into three mutually exclusive groups: 1) TNFi, with or without other DMARDs; 2) methotrexate (MTX), without a TNFi; or 3) other DMARDs, without a TNFi or MTX. Group 3 (other DMARD) was considered the reference group. Subjects were followed until they experienced a hip, humerus, wrist, or pelvis fracture based on diagnosis and procedure codes identified in the health care utilization data. The composite of any of these fracture types was considered the primary outcome. Incidence rates for fractures were compared across exposure groups. In addition, adjusted hazard ratios were calculated in Cox regression with covariates including age, gender, Charlson comorbidity index, prior fractures, oral glucocorticoids, other fracture risk factors, and health services utilization. Secondary analyses focused on groups with oral glucocorticoid use and prior fractures.

Results: The study cohort consisted of 25,988 subjects with RA starting one of the three groups: 5,856 TNFi, 12,554 MTX, and 7,578 other DMARDs. Mean follow-up was 6 months. The three groups' characteristics were similar with respect to age, gender, and comorbidities, but differed with respect to oral glucocorticoid and opioid use, with higher rates for TNFi users. The incidence rates per 1,000 person-years for the composite fracture outcome were 5.11 (95% CI 3.50–7.45) for TNFi, 5.35 (95% CI 4.08–7.02) for MTX, and

6.38 (95% CI 3.78–10.77) for other DMARDs. Adjusted hazard ratios for the primary outcome and secondary analyses are shown in the Table. The risk of fracture was similar across DMARD exposure groups.

Table. Adjusted hazard ratio (95% CI) for fracture among subjects with RA

	Main analysis (n = 25,988)	No recent steroid use (n = 18,157)	No prior fracture (n = 25,752)
Other DMARDs	Reference	Reference	Reference
MTX	1.18 (0.60–2.34)	1.20 (0.62–2.34)	1.17 (0.46–2.98)
TNFi	1.07 (0.57–1.98)	1.25 (0.60–2.61)	1.21 (0.54–2.71)

Conclusions: Among subjects diagnosed with RA, the adjusted risk of fracture was similar across persons starting a TNFi, MTX, or other DMARDs. This result was robust across secondary analyses.

Disclosure: D. H. Solomon: Abbott Immunology Pharmaceuticals, 2, Amgen Inc., 2, Bristol-Myers Squibb, 9; **S. Y. Kim:** None; **J. Liu:** None; **C. Canning:** None; **S. Schneeweiss:** None.

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Traditional and Novel Risk Markers for Atherosclerosis but Not Clinical Measures of Inflammatory Disease Are Associated with Atheromatous Plaque Presence in Early Inflammatory Polyarthritis—Results from the Norfolk Arthritis Register (NOAR). Hoda Mirjafari[3], Suzanne M. M. Verstappen[2], Diane Bunn[6], Helena Edlin[5], Valentine Charlton-Menys[4], Philip Pemberton[5], Tarnya Marshall[6], Paddy Wilson[6], Mark Lunt[2], Deborah P. Symmons[7] and Ian N. Bruce[1]. [1]Arthritis Research UK Epidemiology Unit, Stopford Building, The University of Manchester, Manchester, United Kingdom, [2]Arthritis Research UK Epidemiology Unit, Stopford Building, The University of Manchester, [3]Arthritis Research UK Epidemiology Unit, The University of Manchester, [4]Cardiovascular Research Group, The University of Manchester, [5]Manchester Royal Infirmary, [6]Norfolk and Norwich University Hospital, [7]Univ of Manchester, Manchester, United Kingdom

Purpose: Patients with inflammatory polyarthritis (IP) have an excess risk of cardiovascular (CVD) mortality due to accelerated atherosclerosis. Markers identifying individuals with subclinical atheromatous plaque may allow for attenuation of CVD risk. The objective of this study was to identify risk markers associated with atheromatous plaque in an incident cohort of patients with early IP.

Methods: Consecutive patients with early IP (> or equal to 2 joints swollen for > or equal to 4 weeks) aged 18–65 years, who were within 24 months of symptom onset were recruited as part of a primary-care based inception cohort between 2004–2008. Patients underwent assessment of classic risk factors, completion of a health assessment questionnaire (HAQ) and a 28 joint count for calculation of disease activity score (DAS28). Blood was taken for rheumatoid factor (RF), anti-citrullinated protein antibody (ACPA), C-reactive protein (CRP), high sensitivity CRP (hs-CRP), fasting glucose, novel and traditional lipid levels (LDL, HDL, triglycerides, paroxonase 1 (PON1) apolipoprotein (Apo) A1 and B), markers of vascular damage (E-selectin, vascular adhesion molecule (VCAM)) and adipocytokines (leptin and adiponectin). All patients underwent B mode Doppler ultrasound examination of the carotid arteries to assess for the presence of plaque. In univariate analyses we identified factors that were associated with plaque presence after age and gender adjustment. An additive stepwise multivariable logistic regression model investigated the independence of any associations.

Results: Of the 316 patients studied 93 (29%) patients were male. The median (IQR) age and symptom duration at study entry was 51 (42–58) years and 6.6 (4.2–11.2) months respectively. The patients had a mean (SD) blood pressure of 134/82 (17/10) mmHg, 71(23%) were smokers and 149 (47%) had detectable plaque. From the univariate analysis; age, smoking, total cholesterol, triglycerides, Apo B, hs-CRP, adiponectin and E-selectin were significantly associated with plaque presence. There was no significant association found between HAQ score, DAS28, exposure to steroid therapy and DMARDs, RF and ACPA status and plaque presence at baseline (OR (95% CI); 0.97 (0.68, 1.40), 1.06 (0.85, 1.32), 0.77 (0.39, 1.51), 0.98 (0.58, 1.64), 1.54 (0.92, 2.57), 1.39 (0.81, 2.39)). In an additive stepwise multivariable logistic regression model age, smoking, systolic blood pressure, Apo B, hs-CRP and adiponectin remained significant independent predictors of plaque (Table).

Table. Multivariable logistic regression association with plaque

Variable	Odds Ratio (95% CI)
Age (years)	1.11 (1.07, 1.16)
Smoker (Y/N)	2.91 (1.28, 6.64)
Systolic blood pressure (/mmHg)	1.02 (1.00, 1.04)
Apo B (/g/l)	7.63 (2.28,25.51)
hs-CRP (/mg/L)	1.04 (1.01, 1.07)
Adiponectin (/mg/l)	1.19 (1.05, 1.36)

Conclusion: Markers known to be associated with atherosclerosis in the general population including smoking, higher systolic blood pressure and Apo B are associated with early atherosclerosis in this population. The association with hs-CRP and adiponectin suggests that low grade inflammation, even in early disease, may contribute to atherogenesis in early IP.

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1068

Unaffected First-Degree Relatives of RA Patients Exhibit a High Prevalence of Joint Symptoms That Is Not Explained by the Presence of RA Autoantibodies: Studies in a Predisposed North American Native Population. Irene Smolik[3], Qier Tan[3], Xikui Wang[3], Donna Hart[3], Marianna Newkirk[1], Charles N. Bernstein[3], David B. Robinson[3] and Hani S. El-Gabalawy[2]. [1]McGill University, [2]University of Manitoba, Winnipeg, MB, Canada, [3]University of Manitoba

Purpose: We have previously shown that in a North American Native (NAN) population in Central Canada, the prevalence of RA is 2–3 times higher than that seen in most other populations, with a particularly high frequency of familial disease. We have also demonstrated a high prevalence of anti-citrullinated protein antibodies (ACPA), rheumatoid factor (RF), and of RA-like joint symptoms in the first-degree relatives (FDR) of RA probands from this population. We sought to get a better understanding of the relationship between joint symptoms and RA autoantibodies in disease-free NAN individuals who may be at risk for developing future RA.

Methods: The prevalence of joint symptoms was compared in three distinct groups: 1) FDR of NAN RA patients (n=306), 2) NAN controls (NC, n=330), and 3) Caucasian controls (CC, n=293). The two control groups had no family history of RA or related autoimmune diseases, and NC were from the same geographic areas as FDR. All study subjects completed a questionnaire which included demographic data, health related habits, family health history, and six questions probing into whether they experience pain, swelling, or stiffness of the hands or of other joints. Anti-CCP2 antibodies were tested by ELISA and RF by nephelometry in FDR (n=287), NC (n=198), CC (n=100).

Results: The mean age of FDR= 35±13, NC= 33±11, CC= 42±13, $p<0.0001$. The percentage of females was FDR=69%, NC=63%, and CC=63%, p=ns. In all groups, females reported more joint pain, swelling, and stiffness, and overall had an OR=1.6, $p<0.01$ for having any joint symptom. Compared to both control groups, FDR were more likely to report joint symptoms in the hands: pain (54%, 35%, 18%); swelling (36%, 16%, 7%); stiffness (40%, 23%, 14%); and in other joints: pain (57%, 34%, 32%); swelling (30%, 17%, 11%); stiffness (39%, 24%, 25%) for FDR, NC, CC, respectively; all comparisons $p<0.0001$. The high prevalence of joint symptoms in FDR was confirmed after matching FDR to NC by age and sex. Compared to CC, NC had more joint symptoms ($p<0.01$ for all hand joint symptoms). There was a higher prevalence of joint symptoms in FDR living in urban vs. rural locations (79% vs. 60%, $P<0.0001$). The prevalence of anti-CCP2 was: FDR = 8.3%, NC = 1%, and CC = 1%, $p<0.0001$, and RF was: FDR = 4.5%, NC = 1%, and CC= 1%, $p<0.05$. Logistic regression modeling demonstrated that age and FDR status were strong independent predictors of having any joint symptoms ($p<0.0001$ for both), while gender, RF, and ACPA status were not significant predictors in the model. Similar results were obtained when modeling the individual joint symptoms, although gender was found to be a predictor of hand symptoms.

Conclusion: RA-like joint symptoms are more common in FDR of NAN RA patients than in either NAN or Caucasian individuals having no

family history of RA, a finding that is not explained by the higher prevalence of ACPA and RF in FDR. This finding, combined with the overall higher frequency of joint symptoms seen in NAN compared to Caucasian controls, and in urban compared to rural FDR raises the possibility that pre-clinical joint symptoms based on biological and psychosocial factors may be part of the risk profile for developing future disease in high risk individuals and populations.

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ACR Poster Session B
Rheumatoid Arthritis - Human Etiology and Pathogenesis II
Tuesday, November 9, 2010, 9:00 AM–6:00 PM

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'Shared' T-Cell Clones Identified in Lymph Nodes and Synovial Tissue of Early Rheumatoid Arthritis Patients Using a Novel High Throughput Sequencing Technology. Paul L. Klarenbeek[4], Marjolein J. de Hair[4], Stefano Alivernini[4], Marleen G. van de Sande[4], Marieke E. Doorenspleet[4], Barbera D. van Schaik[3], Ferco H. Berger[2], Rebecca E. Esveldt[4], Antoine H. van Kampen[3], Danielle M. Gerlag[4], Frank Baas[5], Paul P. Tak[1] and Niek de Vries[4]. [1]Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, [2]Dept of Radiology, Academic Medical Center-University of Amsterdam, [3]Dept. of Clin. Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center-University of Amsterdam, [4]Div of Clin Immunology & Rheumatology, Academic Medical Center-University of Amsterdam, Amsterdam, The Netherlands, [5]Lab. For Genome Analysis, Academic Medical Center-University of Amsterdam

Background: T-cells are likely to play important roles in the pathogenesis of rheumatoid arthritis (RA), but the role of T-cell clones remains to be elucidated. Although the synovial tissue (ST) is the primary target tissue in RA, previous observations from our group suggested that other sites might also be involved in the early phases. As a primary site for adaptive immune responses the lymph node (LN) is a likely candidate. Previously, we demonstrated, using newly developed High Throughput Sequencing (HTS) technology, that T-cell clones are present in the ST of RA-patients, and that the T-cell repertoire in the ST is markedly different from that in the peripheral blood (PB). Here, for the first time, we analyzed paired samples from LN, ST and PB to study T-cell clones in early RA.

Objectives: Investigate paired LN, ST, and PB samples of early RA patients for presence of T-cell clones to analyze the relation between these compartments with regard to adaptive immune responses.

Methods: mRNA was isolated from paired LN, ST and PB samples of 2 DMARD-naive anti-CCP+ RA-patients (pt) (fulfilling ACR-criteria at inclusion; disease duration < 1 year) after arthroscopic ST sampling of an arthritic ankle and ultrasound guided needle biopsy sampling of a regional lymph node. A linear amplification with primers for all V(ariable)-genes of the T-cell receptor β-chain was performed. The amplified products contain the Complementarity Determining Region 3 (CDR3), which can be used as 'fingerprint' for each clone. The samples were processed using a Genome Sequencer (454/Roche) analyzing up to 1 million receptors at once. The frequency of each clone was determined by the CDR3 using bioinformatics algorithms. Clones with a frequency of ≥1% were arbitrarily considered as highly expanded.

Results: The LN samples showed only few highly expanded clones when compared to the ST (2 vs. 25 clones (pt1) and 1 vs 24 (pt2) in LN and ST respectively). Few expanded clones were detected in PB as well (0 (pt1) and 2 (pt2)). Evidence of circulation between the compartments was seen in both patients. E.g. of the 24 highly expanded clones in pt2 9 clones were found in the PB and 8 were found in the LN. Of these, 4 were found both in the LN and the PB. Whereas these shared clones were highly expanded in the ST, they were of low frequency in the PB and LN (0.01–0.09% in LN and 0.01–0.52% in PB). Little overlap was seen in the T-cell repertoire between ST and PB/LN. In pt1 only 6% and 8% of the ST clones were shared with the LN and PB respectively. In pt2 this was 9% for both LN and PB.

Conclusions: This is the first analysis of T-cell clones in LN samples compared to ST and PB, using the HTS technology. In these patients we found T-cell clones in both the regional LN and the ST. Only few highly expanded clones were found in the LN while multiple highly expanded clones were found in the ST, perhaps due to epitope spreading in the ST. Many of the highly expanded ST clones could be found back in LN and/or PB. The frequencies of these clones in LN/PB were very low suggesting local retention and/or proliferation of these clones in the inflamed ST. Additional studies are underway to further characterize the roles of T- and B-cell clones in early RA and to investigate the role of the LN in RA.

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1070

Anticitrullinated Peptide Antibodies (ACPAS) in the Sera of Heavy Smokers without Arthritis. A Differential Role of Associated Pulmonary Disease? Virginia Ruiz-Esquide[3], María José Gómara[4], Víctor Peinado[1], José Alfredo Gómez Puerta[3], María Victoria Hernández[2], Joan A. Barberà[1], Julio Ramírez[3], Juan de Dios Cañete[3], Isabel Haro[4] and Raimon Sanmartí[3]. [1]Pneumology Service, Hospital Clínic of Barcelona, Barcelona, Spain, [2]Rheumatology Service, Hospital Clínic of Barcelona, Barcelona, Spain, [3]Rheumatology Service. Hospital Clínic of Barcelona, Barcelona, Spain, [4]Unit of Synthesis and Biomedical Applications of Peptides, IQAC-CSIC, Barcelona, Spain

Background: Anti-citrullinated peptide antibodies (ACPAs) are the most specific serological markers of rheumatoid arthritis (RA). An increased risk of RA has been described in smokers, but only in ACPA-positive RA patients. The frequency of ACPAs in serum of heavy smokers is not known.

Objectives: To analyze the frequency and levels of ACPAs in the serum of heavy smokers subjects, with and without lung disease, and to compare them with a healthy control group.

Methods: Serum samples of 110 heavy smokers (39% women, mean age 56.9 ± 10 years) were obtained. Subjects were selected, from a Pneumology Service data base and from hospital health workers, regardless of wheather they had chronic obstructive lung disease (COPD) or not. Study subjects were compared with a healthy control group who had never smoked (51% women, 41.8 ± 12 years) (n=209). Both groups were tested for two different antibodies against citrullinated proteins, a commercial CCP2 test and a home-made chimeric fibrin/filaggrin citrullinated synthetic peptide (anti-CFFCP). The frequency of positive results and autoantibody levels were compared between groups.

Results: Of the 110 heavy smokers, 54 had COPD and 56 were healthy smokers. None had RA. Mean pack-years were 44.3 ± 36 (53 ± 28 in COPD disease and 36 ± 16 in healthy smokers, $p<0.01$).

The percentage of positive results together with the mean serum levels of the two citrullinated autoantibodies in all the study groups are shown in Table 1.

The prevalence of positive anti-CFFCP was higher in the heavy smoker group than in non smokers, although the difference was not significant. The highest prevalence of positive anti-CFFCP was seen in patients with COPD (7.4%); the difference was at the limit of statistical significance compared with the control group (2.4%) (OR 3.26 95% CI 0.85–12.6 p=0.07). There was no significant difference in the frequency of positive anti-CCP antibodies between groups.

The differences in the mean serum levels of anti-CFFCP and anti-CCP antibodies in heavy smokers compared with never smokers were not statistically significant. Heavy smokers with COPD had significantly higher levels of both autoantibodies than those without pulmonary disease, although almost all patients had serum levels bellow the cut-off values.

Table 1. Frequency (%) of patients with positive autoantibodies and mean serum levels of antibodies in the study groups.

	HEAVY SMOKERS			NON SMOKERS
	A TOTAL n = 110	B COPD n = 54	C NON COPD n = 56	D n = 209
CFFCP+ (%)	5 (4.5%)	4 (7.4%)*	1 (1.7%)	5 (2.4%)*
CFFCP mean ± SD	0.12 ± 0.06	0.15 ± 0.7†	0.09 ± 0.5†	0.10 ± 0.12
CCP2+ (%)	2 (1.8%)	2 (3.7%)	0 (0%)	4 (1.9%)
CCP2 mean ± SD	15.62 ± 4.25	16.2 ± 5.97‡	15.05 ± 0.9‡	16.9 ± 2.78

*B vs D: p = 0.07
†B vs C: p = 0.013
‡B vs C: p = 0.003

Conclusion: ACPAs are rarely seen in the sera of non-arthritic heavy smokers. However the production of these autoantibodies seems to be higher in heavy smokers patients with associated COPD disease. Larger series

studies are necessary to confirm these findings and to ascertain the relationship between ACPAs and inflammatory lung disease.

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1071

Anti-Citrullinated Protein Antibodies (ACPA) in Unaffected Siblings of ACPA-Positive Rheumatoid Arthritis Patients. Lillian Barra[1], Elizabeth Wilson[1], Matthias Scinocca[1], Kelly Summers[1], Ewa Cairns[2] and David A. Bell[2]. [1]The University of Western Ontario, [2]The University of Western Ontario, London, ON, Canada

Background: We have previously reported that ACPA purified from RA patients injected intra-peritoneally (ip) into FcgRIIB-deficient mice induced inflammatory arthritis; whereas, ip injections of IgG devoid of ACPA from the same RA patients did not. ACPA has been shown to be positive in some unaffected first degree relatives of patients with RA (approximately 2% prevalence in a predominantly Caucasian population and 17% in a North American Native population) and its prevalence increases with the presence of the shared epitope (SE).

Objective: To determine whether unaffected siblings of ACPA positive RA probands have RA features and whether their ACPA can induce inflammatory arthritis experimentally.

Methods: Patients were included if they met ACR criteria for RA, had IgG anti-CCP2>50 and had unaffected siblings (confirmed after assessment by a physician). A questionnaire detailing medical history and risk factors for RA was completed. ACPA was affinity purified using a proprietary synthetic citrullinated peptide (JED) and administered ip to pre-autoimmune FcγRIIb deficient mice. IgG and IgM anti-JED and anti-CCP2 were measured by ELISA. All subjects were tested for the presence of the SE; levels of 27 cytokines were determined by Luminex®.

Results: Twelve families were recruited for a total of 33 siblings (32 were unaffected with RA); there were two monozygotic twins discordant for RA. All subjects were Caucasian. Mean age of RA probands was 60, mean age of disease onset was 44, 10/12 (83%) were smokers, and 10/12 (83%) were in complete remission. Mean age of siblings was 51 and 14/29 (48%) were smokers, which was significantly less than RA probands ($p=0.024$). 9/12 probands were also IgG anti-JED positive and 7/12 were IgM anti-JED positive. One sibling was IgG anti-JED and anti-CCP2 positive. 10/31 siblings were IgM anti-JED positive; whereas, all normals ($n=9$) were negative. The monozygotic twins were also discordant for the presence of anti-JED and anti-CCP2. The results of HLA-typing and ip ACPA transfers are pending. Pro-inflammatory cytokines were elevated in RA patients compared to siblings and normals ($p<0.05$). Siblings did not have higher levels of pro-inflammatory cytokines than normals; however, the levels in smokers were higher than non-smokers ($p<0.05$).

Conclusions: Siblings of IgG anti-CCP2 postive RA probands had an increase in IgM anti-JED, but rarely had IgG anti-JED and IgG anti-CCP2 and also lacked elevation of pro-inflammatory cytokines characteristic of RA. Interestingly, monozygotic twins discordant for RA were also discordant for the presence of anti-CCP2 and anti-JED antibodies. Future work aims to determine whether IgM and IgG anti-JED isolated from these unaffected siblings is pathogenic in a mouse model of inflammatory arthritis.

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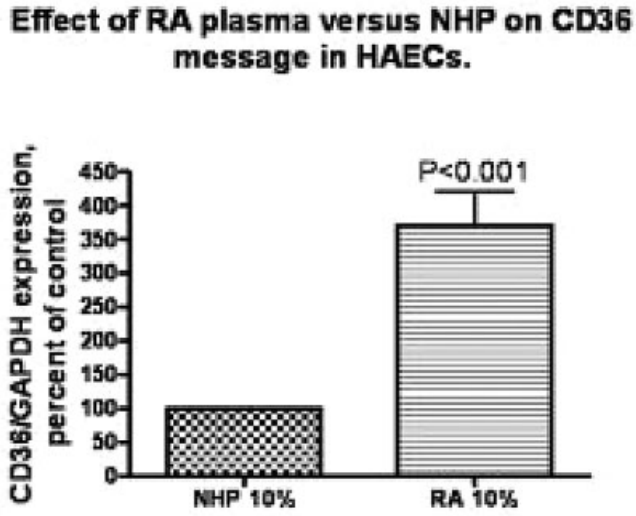
Atherogenic Properties of Rheumatoid Arthritis Plasma: Effect on Cholesterol Transport Genes. Allison B. Reiss[1], Iryna Voloshyna[1], Michael Littlefield[1], Elise Belilos[1], Kristina Belostocki[2], Lois A. Bonetti[1], Gary C. Rosenblum[1] and Steven E. Carsons[1]. [1]Winthrop University Hospital, Mineola, NY, [2]Winthrop University Hospital, Jamaica, NY

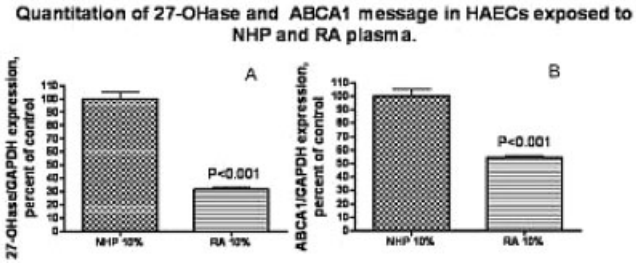
Purpose: The risk of cardiovascular (CV) morbidity and mortality is profoundly increased in patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). We have reported that SLE patients manifest a pattern of disturbance in expression of genes involved in lipid transport that is atheroma-promoting. When THP-1 human monocytes/macrophages are exposed to lupus plasma, the cholesterol efflux proteins 27-hydroxylase (27-OHase) and ATP binding cassette transporter (ABC)A1 are suppressed while the scavenger receptor CD36 that facilitates cholesterol uptake is augmented, leading to cholesterol overload and foam cell formation (FCF). This study examines whether RA patients exhibit comparably atherogenic plasma. In addition to the genes already mentioned, we look at the nuclear hormone receptor liver X receptor (LXR), which stimulates cholesterol efflux and induces expression of ABC transporters.

Methods: CD36, ABCA1, 27-OHase and LXR expression were evaluated in THP-1 human monocytes and human aortic endothelial cells (HAEC), cell types relevant to atherogenesis. Cells were incubated for 18h and 24h in medium containing 0, 10 or 25% of either RA patient plasma or normal human plasma (NHP). Following the 18h incubation, mRNA was isolated and reverse transcribed. The resulting cDNA was subjected to quantitative PCR using specific primers for each gene. Cellular extracts were prepared for Western immunoblotting after 24h.

Results: Pooled plasma from RA patients in this study population was compared to NHP. The presence of 10% RA plasma upregulated CD36 message by 270.8 ± 88.0% in HAEC ($n=3$, $P<0.001$) above NHP (Figure 1).



In THP-1 and HAEC, 27-OHase message level fell by 46.23 ± 12.5% and 69.1 ± 4.12% (Figure 2A) ($n=3$, $P<0.001$) below NHP, respectively and ABCA1 fell by 50.6 ± 15.0% ($n=3$, $P<0.001$) and 45.6 ± 8.7% (Figure 2B) ($n=3$, $P<0.01$) below NHP, respectively. LXR levels fell concomitantly: by 26.6 ± 3.9% and 56.6 ± 7.4% % ($n=3$, $P<0.001$) below NHP, respectively. Western blot analysis confirmed PCR results.



Conclusion: Traditional CV risk assessment is inadequate in RA. This study demonstrates pro-atherogenic properties of RA plasma that may promote atherosclerosis by increasing vulnerability to cholesterol overload. Demonstration of disrupted cholesterol homeostasis in this select group of patients provides further evidence of the involvement of the immune system in atherogenesis. Our findings may lead to the use of a cholesterol transport gene profile for evaluation of CV risk in this susceptible population.

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Circulating Cytokines Influence the Fetal Growth in Pregnant Women with Rheumatoid Arthritis. Florentien D. O. de Steenwinkel[2], Johanna M. W. Hazes[1], Yaël A. de Man[1], Anita C. S. Hokken[2], Yolanda B. de Rijke[2] and Radboud J. E. M. Dolhain[1]. [1]Erasmus Medical Center, Rotterdam, The Netherlands, [2]Erasmus Medical Center/Sophia Children's Hospital, Rotterdam, The Netherlands

Background: High RA disease activity during pregnancy is associated with lower birth weight. Lower birth weight, even within the normal range, has been linked with cardiovascular diseases and metabolic syndromes later in life. Outside pregnancy, active RA is associated with high levels of circulating cytokines.

Purpose: To asses the levels of IL-10, IL-6 and TNFa in pregnant women with RA and to evaluate correlations between these levels, disease activity, and birth weight.

Methods: Current study is embedded in the PARA-study, a prospective study on RA and pregnancy. 134 pregnant RA patients are enrolled in first and 168 in third trimester. 33 healthy pregnant women served as control. We analyse data using birth weight standard deviation scores (bwsds), a measure for birth weight adjusting for gestational age and sex of the child. Maternal disease activity is based on DAS28. IL-10, IL-6 and TNFa are determined by Immulite 1000.

Results: Levels of IL-10, IL-6 and TNFa decrease during pregnancy. Strong correlations are found between these cytokines in first and third trimester and between DAS28 and IL-10, IL-6.

First trimester patients with detectable IL-10 (n=12) show a higher disease activity than the IL-10 negative patients, a mean DAS28 4.4 (SD 1.2) and 3.6 (SD 1.1) respectively. To diminish the influence of disease activity on birth weight we match the IL-10 positive to an IL-10 negative group. Matching is on disease activity, parity and prednisone use. Mean bwsds is significantly higher ($p=0.02$) in the IL-10 positive group 0.92 (SD 0.7), than in the IL-10 negative match, 0.15 (SD 0.7). No such association is found in third trimester.

To determine the additional effect of IL-6 to disease activity on bwsds stratification is done. In first trimester we stratify IL-6 and DAS28 in high and low group based on their median, resulting in 4 groups. In the two high DAS28 groups (defined median over 3.8), bwsds is significantly lower in high IL-6 than in low IL-6 ($p<0.05$). In the high IL-6 group bwsds is −0.19 (SD 1.12) in the low IL-6 group bwsds is 0.36 (SD 0.93). No such association is found in third trimester.

TNFa is stratified the same way. In third trimester, only in patients with low disease activity, bwsds is lower in the low TNFa group than in the high TNFa group, bwsds of 0.05 (SD 0.97) and 0.52 (SD 0.96) respectively ($p<0.05$). Same trend is seen in the healthy cohort group, although not significant. No such association is found in first trimester or in patients with high RA disease activity.

Conclusion: Circulating cytokines influence fetal growth in pregnant women with RA. In first trimester elevated IL-10 seems to protect against the negative influence of RA disease activity on birth weight, IL-6 seems to amplify this negative influence. Both cytokines create a bwsds deviation of more than 0.50 which is considered clinically relevant. In third trimester there is no influence suggesting an early critical window.

Finally, our data might indicate a physiological role of TNFa in fetal growth during third trimester in healthy controls and patients with low disease activity. Underscoring that TNF-blockers should be used with caution during pregnancy.

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Citrullination and Peptidylarginine Deiminase (PAD) Expression Is Detected in the Oral Mucosa and Periodontium in the Absence of Rheumatoid Arthritis. Clifton O. Bingham[1], Mark A. Reynolds[3], Jon Giles[2], Felipe Andrade[2], Joan M. Bathon[2], Karen Fox-Talbot[2] and Marc K. Halushka[2]. [1]Johns Hopkins, Baltimore, MD, [2]Johns Hopkins, [3]University of Maryland Dental School

Background: There is growing interest in the association of periodontal disease (PD) and rheumatoid arthritis (RA). It has been proposed that *P. gingivalis*, an important periodontal bacteria with an endogenous PAD enzyme (Pg-PAD), is responsible for oral citrullination leading to a break in tolerance with attendant anti- citrullinated peptide antibody (ACPA) formation in RA. There is limited data on the protein citrullination and endogenous PAD expression in the oral cavity.

Methods: Using immunohistochemistry, we have examined formalin-fixed, paraffin-embedded gingival tissue from 4 patients with PD. Additional oral tissues examined included buccal mucosa and tonsil. All samples were from patients without known inflammatory arthritis. We used an anti-modified citrulline kit (Upstate) to detect citrullination. Expression of PAD2, PAD3, PAD4, and PAD6 were evaluated with rabbit-anti human polyclonal antibodies using an avidin-biotin complex detection system with DAB as the chromogen and with appropriate controls.

Results: Citrullination was detected in keratinized epithelium in gingiva and in normal buccal mucosa. Variable levels of citrullination were also detected in blood vessels and inflammatory cells in normal mucosa and periodontitis. Expression of PAD2 was abundant in buccal mucosa and periodontal tissues in epithelium, vascular endothelium, and inflammatory cells. PAD3 was similarly localized in the epithelium, endothelium, and inflammatory cells. PAD4 was only minimally expressed in the epithelium and weakly in the endothelium, but seen in some infiltrating cells including neutrophils and in inflammatory cells in tonsil. PAD6 was seen in the epithelium and endothelium with variable expression in inflammatory cells. In some tissue with skeletal muscle, bundles were variably stained with PAD2 and PAD6 with concomitant citrullination. Studies to examine PAD1 expression and additional diseased and control tissues are in progress.

Conclusions: This is the first comprehensive examination of protein citrullination and PAD expression in oral tissues. Citrullination is ubiquitously present in multiple oral locations and is not limited to inflamed periodontium. Similarly, PADs 2, 3, 4 and 6 are all localized in oral tissue in the presence or absence of inflammation. Our studies indicate that there are multiple potential pathways responsible for post-translational citrullination in the oral mucosa: endogenous PAD expression, upregulated PADs at inflammatory foci, in addition to Pg-PAD providing an exogenous source. Additional studies are necessary to determine the specific substrates of different human and bacterial PADs in the periodontal microenvironment and to establish their relationship with ACPA formation, and disease initiation or propagation in RA.

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1075

Common Genetic Background for Rheumatoid Arthritis and Systemic Lupus Erythematosus. Gisela Orozco, Steve Eyre, Anne Hinks, Wendy Thomson, Jane Worthington and Anne Barton. Arthritis Research Campaign Epidemiology Unit, The University of Manchester

Background: Evidence is beginning to emerge that there may be susceptibility loci for rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) that are common to both diseases.

The aim of this study was to investigate single nucleotide polymorphisms (SNP) that have been reported to be associated with SLE in a UK cohort of RA cases and controls.

Methods: 3,962 RA patients and 9,275 controls were included in the study. Of the SLE loci identified to date (1), eleven SNPs mapping to confirmed SLE loci were investigated. These mapped to the *TNFSF4, BANK1, TNIP1, PTTG1, UHRF1BP1, ATG5, JAZF1, BLK, KIAA1542, ITGAM* and *UBE2L3* loci. Genotyping was undertaken using a Sequenom platform with iPlex chemistry. Genotype frequencies were compared between RA cases and controls using the trend test implemented in PLINK software. *P*-values <0.0045 were regarded as significant after correcting for multiple testing.

Summary of Results: The SNPs mapping to the *BLK* and *UBE2L3* loci showed significant evidence for association with RA (rs2736340, $P = 3.0 \times 10^{-4}$, OR 1.11 95% CI 1.05–1.17; rs5754217, $P = 2.4 \times 10^{-3}$, OR 1.11 95% CI 1.04–1.19). Two other SNPs, mapping to *ATG5* and *KIAA1542*, showed nominal evidence for association with RA ($P=0.02$ and $P=0.02$, respectively) but these were not significant after applying a Bonferroni correction. Additionally, we found a significant global enrichment in carriage of SLE alleles in RA patients compared to controls ($P=$

9.1×10^{-7}). Meta-analysis of this and previous studies confirm the association of the *BLK* and *UBE2L3* gene with RA at genome-wide significance levels ($P<5\times10^{-8}$). Together, we estimate that, after excluding *HLA-DRB1* alleles, the overlapping loci identified so far explain ~5.8% of the genetic susceptibility to RA as a whole.

Conclusions: The findings confirm the association of the *BLK* and *UBE2L3* loci with RA thus adding to the list of loci showing overlap between RA and SLE, which currently include *HLA-DRB1, PTPN22, STAT4, TNFAIP3, FCGR2A, PRDM1, IRF5* and *PXK*.

References:

(1) Gateva V, Sandling JK, Hom G, Taylor KE, Chung SA, Sun X et al. A large-scale replication study identifies *TNIP1, PRDM1, JAZF1, UHRF1BP1* and *IL10* as risk loci for systemic lupus erythematosus. Nat Genet 2009; 41(11):1228–33.

Disclosure: G. Orozco: None; **S. Eyre:** None; **A. Hinks:** None; **W. Thomson:** None; **J. Worthington:** None; **A. Barton:** None.

1076

Confirmation of the Especial Interaction of Autoimmunity Against Citrullinated α-Enolase with Genotypes Predisposing to Rheumatoid Arthritis. Antonio Gonzalez[1], Ariana Montes[2], Rebeca Dieguez-Gonzalez[2], Manuel Calaza[2], Eva Perez-Pampin[2], Antonio Mera[2] and Juan J. Gomez-Reino[2]. [1]Hospital Clinico Universitario de Santiago, Santiago de Compostela, A Coruña, Spain, [2]Hospital Clinico Universitario de Santiago

Background: Autoimmunity against citrullinated α-enolase has been proposed as a major component of the anti-citrullinated proteins response characterizing rheumatoid arthritis (RA) patients with worse spontaneous disease evolution. This claim was based on the extraordinary interaction between the presence of antibodies against the immunodominant peptide of α-enolase (CEP-1) and genetic and environmental susceptibility factors for RA.

Methods: DNA and serum samples from 451 patients with RA and 277 healthy controls of Spanish ancestry were obtained. Antibodies to CCP-2 and CEP-1 were measured by ELISA. HLA-DRB1 was genotyped by the sequencing-based-typing method (SBT) and the R620W SNP of PTPN22 by a Taqman genotyping assay. Interactions between factors were evaluated as departures from additivity of the individual effects.

Results: Anti-CEP-1 antibodies were detected in 26.8 % of the RA patients whereas 71.2 % were anti-CCP positive. Most of the patients with anti-CEP-1 antibodies, 86.6 %, were also positive in the anti-CCP2 test. This group of patients with RA positive for the two antibodies were disproportionally associated with the SE (Fig. 1), especially with the DRB1*04 allele (not shown), and with the 620W risk allele of PTPN22 (Fig. 2).

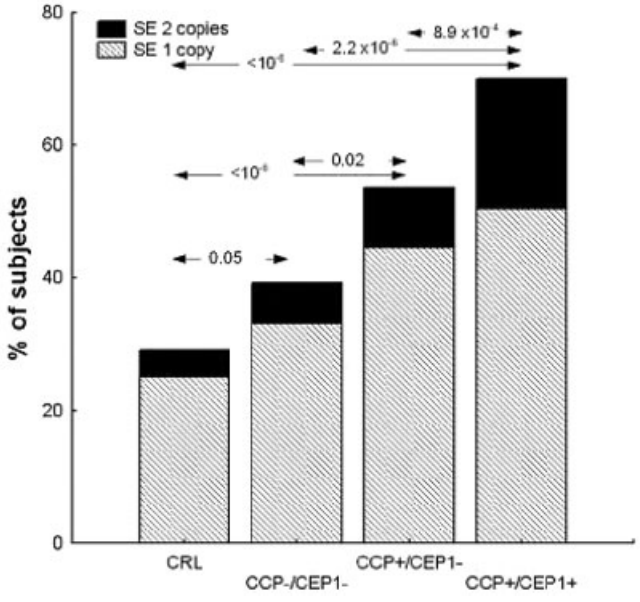

Figure 1.

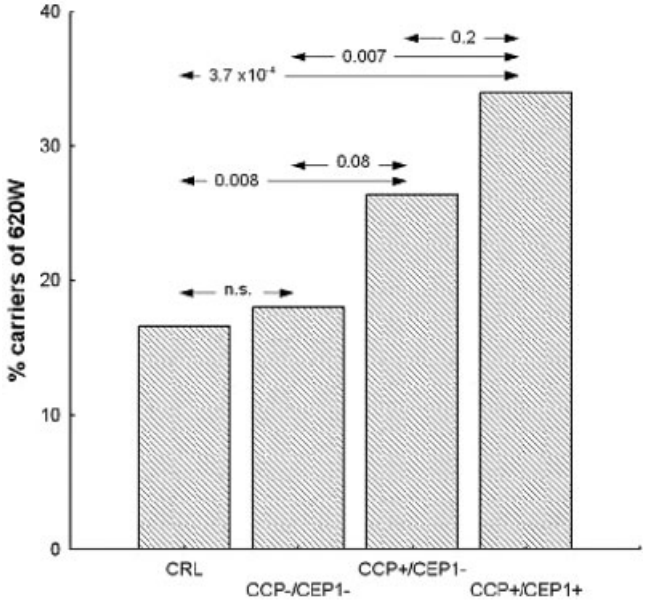

Figure 2.

There was significant evidence of epistasis between the two genetic factors only when considering the patients that were positive for the two antibodies (p = 0.002, Fig. 3).

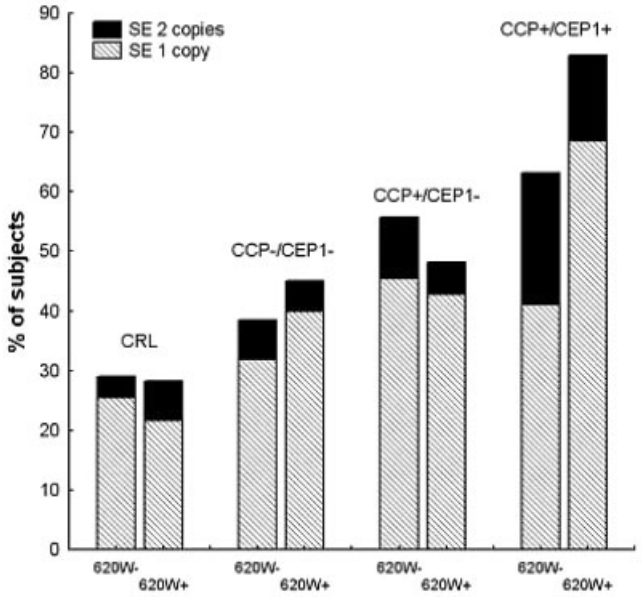

Figure 3.

The patients that were anti-CCP+ but anti-CEP-1- showed also association with these susceptibility genetic factors although of a lower magnitude and without significant interaction.

There was not association of any of the subgroups of patients with the smoking habit, probably in relation with the much lower prevalence of this habit among our patients (18.7 %) than in other published series.

Conclusions: We have confirmed that autoimmunity against citrullinated α-enolase accounts for a disproportionally large part of the effect of the genetic susceptibility alleles of HLA-DRB1 and PTPN22 among patients positive for anti-CCP antibodies. However, other citrullinated proteins seem to be also important targets in RA pathogenesis. In contrast with a previous report, we did not find any evidence of association with the smoking habit, but we have a small percentage of smokers among our patients.

Disclosure: A. Gonzalez: None; **A. Montes:** None; **R. Dieguez-Gonzalez:** None; **M. Calaza:** None; **E. Perez-Pampin:** None; **A. Mera:** None; **J. J. Gomez-Reino:** None.

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C-Reactive Protein (*CRP*) Single Nucleotide Polymorphisms (SNPs) Are Associated with Radiographic Damage and Plasma CRP Levels in African Americans (AAs) with Early Rheumatoid Arthritis (RA). Maria I. Danila[6], Lang Chen[5], Desiree M. Van Der Heijde[2], Doyt L. Conn[1], Beth L. Jonas[7], Leigh F. Callahan[8], Edwin A. Smith[3], Richard Brasington[10], Larry W. Moreland[9], S. Louis Bridges[6] and Laura B. Hughes[4]. [1]Emory Univ Schl of Med, Atlanta, GA, [2]Leiden University Medical Center, Meerssen, The Netherlands, [3]Med Univ of South Carolina, Charleston, SC, [4]Univ of Alabama Birmingham, Birmingham, AL, [5]Univ of Alabama-Birmingham, [6]Univ of Alabama-Birmingham, Birmingham, AL, [7]Univ of N Carolina-Chapel Hill, Chapel Hill, NC, [8]Univ of North Carolina, Chapel Hill, NC, [9]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [10]Washington Univ Schl of Med, St Louis, MO

Background: Plasma CRP levels are associated with disease activity in RA and influence clinical management. *CRP* SNPs correlate with plasma CRP levels and cardiovascular events. There are large differences in minor allele frequencies (MAF) of some clinically relevant *CRP* SNPs between Caucasians and AAs.

Objective: To test the hypotheses that, after accounting for other variables, *CRP* SNPs are associated with radiographic severity or plasma CRP levels in AAs with early RA (< 2 years disease duration).

Methods: Genotyping of *CRP* SNPs (rs3093058, rs3093059, rs2794521, rs3093061, rs3093062, rs3091244, rs1417938, rs1800947, rs3093066 rs1205, rs2808630), baseline plasma CRP level measurement and baseline radiographs of hands/feet scoring (Sharp/van der Heijde score) were performed on 357 AA RA patients and 150 AA controls enrolled in the CLEAR study. Differences in MAF were analyzed using chi square analysis. Univariable and multivariable negative binomial regression was used to evaluate the association of *CRP* SNPs with baseline radiographic erosions scores and CRP levels. Other relevant variables examined in univariable analyses were: HLA-DRB1 shared epitope, RF, anti-CCP antibody, age, gender, disease duration, body mass index (BMI), use of DMARDs, biologic agents, and corticosteroids. Those obtaining a p value < 0.1 in the univariable analyses were included as covariates in the multivariable analyses.

Results: 40% of RA subjects had radiographic erosions at baseline. Mean age of RA onset was 49 years, median disease duration was 1.5 years, 82.4% were female, mean BMI was 31.2; DMARD use (62.8%), corticosteroid use (77.7%), biologic use (4.0%), and mean baseline plasma CRP was 17.9 mg/L.

There were no significant differences in the distribution of the *CRP* SNPs between RA cases and controls. In the multivariable analysis, significant associations were found between 5 *CRP* SNPs and plasma CRP levels: rs3093058 (p=0.0002), rs3093061 (p=0.0042), rs3093062 (p=0.002), rs3091244 (p=0.0212), rs1205 (p=0.0425) after adjusting for BMI, age at RA onset, and biologic use (Table 1a). The majority of the observed effect was due to the rs3091244 T and rs1205 T alleles (Table 1a). In the multivariable analysis of radiographic erosions, 5 CRP SNPs demonstrated significance: rs3093059 (p=0.0096), rs2794521 (p=0.0238), rs3091244 (p=0.0026), rs3093066 (p=0.0090), rs2808630 (p=0.0081) after adjusting for disease duration and biologic use (Table 1b). The majority of the observed effect was due to the rs2794521G allele (Table 1b). There was no association between baseline plasma CRP levels and radiographic erosions.

Table 1a. Multivariate analysis of *CRP* SNPs and CRP levels, adjusted for factors found to be significant in the univariate analysis: BMI, age at RA onset, and biologic use.

		P value Conditioned on				
Marker	**Original**	**rs3093058**	**rs3093061**	**rs3093062**	**rs3091244**	**rs1205**
rs3093058	0.0002	–	0.7958	0.001	**0.7235**	**0.2344**
rs3093061	0.0042	0.014	–	0.0135	**0.3191**	**0.1087**
rs3093062	0.0002	0.001	0.8484	–	**0.7135**	**0.2229**
rs3091244	0.0212	0.002	0.0443	0.002	–	**0.1831**
rs1205	0.0425	0.0008	0.0134	0.0008	**0.0882**	–

Table 1b. Multivariate analysis of *CRP* SNPs and erosions, adjusted for factors found to be significant in the univariate analysis: disease duration and biologic use.

		P value Conditioned on				
Marker	**Original**	**rs3093059**	**rs2808630**	**rs3091244**	**rs3093066**	**rs2794521**
rs3093059	0.0097	–	0.0236	0.1961	0.3508	**0.0606**
rs2794521	0.0238	0.012	0.128	0.0036	0.0191	–
rs3091244	0.0026	0.6683	0.0409	–	0.9883	**0.0999**
rs3093066	0.0090	0.1752	0.0164	0.0962	–	**0.0449**
rs2808630	0.0064	0.0129	–	0.0045	0.0190	**0.5359**

Conclusions: In AAs with early RA, *CRP* variants are associated with CRP levels and baseline radiographic erosions independent of other clinical factors. These findings have important implications for assessment of disease activity and risk of erosive disease in AAs with early RA.

Disclosure: M. I. Danila: None; **L. Chen:** None; **D. M. Van Der Heijde:** Receiving remuneration for reading radiographs, 5; **D. L. Conn:** None; **B. L. Jonas:** None; **L. F. Callahan:** None; **E. A. Smith:** None; **R. Brasington:** None; **L. W. Moreland:** None; **S. L. Bridges:** None; **L. B. Hughes:** None.

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Differential Association of IL23R Genetic Variants with Anti-CCP Positive and Negative Rheumatoid Arthritis Patients. Antonio Gonzalez[6], Aida Ferreiro[5], Eva Perez-Pampin[5], Manuel Calaza[5], Francisco J. Lopez-Longo[13], Jose Luis Marenco[12], Francisco J. Blanco[9], Rafael Caliz[14], Javier Narvaez[10], Federico Navarro[15], Juan Cañete[3], Arturo R. de la Serna[8], Isidoro Gonzalez-Alvarez[11], Gabriel Herrero-Beaumont[1], Jose Luis Pablos[2], Alejandro Balsa[7], Benjamin Fernandez-Gutierrez[4] and Juan J. Gomez-Reino[5]. [1]Fundacion Jimenez Diaz. Madrid, [2]Hospital 12 de Octubre, Madrid, [3]Hospital Clinic. Barcelona, [4]Hospital Clinico San Carlos, Madrid, [5]Hospital Clinico Universitario de Santiago, [6]Hospital Clinico Universitario de Santiago, Santiago de Compostela, Spain, [7]Hospital La Paz. Madrid, [8]Hospital Santa Creu e San Pau. Barcelona, [9]Hospital Universitario A Coruña, [10]Hospital Universitario de Bellvitge. Barcelona, [11]Hospital Universitario de la Princesa, [12]Hospital Universitario de Valme. Sevilla, [13]Hospital Universitario Gregorio Marañon, Madrid, [14]Hospital Universitario Virgen de las Nieves, Granada, [15]Hospital Universitario Virgen Macarena, Sevilla

Background: Several polymorphisms in the interlekin-23 receptor gene (IL23R) have shown strong association to autoimmune diseases including ankilosing spondylitis, Crohn's disease and psoriasis. There have been also some less convincing reports of association with rheumatoid arthritis (RA). These associations are interpreted as highlighting a significant involvement of the IL23/IL17 pathway in disease pathogenesis and, therefore, are of great interest for the understanding of disease pathogenesis.

Methods: We have examined 5 SNPs in the IL23R gene (rs11209026, rs1343151, rs7530511, rs2201841, rs11209032) that were strongly associated with other autoimmune diseases in 1655 patients with AR and 1601 healthy controls of Spanish ancestry. Genotyping was done by minisequencing. Statistical analyses were done with the Statistica software. Haplotype estimation was conducted with PHASE2.

Results: One of the SNPs was rejected due to lack of Hardy-Weinberg equilibrium. Comparison of allele frequencies of the other 4 SNPs in patients with RA and healthy controls revealed no differences in the distribution of IL23R allele frequencies. However, there were differences between anti-CCP$^+$ and anti-CCP$^-$ patients and between the two subgroups of patients and the controls (Table 1).

	anti-CCP$^+$	**anti-CCP$^-$**	**CRL**	**anti-CCP$^+$ vs CRL p-value**	**anti-CCP$^-$ vs CRL p-value**	**anti-CCP$^+$ vs anti-CCP$^-$ p-value**
rs11209026	6.7% (80/1188)	10.2% (89/870)	8.0% (255/3200)	0.2	0.034	0.0043
rs1343151	33.8% (401/1188)	41.6% (362/870)	37.3% (1193/3200)	0.031	0.02	0.00027
rs2201841	32.3% (384/1188)	27.3% (237/868)	31.1% (995/3198)	0.4	0.03	0.014
rs7530511	12.8% (152/1188)	13.0% (113/868)	12.6% (402/3198)	0.8	0.7	0.9

Conditional logistic regression analysis showed that rs1343151 could account for all the associations in the locus, both in anti-CCP$^+$ and anti-CCP$^-$ patients, but with a stronger effect in the latter. Haplotype analysis also indicated that this SNP was able to explain all association in the locus.

Conclusions: Our results showed evidence of a differential effect of polymorphisms in the IL23R gene in anti-CCP$^+$ and anti-CCP$^-$ patients with

RA. The effect was of an increased risk for the anti-CCP$^-$ phenotype in the patients bearing the minor allele of rs1343151, and of an opposed trend for the anti-CCP$^+$ phenotype. These contrasting associations may explain previous results of genetic studies of this locus in RA that have shown a predominant effect of the rs1343151 SNP but some variation between patient cohorts. They also rise the intriguing possibility of their contribution to the differentiation of these two major subgroups of RA patients. This possibility together with the evidence of multiple independent associations in other diseases increase the interest in the dissection of the mechanisms affected by the IL23R polymorphisms.

Disclosure: A. Gonzalez: None; **A. Ferreiro:** None; **E. Perez-Pampin:** None; **M. Calaza:** None; **F. J. Lopez-Longo:** None; **J. L. Marenco:** None; **F. J. Blanco:** None; **R. Caliz:** None; **J. Narvaez:** None; **F. Navarro:** None; **J. Cañete:** None; **A. R. de la Serna:** None; **I. Gonzalez-Alvarez:** None; **G. Herrero-Beaumont:** None; **J. L. Pablos:** None; **A. Balsa:** None; **B. Fernandez-Gutierrez:** None; **J. J. Gomez-Reino:** None.

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DNA Damage, T Cell Lymphopenia and Immunosenescence in Rheumatoid Arthritis. Lan Shao[1], Hiroshi Fujii[2], Jorg J. Goronzy[1] and Cornelia M. Weyand[1]. [1]Stanford University School of Medicine, Stanford, CA, [2]Tohoku University School of Medicine, Sendai, Japan

Background/Purpose: In RA, immune aging is accelerated by 25–30 years. The immune system is homeostatically controlled; lymphocyte regeneration/proliferation compensates for cell attrition. Lymphocytes age prematurely if they proliferate excessively; imposed by too much loss or too little cell input. We have examined whether RA patients have higher T cell loss than age-matched controls by focusing on naive CD4 T cells which have not yet been recruited into any immune response. Specifically, we have examined signals and molecular mechanisms regulating survival of naive T cells that build the immune reserve.

Methods: Naive CD4 T cells from sero-positive RA patients and demographically matched controls were tested ex vivo for their susceptibility to apoptosis by cytometric analysis of 7AAD and Annexin V with and without T cell receptor stimulation. The load of damaged DNA was quantified by Comet assay and telomeric length was measured by modified qPCR. Repair mechanisms for telomeric and non-telomeric DNA were assessed through the analysis of three enzymatic systems involved in DNA repair/telomeric maintenance; telomerase and the phosphoinositide-3-kinase-related protein kinases Ataxia-telangiectasia mutated (ATM) and DNA-dependent protein kinase catalytic subunit (DNA-PKcs). DNA damage sensing enzymes were knocked down by si-RNA technology or forcefully overexpressed by transfection.

Summary of Results: Naive human CD4 T cells, both resting and triggered with anti-CD3/CD28, died through the intrinsic death pathways, regulated by pro- and anti-apoptotic Bcl-2 family members. RA CD4 T cells freshly isolated from patients or kept without stimulation ex vivo were highly susceptible to apoptosis with doubling of death rates (28.2% RA T cells vs. 15.1% control T cells; p=0.01). Increased apoptotic susceptibility coincided with accumulation of DNA double strand breaks (p=0.0001), suggesting that unrepaired DNA and telomeres shorten survival of naive T cells. Induction of the telomere repair enzyme telomerase was impaired in RA T cells (p=0.0001). Also, RA T cells insufficiently upregulated the damage-sensing enzyme ATM (p=0.008) but expressed high levels of DNA-PKcs transcripts and protein (p=0.03). Forced overexpression of telomerase or ATM and blockade of DNA-PKcs rescued RA T cells from apoptosis (p=0.008, 0.001 and 0.005, respectively). The shift in apoptotic threshold setting was not a consequence of therapy but was equally present in untreated RA patients (p=NS, Tx vs. non-Tx).

Conclusions: Naive CD4 T cells in RA patients are under genotoxic stress. Telomeres are shortened and insufficiently repaired and DNA doubles strand breaks accumulate. Repair pathways involving the enzyme ATM are suppressed. Chronic repair activity signaled by the DNA-PKcs pathway sustains cell-internal stress signals that harm the cells and lead to apoptosis. Excessive T cell loss strains homeostatic mechanisms and, by depleting the proliferative reserve of long-lived T cells, leads to premature immune aging. Mechanisms regulating intactness of telomeric and non-telomeric DNA should be considered in attempts to reset the dysfunctional immune system of RA patients.

Disclosure: L. Shao: None; **H. Fujii:** None; **J. J. Goronzy:** NIAMS-NIH, 2, NIH, 2; **C. M. Weyand:** NHBLI, 2, NIAMS-NIH, 2, NIH, 2.

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Do Patients with Rheumatoid Arthritis Exhibit Differential Cellular Responses to Implant Wear Debris and Do the Implant Failure Mechanisms Differ from Non-RA Patients? Anant Vasudevan[5], Edward F. DiCarlo[3], Timothy Wright[2], Dan Chen[2], Steven R. Goldring[1] and Lisa A. Mandl[4]. [1]Chief Scientific Officer, Hospital for Special Surgery, [2]Department of Biomechanics, Hospital for Special Surgery, [3]Department of Pathology and Laboratory Medicine, Hospital for Special Surgery, [4]Hospital for Special Surgery, New York, NY, [5]Yale School of Medicine, New York, NY

Background: Peri-implant osteolysis is the major reason total elbow replacements (TER) fail. Osteolysis is caused by implant wear debris, and evidence exists that patients with rheumatoid arthritis (RA) may respond differently to foreign material compared to patients without RA. This study was performed to determine whether TER patients with RA exhibit differential cellular responses to implant wear debris compared to TER patients without inflammatory joint disease.

Materials and Methods: Thirty-eight patients who had their first TER revision for osteolysis were reviewed. All had similar prosthetic devices removed between 1996 and 2008. Twenty-five had RA, and thirteen had no autoimmune disease. Histopathology, clinical data, and gross wear of the removed prostheses were evaluated and compared in RA and non-RA patients.

Results: Structural evaluation of the retrieved prostheses showed increased material loss was significantly associated with the generation of more, large polyethylene particles (p-value < 0.01) and a trend towards more metal particles (p-value $= 0.05$). The amount of wear debris in the tissue was similar regardless of underlying diagnosis (p-value > 0.65). In the presence of large particulate polyethylene debris, RA patients not on anti-TNF therapy showed a trend towards more plasma cell infiltration within lymphocytic aggregates in the periprosthetic tissue compared with non-RA patients (p-value $= 0.07$). This difference was attenuated in RA patients who had received anti-TNF therapy (p-value $= 1.0$). Among patients with high levels of plasma cells within lymphocytic aggregates, non-RA and RA patients on anti-TNF inhibitors showed similar perivascular patterns of lymphocytic aggregation, whereas RA patients not on anti-TNF inhibitors showed no perivascular aggregates (p-value $= 0.01$).

Conclusion: RA patients exhibit a distinct pattern of cellular response to implant wear debris when compared with non-RA patients, which was not due to differences in the type or amount of particulate debris. The increased number of plasma cells within lymphoid aggregates indicates that RA patients mount an adaptive immune response to implant wear particles, which is mitigated by anti-TNF therapy. These observations provide insights into the pathogenic link between the innate and adaptive immune systems in RA and have implications for future approaches to treating osteolysis in RA patients.

Disclosure: A. Vasudevan: New York Chapter of the Arthritis Foundation, 2, Yale University School of Medicine, 2; **E. F. DiCarlo:** None; **T. Wright:** None; **D. Chen:** None; **S. R. Goldring:** Boehringer Ingelheim, 2, Bone Therapeutics, 5, Merck Pharmaceuticals, 5, Novartis Pharmaceuticals Corporation, 5, Roche, 5, Serono, 5; **L. A. Mandl:** NIH 5 K23 AR050607-05; Arthritis Investigator Award, 2, NIH, 2.

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Dual Roles of Heme Oxygenase-1 on Rheumatoid Arthritis: Anti-Inflammation Versus Angiogenesis. Kaoru Takase[2], Shigeru Ohno[1], Mitsuhiro Takeno[3] and Yoshiaki Ishigatsubo[4]. [1]Center for Rheumatic Diseases, Yokohama City University Medical Center, [2]Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Japan, [3]Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Japan[4]Yokohama City Grad Sch of Med, Yokohama, Japan

Objectives: Heme oxygenase 1 (HO-1) plays cytoproptective roles on various pathological conditions including inflammatory disorders. However, the roles of HO-1 in development of rheumatoid arthritis (RA) have been controversial. We and others have demonstrated an anti-inflammatory role of HO-1 in synovitis *in vitro* and *in vivo*, whereas hemin, a potent HO-1 inducer, is not necessarily beneficial for animal model arthritis. Some studies have suggested the protein promotes angiogenesis, leading to exacerbation of arthritis. We here examined relationship between HO-1 expression and angiogenesis in synovial tissues from RA patients and animal arthritis model.

Materials and Methods: 1) Human samples of synovial tissues were obtained form 10 RA patients and 5 OA patients during knee surgery. Expression of HO-1, and CD31 as a marker for endothelial cells, and CD68,

a marker for macrophages, in the tissues were semiquantitatively determined by immunohistochemistry using a digital image analyzer.

2) Arthritis was induced by cocktails of anti-type II collagen antibody in CB57/B6 mice (CAIA). Mice were pretreated with an HO-1 inducer, hemin or PBS, followed by induction of arthritis. Macroscopic arthritis score (0–3) and thickness of foot pad were evaluated.

Results: 1) HO-1 expressing cells were significantly more abundant in synovial tissues from RA than those from OA.

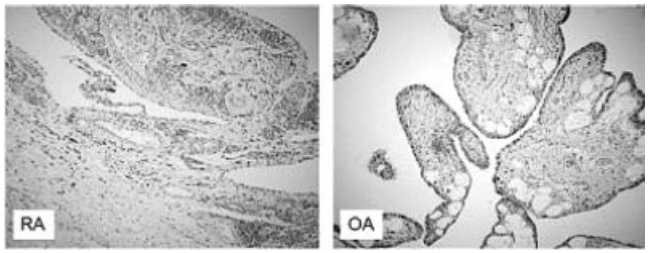

Figure 1. Expression of HO-1 proteins in synovial tissue.

While HO-1 expression was localized in the lining layer of OA synovium, analysis of serial sections revealed that HO-1 expression was detected in CD68+ synovial sublining macrophages and CD31+ vascular endothelial cells of RA synovium. Number of HO-1 expressing cells was correlated with those of CD68+ cells (r=0.81) and those of CD31+ cells (r=0.78), respectively.

2) Arthritis score and thickness of foot pad were significantly higher in CAIA mice pretreated with hemin than controls. In concordant with the clinical score, more abundant HO-1 expressing cells and angiogenesis were found in synovial tissues of hemin-treated group than controls.

Conclusions: The present study demonstrates HO-1 is associated with angiogenesis which potentially promotes development of arthritis in both human RA and arthritis in animal models, whereas HO-1 suppresses inflammatory responses by the innate immune systems including RA synoviocytes. Both features of HO-1 should be considered in the clinical application for inflammatory arthritis.

Disclosure: K. Takase: None; **S. Ohno:** None; **M. Takeno:** None; **Y. Ishigatsubo:** None.

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Epstein Barr Virus Serologies and Future Risk of Rheumatoid Arthritis among Women. Barbara L. Goldstein[2], Lori B. Chibnik[2], Elizabeth W. Karlson[2] and Karen H. Costenbader[1]. [1]Brigham & Women, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA

Background: Exposure to EBV and/or the humoral immune response it creates may be involved in the pathogenesis of rheumatoid arthritis (RA). Several past studies suggest an association between EBV and RA, but no study has examined EBV serologies prior to RA onset.

Methods: We studied the association between EBV serologies and future RA risk in a nested case-control sample among women enrolled in the Nurses' Health Study (NHS). We confirmed 93 incident RA cases with blood collected prior to RA symptoms by questionnaire and medical record review, excluding all self-reports not confirmed as RA. In a nested case-control design, each incident RA case was matched to a participant without RA by time of day and date of blood collection, year of birth, menopausal status and postmenopausal hormone use. Immunofluorescence assays were used to measure IgG serologic responses to EBV peptides: viral capsid antigen (VCA), early-antigen-diffuse and early antigen-restricted (EA-D and EA-R-D), EA-complex, Epstein Barr nuclear antigen (EBNA)-1, EBNA-2, and BZLF-1 (an EBV immediate early protein); all of which were reported as titers, except for BZLF-1 which was reported as positive or negative. Six ANA positive samples and their matched controls were excluded. We employed conditional logistic regression analyses of the risk of RA associated with two-fold elevations in the geometric mean titer (GMT) of the viral antibodies or presence/absence of BZLF-1. Multivariate models further adjusted for age and smoking.

Results: Mean time to RA after blood draw was 5.2 years (range = 0.3–12 years) among 87 incident RA cases, who were matched to 87 healthy female controls. Mean age at RA diagnosis was 60.5 ± 9.7 years. Forty-seven (54%) cases were RF positive at diagnosis. In unadjusted and multivariate models, two-fold elevations in EBV antibody GMTs, as well as anti- BZLF-1 positivity, were not associated with increased RA risk.

Table 1. Risk of RA associated with EBV Serologies

IgG Serology	Unadjusted OR* (95% CI)	MV** OR* (95% CI)
VCA	1.01 (0.87, 1.18)	1.02 (0.87, 1.18)
EBNA-1	1.02 (0.87, 1.20)	1.03 (0.88, 1.21)
EBNA-2	1.03 (0.89, 1.19)	1.02 (0.89, 1.18)
EA-D	2.68 (0.73, 9.81)	2.88 (0.75, 10.99)
EA-R-D	0.98 (0.82, 1.16)	0.98 (0.82, 1.18)
BZLF-1 (+)	0.75 (0.36, 1.59)	0.72 (0.34, 1.55)

VCA: viral capsid antigen, EA-D and EA-R-D: early-antigen-diffuse and early-antigen-restricted EA-complex, EBNA: Epstein Barr nuclear antigen, BZLF-1: an EBV immediate early protein
*Odds ratio of a 2-fold elevation in the IgG geometric mean titer, or presence of IgG antibody to BZLF-1.
**Multivariate conditional logistic regression model controlling for age and smoking.

Conclusions: Two-fold elevated anti-EBV GMTs, and BZLF-1 positivity, were not associated with future risk of RA, diagnosed a mean of 5.2 years later, in these women.

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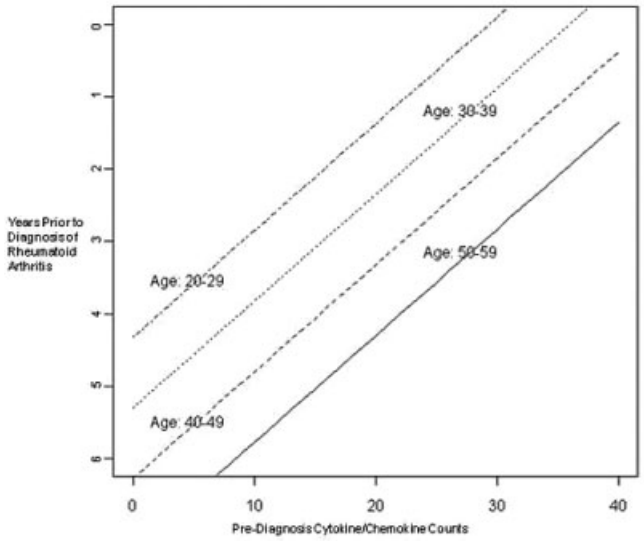
1083

Expanded Cytokine/Chemokine Testing Improves Prediction of Time to Future Diagnosis of Seropositive Rheumatoid Arthritis (RA) in an Age-Dependent Manner. Kevin D. Deane[8], Colin I. O'Donnell[2], Lezlie A. Derber[3], Jess D. Edison[10], William R. Gilliland[1], Wolfgang Hueber[4], Jeremy Sokolove[6], Piyanka E. Chandra[7], Jill Norris[9], William Robinson[5] and V. Michael Holers[8]. [1]Department of Medicine, Rheumatology Section, Walter Reed Army Medical Center, Washington, DC, [2]Department of Preventive Medicine and Biometrics, University of Colorado Denver, Denver, CO, [3]Division of Rheumatology, University of Colorado School of Medicine, Aurora, CO, [4]Novartis Institutes for BioMedical Research, Basel, Switzerland, [5]Stanford Univ School of Med, Stanford, CA, [6]Stanford University School of Medicine, Palo Alto, Mountain View, CA, [7]Stanford University School of Medicine, Palo Alto, CA, [8]Univ of Colorado School of Med, Aurora, CO, [9]University of Colorado Denver, Aurora, CO, [10]Walter Reed Army Med Ctr, Washington, DC

Purpose: We have previously shown using testing for 14 cytokines/chemokines that the number of elevated cytokines/chemokines predicted time to diagnosis of future RA in an age-dependent manner. However, with this limited number of cytokines/chemokines, accurate prediction was limited to <5 years prior to RA diagnosis. Herein we examine the effect of testing for increased numbers of cytokines/chemokines (N=48 current versus 14 prior) on the prediction of time to diagnosis of future RA.

Methods: For this analysis we selected 101 stored pre-RA diagnosis serum samples from 51 military cases (69% male, mean age at RA diagnosis 39) that would develop future rheumatoid factor (RF) and/or CCP positive RA. These pre-diagnosis samples were selected based on positivity for anti-CCP and/or 2 or more RF isotypes, an autoantibody profile shown prior to have 74% sensitivity and >96% specificity for future RA. Each of these pre-diagnosis samples was tested for 48 cytokines/chemokines using a magnetic bead-based assay. Cytokine/chemokine positivity was established using additional military post-RA diagnosis case versus matched control samples (N=43 each group), with cutoff levels selected for positivity >90% specific for RA. The time from pre-diagnosis sample collection to RA diagnosis was analysed using mixed-model regression analysis, with predictor variables age-at-diagnosis (stratified by decade) and cyotkine/chemokine counts.

Results: The number of elevated cytokines/chemokines (cytokine/chemokine counts) increased as the time of diagnosis of RA approached, with the highest cytokine/chemokine counts present <2 years prior to RA diagnosis. Increasing cytokine/chemokine counts predicted time to diagnosis in an age-dependent manner (Figure). The regression coefficients for age-at-diagnosis (by decade) and cytokine/chemokine counts were respectively beta1= −0.975 ($p<0.01$) and beta2= 0.147 ($p<0.01$). In contrast to prior analysis with 14 markers, testing for 48 markers allowed for accurate prediction of time of onset of future RA more than 6 years prior to diagnosis as well as allowing for finer prediction of time to diagnosis in times <3 yrs prior to diagnosis.



Increasing Cytokine/Chemokine Counts Predict Time to Future Diagnosis of Seropositive Rheumatoid Arthritis. All subject samples (N=101 from 51 RA cases) included in this analysis were positive for anti-CCP and/or 2 or more RF isotypes, an autoantibody profile >96% specific for future RA. In regression analysis, time to diagnosis for future RA was the outcome, and cytokine/chemokine counts and age (by decade) were predictor variables. For example, in a subject 45 years-old at assessment, a cytokine/chemokine count of 30 positive predicts a time to diagnosis of future RA of ~2 years.

Conclusions: In pre-clinical case samples positive for autoantibodies highly specific for future RA, increasing cytokine/chemokine counts from a panel of 48 cytokines/chemokines predicts time-to-diagnosis in an age-dependent manner, improving a prior model using 14 cytokines/chemokines. These findings provide insight into the biology of pre-clinical RA as well as provide a methodology for identification of currently arthritis-free subjects at risk for imminent RA who may be candidates for intervention studies.

Disclosure: K. D. Deane: Patent application, 9, The views expressed in this presentation are those of the authors and do not reflect the official policy or the Department of the Army, Department of Defense, or U.S. Government, 9; **C. I. O'Donnell:** None; **L. A. Derber:** None; **J. D. Edison:** None; **W. R. Gilliland:** None; **W. Hueber:** Patent application, 9; **J. Sokolove:** None; **P. E. Chandra:** None; **J. Norris:** None; **W. Robinson:** Patent application, 9; **V. Holers:** Patent application, 9.

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Gene Expression Profiling in Rheumatoid Arthritis Patients Following B Cell Depletion with Rituximab Reveals Changes in Type I IFN Activity Related to Clinical Responsiveness. Saskia Vosslamber[1], Hennie G. Raterman[2], Tineke C. T. M. van der PouwKraan[2], Micheal T. Nurmohamed[2], Willem F. Lems[2], Ben A. C. Dijkmans[2], Alexandre E. Voskuyl[2] and Cornelis L. Verweij[2]. [1]VU University Medical Center, Amsterdam, The Netherlands, [2]VU University Medical Center

Background: Targeting of B cells using rituximab, a monoclonal antibody directed against the B cell marker CD20, is one of the options for treatment of rheumatoid arthritis (RA). Despite the fact that rituximab depletes the B cells in all the patients treated, the fact that not all patients show a favorable clinical response raised questions about the mechanism of action. In order to provide insight in the biological basis of the clinical response to rituximab we evaluated the pharmacological effects of rituximab using genome-wide gene expression technology on whole blood of RA patients

Methods: RNA was isolated from peripheral blood (PB) samples collected from 13 RA patients before, three and six months after start of treatment with rituximab. Gene-expression profiling was performed using Illumina HumanHT 12-vs bead chips. Clinical responder status was determined after three and six months using ΔDAS28 (7 responders and 6 non-responders) and EULAR (4 responders, 5 moderate responders and 4 non-responders) response criteria. Hierarchical cluster analysis, Significance Analysis of Microarrays and MetaCore pathway level analysis were used for data analysis and interpretation. Differences in type I IFN response gene expression levels between responders and non-responders were analyzed using Student's unpaired t-test.

Results: Pharmacogenomic analyses demonstrated that despite the overall decrease in the expression of B cell markers RA patients exhibited interindividual differences in their pharmacological responses towards rituximab therapy. Genes that were differentially regulated between patients after rituximab treatment represented the following biological processes: humoral immunity, cytotoxic T and NK cell mediated immunity, type I Interferon (IFN) response, IL17 signalling, granulocyte development, chemotaxis and adhesion, and genes related to the ubiquitin proteosomal pathway and Activin A signaling.

When we investigated the pharmacological differences between patients in relation to clinical response we observed that only the cluster of IFN type I response genes correlated with the treatment response to rituximab as defined by ΔDAS28 and EULAR response measurements. Good responders exhibited a selective induction of the expression of type I IFN response genes after three months of treatment, whereas non-responders showed no induction under the influence of rituximab ($p=0.0397$ and $p=0.0478$ for ΔDAS28 and EULAR respectively). The increase in IFN type I activity in the good responders correlated with a low baseline level IFN type I activity and returned to baseline values at 6 months after the start of therapy. These results indicate that the pharmacological induced change in type I IFN response gene activity correlates with the clinical response of rituximab treatment in RA.

Conclusions: An increase in IFN-response activity during rituximab treatment is associated with a favorable response and may provide insight in the biological mechanism underlying the therapeutic response. Moreover, this information could be used to develop surrogate markers to monitor efficacy of rituximab.

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Heterogeneity in the Bone Marrow B Cell Compartment: Implications for Pathogenesis of Human RA. Arumugam Palanichamy, Chris Cistrone, Jennifer Hossler, Chungwen Wei, James Kobie, Inaki Sanz and Jennifer Anolik. University of Rochester Medical Center

Purpose: Recent studies suggest that the bone marrow (BM) may be an active compartment in the development of autoimmune responses in RA. However the precise phenotype, function and regulation of mature B cells in BM remain largely unexplored in humans. Investigation of BM compartment may provide critical insights into the role of B cells in the pathogenesis of RA

Methods: B cells in BM and matched peripheral blood (PB) samples from 10 subjects (5 RA and 5 normal controls (NC)) were analyzed by 11 color flow cytometry. For analysis DAPI+ dead, CD3+ T and CD24hi/CD38hi early B cells were negatively gated and CD19+ mature B cells were divided into memory subsets (switched (SM): IgD-, CD27+; unswitched (USM): IgD+, CD27+; double negative (DN): IgD-, CD27-) and true naïve (N: IgD+, CD27-) population and expression of markers associated with activation and differentiation including FcRH4 and B220 were examined. In 2 NC, single B cells from memory subsets were sorted, reverse transcribed, Ig-VH3 genes amplified by nested PCR, sequenced and mutational imprints compared between BM (n=58) and PB (n=57).

Results: Frequency of CD27+ memory B cells in RA BM remained lower compared to matched PB or normal BM (18.24±2.9 v 29.04±13.2 or 25.16±13.0; RA BM v RA PB or normal BM) which reflected in a reduction of SM B cells (7.87±3.0 v 16.86±13.6; RA BM V NC BM). Examination of expanded markers, such as B220 (which is previously shown to be expressed on a majority of CD27- and a subset of CD27+ B cells) revealed an increased number of B220 expressing BM mature naïve and USM cells in RA as opposed to NC ($P<0.05$). Furthermore elevated levels of B220 expressing cells were noticed in naïve and memory subsets in RA PB compared to BM suggesting tissue specific differential expression. Analysis of the FcRH4 (an inhibitory FcR homolog,) showed a slightly higher number of USM and naïve B cells from RA PBL that was FcRH4+ compared to the BM. On the molecular level, Ig gene analysis of memory subsets between BM and PB of normal controls showed no differences in the overall mutational frequencies between BM and PB. However significant changes were noted in the pattern of mutational targeting in Ig-VH framework (FR1–3) and hypervariable regions (CDR1 and 2). Of note, SM B cells from BM exhibited a 2 fold higher mutations in FR2 compared to PB, whereas in USM B cells, a 2 fold increased mutations were seen in CDR1 compared to PB. Both SM and USM had higher numbers of G mutations in hotspot motifs in PB. Mutational analyses of RA BM and PB memory subsets are underway.

Conclusion: Molecular analysis of BM and matched PB hints increased AICDA enzymatic activity in PB revealed by G mutations and tissue specific generation/selection of distinctly targeted B cell subsets. Distinct mature B cells with consistent heterogeneity in RA BM suggest that these cells may

play a role in the mounting autoimmune responses. Further analyses are needed to elucidate the functionality of these cells.

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High Level of Serum Matrix Metalloproteinase-3 Could Be Implicated in the Pathogenesis of Rheumatoid Interstitial Lung Disease. Yoshinobu Koyama[3], Kosuke Tsuruno[1], Toshiyuki Ota[2] and Kenji Fujii[1]. [1]Center for Rheumatic Diseases, Iizuka Hospital, [2]Department of Laboratory and Transfusion Medicine, University of Occupational and Environmental Health, [3]Iizuka Hospital, Iizuka, Japan

Background: Pulmonary complications such as interstitial lung disease (ILD) are common in patients with rheumatoid arthritis (RA) even in the absence of symptoms. Presentation of ILD has been reported to associate with seropositive and erosive joint disease. Although the etiology of ILD in RA is still unclear, matrix metalloproteinase (MMP)s are believed to play important roles in the pathogenesis of idiopathic pulmonary fibrosis recently. Among them, MMP-3 is known to be one of the most established markers indicating RA activity. However, the correlation between ILD and level of serum MMP-3 in RA has not been well discussed.

Objectives: To identify whether serum MMP-3 level has implication for the pathogenesis of ILD in RA.

Methods: Newly diagnosed RA patients (n=86) were enrolled in this study. As a loss of carbon monoxide diffusing capacity (DLCO) is quantitative and one of the most sensitive marker for ILD, correlations between a loss of DLCO and serum indices for diagnosis of RA were evaluated. Before the patients were exposed to medication, the activity of RA (DAS-28) and the level of laboratory data such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), matrix metalloproteinase-3 (MMP-3), serum amyloid A protein (SAA), rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP) antibody and %DLCO were evaluated. RA patients were classified in three groups by the %DLCO based on the criteria of the American Thoracic Society (group A; DLCO>70%; normal to slight decrease, group B; 50%<DLCO<70%; moderate decrease, group C; DLCO<50%; severe decrease). Statistical analysis was performed to identify the characteristic pattern of serum markers in the three groups.

Results: At the time of diagnosis for RA, the titer of RF and anti-CCP antibody seemed to be no significant influence on a loss of DLCO. Although DAS28, CRP or SAA seemed to be no direct impact on %DLCO, a weak association between high ESR and the loss of DLCO was found (P<0.05). The serum level of MMP-3 was the most significant index correlating with a loss of DLCO (P<0.01). The significant negative correlation between MMP-3 and %DLCO was also detected (P<0.05). If the level of MMP-3≥450ng/ml, the relative risk of severe decrease of DLCO (DLCO<50%) was 6.1.

Conclusion: Although the elevation of inflammatory markers such as ESR or CRP is known to be associated with the elevation of serum MMP-3, we found the MMP-3 was the most significant index correlating with a loss of DLCO. In our study, titer of RF or CCP antibody seems no significant association with rheumatoid ILD at the time of diagnosis for RA. As MMPs are believed to play important roles in the pathogenesis of idiopathic pulmonary fibrosis recently, our finding suggests that MMP-3 is possible to play an important role in the developing of ILD associated with RA. The novel approach such as the correction of inappropriate expression of MMP-3 would be worth to discuss for preventing progression of ILD in RA patients.

Disclosure: Y. Koyama: None; **K. Tsuruno:** None; **T. Ota:** None; **K. Fujii:** None.

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Identification of Genes Associated with Erosion in Cohorts of Patients with Early Arthritis. Amir Kadi[5], Brigitte Izac[5], Jean-Philippe Jais[3], Thierry Lequerre[4], Olivier Vittecoq[4], Xavier Le Loet[4], Philippe Dieude[1], Corinne Miceli[3], Maxime Breban[2] and Gilles Chiocchia[5]. [1]AP-HP, Paris, France, [2]AP-HP, Boulogne-Billancourt, France, [3]AP-HP, [4]CHU Rouen, [5]Inserm U1016/CNRS UMR8104, Paris, France

Background: Rheumatoid arthritis (RA) is a complex disease influenced by both genetic and environmental factors. Several studies showed a large number of polymorphisms associated with this disease. Here, we selected a subset of 137 of these single nucleotide polymorphisms (SNP) to dissect and identify genes implicated in disease susceptibility and structural severity.

Objectives: The aim of this work was to evaluate the predictive SNP, and to test the value of their combination as susceptibility markers for RA diagnosis and as markers of structural severity in two different cohorts of patients with early arthritis (VErA and ESPOIR).

Methods: VeRA cohort: 244 European Caucasian who had persistent swelling of at least two joints for more than 4 weeks with evolution lasting for less than 6 months before inclusion. The erosion was evaluated and classified at 3 separate time-points (1, 2 and 5 years of follow up) according to ACR criteria 1987. ESPOIR cohort: Patients were recruited if they had undifferentiated arthritis or rheumatoid arthritis, of less than 6 months disease duration. TRhe erosion was evaluated and classified at 3 separate time-points (0, 1, 2 years of follow up) according to ACR criteria 1987. SNP genotyping was performed using the SNPlex platform from Applied Biosystems. The association studies were performed using standard chi-square tests implemented in PLINK program. Correction for the significance level of statistical tests was applied to account for the multiplicity of tests. Genotype and allele frequencies did not deviate significantly from those expected under Hardy-Weinberg Equilibrium (HWE) either in RA or in non RA patients.

Results: Seventeen SNPs were discarded because insufficient quality control. The analysis was performed on the 120 remaining SNPs. In the VeRA cohort, we found that there was a significant association of 4 SNPs lying in 4 distinct genes with the presence of erosion. The strongest association was observed for Ficolin (collagen/fibrinogen domain containing) 1 (rs2989727) (P = 2×10-3, OR, 0.41, 95% CI, 0.23–0.73), at 1 year. The second most significant association was with Tumor necrosis factor type 2 gene (rs1061622) (P = 7×10-3, OR, 2.12, 95% CI, 1.21–3.70), at all time-points. Two others polymorphisms (CTLA4 rs3087243 and IL-1F8 rs1900287) were also significantly associated with the first year of erosion ($p < 0.05$). We are now in the replication step of these results in the independent French cohort "Espoir" including 810 early rheumatoid arthritis

Conclusion: Our findings suggest that at least four SNPs are associated with erosion in RA and that combining detection of these SNPs could be useful to predict early progression of structural damage in patients with very early arthritis.

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In Early RA, Serum Increase of IL-21 Is Associated with Serum Level of IL-6, Autoantibody Secretion, Markers of B-Cell Activation, and Radiographic Progression. Jacques-Eric Gottenberg[4], Pascale Roux-Lombard[2], Alain Cantagrel[5], Alain Saraux[1], Cedric Lukas[3], Jean-Michel Dayer[2] and Xavier Mariette. [1]Brest Hospital, [2]Geneva Hospital, [3]Montpellier Hospital, [4]Strasbourg Hospital, [5]Toulouse Hospital

Rationale and Objectives: IL-21, a cytokine mainly expressed by CD4 T cells, was recently suspected to play a pathogenic role in rheumatoid arthritis (RA). However, levels of serum IL-21 have never been assessed in a prospective cohort of early RA. We recently reported that IL-6 and serum markers of B-cell activation were correlated and increased in early RA. IL-6 is a strong inducer of IL-21. We therefore investigated serum IL-21 level in early RA.

Patients and Methods: In the ESPOIR early arthritis cohort (at least 2 swollen joints for more than 6 weeks but less than 6 months), serum IL-21 and diagnosis of RA using the new 2010 ACR/EULAR criteria were assessed at enrollment in 723 patients with early arthritis, naïve to corticosteroid and DMARD treatment. Results for serum levels of IL-1beta, IL-1Ra, IL-2, IL-4, IL-6, IL-10, IL-17, TNF-alpha, IFN-gamma, MCP1, BAFF and markers of B-cell activation (beta2-microglobulin, total IgG, IgA, IgM and free light chains of Igs) were previously reported. Radiographic progression was defined as an increase of total Sharp/van der Heijde score (SHS) greater or equal to 1 between inclusion and 1 year.

Results:

- Higher levels of IL-21 in patients with early RA compared to other early arthritides

There was a trend in favor a higher frequency of detection (21.5% vs 15.3%, p=0.07) and a higher level of serum IL-21 (391.3 pg/ml [181.9–593.9] versus 191.6 pg/ml [142.5–543.4], p= 0.08) in the 523 patients with early RA versus the other patients with undifferentiated arthritis.

- Association between baseline IL-21 and autoantibody secretion, markers of B-cell activation and IL-6 in patients with early RA

IL-21 was significantly more frequently detected in RF-positive patients (30.2% vs 7.5% in RF-negative patients, P< 0.0001) and in anti-CCP-positive patients (28.5% vs 13.5%, P< 0.0001). Serum IL-21 could be detected in 33.3% of patients with detectable IL-6 levels compared to 14.6%

in patients without detectable IL-6 (P= 0.02). No association was observed between IL-21 and BAFF, or the other 9 assessed cytokines.

Patients with detectable IL-21 had significantly higher levels of serum beta-2 microglobulin, IgG, kappa and lambda free light chains (P= 0.003, 0.02, 0.0003, 0.0003, respectively).

- Association between baseline IL-21, early RA erosions and radiographic progression

Patients with early RA and erosions at enrollment had significantly more frequently detectable IL-21 (29.6% of patients with detectable IL21 compared to 19.6% in patients without erosions, P= 0.05).

Radiographic progression after 1 year of follow-up was significantly higher in patients with detectable IL-21 at enrollment (mean increase in SHS of 2.9±0.6 compared to 1.3±0.2 in patients without detectable IL-21, P= 0.005).

Conclusion: In early RA, increase in serum IL-21 is strongly correlated with autoantibody secretion, B-cell biomarkers levels, IL-6 increase and radiographic progression. This suggests that IL-21 could be the intermediate between IL-6 overexpression and B-cell activation. This study suggests that targeting IL-21 might be a useful therapeutic strategy in early RA.

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Strong Activation of Dopamine Pathway in Synovial Tissue from Rheumatoid Arthritis Patients: New Target of Pathology? Silvia Capellino[1], Christine Wolff[2], Franca Marino[3], Alessandra Luini[3], Marco Cosentino[3] and Rainer H. Straub[1]. [1]University Hospital Regensburg, Dept. of Internal Medicine I, Regensburg, Germany, [2]University Hospital Regensburg, Dept. of Internal Medicine I, Regensburg, Germany, [3]University of Insubria, Varese, Italy

Introduction: Synovial cells produce catecholamines in osteoarthritis (OA) and rheumatoid arthritis (RA) patients. Dopamine (DA) is the most abundant catecholamine locally produced during arthritis. However, expression of DA receptors in synovial tissue and role of DA on synovial inflammation are still unknown. Aim of this study is to investigate the presence of DA receptors and DA transporter (DAT) on synovial cells in OA and RA and to study their role on immune response.

Material & Methods: Synovial tissue was collected from 10 OA and 10 RA patients. Control synovial tissue samples were obtained by 5 joint trauma patients. For immunofluorescence analysis D1, D3, D4, D5 and DAT were analyzed alone or in combination with CD45 (lymphocyte marker), CD163 (macrophages) or prolyl-4-hydroxylase (fibroblasts). For real-time PCR, isolated synovial fibroblasts were used. Expression of all dopamine receptors (D1 to D5) was evaluated. For cell culture, mixed synovial cells were treated with SCH23390, a D1-like antagonist. After 24hrs treatment, supernatants were collected and IL-6, IL-8, TNF and IL-10 were measured.

Results: In RA patients a large amount of synovial cells are positive for D1, D3, D4, D5 and DAT compared to OA patients. No positive cells are found in control synovial tissue. Doublestaining immunofluorescence reveals that mostly fibroblasts are positive for D5 receptor. Quantitative PCR analysis shows a very strong expression of all DA receptors in RA fibroblasts compared to OA. Treatment with SCH23390 inhibits IL-8 both in OA and RA, and IL-6 in RA patients.

Conclusions: These results show strong upregulation of dopamine pathway in RA synovial cells, especially in fibroblasts. The initiation of dopamine pathway is related to chronic inflammation, as neither dopamine receptor-positive cells nor dopamine-producing cells are present in normal synovial tissue. Functional experiments demonstrate that the blockade of D1-like receptors influence cytokines production during arthritis. Taken together, these results suggest that peripheral upregulation of DA pathway in rheumatoid arthritis patients influence the immune response.

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T-Cell Subsets Dys-Regulation and Cytokines Are Predictive of RA Pathogenesis in an ACPA-Positive Background. Richard Cuthbert[2], Rekha Parmar[2], Jackie Nam[2], Edith Villeneuve[2], Diane Corscadden[2], Karen Henshaw[2], Paul Emery[1] and Frederique Ponchel[2]. [1]Chapel Allerton Hospital, Leeds, United Kingdom, [2]University of Leeds

Background: We reported that T-cell subset dys-regulation can predict response to treatment in early RA independently of the treatment received as well as relapse in patients who achieved clinical remission. Naïve cells frequency were the most significant circulating T-cells in early disease although, a subset of regulatory T-cell expressing CD62L showed significance. Cytokine activated T-cells (IRC) were less informative as systemic inflammation was low. The aim of the current study is to determine whether T-cell subset analysis done within 4 hours of blood collection can predict future diagnostic in early inflammatory arthritis.

Methods: 60 patients with < 12 months inflammatory arthritis (IA) were enrolled; age, DAS, CRP, symptom duration, RF, ACPA and shared epitope status were included in the analysis. 6 colour flowcytometry was performed using standard protocols. 36 healthy controls were used to build the age relationship with naïve cell frequency. ELISA were used to measure cytokines and chemokines.

Results: Of the 60 IA patients, 25 satisfied the ACR criteria for RA at baseline, the 35 remained classified as undifferentiated (UA). There was no difference at baseline between groups for age and CRP however DAS was higher in the RA group (P=0.04). There were also no difference between RA and UA for T-cell subsets with the exception of a trend for lower naïve T-cell frequency in RA (P=0.075). In relation with higher CRP, IRC frequency was also higher in RA and the relationship between CRP and IRC was confirmed using both groups (R=0.460, P=0.040). $CD25^{high}FoxP3+$ Treg were reduced in both groups with no difference in CD62L+Treg. Using ACPA positivity as criteria, ACPA+ disease was associated with a trend for higher CRP (n=42, P=0.099) and lower naïve T-cell (P=0.150). In contrast naïve cell in ACPA-negative disease were close to healthy controls. IRC were only increased in ACPA+ disease with normal frequency in ACPA- patients. Similarly, both Treg and CD62L+Treg were lower and higher respectively in ACPA-positive and closer to normal in ACPA-negative disease. Serum levels of all tested cytokines differed in patients compared to healthy controls using both ACR and ACPA as criteria. IL-12 and IL-7 were reduced in both RA (P<0.001) and UA (P<0.001) and MIP-1alpha increased (P=0.02 and P=0.0001). There was no difference between ACPA-positive and negative disease for levels of MIP-1alpha and IL-7 however, IL-12 reduction was more marked in ACPA-negative disease (both P<0.001). The added value of IL7 and MIP for the diagnostic of ACPA-negative RA needs to be further anlysed.

Conclusion: The development of RA appears clearly associated with profoundly abnormal immunological parameters at baseline however more closely associated with ACPA-positive disease. Associated with differences in genetic background between ACPA-positive and negative diseases, these data support two divergent pathogenesis, one involving T-cell in ACPA-positive disease. Providing novel diagnostic criteria by transferring flow cytometry protocols and ELISA from research lab to routine hospital services appears promising.

Disclosure: R. Cuthbert: None; **R. Parmar:** None; **J. Nam:** None; **E. Villeneuve:** None; **D. Corscadden:** None; **K. Henshaw:** None; **P. Emery:** None; **F. Ponchel:** None.

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The Development of the ACPA Repertoire Prior to the Onset of Clinical RA. Lotte A. van de Stadt[4], Margret de Koning[2], Rob J. van de Stadt[1], Gertjan Wolbink[2], B. A. C. Dijkmans[5], Dörte Hamann[3] and Dirkjan van Schaardenburg[2]. [1]Jan van Breemen Instituite, [2]Jan van Breemen Institute, [3]Sanquin Diagnostics, [4]Sanquin Research, [5]VU Medical Centre, Amsterdam, The Netherlands

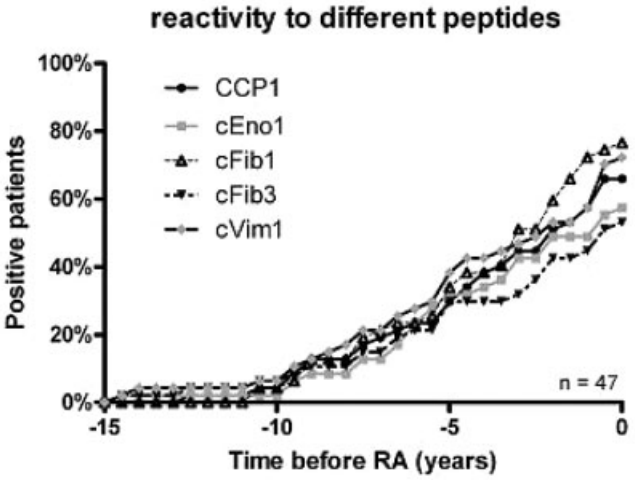
Background: Rheumatoid Arthritis is an auto-immune disease in which anti-citrullinated protein antibodies (ACPA) probably play a pathogenic role. The ACPA response is already expanded before the first symptoms of RA and remains stable thereafter [1].

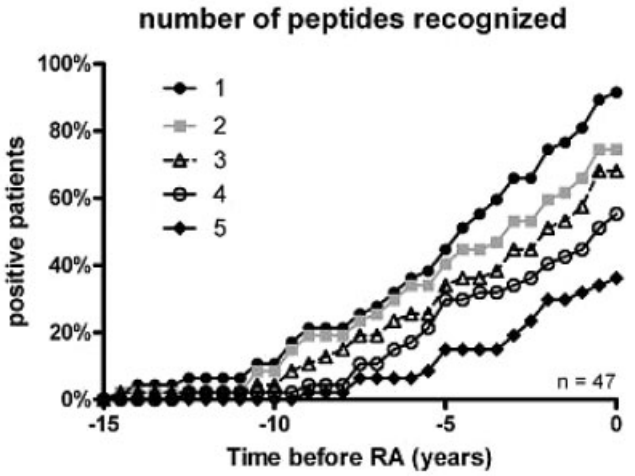
Objectives: To explore the degree of epitope spreading prior to onset of clinical RA and the pattern of auto-antigen reactivity at the start of the immune response.

Methods: Multiple serial serum samples of 79 RA patients who donated blood before disease onset were available for analysis. 47 patients tested aCCP2 positive prior to onset of clinical RA. Of these patients a median of 5 (IQR 3–7) sequential pre-RA sera spaced one to two years apart were tested for reactivity to 5 distinct citrullinated peptides in an ELISA. Two fibrinogen, 1 vimentin, 1 alpha-enolase and 1 cyclic citrullinated peptide (CCP1) were tested. Reactivity to the 5 corresponding arginine peptides was also tested.

Results: Four anti-CCP2 positive patients (9%) did not show reactivity to any peptide. In the selected patient samples seroconversion to ACPA was detected in 24 patients (51%). In 14 of these patients (58%) the immune response started with reactivity to one peptide. In four patients (17%) it started with two peptides, in four (17%) it started with three peptides and in two (8%) it started with four peptides. The number of recognised peptides increased

over time (figure 1). Median antibody titers directed to all peptides also increased over time. The ACPA response did not start with reactivity to one particular peptide (figure 2).





Conclusion: ACPA epitope spreading occurs over several years prior to onset of clinical RA. None of the tested auto-antigens is solely responsible for the initial auto-immune response.

1. van der Woude D., et.al., Ann Rheum Dis, 2010, doi:10.1136/ard.2009.124537.

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1092

The Differential Effect of HLA-DRB1 *0901 Allele from Shared Epitope on the Development of Rheumatoid Arthritis. So-Young Bang[1], Hye-Soon Lee[1], Ji-Seon Lee[1], Eun-Mi Kim[1], Kyung Wha Lee[2] and Sang-Cheol Bae[1]. [1]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Korea, Republic of, [2]Hallym Institute for Genome Application, Hallym University Sacred Heart Hospital, Anyang, Korea, Republic of

Objectives: Smoking is associated with rheumatoid arthritis (RA) in individuals with the HLA-DRB1 shared epitope (SE) alleles encoding conserved amino acid sequence (*0101,*0404, *0405, *0410 [^{70}QRRAA^{74}], *0401 [^{70}QKRAA^{74}], *1001 [^{70}RRRAA^{74}]). The HLA–DRB1*0901 [^{70}RRRAE^{74}], non-SE allele, is significantly associated with RA in Asian, but it is rare in Caucasian. We aimed to investigate interactions between HLA–DRB1 susceptible alleles and smoking, to examine the quantitative effects of these alleles on anti-CCP titers, and to study which distinct HLA–DRB1 alleles involve for developing anti-CCP-positive/negative RA in Korean populations with RA.

Methods. All RA patients (n =1482) and controls (n = 1119) were Korean. Four-digit HLA-DRB1 typing was performed by a conventional PCR-SBT method. Information about smoking history was obtained through a questionnaire by interviewers.

Results: Smoking interacted with SE alleles, but no significant interaction was found between *0901 allele and smoking. The SE alleles and smoking were associated with markedly increased titers of anti-CCP. But *0901 allele was significantly associated with reduced median titer of anti-CCP. In addition, DRB1*0405/*0901 heterozygote dramatically increased the risk in anti-CCP-positive RA smokers (OR 120.29 [12.83–1127.63]) and anti-CCP-negative RA smokers (OR 37.96 [2.06–693.47]) compared with nonsmokers without HLA-DRB1 risk alleles.

Table 1. Risk for developing RA according to HLA-DRB1 susceptible alleles and smoking†

HLA-DRB1/Smoking	No. of cases/controls	OR (95% CI)
Shared Epitope alleles		
−/−	218/503	reference
−/+	45/63	3.28 (1.80–6.00)
+/−	803/327	6.28 (4.91–8.02)
+/+	162/46	15.68 (9.04–27.18)
***0901 allele**		
−/−	218/503	reference
−/+	45/3	3.29 (1.77–6.10)
+/−	318/162	4.43 (3.34–5.89)
+/+	59/33	7.73 (3.97–15.06)

†All odds ratio (OR) and 95% confidence intervals (95% CI) were calculated by comparing each group with reference [individuals without HLA-DRB1 risk alleles (*0101, *0401, *0404, *0405, *0410, *0901, *1001)] and were adjusted for age and sex. The attributable proportions (AP) was 0.45 (0.19–0.72) for smoking and SE alleles, and 0.17 (−0.44–0.79) for smoking and *0901 allele.

Conclusions: Gene-environment interaction of HLA-DRB1 *0901 allele is differ from SE alleles. The DRB1*0405/*0901 heterozygote enhances the susceptibility to both anti-CCP-positive and anti-CCP-negative RA.

Disclosure: S.-Y. Bang: None; **H.-S. Lee:** None; **J-S. Lee:** None; **E.-M. Kim:** None; **K. W. Lee:** None; **S.-C. Bae:** None.

1093

The Smoking-Induced Heat Shock Protein DNAjC6 Is Downregulated in Rheumatoid Arthritis. Caroline Ospelt[1], Joanna Stanczyk[2], Christoph Kolling[3], Renate E. Gay[1] and Steffen Gay[4]. [1]Center of Experimental Rheumatology and Center of Integrative Human Physiology, Zurich, Switzerland, [2]Center of Experimental Rheumatology and Center of Integrative Human Physiology, Zurich, Switzerland, [3]Schulthess Clinic Zurich, Switzerland, [4]University Hospital Zurich, Zurich, Switzerland

Background: Previously we had found that the heat shock protein DNAjC6 is upregulated in joints of mice after exposure to cigarette smoke as well as in the synovium of human smokers compared to non-smokers. Smoking has repeatedly been shown to be a risk factor for the development of rheumatoid arthritis (RA) in susceptible individuals. On the other hand nicotine has also been found to have anti-inflammatory properties and smoke exposure delays the onset of collagen-induced arthritis in mice. Also heat shock proteins have been described to protect cells from environmental damage and act as tumor suppressors, as well as to elicit aberrant immune responses. In the current work we aimed at elucidating the effect of increased levels DNAjC6 in joints of smokers and its possible role in pathogenesis of RA.

Material and Methods: Expression of DNAjs, MMPs, IL-6, IL-8 and microRNAs (miRs) in synovial fibroblasts (SFs) and tissues was measured by Real-time PCR. Relative quantification with 18S or let7a as reference genes was used to quantify levels of gene expression. Synovial fibroblasts were transfected with siRNA targeting DNAjC6 or siRNA control by nucleoporation.

Results: Basal mRNA expression levels of 6 DNAj family members representing different subtypes of DNAjs namely DNAjA3, B4, B9, C6, C9 and C15 were measured in RA (n=6) and osteoarthritis (OA; n=8) SFs. Except for DNAjB9, SFs expressed all of the measured DNAjs, but only DNAjC6 was differentially expressed between RA and OA. Thereby, transcript levels of DNAjC6 were 2.3 fold downregulated in RASFs compared to OASFs (dCT 13.6 ±0.4 vs 12.4 ±0.2; p=0.04). Decreased expression of DNAjC6 in RA was also measured in synovial tissues, where it was 3.3 fold lower in RA (n=16) than in OA patients (n=6) (dCT 13.7 ±0.2 vs 12.0 ±0.6; p=0.01). To see the effect of lowered DNAjC6 levels in SFs we silenced its expression in OASFs (n=4) and measured expression levels of MMPs, IL-6 and IL-8. Whereas the expression of the interleukins, MMP-9 and MMP-13 was not altered, expression of MMP-1 and MMP-3 significantly increased by silencing of DNAjC6 (1.9 ±0.2 and 1.7 ±0.2 respectively; p=0.03). In search of mechanisms leading to lowered expression of DNAjC6 in RA, we used computational miR target prediction programs and found that miR-323 potentially targets DNAjC6, but no other members of the DNAj family. In accordance, expression of miR-323 was significantly higher in RASFs (n=6) than in OASFs (n=4) (dCT 8.6 ±0.3 vs 9.4 ±0.1; p=0.04) and basal expression levels of miR-323 in SFs (n=10) negatively correlated with expression of DNAjC6 (Spearman r: −0.8; p=0.006).

Conclusion: In the current work, we identified a novel pathway contributing to the imprinted activated phenotype of SFs in RA. Elevated expression of miR-323 in RASFs causes downregulation of DNAjC6 mRNA which leads to higher expression of MMPs promoting joint destruction. Therefore, increased expression of DNAjC6 in joints of smokers might be a protective mechanism against environmental damage.

Disclosure: C. Ospelt: None; **J. Stanczyk:** None; **C. Kolling:** None; **R. E. Gay:** None; **S. Gay:** None.

1094

Variability of Anti-CCP Kit Testing in Cohorts with and without RA.

Kevin D. Deane[7], Kristen Demoruelle[10], Mark Parish[4], Whitney Hilton[4], Lauren Harrington[4], Lezlie Derber[4], Jason R. Kolfenbach[6], Jan M. Hughes-Austin[4], Michael H. Weisman[3], Ted R. Mikuls[14], James R. O'Dell[8], Richard M. Keating[1], Peter K. Gregersen[5], Jane Buckner[2], Irene Smolik[13], Donna Hart[13], Charles N. Bernstein[13], David B. Robinson[12], Jill Norris[9], V. Michael Holers[7] and Hani S. El-Gabalawy[11]. [1]Oak Park, IL, [2]Benaroya Research Institute at Virginia Mason, Seattle, WA, [3]Cedars-Sinai Medical Center, Los Angeles, CA, [4]Division of Rheumatology, University of Colorado School of Medicine, Aurora, CO, [5]N Shore Univ Hosp Rsch Ctr, Manhasset, NY, [6]Univ of CO Schl of Med, Aurora, CO, [7]Univ of Colorado School of Med, Aurora, CO, [8]University of Nebraska Medical Center, Omaha, NE, [9]University of Colorado Denver, Aurora, CO, [10]University of Colorado School of Medicine, [11]University of Manitoba, Winnipeg, MB, Canada, [12]University of Manitoba, Winnipeg, MB, Canada, [13]University of Manitoba, [14]University of Nebraska Medical Center, Omaha, NE

Purpose: Anti-CCP positive (CCP+) subjects without current symptoms of RA are important to identify in order to investigate the biology and evolution of RA development. However, it is unknown how clinically-available CCP tests identify CCP+ in individuals who do not currently have RA. Here we examine the sensitivity (SENS) and specificity (SPEC), prevalence and test agreement of 3 CCP kits in RA cases and currently healthy first-degree relatives (FDRs) of probands with RA.

Methods: CCP testing was performed in a single laboratory using standard protocols for 3 ELISA kits: CCP2 (IgG) (Axis-Shield), CCP3 (IgG) and CCP3.1 (IgG, IgA) (INOVA). Sera from 2 established RA cohorts were tested with each kit: a Cree/Ojibway North American Native (NAN) population from Central Canada, and the RA population from the U.S.-based Studies of the Etiologies of RA [SERA] (Caucasian 85%). The SENS/SPEC of kits for RA were calculated compared to non-RA controls (NAN, N=100; SERA random blood donor controls, N=200). Sera from 2 FDR cohorts (NAN and SERA) were also tested with each kit. The NAN FDRs were selected on the basis of CCP2+ at least once during the course of their longitudinal follow-up in the study. SERA FDRs were randomly selected regardless of CCP+ from a cohort of ~1600 subjects. Kappa testing was performed to assess agreement of CCP tests.

Results: See Table 1: The SENS of CCP for RA by any kit was higher in NAN RA cases compared to SERA cases, and the SENS of CCP+ in RA cases was highest using combined kit testing, although SPEC was lower. In NAN and SERA FDRs, CCP3 and 3.1 kits had higher prevalence of positivity compared to CCP2, with differences most pronounced in SERA FDRS: CCP2+(2%), CCP3+(4%) CCP3.1+(9%). Median levels of CCP were lowest in SERA FDRs.

Table 1. Anti-CCP Kit Test Results (Sensitivity/Specificity, Prevalence, and Titers) in Established RA and Healthy First-Degree Relative (FDR) Cohorts

Cohort	CCP2	CCP3	CCP3.1	≥1 of 3 Kits Positive
NANRA (N = 112) vs Non-RA Controls (N = 100)				
SENS	71%	67%	69%	75%
SPEC	97%	98%	96%	95%
SERA RA (N = 230) vs Non-RA Controls (N = 200)				
SENS	54%	63%	65%	67%
SPEC	99%	95%	94%	91%
NAN FDR (N = 31)				
Prevalence of CCP positivity	13/31 (42%)	15/31 (48%)	14/31 (45%)	16/31 (52%)
SERA FDR (N = 299)				
Prevalence of CCP positivity	7/299 (2%)	12/299 (4%)	26/299 (9%)	31/299 (10%)
Median level (range) [levels calculated only in those positive]				
NAN RA	104 (>5–134)	315 (38–401)	366 (39–401)	N/A
NAN FDR	107 (47–127)	280 (25–401)	327 (30–401)	
SERA RA	78 (>5–201)	296 (21–420)	286 (23–406)	
SERA FDR	22 (>5–113)	43 (21–401)	28 (21–401)	

Abbreviations: NAN = North American Native cohorts; SERA = Studies of the Etiologies of Rheumatoid Arthritis cohorts; SENS = sensitivity; SPEC = specificity

See Table 2: Test agreement (kappa) was lowest in SERA FDRs, although kappa improved when anti-CCP cutoffs for positivity were set at 3-times established kit cut-offs.

Table 2. Anti-CCP Kit Agreement, By Cohort

Cohort	CCP2 and 3 (kappa*)	CCP2 and 3.1 (kappa*)	CCP3 and 3.1 (kappa*)
NAN RA	0.81	0.77	0.96
SERARA	0.72	0.71	0.93
NANFDRs			
Standard kit cut-off**	0.74	0.80	0.94
Cut-off >3× normal**	0.87	0.87	1.0
SERAFDRs			
Standard kit cut-off**	0.19	0.15	0.55
Cut-off >3× normal**	0.44	0.44	0.39

*Cohen's kappa
**For CCP2 standard kit cut-off >5 units, ×3 = >15 units, for CCP3, 3.1 standard cut-off >20 units, ×3 = >60 units
Abbreviations: NAN = North American Native cohorts; SERA = Studies of the Etiologies of Rheumatoid Arthritis Cohorts

Conclusion: In this study CCP kits differ in SENS/SPEC for RA, prevalence in FDRs and cohort-related kit agreement. In particular, in SERA FDRs the differential prevalence of CCP+ by kit and decreased kit agreement may indicate that CCP reactivity in these currently healthy individuals, who have perhaps early RA-specific autoimmunity, is fundamentally different than in established disease, possibly due to differences in autoantigen specificity or autoantibody isotypes. Further study is needed to understand the biologic factors behind these CCP results and the role of these CCP tests for identification of pre-clinical RA-specific autoimmunity.

Disclosure: K. D. Deane: None; **K. Demoruelle:** None; **M. Parish:** None; **W. Hilton:** None; **L. Harrington:** None; **L. Derber:** None; **J. R. Kolfenbach:** None; **J. M. Hughes-Austin:** None; **M. H. Weisman:** None; **T. R. Mikuls:** None; **J. R. O'Dell:** None; **R. M. Keating:** None; **P. K. Gregersen:** None; **J. Buckner:** None; **I. Smolik:** None; **D. Hart:** None; **C. N. Bernstein:** None; **D. B. Robinson:** None; **J. Norris:** None; **V. Holers:** None; **H. S. El-Gabalawy:** None.

ACR Poster Session B
Rheumatoid Arthritis Treatment - Small Molecules, Biologics and Gene Therapy: Predicting and Measuring Outcomes, Novel Compounds II

Tuesday, November 9, 2010, 9:00 AM–6:00 PM

1095

A Phase IIa, Randomized, Double-Blind, Placebo-Controlled Clinical Study of Apilimod Mesylate, an Oral IL-12/IL-23 Inhibitor, in Patients with Active Rheumatoid Arthritis. Sarah Krausz[3], Maartje J. H. Boumans[3], Daniëlle M. Gerlag[3], Joelle Lufkin[4], Arno W. R. van Kuijk[2], Alian A. B. Bakker[3], Maarten de Boer[3], Beatrijs M. Lodde[3], Kris A. Reedquist[3], Eric W. Jacobson[4], Michael O'Meara[4] and Paul P. Tak[1]. [1]Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, [2]Academic Medical Center/University of Amsterdam, [3]Academic Medical Center-University of Amsterdam, [4]Synta Pharmaceuticals Corp

Objective: Apilimod mesylate (STA-5326) is an oral small-molecule compound. It selectively inhibits production of interleukin (IL)-12 and IL-23, which play an important role in regulating the immune response, and has demonstrated safety and efficacy in a phase I/IIa trial for Crohn's disease. We investigated the efficacy, safety and tolerability of STA-5326 in patients with active rheumatoid arthritis (RA).

Methods: We performed a phase IIa, single-center, randomized, double-blind, placebo-controlled, proof-of-principle study of STA-5326 in combination with methotrexate (MTX) in 29 patients with active RA (3:1, STA-5326 to placebo). In stage I, 9 patients were treated with STA-5326 100 mg QD and 2 with placebo for 4 weeks. In stage II, 8 patients received STA-5326 100mg QD and 3 placebo for 8 weeks. In stage III, 5 patients received STA-5326 100 mg BID and 2 placebo for 8 weeks, with an optional extension of 4 weeks. Clinical response was assessed according to DAS28 and ACR response criteria. Synovial tissue samples were obtained at baseline and day 29 (stage I/II) or day 57 (stage III), and stained for CD3, CD22, CD55, CD68 and IL-1β by immunohistochemistry, and evaluated by digital image analysis.

Results: STA-5326-treated patients (100mg QD) showed a modest, but statistically significant reduction in DAS28 compared to baseline at day 29 and day 57, but an ACR20 response was reached in only 6% of patients at day 29 and 25% at day 57 (Table). This was similar to the response in placebo treated patients. The increased dosage (100mg BID) did not improve clinical efficacy. Consistent with the clinical results, there were no clear cut changes in expression of synovial biomarkers between baseline and day 29 in stages I/II or day 57 in stage III. While only mild adverse events (mainly gastro-intestinal and dizziness) were observed in stages I/II, in stage III all patients experienced debilitating side-effects (nausea and headache) causing 2 of 5 STA-5326-treated patients to withdraw prior to day 57 and only 1 patient to extend the study until day 85.

Table. Changes in DAS28 and ACR responses in RA patients treated with STA-5326 100mg QD, 100mg BID or placebo

Stage I/II, 100mg QD	**Day 29 (n = 17)**	**Day 57 (n = 8, stage II only)**	
ΔDAS28	−0.41 (*p = 0.03*)	−0.61 (*p = 0.004*)	
ACR20	1 (6%)	2 (25%)	
ACR50	0	0	
ACR70	0	0	
Stage III, 100 mg BID	**Day 29 (n = 4)**	**Day 57 (n = 3)**	**Day 85 (n = 1)**
ΔDAS28	−0.67 (*ns*)	−0.47 (*ns*)	−0.50
ACR20	0	1 (33%)	1 (100%)
ACR50	1 (25%)	0	0
ACR70	0	0	0
Placebo (n = 7, pooled)	**Day 29 (n = 7)**	**Day 57 (n = 4)**	**Day 85 (n = 2)**
ΔDAS28	−0.21 (*ns*)	−0.92 (*ns*)	−0.90
ACR20	0	1 (25%)	0
ACR50	0	0	0
ACR70	0	0	0

In stage III, 1 patient withdrew prior to day 29 and 1 patient prior to day 57 due to side effects. Only 1 out of 5 decided to extend the study until day 85. Changes in DAS28 (*p*-value) are compared to baseline, *ns* = not significant

Conclusion: The results presented here do not support the notion that STA-5326 treatment is able to induce robust clinical improvement of RA.

Disclosure: S. Krausz: None; **M. J. H. Boumans:** None; **D. M. Gerlag:** None; **J. Lufkin:** Synta Pharmaceuticals, 1, 3; **A. W. R. van Kuijk:** None; **A. A. B. Bakker:** None; **M. de Boer:** None; **B. M. Lodde:** None; **K. A. Reedquist:** None; **E. W. Jacobson:** None; **M. O'Meara:** Synta Pharmaceuticals, 1, 3; **P. P. Tak:** None.

1096

ALD518 (BMS945429), a High-Affinity Anti-Interleukin-6 Monoclonal Antibody, Provides Improvements in Health-Related Quality of Life (HRQoL) in Patients with Rheumatoid Arthritis (RA) and an Inadequate Response to Methotrexate. Vibeke Strand[3], Levan Shalamberidze[6], Aleksandar Dimic[4], Jeffrey Smith[1], Robin Mukherjee[2] and Philip Mease[5]. [1]Alder Biopharmaceuticals Inc., Bothell, WA, [2]Bristol-Myers Squibb, Princeton, NJ, [3]Division of Immunology/Rheumatology, Stanford University, Palo Alto, CA, [4]Institute of Rehabilitation and Treatment, Niska Banja, Serbia, [5]Swedish Medical Center and University of Washington, Seattle, WA, [6]V. Tsitlanadze Scientific Practical Centre of Rheumatology, Tbilisi, Georgia

Background: ALD518 (BMS945429) is a monoclonal antibody directed against IL-6. Rapid and significant ACR responses have previously been demonstrated with ALD518 in patients with RA through 16 weeks[1]. Here, the authors report HRQoL outcomes from a Phase II randomized controlled trial of intravenous ALD518 in patients with active RA and inadequate responses to methotrexate (MTX).

Methods: This was a 16-week, double-blind, placebo (PL)-controlled study in which patients with active RA were randomized 1:1:1:1 to ALD518 80, 160 or 320 mg or PL. Two infusions were given (at Day 1 and Week 8), and patients were maintained on stable doses of MTX (≥10 mg/week) throughout. HRQoL was evaluated by the Medical Outcomes Survey Short Form-36 (SF-36). Analyses were performed on the modified intent-to-treat population for patients with data available at the visit of interest (as observed). Minimum clinically important differences (MCID) were 2.5–5.0 for physical and mental component summary scores (PCS and MCS, respectively); 5.0–10.0 for domain scores and MID for SF-6D=0.041[2,3].

Results: 127 patients were randomized and treated, and 116 completed the trial (80 mg, 29/32; 160 mg, 33/34; 320 mg, 25/28; PL, 29/33); mean age was 52.3 years; mean RA duration was 6.8 years; and mean tender and swollen joint counts were 26.1 and 16.7, respectively. Mean baseline PCS and MCS were 31.0 and 35.0, 2 and 1.5 standard deviations less than normative values of 50, respectively. At Week 12, improvements in PCS and MCS were 7.1 and 12.3 in the 80 mg group, 6.1 and 7.6 in the 160 mg group and 8.5 and 13.5 in the 320 mg group versus 4.2 and 1.8 in the PL group. At Week 16, in the ALD518 80, 160 and 320 mg groups, respectively, improvements in PCS were 6.7, 6.6 and 8.3 versus 4.7 with PL; improvements in MCS were 10.8, 9.4 and 11.0, respectively, versus 3.8 for PL. Improvements at Week 16 in MCS scores were observed to be greater in the ALD518 80 and 320 mg groups (p=0.05 each) when compared with PL, and ≥MCID. Observed mean changes from BL in bodily pain, general health and social functioning in the ALD518 80,160 and 320 mg groups exceeded those with PL; and in vitality in the 160 and 360 mg groups and mental health in 360 mg group. Changes ≥MCID were observed in all domains, including SF-6D (Table).

Domain* (+ age/ gender norm)	**Time point**	**ALD518 80 mg (n = 32)**	**ALD518 160 mg (n = 33)**	**ALD518 320 mg (n = 29)**	**Placebo - (n = 32)**
Physical functioning (79.6)	Baseline score	41.6	49.7	43.8	42.4
	Mean change to Wk 16	15.2	14.8	20.0	13.9
Role physical (80.1)	Baseline score	29.9	30.7	32.5	33.5
	Mean change to Wk 16	18.8	22.0	24.6	14.8
Bodily pain (68.3)	Baseline score	25.3	28.6	29.1	29.2
	Mean change to Wk 16	22.3†	23.0	26.3†	10.0
General health (69.5)	Baseline score	35.6	37.2	38.0	37.6
	Mean change to Wk 16	9.5†	10.1	10.1†	3.0
Vitality (58.2)	Baseline score	32.2	32.8	36.6	40.2
	Mean change to Wk 16	14.5	20.1†	19.8	6.4
Social functioning (83.6)	Baseline score	39.1	40.2	44.8	45.5
	Mean change to Wk 16	24.6†	26.5†	23.7†	7.2
Role emotional (86.8)	Baseline score	39.1	46.2	38.8	42.9
	Mean change to Wk 16	20.1	15.2	21.0	11.6
Mental health (74.9)	Baseline score	44.1	49.1	42.9	51.1
	Mean change to Wk 16	12.6	15.5	20.9†	5.2
SF-6D (0.831)	Baseline score	0.556	0.584	0.579	0.592
	Mean change to Wk 16	0.140	0.150	0.170	0.070

*0–100 scores are presented for each domain to enable interpretation within the context of the MCIDs; shading indicates changes ≥MCID in domain scores and ≥MID in SF-6D; †p < 0.05

Conclusions: Treatment over 16 weeks with the IL-6 inhibitor ALD518 resulted in improvements in physical, mental and emotional aspects of HRQoL that were clinically meaningful. These improvements were statistically significant in some but not all SF-36 domains, which may be due to large changes in the placebo group. These data support continued evaluation of ALD518 for treatment of patients with active RA and inadequate responses to MTX.

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Assessment of Inflammation and Damage by MRI in Established RA Patients with Methotrexate Inadequate Response Receiving Golimumab: Results of the GO-FORWARD Trial.

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Background: Previously reported results of the GO-FORWARD trial have shown the beneficial effects of adding the human monoclonal antibody golimumab (GLM) on signs and symptoms and physical function in an established RA cohort with methotrexate (MTX) inadequate response. Magnetic resonance imaging (MRI) provides a sensitive tool for the objective assessment of both inflammation and damage.

Objective: To evaluate the effect of GLM on the inflammation and structural damage detected by MRI in pts with active RA despite MTX.

Methods: Patients (n=444) were randomly assigned to receive placebo (PBO) + MTX, GLM 100mg + PBO, GLM 50mg + MTX, or GLM 100mg + MTX. A subset of study sites capable and willing participated in the MRI substudy. All pts from each substudy site were eligible for the substudy (n=240). GLM and PBO were administered via subcutaneous injection q4 wks. At wk16, pts in the PBO + MTX, GLM 100mg + PBO, and GLM 50mg + MTX groups with <20% improvement in both tender and swollen joint counts entered early escape to receive GLM 50mg + MTX, GLM 100mg + MTX, and GLM 100mg + MTX, respectively. The main comparison was between the combined GLM + MTX and PBO + MTX groups. MRIs of the pt's dominant wrist and metacarpophalangeal joints were obtained at baseline and wks12, 24, 52 and 104 using 1.5T MRI with contrast enhancement. Results through wk24 are presented here. Images were scored by 2 independent expert readers who were blinded to image time point or sequence, pt identity, or treatment group. Readers scored synovitis (0–21), bone erosions (0–230), and bone edema (osteitis; 0–69) using the Rheumatoid Arthritis MRI Scoring (RAMRIS) system; the average of each RAMRIS score provided by the readers was used in the analysis. Pts who entered early escape at wk16 had their last observation carried forward in the MRI analysis at wk24.

Results: Significant improvements in synovitis and bone edema (osteitis), which are known prognosticators of future structural damage, were observed in the combined GLM + MTX groups versus the PBO + MTX group. The minimal changes in bone erosions observed in all treatment groups (Table), precluded the adequate evaluation of GLM's effect on bone erosions, which is consistent with previously published radiographic data. This could be because the overall GO-FORWARD study population had less active inflammation at baseline (median CRP concentrations ranging from 0.60 to 0.95mg/dL), indicating this population would have minimal changes in bone erosion.

Conclusion: Results of MRI assessments showed that GLM + MTX significantly improved synovitis and bone edema (osteitis) relative to PBO plus MTX as early as wk12 and also at wk24. The effect of GLM on bone erosions could not be determined by semi-quantitative scoring in this population of RA pts who had minimal changes in bone erosion during this study.

Table. RAMRIS scores including at baseline and changes from baseline to weeks 12 and 24

RAMRIS scores: values are mean÷dian (interquartile range)	Placebo + MTX (n = 72)	GLM 100mg + PBO (n = 72)	GLM 50mg + MTX (n = 47)	GLM 100mg + MTX (n = 49)	Combined GLM + MTX (n = 96)
Synovitis*					
Baseline	6.7 6.8 (3.3, 9.30)	7.3 7.5 (2.5, 10.5)	7.6 7.8 (4.1, 10.5)	6.3 6.6 (3.0, 8.5)	7.0 7.0 (4.0, 9.5)
Week 12	−0.2 −0.5 (−1.5, 1.5)	−0.8 −0.3 (−2.0, 0.5)	−2.0 −2.0 (−3.0, −0.5)	−1.5 −2.0 (−3.2, 0.5)	−1.8 −2.0 (−3.2, 0.0)
p value		0.299	<0.001	0.014	<0.001
Week 24	−0.4 −0.5 (−1.5, 1.0)	−1.0 −1.0 (−1.5, 0.0)	−1.9 −1.8 (−3.0, −0.5)	−2.0 −1.0 (−4.5, 0.0)	−1.9 −1.0 (−3.1, −0.33)
p value		0.202	<0.001	0.003	<0.001
Bone edema (Osteitis)					
Baseline	7.1 2.0 (0.0, 12.0)	6.9 2.3 (0.0, 10.0)	7.6 4.0 (0.5, 12.5)	6.0 2.0 (0.0, 7.0)	6.8 2.5 (0.0, 11.8)
Week 12	0.2 0.0 (−1.0, 1.5)	−2.1 0.0 (−2.1, 0.0)	−2.8 −0.5 (−4.5, 0.0)	−1.3 0.0 (−1.5, 0.0)	−2.0 −0.5 (−2.1, 0.0)
p value		0.007	0.002	0.071	0.003
Week 24	0.7 0.0 (−0.5, 0.5)	−1.3 0.0 (−1.5, 0.0)	−2.6 −0.5 (−4.1, 0.0)	−0.9 0.0 (−1.6, 0.0)	−1.7 0.0 (−2.2, 0.0)
p value		0.109	<0.001	0.177	0.004
Bone erosion					
Baseline	25.5 12.8 (8.0, 28.3)	25.2 17.4 (5.5, 35.5)	23.9 11.0 (5.5, 29.0)	22.1 13.5 (6.0, 20.7)	23.0 12.5 (6.0, 25.0)
Week 12	−0.8 0.0 (−0.5, 0.1)	0.5 0.0 (0.0, 0.5)	−1.3 0.0 (−0.5, 0.0)	−0.8 0.0 (−0.1, 0.4)	−1.0 0.0 (−0.5, 0.0)
p value		0.038	0.364	0.320	0.899
Week 24	−0.5 0.0 (−0.5, 0.0)	0.4 0.0 (0.0, 0.0)	−1.1 0.0 (−0.5, 0.0)	−0.8 0.0 (−0.1, 0.2)	−0.9 0.0 (−0.2, 0.0)
p value		0.139	0.207	0.680	0.622

*Given that several sites did not have the capability to obtain postgadolinium images, synovitis evaluations of the wrist and MCP joints were obtained in 56, 53, 38, and 39 patients in the PBO + MTX, 100 mg + PBO, 50 mg + MTX, and 100 mg + MTX groups, respectively.

Disclosure: P. G. Conaghan: Centocor Research and Development, Inc., 2, 9; **P. Emery:** Centocor Research and Development, Inc., 2, 9; **M. Østergaard:** Centocor Research and Development, Inc., 2, 9; **E. C. Keystone:** Centocor Research and Development, Inc., 2, 9; **M. C. Genovese:** Centocor Research and Development, Inc., 2, 9; **L. Klareskog:** Centocor Research and Development, Inc., 2, 9; **W. Xu:** Centocor Research and Development, Inc., 3; **E. C. Hsia:** Centocor Research and Development, Inc., 3; **M. U. Rahman:** Centocor Research and Development, Inc., 3.

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Biomarkers Predictors of Good EULAR Response to B Cell Depletion Therapy (BCDT) in Seropositive Rheumatoid Arthritis Patients.

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Background: The best predictor of a good response to BCDT in Rheumatoid Arthritis (RA) is IgM rheumatoid factor (RF) positivity. No data are available on which biomarkers can identify the best profile of a good responder to BCDT in strictly seropositive RA patients.

Objective: To define possible biomarkers of a 6th months good EULAR response in RA patients strictly seropositive for one or more autoantibodies.

Methods: One hundred and forty eight RA patients (122 female; disease duration: 13.0±10.6 years) who did not respond to previous DMARDs and/or TNF-α blockers were enrolled in a multicentric Italian study to evaluate the efficacy of BCDT. All the RA patients were seropositive to at least one of the Autoantibodies (AAB) tested: RF IgG, RF IgM, RFIgA, anti-CCP2 and anti-MCV (Axis-Shield and Orgentec Diagnostika GmbH). At baseline and every 3 months, demographic, clinical, previous TNF blocker therapies and current therapy with glucocorticoids (GC), immunological and laboratory data, HAQ, DAS score were recorded. Plasma levels of IL6 and BAFF were determined at baseline with ELISA methods. A logistic regression models

was evaluated to determine the influence of the independent variables that reached the value of $p<0.25$ at the univariate analysis, considering the optimal cut-off value resulted by the analysis with receiver operating characteristic (ROC) curves on the dependent variable "good EULAR response at 6th month". A p value at the 0.05 level was accepted as statistically significant.

Results: 74.7% of RA patients were positive for anti-CCP2 antibodies, 79.5% for RF IgG, 63.0% for RF IgM, 53.7% for RF IgA, 88.4% for anti-MCV; 10.1%, 12.2%, 18.2%, 23.0% and 36.5% of RA patients were positive for 1, 2, 3, 4, 5 AAB, respectively. 73.7 % of the patients had been treated with one or more TNFa-blockers and 78.9% were on steroid therapy. A EULAR good response was obtained in 23.9% of subjects at the 6th month FU visit.

On multivariate analysis, "EULAR good response to BCDT after 6th months FU" was closely correlated with baseline lymphocytes count <1875/uL (OR (95% CI): 5.78 (1.56–21.45)), RF IgG levels > 52.1 IU/ml (OR (95% CI): 4.48 (1.05–19.24)), plasma BAFF levels < 1011 pg/ml (OR (95% CI): 6.27 (1.13–34.79)) and no current steroid therapy (OR (95% CI): 0.12 (0.03– 0.51)).

Discussion: Two easy markers (no current steroids and a low lymphocyte count) and two immunological parameters (high RF IgG and low plasma BAFF levels) identify the best responder to BCDT. Data support the original theory that IgG RF could be the main driver of the AAB mediated rheumatoid inflammation.

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1099

Candidate Gene Analysis in US Veteran Rheumatoid Arthritis Patients with Clinical Improvement during Treatment with Anti-Tumor Necrosis Factor Agents in the Veterans Affairs Rheumatoid Arthritis (VARA) Registry. Grant W. Cannon[5], Roger K. Wolff[5], Jian Ying[8], Candace L. Hayden[6], Brian C. Sauer[6], Jeffrey R. Curtis[7], Dannette S. Johnson[3], Gail S. Kerr[9], J. Steuart Richards[10], Liron Caplan[2], Andreas Reimold[1] and Ted R. Mikuls[4]. [1]Dallas VA and University of Texas Southwestern, [2]Denver VA and University of Colorado, [3]Jackson VA and University of Mississippi, [4]Omaha VA and University of Nebraska, [5]Salt Lake City VA and University of Utah, Salt Lake City, UT, [6]Salt Lake City VA and University of Utah, [7]University of Alabama, [8]University of Utah, [9]Washington DC VA and Georgetown and Howard Universities, [10]Washington DC VA and Georgetown University

Purpose: While anti-tumor necrosis factor (anti-TNF) agents are effective in rheumatoid arthritis (RA) patients, these benefits are not universal. Several genes are associated with either RA susceptibility or severity. In RA patients being treated with adalimumab, etanercept, or infliximab, multiple SNPs of known RA susceptibility genes were measured and correlated with 28 joint count disease activity scores (DAS28).

Methods: Effectiveness of anti-TNF therapy in RA patients enrolled in the Veterans Affairs RA (VARA) registry was defined by two methods. In method #1, patients receiving ≥90 days of anti-TNF in the VA pharmacy benefits management database were compared. Clinical effectiveness required an average DAS28 ≤3.2 during the observation period from 90 days after initiation of anti-TNF treatment until the end of the anti-TNF course. In method #2, VARA patients initiating an anti-TNF and sustaining a DAS28 ≤3.2 after one year (±2 months) while on continued treatment with the same anti-TNF were defined as having clinical effectiveness. In addition, these patients evaluated by method #2 could not have initiated or escalated corticosteroid therapy, initiated a traditional disease modifying antirheumatic drug, or had more than one joint injection to be classified as having clinical effectiveness.

Caucasian men VARA patients were genotyped for polymorphisms within CTLA4 (5 SNPs), PADI1 (15 SNPs), PTPN22 (5 SNPs), STAT4 (26 SNPs), TRAF1-C5 (17 SNPs), IL10 (4 SNPs), TNF-alpha (3 SNPs) and shared epitope (SE). Using SAS, logistic regression was performed to test the effects of genotypes on the response to the treatment. We assessed significance with a Bonferroni correction ($P_{cutoff}=0.0005$)

Results: Method #1 classified 106 (34%) of 307 eligible patients and method #2 classified 73 (36%) of 201 as having an effective clinical response. With method #1, the increase of each copy of SE was associated with an increase of 67.8% (15.8%, 143.1%) in odds of response to anti-TNF. Comparing to null, compound heterozygous SE is significantly ($p=0.005$) associated with a higher odds of response ((OR 3.1, 95% CI (1.4, 6.7)). The odds of response for homozygous and heterozygous SE were 51.1% and 42.5% higher respectively, but did not reach statistical significance. No association of SE with clinical response was seen with SE by method #2. Neither method demonstrated a significant association with clinical response for the other candidate gene SNPs. Given the small sample size, the power to detect genetic effect is not high, we only have a power of 35% to detect of a 2-fold effect a SNP given the minor allele frequency (MAF) of the SNP is as high as 0.2, and the power would be even lower when either the genetic effect or the MAF is smaller.

Conclusion: This analysis suggests that SE genotype may be associated with anti-TNF effectiveness but failed to demonstrate any statically significant difference in other RA susceptibility gene polymorphism in US veterans with and without clinical effectiveness during anti-TNF therapy. The different results with these two methods emphasize the importance of phenotype definition in these genetic analyses.

Disclosure: G. W. Cannon: None; **R. K. Wolff:** None; **J. Ying:** None; **C. L. Hayden:** None; **B. C. Sauer:** None; **J. R. Curtis:** None; **D. S. Johnson:** None; **G. S. Kerr:** None; **J. S. Richards:** None; **L. Caplan:** None; **A. Reimold:** None; **T. R. Mikuls:** None.

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CCR1 Antagonist CCX354-C in Phase 2 Clinical Development for Rheumatoid Arthritis. Daniel J. Dairaghi, Vittorio Marchesin, Daniel A. Johnson, Shichang Miao, Lisa C. Seitz, Yu Wang, Penglie Zhang, Jay P. Powers, Bert Ho, Pirow J. Bekker, Juan C. Jaen and Thomas J. Schall. ChemoCentryx

Purpose: CCX354-C is an oral drug targeting the chemokine receptor CCR1, which is instrumental in monocyte/macrophage infiltration into the joints of RA patients. The purpose of the preclinical and clinical studies conducted to date was to determine the safety, pharmacokinetic (PK) and pharmacodynamic (PD) properties of CCX354-C. This paved the way for a Phase 2 clinical trial in patients with RA.

Methods: PK/PD requirements for complete inhibition of CCR1-mediated leukocyte infiltration were defined in rabbits (LPS injection into the knee joint) and rats (thioglycollate-induced sterile peritonitis), following oral dosing of CCX354-C. In the Phase 1 program, 84 male or female healthy volunteers (HVs) received either placebo or CCX354-C orally at doses ranging from 1 to 300 mg in the single-dose study and from 3 to 300 mg/day in the multiple-dose study. In total, 70 HVs received CCX354-C. Blood was collected at pre-specified time points for PK and PD analyses. In the 10, 30, and 100 mg dose cohorts, blood was collected for *ex vivo* analysis of CCR1 receptor coverage on blood monocytes using a flow-cytometric assay with Alexa647-CCL3. Based on this information, 24 patients with stable RA were randomized to receive either placebo or daily doses of 100 to 200 mg CCX354-C for 14 days. In total, 18 RA patients received CCX354-C. Safety, PK and potential effects on concomitant methotrexate administration were assessed in this study.

Results: CCX354-C blocked chemotaxis of human monocytic cells towards 17 separate RA synovial fluids. In the preclinical models, leukocyte infiltration into inflamed rabbit knee or rat peritoneum was effectively blocked if plasma levels of CCX354 were maintained sufficiently high to produce 90% CCR1 blockade on circulating leukocytes.

CCX354-C was well tolerated, displayed excellent oral bioavailability and dose-proportional increases in exposure in all 3 clinical trials conducted in HVs and RA subjects. No serious adverse events or withdrawals due to adverse events have been observed. Plasma levels as high as 5,000 ng/mL and 3,700 ng/mL were reached in the single and multiple-dose studies, respectively. These levels of CCX354 far exceed those required for CCR1 blockade (e.g., 90% inhibition (IC_{90}) of CCR1-mediated chemotaxis of human monocytes in 100% human plasma required 110 ng/mL). The plasma half-life of the drug approached 7 hours at the 300 mg dose. In the RA study, co-administration of CCX354-C with methotrexate had no influence on the plasma levels of either drug. In the clinical *ex vivo* PD assay, high levels of receptor coverage (> 90%) at the 12-hour time point were achieved in blood after a single dose of 100 mg CCX354-C.

Conclusions: The oral CCR1-specific antagonist CCX354-C showed an excellent safety and tolerability profile in Phase 1 studies in 70 HVs and 18 RA patients. PK and PD data indicate that daily doses of 200 mg CCX354-C produce greater than 90% receptor coverage in blood at all times. No drug-drug interactions were noted between CCX354-C and methotrexate. Based on results from these clinical trials and supportive preclinical studies,

a Phase 2 clinical trial has been initiated in 150 patients with active RA with an inadequate response to methotrexate.

Disclosure: D. J. Dairaghi: Chemocentryx, 3; **V. Marchesin:** Chemocentryx, 3; **D. A. Johnson:** Chemocentryx, 3; **S. Miao:** Chemocentryx, 3; **L. C. Seitz:** Chemocentryx, 3; **Y. Wang:** Chemocentryx, 3; **P. Zhang:** Chemocentryx, 3; **J. P. Powers:** Chemocentryx, 3; **B. Ho:** Chemocentryx, 3; **P. J. Bekker:** Chemocentryx, 3; **J. C. Jaen:** Chemocentryx, 3; **T. J. Schall:** Chemocentryx, 3.

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Change in CRP at 12 Weeks Predicts the Risk of Rapid Radiographic Progression at 2 Years in Methotrexate-Treated Patients with Early Rheumatoid Arthritis. Boulos Haraoui[4], Paul Emery[3], Neelufar Mozaffarian[1], Benoit Guerette[2], Hartmut Kupper[2], Kaushik Patra[2] and Ed C. Keystone[5]. [1]Abbott Laboratories, Abbott Park, IL, [2]Abbott Laboratories, [3]Chapel Allerton Hospital, Leeds, United Kingdom, [4]Institut de Rhumatologie, Montreal, QC, Canada, [5]University of Toronto, Toronto, ON, Canada

Background: In patients with rheumatoid arthritis (RA), radiographic progression is an important contributor to long-term disability. Hence, identifying patients at risk of rapid radiographic progression (RRP) early in the course of disease is an important goal of medical management, as it affects therapeutic decision-making.

Objective: To determine whether change in CRP after 12 weeks of treatment can indicate risk of RRP in patients with early RA.

Methods: We examined data from methotrexate (MTX)-naïve patients with early RA in the PREMIER study, a 104-week, phase III, placebo-controlled trial in which patients were randomized 1:1:1 to: weekly MTX, adalimumab (ADA) 40 mg every other week, or ADA + MTX. This post hoc analysis evaluated patients from the intention to treat population who had CRP measures at baseline and at week 12, as well as radiographs at baseline and week 104. RRP was defined as an increase of >3 units/year in the modified Total Sharp Score (mTSS). Using week 12 data, quartiles (Qs) of CRP absolute values and percent change from baseline (%ΔCRP) were used to assess relationships with RRP following 2 years of treatment.

Results: Overall, RRP was significantly more likely to occur among patients treated with MTX monotherapy (33.5%) than among patients treated with ADA + MTX (6.7%). In the MTX-treated population, there was an association between increasing Qs of %ΔCRP (less improvement) and RRP prevalence (Table); however, this association was absent in the ADA + MTX population, where the risk of RRP was universally low. Specifically, MTX-treated patients who fell into the top Q (least improvement) of %ΔCRP at week 12 demonstrated 48.5% RRP; ADA + MTX-treated patients in the same Q of %ΔCRP displayed only 6.9% RRP. In both treatment groups, lower CRP improvement at week 12 was observed in the majority of patients ultimately identified with RRP at year 2; 84% of the MTX-treated RRP patients and 54% of the ADA + MTX-treated RRP patients exhibited CRP improvement ≤80% after 12 weeks of treatment. Interestingly, increasing Qs of CRP at 12 weeks produced comparable results to those from the %ΔCRP.

Table. Association of Quartiles (Qs) of %ΔCRP From Baseline to 12 Weeks With % Rapid Radiographic Progression (RRP) From Baseline to 2 Years

%ΔCRP, Qs	MTX (N = 169) n/N (%) of RRP	ADA + MTX (N = 201) n/N (%) of RRP
Min-Q1: −98.61-<−80.34	9/34 (26.5)	6/89 (6.7)
Q1-Q2: −80.34-<−61.28	12/43 (27.9)	3/58 (5.2)
Q2-Q3: −61.28-<−16.67	19/59 (32.2)	2/25 (8.0)
Q3-Max: −16.67-661.36	16/33 (48.5)	2/29 (6.9)

Conclusions: CRP changes from baseline to 12 weeks or absolute CRP levels at 12 weeks were associated with the prevalence of RRP. Of note, association of CRP with poor radiographic prognosis applied mainly to patients treated with MTX monotherapy, as RRP rates were low in patients treated with ADA + MTX and CRP changes were not correlative with frequency of RRP during combination therapy. Based on these data, changes in CRP or CRP levels at 12 weeks appear to be useful tools for early identification of MTX-treated patients who will fail to achieve long-term disease control, as evidenced by significant radiographic damage.

Disclosure: B. Haraoui: None; **P. Emery:** Abbott Laboratories, 2, 5, Bristol-Myers Squibb, 2, 5, Merck Pharmaceuticals, 2, 5, Pfizer Inc, 2, 5, Roche, 2, 5; **N. Mozaffarian:** Abbott Laboratories, 1, 3; **B. Guerette:** Abbott Laboratories, 3; **H. Kupper:** Abbott Laboratories, 1, 3; **K. Patra:** Abbott Laboratories, 1, 3; **E. C. Keystone:** Abbott Laboratories, 5, Amgen Inc., 5, Bristol-Myers Squibb, 5, Pfizer Inc, 5, Roche, 5, UCB, Inc., 5.

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Clinical and Radiographic Implications of Time to Treatment Response in Patients with Early Rheumatoid Arthritis. Ed C. Keystone[7], Michael E. Weinblatt[4], Boulos Haraoui[5], Benoit Guerette[2], Neelufar Mozaffarian[1], Kaushik Patra[3] and Arthur Kavanaugh[6]. [1]Abbott Laboratories, Abbott Park, IL, [2]Abbott Laboratories, France, [3]Abbott Laboratories, [4]Brigham & Womens Hospital, Boston, MA, [5]Institut de Rhumatologie, Montreal, QC, Canada, [6]University of California-San Diego, La Jolla, CA, [7]University of Toronto, Toronto, ON, Canada

Background: For patients with rheumatoid arthritis (RA), there has been increased interest in treating to target early and quickly. While some advocate treatment adjustment at 12 weeks (wks), data support the possibility of later responses to therapy. The longer-term radiographic implications of such a delay in response have not been examined previously.

Objective: To evaluate the association of early (12 wks) and delayed (24 wks) clinical responses with rates of clinical remission, low-disease activity (LDAS), and rapid radiographic progression (RRP) at 52 wks in patients with early RA treated with methotrexate (MTX) monotherapy or adalimumab (ADA) + MTX combination therapy in the PREMIER trial.

Methods: PREMIER was a 104-wk, phase III, randomized, placebo-controlled trial in MTX-naïve patients with early RA, who were randomized 1:1:1 to one of three treatment groups: MTX, ADA 40 mg every other wk (eow), or ADA 40 mg eow + MTX. In this post hoc analysis, observed data comparing MTX with ADA + MTX therapy are presented. Clinical outcome measures included the 28-joint Disease Activity Score (DAS28) and mean change from baseline in modified Total Sharp Score (ΔmTSS) at 52 wks. Patients were categorized on the basis of clinical response (DAS28 improvement ≥1.2 or 20/50/70% improvement in ACR score) at 12 and 24 wks as responders or non-responders: "early responders" achieved the clinical target at wk 12 and maintained the response at wk 24; "delayed responders" did not meet the clinical target until wk 24. The percentages of patients at 52 wks with LDAS (DAS28 <3.2), clinical remission (DAS28 <2.6), and RRP (ΔmTSS >3 units/year) in each group were determined.

Results: In both treatment groups, early clinical responses were associated with better long-term outcomes than delayed responses (Table). Achieving early or delayed ACR70 responses did not result in treatment group differences in the proportion of patients achieving LDAS or clinical remission at wk 52. Importantly, delayed responses to MTX resulted in a high proportion of patients with RRP. Indeed, delayed ACR70 responses were associated with an RRP prevalence of 40%. In addition, an early improvement in DAS28 ≥1.2 with MTX was insufficient to slow radiographic progression (41% RRP). In contrast, early or delayed clinical responses to ADA + MTX resulted in low proportions of RRP at 52 wks, even for patients with a delayed ACR20 response (11% RRP). Of note, ADA + MTX-treated delayed responders had less RRP than MTX-treated early responders.

Table. Association of Treatment and Time to Clinical Reponse With Long-term Outcome

Treatment	Responder Type	Response at Week 12st	Response at Week 24st	% DAS28 <3.2 (LDAS)	% DAS28 <2.6 (Remission)	% ΔmTSS < Uiyr (RRP)
MTX	Early	ACR70R	ACR70R	94	89	18
MTX	Delayed	ACR70NR	ACR70R	70	47	40
ADA-MTX	Early	ACR70R	ACR70R	98	85	5
ADA-MTX	Delayed	ACR70NR	ACR70R	82	41	13**
MTX	Early	ΔDAS28≥1.2	ΔDAS28≥	51	32	41
MTX	Delayed	ΔDAS28≤1.2	ΔDAS28≥	24	10	53
ADA-MTX	Early	ΔDAS28≥1.2	ΔDAS28≥	67**	46*	11*
ADA-MTX	Delayed	ΔDAS28≤1.2	ΔDAS28≥	45	25	5**

*P <0.05; **P <0.01; ***P <0.001 for between treatment group companies of MTX and ADA + MTX
#ΔDAS28 are improvements, values are considered less than prior assessment; R = Responder; NR = Non-responder

Conclusions: MTX-treated patients with early RA who fail to achieve high-level response (*e.g.* ACR70) within 12 wks are at risk for RRP and should be considered for treatment adjustment. ADA + MTX treatment is associated with better clinical outcomes and less severe radiographic progression at 52 wks, even among patients with a delayed clinical response.

Disclosure: E. C. Keystone: Abbott Laboratories, 5, Amgen Inc., 5, Bristol-Myers Squibb, 5, Pfizer Inc, 5, Roche, 5, UCB, Inc., 5; **M. E. Weinblatt:** Abbott Laboratories, 2, 5, Amgen Inc., 5, Bristol-Myers Squibb, 5, Centocor Ortho Biotech Inc., 5, Pfizer Inc, 5, Roche, 5, UCB, Inc., 5; **B. Haraoui:** None; **B. Guerette:** Abbott Laboratories, 3; **N. Mozaffarian:** Abbott Laboratories, 1, 3; **K. Patra:** Abbott Laboratories, 1, 3; **A. Kavanaugh:** Abbott Laboratories, 2.

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Composite Remission Using Clinical, Structural, and Functional Criteria in Patients with Rheumatoid Arthritis (RA) Treated with Etanercept. Mark C. Genovese[4], Andrew S. Koenig[3], Grace S. Park[1] and Scott W. Baumgartner[2]. [1]Amgen Inc., Thousand Oaks, CA, [2]Amgen, Inc., Thousand Oaks, CA, [3]Pfizer Inc., Blue Bell, PA, [4]Stanford University, Sunnyvale, CA

Background: Remission, a goal of treatments for patients with RA, can be defined in terms of signs and symptoms (clinical remission), radiographic progression (structural remission), and function (functional remission). The purpose of this analysis was to examine the incidence of "composite remission" using clinical, structural, and functional criteria in patients receiving etanercept (ETN).

Methods: Data from a clinical trial of patients with early RA (ERA) and established RA (TEMPO) were retrospectively analyzed for 2-year outcomes. Patients in ERA received ETN 10 mg or 25 mg twice weekly (BIW) or methotrexate (MTX). Patients in TEMPO received ETN 25 mg BIW, MTX, or both. Composite remission was defined as: Disease Activity Score based on 28 or 44 joints with erythrocyte sedimentation rate as the indicator of inflammation (DAS28ESR) < 2.6 or DAS44ESR < 1.6 (clinical remission), Total modified Sharp Score annualized progression rate (TSSRATE) ≤ 0 (structural remission), and Health Assessment Questionnaire Disability Index (HAQ-DI) score ≤ 0.5 (functional remission).

Results: Patients had similar baseline clinical characteristics across treatment groups within each study. In the ERA study, mean baseline DAS28ESR scores were 6.3 and mean DAS44ESR scores ranged from 5.2 to 5.3; mean baseline HAQ-DI scores ranged from 1.4 to 1.5. In TEMPO, mean baseline DAS28ESR scores ranged from 6.7 to 6.9, and mean DAS44ESR scores ranged from 5.5 to 5.7; mean baseline HAQ-DI scores ranged from 1.7 to 1.8. Patients achieving composite remission are shown in the table.

Rates of Clinical, Structural, and Functional Composite Remission

	ERA			TEMPO		
	ETN 10 mg (N = 208) nN1 (%)	ETN 25 mg (N = 207) nN1 (%)	MTX (N = 217) nN1 (%)	ETN (N = 223) nN1 (%)	MTX (N = 228) nN1 (%)	ETN + MTX (N = 231) nN1 (%)
Composite Remission using DAS28ESR						
6 mo[a]	17/196 (8.7)	20/195 (10.3)	16/208 (7.7)	3/185 (1.6)	7/190 (3.7)	13/175 (7.4)
1 yr	10/189 (5.3)	17/191 (8.9)	17/197 (8.6)	22/182 (12.1)	18/182 (9.9)	43/195 (22.1)
2 yr[b]	14/149 (9.4)	20/170 (11.8)	13/159 (8.2)	19/167 (11.4)	17/163 (10.4)	52/173 (30.1)
Composite Remission using DAS44ESR						
6 mo[a]	13/196 (6.6)	19/19 (9.7)	17/208 (8.2)	3/187 (1.6)	7/190 (3.7)	12/168 (7.1)
1 yr	7/189 (3.7)	21/190 (11.1)	22/197 (11.2)	19/181 (10.5)	18/182 (9.9)	44/195 (22.4)
2 yr[b]	12/149 (8.1)	18/169 (10.7)	12/159 (7.5)	19/167 (11.4)	17/162 (10.5)	48/173 (27.7)

[a]Radiographic assessments were performed at 24 weeks in TEMPO
[b]HAQ-DI and DAS28ESR were assessed at Week 100 in TEMPO
ERA, Early rheumatoid arthritis; TEMPO, Trial of Etanercept and methotrexate with Radiographic Patient Outcomes; ETN, etanercept; MTX, methotrexate; ND, not done; n, number of patients with composite remission; N, number of patients in cohort; N1, number of patients who had assessment

Conclusions: In both trials the rates of composite remission were similar whether using DAS28ESR or DAS44ESR. Similar remission rates were observed in monotherapy arms across all trials, including ETN 10 mg BIW. These data reinforce the value of monotherapy with ETN or combination therapy with ETN and MTX in early and established RA, and demonstrate that up to a third of patients receiving combination therapy with ETN and MTX are able to attain a composite remission using stringent criteria.

Disclosure: M. C. Genovese: Amgen Inc., 5, Pfizer Inc, 5; **A. S. Koenig:** Pfizer Inc, 1, 3; **G. S. Park:** Amgen Inc., 1, 3; **S. W. Baumgartner:** Amgen Inc., 1, 3.

1104

DAS-Driven Therapy Versus Routine Care in Patients with Recent-Onset Active Rheumatoid Arthritis: Data from the GUEPAR Trial and ESPOIR Cohort. Martin Soubrier[1], Cédric Lukas[2], Jean Sibilia[3], Bruno Fautrel[5], Laure Gossec[4], Simon Patternotte[4] and Maxime Dougados[4]. [1]CHU Clermont-Ferrand, Sevice de Rhumatologie, F-63003, Clermont-Ferrand, Puy-de-dôme, France, [2]CHU Montpellier, Service de Rhumatologie, F-34295 Montpellier, France, [3]CHU Strasbourg, Service de Rhumatologie, Strasbourg, France, [4]Hôpital Cochin, Service de Rhumatologie, F-75014, Paris, France, [5]Hôpital Pitié-Salpétrière, Service de Rhumatologie, F-75013, Paris, France

Objectives: To compare the efficacy of disease activity score (DAS28ESR)-driven therapy and routine care in patients with recent-onset rheumatoid arthritis.

Methods: Patients with recent-onset RA from either the GUEPARD study (tight control) or ESPOIR cohort (routine practice group). GUEPARD is a prospective unblinded randomized multicenter controlled one-year trial comparing two initial treatment strategies (initial methotrexate monotherapy versus its combination with adalimumab) in patients with early and active RA (<6 months, DAS28 $>5,1$). In both groups, treatment was adjusted every 3 months with the aim of achieving a low DAS (DAS <3.2) with the use of TNF blockers. ESPOIR is a French, multi-centric early arthritis cohort in which treatment was left to the discretion of the treating physician. The propensity score was used to match the patients (one patient from the GUEPARD trial for two patients from the ESPOIR cohort).

Results: At baseline, all patients in the tight control group (n=65) and routine practrice group (n=130) fulfilled the ACR1987 criteria. They had comparable demographic characteristics (female 77%, age 48.0 $\pm$13.0 years), RF and anti-CCP positivity (67.2% and 63.6%), swollen and tender joint counts (10.5 $\pm$5.5 and 14.0 $\pm$6.8), patient's and doctor's assessment of global disease activity (68.0 $\pm$20.8 mm and 66.5 $\pm$17.8 mm respectively), pain (57.0 $\pm$21.2 mm), fatigue (54.7 $\pm$26.3 mm), on a 0–100 mm VAS, ESR (38.7 $\pm$24.6 mm first hour), CRP (29.4 $\pm$ 32.6 mg/l), typical erosive disease (17.9%), modified total Sharp/VDH score (SHS) (6.5 $\pm$ 10.1), erosion score (2.4 $\pm$ 4.2), narrowing score (4.1 $\pm$7.1), HAQ (1.3 $\pm$0.6). All patients had a DAS score above >5.1 (mean 6.26 $\pm$ 0.87). The tight control group had a longer mean disease duration than the routine practice group (5.6 $\pm$4.6 vs 3.5 $\pm$2.0 months, $p<0.001$)

After one year, the percentage of patients in remission with an HAQ (<0.5) and an absence of radiologic progression was higher in the tight control group (32.3% vs 10.2%, p = 0.011). However, there was no difference in the decrease in DAS (tight control: -3.12 $\pm$1.82, routine practice: -2.65 $\pm$1.66, p=0.12), nor in the percentage of patients in low DAS (tight control: 63.1%, routine practice: 43.8%, p=0.64) and in remission (tight control: 47.7%, routine practice: 29.2%, p=0.35). There was no statistically significant difference in EULAR, ACR20, ACR50, and ACR70 responses. The improvement in HAQ was similar but more patients in the tight control group had an HAQ below 0.5 (70.2% vs 45.2%, p=0.005). Overall, pain, patient and physician assessment, and fatigue decreased more in the tight control group than in the routine practice group. The mean SHS progression was similar in the two groups (tight control: 0.95 $\pm$ 4.6; routine practice: 1.5 $\pm$ 4.1, p=0.46) as was the percentage of patients without progression (71.19% vs 69.23%, p=0.37).

Conclusion: In patients with recent onset active rheumatoid arthritis, a tight control of disease activity with TNF blockers allows more patients to achieve remission without disability and radiographic progression.

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1105

Differential Serum Glycosylation Changes in Rheumatoid and Psoriatic Arthritis—In Response to Anti-TNF Therapy. Azita Alavi[1], Oliver M. FitzGerald[3], Emily S. Collins[4], Owen Fraser[2], Edward Tarelli[1], Chin Teck Ng[4], Barry Bresnihan[5], Douglas J. Veale[4] and John S. Axford[1]. [1]St. Georges University of London, United Kingdom, [2]St. Georges University of London, United Kingdom, [3]St. Vincent's University Hospital, Dublin, Ranelagh Dublin, Ireland, [4]St. Vincent's University Hospital, Dublin, Ireland, [5]St. Vincent's University Hospital, Dublin, Ireland

Background: Our earlier research into IgG glycosylation changes associated with rheumatoid arthritis (RA) and other rheumatic diseases has indicated the presence of disease specific glycosylation profiles, which in the case of RA have been shown to correlate with disease activity and to revert to normal in pregnancy induced remission. We have since extended these studies using whole serum to assess the direct diagnostic and prognostic potential of serum sugar biomarkers.

Objectives: Evaluate the influence of anti-TNFα therapy on the serum *N*-glycosylation profile of RA and psoriatic arthritis (PsA) patients and to assess the potential of these sugar biomarkers as a measure of disease response.

Methods: Serum *N*-glycan profile of a cohort of RA (n=24) and PsA (n=18) patients on anti-TNFα therapy, at baseline and 1 year after starting treatment, were investigated. Enzyme released *N*-glycans were analysed by MALDI-TOF mass spectrometry. Direct comparisons of the sugar profiles (mass / charge ratio) indicated significant changes in the profile of several biantennary *N*-glycan structures; distinguished by the presence / absence of galactose (G), fucose (F), bisecting GlcNAc (bis) and sialic acid (A) attached to the core biantennary heptasaccharide [GlcNAc(β1–2)Man(α1–6)] [GlcNAc(β1–2)Man(α1–3)]-Man(β1–4)GlcNAc(β1–4)GlcNAc. The glycans comprised of G0 (non-galactosylated), G2F (fucosylated di-

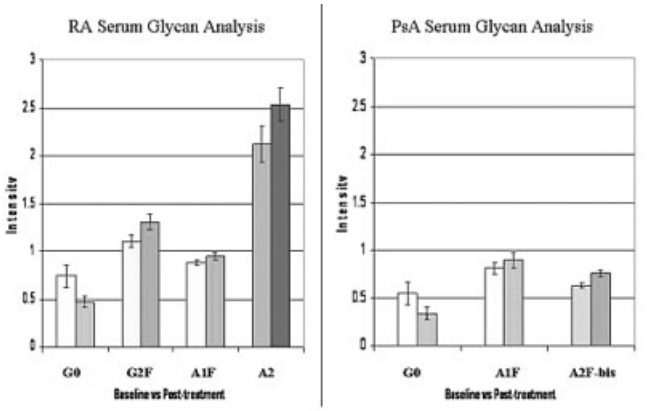
galactosylated), A1G2F (mono-sialylated G2F), A2 (di- sialylated G2) and A2bisF (fucosylated di-sialylated G2 with a bisecting N-acetylglucosamine).

Results: RA and PsA were found to have distinct serum glycan profiles, which underwent significant changes in response to treatment with anti-TNFα (Figure). Levels of G0 decreased significantly in both RA ($p=0.012$) and PsA ($p=0.028$). This was accompanied by a moderate, but significant, increase in A1G2F (RA; $p=0.018$ and PsA; $p=0.010$).

Anti-TNFα treatment also resulted in significant increase (19–20%; $p<0.05$) in the levels of other glycan structures; G2F and A2G2 in RA, and A2G2bisF in PsA. The G2F glycan values were found to significantly correlate with changes in diseases activity (DAS-28) in RA patients ($n=24$) after one year of anti-TNFa therapy(Pearson; $r(22)=0.421>p>0.04$).

Interestingly, there were also marked differences between Etanercept and Adalimumab, with the RA Adalimumab treated group showing significantly more pronounced changes in G0 and A2 (PsA cohort too small for analysis).

Conclusion: RA and PsA have distinct serum N-glycan profiles which undergo significant changes in response to anti-TNFα therapy. These differential changes which include galactosylation as well as sialylation could be a useful marker of disease response, and may provide a better insight into the different mechanistic action of TNF antagonists currently used for treatment of inflammatory arthritis.



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1106

Double-Blind, Randomized, Controlled, Placebo-Included, Pilot Study Comparing Classical Ayurvedic Medicine, Methotrexate, and Their Combination in RA. Daniel E. Furst[3], Manorama M. Venkatraman[4], Mary McGann[1], P. Ram Manohar[1], Cathryn Booth-LaForce[4], Dinesh Khanna[2], K. G. Raveendran[1], Reshmi Sarin[1], Anita Mahapatra[1], Jidesh Gopinath[1] and P. R. Krishna Kumar[1]. [1]The Ayurvedic Trust, [2]UCLA, [3]University of California Los Angeles Medical School, Los Angeles, CA, [4]University of Washington

Background: Classical Ayurveda is a 3000 year old complete system of natural medicine, which is used by millions in India and elsewhere. It is a holistic, multifaceted treatment system which includes complex herbal-mineral formulations, dietary and lifestyle modification, and detoxification routines. Its description of rheumatic diseases is similar to modern descriptions of RA features. Classical Ayurveda for RA has hitherto never been tested in an RCT. The aim of this study was to compare classical Ayurveda, methotrexate (MTX), and their combination in a randomized, double-blind, double dummy pilot trial of RA over 36 weeks.

Methods: In a pilot study, 43 seropositive RA patients by ACR criteria with disease duration ≤7 years were assigned to the following treatment groups: MTX plus Ayurvedic placebo (n= 14), Ayurveda plus MTX placebo (n=12), Ayurveda plus MTX (n=17). DAS28-CRP, ACR20/50/70, and HAQ-DI were obtained every 12 weeks for 36 weeks. Analyses included descriptive statistics, ANOVA, Chi-Square or Student's t-test. The unique features of this study included the development of placebos for each of 7 Ayurvedic pharmacological dosage forms and individualization of Ayurvedic therapy. Neither medications nor placebos contained any heavy metals or foreign substances (e.g., steroids) as shown by HPLC.

Results: All patient groups and physicians were shown to remain blinded throughout. All 3 groups were comparable (p=ns) at baseline (means): age: 45–47.9 years; RA duration: 1.1–2.7 years; RF+: 71–78%; CCP+: 8–29%; % erosions: 61–69%; DAS28-CRP: 6.5 (high disease activity); CRP: 27–42 mg/dl; female: 83–88%. No statistical differences in response were found except in patient pain VAS (see Table 1 & Figure 1). There were no statistically significant differences in the occurrence of Adverse Events (AE) among groups although the groups using MTX had more frequent AE (MTX: 174; Ayurveda: 112; Combination: 176). No deaths occurred.

Conclusion: In this first ever, double dummy, double-blind, randomized, controlled pilot study comparing Ayurveda, MTX, and their combination, MTX and Ayurvedic treatments were approximately equivalent although the trial size and pilot nature of the trial precludes definitive conclusions. AE were numerically but not statistically fewer in the Ayurveda group. These results also show that double-blind, placebo-included, randomized controlled studies are possible when testing classical Ayurvedic versus allopathic treatment in ways acceptable to western standards and to Ayurvedic physicians.

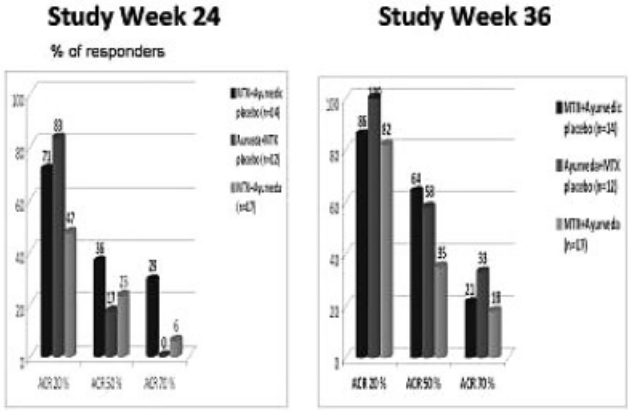


Table 1. Mean Differences (+/− SD) from Baseline to 36 weeks*

	MTX + Ayurvedic placebo (n = 14)	Ayurveda + MTX placebo (n = 12)	MTX + Ayurveda (n = 17)	*p value by ANOVA*
Outcome Measure	**0–36 wks**	**0–36 wks**	**0–36 wks**	
DAS28-CRP (0–10 units)	−2.4 (1.5)	−1.7 (1.4)	−2.4 (1.5)	.379
Tender Joint Count (max = 28)	−13.7 (7.0)	−11.3 (8.2)	−13.8 (5.2)	.581
Swollen Joint Count (max = 28)	−11.3 (7.7)	−8.2 (8.8)	−11.6 (7.4)	.492
Patient's assessment of pain (100 mm VAS)	−44.0 (25.4)	−44.9 (14.4)	−23.2 (27.9)	.026
Patient's global assessment of disease activity (100 mm VAS)	−43.8 (23.8)	−45.2 (18.7)	−25.4 (31.1)	.073
Ayurvedic physician's global assessment of disease activity (100 mm VAS)	−22.8 (8.6)	−15.7 (7.4)	−17.8 (13.9)	.223
Allopathic physician's global assessment of disease activity (100 mm VAS)	−45.1 (13.0)	−44.6 (19.4)	−46.3 (18.1)	.959
CRP (mg/dL)	−12.9 (37.4)	−2.8 (41.0)	−26.2 (44.8)	.327
HAQ-DI SCORE	−.87 (.72)	−.86 (.58)	−.64 (.55)	.508

*includes Intent to Treat Population (ITT) with Last Observation Carried Forward (LOCF)

Disclosure: D. E. Furst: Abbott Laboratories, 2, Actelion Pharmaceuticals US, 2, Amgen Inc., 2, BMS, 2, Genentech and Biogen IDEC Inc, 2, Gilead Sciences, Inc., 2, GSK, 2, Nitec, 2, Novartis Pharmaceuticals Corporation, 2, Roche, 2, UCB, Inc., 2, Wyeth; **M. M. Venkatraman:** None; **M. McGann:** None; **P. R. Manohar:** None; **C. Booth-LaForce:** None; **D. Khanna:** Actelion Pharmaceuticals US, 2, 8, Gilead Sciences, Inc., 2, 8, NIAMS-NIH, 2; **K. G. Raveendran:** None; **R. Sarin:** None; **A. Mahapatra:** None; **J. Gopinath:** None; **P. R. Krishna Kumar:** None.

1107

HM-A42, a Novel Inhibitor of IKKβ Kinase Reverses Clinical and Histological Disease Parameters in Multiple Autoimmune Disease Models. Yu Cai[1], Xinrong Wang[1], Ping Ren[1], Changwu Lu[1], Jianlin He[1], Xiaoming Dai[3], Qianqian Dong[1], Jun Yu[3], Lei Fang[2], Xiaoning Yang[1], Lei Jiang[3], Jia Li[1], Weifang Xue[1], Pingmin Tang[1], Jian Wang[1], Fang Yin[3], Yongjuan Yu[3], Jingshui Li[3], Yang Sai[3], James Yan[3], Jianguo Ji[3], Weiguo Qing[3], Weiguo Su[3] and Haoran Zhao[1]. [1]Hutchison MediPharma Ltd, Shanghai, China, [2]Hutchison MediPharma Ltd, Shanghai, China, [3]Hutchison MediPharma Ltd

Purpose: NF-κB activation has been demonstrated to be involved in the pathogenesis of multiple inflammatory diseases including rheumatoid arthritis

(RA), multiple sclerosis (MS), and respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). The central role that IκB kinase β (IKKβ) plays in regulating NF-κB signaling in response to inflammatory stimuli has made this enzyme as an attractive target for therapeutic intervention. Here we report the identification and preclinical characterization of HM-A42, a potent, selective, and orally bioavailable inhibitor of IKKβ kinase.

Methods and Results: HM-A42 is a potent and highly selective inhibitor of IKKβ kinase (IC50 = 0.006–0.058uM) and demonstrated 127-fold selectivity against IKKα kinase. In OVA-induced asthma model in BN rat, HM-A42 treatment led to reduced inflammatory cell number in the BAL fluid with an ED50 of 0.49 mg/kg. In an acute PLP139–151 peptide-induced EAE mouse model of MS, HM-A42 treatment resulted in rapid and substantial regression of EAE relapses. It also significantly reduced EAE clinical score in a dose dependent manner over a 6 week period with an ED50 of 3.7 mg/kg. Histopathological examination of the spinal cords showed that disease scores for inflammation and the area of demyelination were all significantly lower in HM-A42 treated animals versus vehicle control group. HM-A42 was also tested in a murine collagen-induced arthritis model of RA in a prophylactic setting. Oral administration of HM-A42 resulted in significant reduction of disease symptom that continued through the course of treatment with an ED50 of 4.3mg/kg. In addition, HM-A42 exhibited favorable pharmacokinetic profile including good oral absorption and bioavailability in various species and low potential for CYP450 inhibition. Moreover, from safety point of view, HM-A42 had low affinity for hERG and was negative in AMES test. Its no adverse effect level (NOAEL) was 500 mg/kg in rat, showing a big safety window over efficacy doses in multiple disease models.

Conclusion: The administration of HM-A42, a potent and highly selective IKKβ kinase inhibitor, resulted in substantial efficacy in aggressive models of asthma, rheumatoid arthritis (RA) and multiple sclerosis (MS). These studies support further development of HM-A42 in clinical studies.

Disclosure: Y. Cai: Hutchison MediPharma Ltd, 3; **X. Wang:** Hutchison MediPharma Ltd, 3; **P. Ren:** Hutchison MediPharma Ltd, 3; **C. Lu:** Hutchison MediPharma Ltd, 3; **J. He:** Hutchison MediPharma Ltd, 3; **X. Dai:** Hutchison MediPharma Ltd, 3; **Q. Dong:** Hutchison MediPharma Ltd, 3; **J. Yu:** Hutchison MediPharma Ltd, 3; **L. Fang:** Hutchison MediPharma Ltd, 3; **X. Yang:** Hutchison MediPharma Ltd, 3; **L. Jiang:** Hutchison MediPharma Ltd, 3; **J. Li:** Hutchison MediPharma Ltd, 3; **W. Xue:** Hutchison MediPharma Ltd, 3; **P. Tang:** Hutchison MediPharma Ltd, 3; **J. Wang:** Hutchison MediPharma Ltd, 3; **F. Yin:** Hutchison MediPharma Ltd, 3; **Y. Yu:** Hutchison MediPharma Ltd, 3; **J. Li:** Hutchison MediPharma Ltd, 3; **Y. Sai:** Hutchison MediPharma Ltd, 3; **J. Yan:** Hutchison MediPharma Ltd, 3; **J. Ji:** Hutchison MediPharma Ltd, 3; **W. Qing:** Hutchison MediPharma Ltd, 3; **W. Su:** Hutchison MediPharma Ltd, 3; **H. Zhao:** Hutchison MediPharma Ltd, 3.

1108

Impact of Genetic Interactions on Response to Adalimumab Plus Methotrexate Versus Methotrexate Alone: Six Month Results of the OPTIMA Trial. Alla Skapenko[3], Kaushik Patra[2], Hartmut Kupper[1] and Hendrik Schulze-Koops[3]. [1]Abbott GmbH & Co. KG, Ludwigshafen, Germany, [2]Abbott Laboratories, Abbott Park, IL, [3]University of Munich, Munich, Germany

Background: Identification of genetic factors that affect rheumatoid arthritis (RA) disease severity and response to treatment can guide personalized therapeutic approaches.

Objective: To explore the impact of candidate genetic factors on changes in disease activity following treatment with adalimumab (ADA) plus methotrexate (MTX) or MTX alone.

Methods: OPTIMA is an ongoing 78-week study with 26- and 52-week periods. Eligible patients had RA <1 year, DAS28 >3.2, ≥6 SJC, ≥8 TJC. ESR ≥28 mm/h or CRP ≥1.5 mg/dL, and ≥1 of the following: >1 erosion, RF+, or anti-CCP+. MTX-naive patients were randomized to ADA 40 mg every other week+MTX or placebo (PBO)+MTX. Patients were genotyped by allele-specific polymerase chain reaction (PCR) and direct sequencing as needed for the presence of the HLA-DRB1 shared epitope (SE), the FcγRIIb I232T single nucleotide polymorphism (SNP), and the IL4R I50V SNP. Clinical responses to 26 weeks of treatment were examined by genetic background for each allele independently, and in the allele combinations of SE and IL4R.

Results: Subjects in the treatment groups demonstrated a comparable distribution of 0, 1, or 2 copies of the HLA-DRB1 SE (PBO+MTX: 37%, 48%, 15%; ADA+MTX: 33%, 49%, 19%, $P=0.28$). Likewise, the IL4R alleles, AA, AG, and GG, were distributed similarly between treatment groups (PBO+MTX: 29%, 52%, 20%; ADA+MTX: 33%, 47%, 20%, $P=0.38$). The FcγRIIb alleles, however, were dissimilarly appropriated between treatment groups, and no further analysis was conducted on this SNP. Presence of the SE did not affect treatment response to MTX alone (e.g., ACR50 of 40%, 33%, and 29% for 0, 1, or 2 copies, $P=0.23$). Conversely, treatment response rates were correspondingly enhanced with increasing copies of the SE in subjects receiving ADA+MTX (ACR50 of 42%, 53%, and 65% for 0, 1, 2 SE, $P=0.004$). Thus, presence of 1 copy of the SE afforded a 20% increase in ACR50 for ADA+MTX subjects relative to the PBO+MTX group ($P<0.001$), and 2 copies of SE increased ACR50 in ADA+MTX by 36% over PBO+MTX ($P<0.001$). Similarly, clinical responses to MTX were not affected by IL4R alleles, while treatment outcomes with ADA+MTX was enhanced in subjects with AA or AG IL4R alleles. Examination of treatment responses for the SE and IL4R allele combinations in the PBO+MTX group shows no alteration in responses by genotype, supporting results from analysis of the individual alleles. In the absence of the SE, IL4R genotype affects treatment response to ADA+MTX, while presence of the SE masks effects of the IL4R alleles (table).

		HLA-DRB1 SE copy #		
ACR50, n/N (%)	**IL4R allele**	**0**	**1**	**2**
PBO+MTX	AA	15/34 (44%)	23/56 (41%)	7/23 (30%)
	AG	33/78 (42%)	34/92 (37%)	12/32 (38%)
	GG	18/38 (47%)	14/35 (40%)	1/2 (50%)
ADA+MTX	AA	27/46 (59%)	32/57 (56%)	16/23 (70%)
	AG	24/55 (44%)	58/94 (62%)	28/40 (70%)
	GG	10/26 (39%)	24/41 (59%)	9/12 (75%)

Conclusion: Clinical responses to adalimumab plus methotrexate are independently affected by both the HLA-DRB1 shared epitope and IL4R alleles, while there was no impact of genotype on the response to methotrexate monotherapy. There appears to be an interaction between the HLA-DRB1 shared epitope and IL4R alleles in response to treatment with adalimumab plus methotrexate.

Disclosure: A. Skapenko: None; **K. Patra:** Abbott Laboratories, 1, 3; **H. Kupper:** Abbott Laboratories, 1, 3; **H. Schulze-Koops:** Abbott Laboratories, 5.

1109

Improved Disease Control in Response to Tocilizumab Therapy Is Accompanied by Decreased Platelet Reactivity in Patients with Rheumatoid Arthritis. Paul A. MacMullan[3], Anne M. Madigan[1], Paola Bagaglia[2], Dermot Kenny[3] and Geraldine M. McCarthy[1]. [1]Mater Misericordiae Univ. Hosp, Dublin, Ireland, [2]Mater Misericordiae Univ. Hosp, Dublin, Ireland, [3]RCSI, Dublin, Ireland

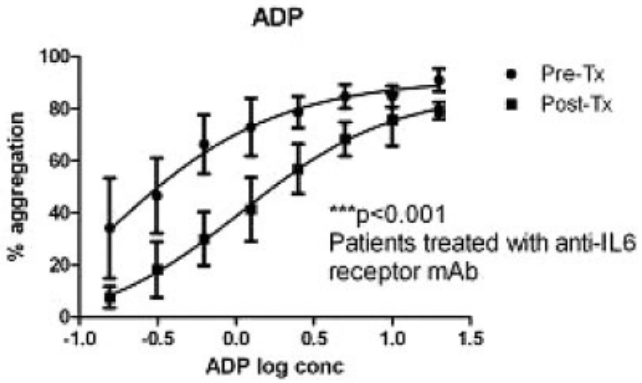
Background: Patients with rheumatoid arthritis (RA) die prematurely of cardiovascular disease (CVD). Platelets play a crucial role in the pathogenesis of CVD. Our previous work demonstrates increased platelet reactivity in patients with active inflammatory arthritis, mediated by the adenosine diphosphate (ADP) pathway [1]. Interleukin 6 (IL-6) plays a key pathogenic role in both inflammation and CVD.

Objective: To prospectively evaluate the impact of IL-6 receptor inhibition on platelet function in patients with RA.

Methods: This work was conducted alongside a PHASE IV study evaluating IL-6 receptor inhibition with tocilizumab in patients with RA. Patients with seropositive RA who had failed conventional and biologic treatment were recruited. Those receiving anti-platelet therapy or with a history of CVD were excluded. All were treated with intravenous infusions of tocilizumab(8mg/kg) at 4-weekly intervals for a minimum of 6 months. 2 patients discontinued treatment due to dermatitis and raised transaminases, respectively. Pre and post-treatment platelet function analyses were performed using a modification of light transmission aggregometry. The *ex vivo* aggregation responses to arachidonic acid, collagen, ADP, epinephrine and thrombin receptor activating peptide (TRAP) were tested. Disease activity was measured using standard inflammatory biomarkers (ESR, CRP, fibrinogen) and the internationally validated DAS-28 Score (<2.6=remission, >5.1=severe disease). The direct effect of elevated IL-6 on platelet ADP responsiveness was examined *in vitro* in samples obtained from 6 healthy volunteers. Platelet-rich plasma (PRP) was incubated with 10ng/ml of IL-6 or vehicle control and the aggregation responses to increasing concentrations of ADP were tested.

Results: Pre and post-treatment data from n=6 female patients were analysed. Disease activity improved significantly in the entire cohort (Mean DAS-28 Scores:5.1+/−0.37 at baseline, and 2.9 +/−0.47 at 6 months, $p<0.01$). Platelet reactivity decreased across a range of agonists in most

subjects, with all subjects displaying a significant decreased response to ADP ($p<0.001$)-see figure. The addition of IL-6 to PRP samples from healthy volunteers increased the platelet response to all concentrations of ADP compared to vehicle control ($p<0.001$).



Control of inflammation *decreases* platelet response to ADP (n=6 RA patients).

Conclusion: Improved disease control with IL-6 receptor inhibition is accompanied by significantly decreased platelet reactivity in patients with refractory RA. This is a novel demonstration of a potential cardioprotective benefit in a cohort of patients at high risk of CVD.

[1] Mac Mullan PA, Peace AJ, Madigan AM, Tedesco AF, Kenny D, McCarthy GM. Platelet hyper-reactivity in active inflammatory arthritis is unique to the adenosine diphosphate pathway: a novel finding and potential therapeutic target. *Rheumatology (Oxford). Feb;49(2):240–5.*

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1110

In Patients with Early Inflammatory Polyarthritis, ACPA Positivity and Inefficacy of the First DMARD Are Associated with the Need To Start a Biologic Later on: Results from the Norfolk Arthritis Register (NOAR).

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Background: Biologics have been available for the management of rheumatoid arthritis (RA) and inflammatory polyarthritis (IP) for almost a decade. Very few data are available on possible predictors, obtained early in the disease, of the need to start a biologic later on. The objectives of this study were (i) to identify baseline disease related predictors in patients with early IP for starting a biologic and (ii) to determine if patients who fail their first non-biologic DMARD within six months are more likely to need a biologic later on.

Methods: Consecutive patients with early IP ($\geq$ 2 swollen joints for $\geq$ 4 weeks) from a primary-care based inception cohort (NOAR), recruited between 2000 and 2004, with a disease duration $\leq$24 months at registration and using at least one DMARD during follow-up were included in this study. Baseline clinical assessments included the DAS28 and the HAQ-score. Blood was collected to determine CRP, RF and ACPA. The use of, including start and stop dates and reason for stopping, DMARDs and biologics was recorded at each visit. DMARD failure was defined as: first DMARD stopped due to inefficacy within six months and/or a second DMARD was started within six months after starting the first DMARD, except if the first DMARD was stopped because of an adverse reaction. The association of baseline disease characteristics and failure of the first DMARD with the start of a biologic was assessed using Cox proportional hazards regression models. Hazard ratios (HRs, 95%CI) were adjusted for age, gender and symptom duration at inclusion. For the association between failure of the first DMARD and the use of a biologic, the survival time started six months after starting the first DMARD.

Results: 45 of 420 (10.7%) patients started to use a biologic during follow-up; the median age of patients at symptom onset in the biologic group was 51 [45 – 55] yrs and 58 [48 – 70] in the non-biologic group and, respectively, 78% (31/40) and 41% (138/334) were ACPA positive. 8.8% patients failed their first DMARD within six months, respectively 17.8% in the biologic group and 7.7% in the non-biologic group. On average, patients started to use a biologic 45 (SD 26) months after symptom onset and used 2.6 (SD 0.9) DMARDs before starting the first biologic. Younger patients and ACPA positive patients were more likely to receive a biologic (see Table).

	HR (95% CI)*
Age (/yr)	**0.97 (0.95, 0.99)**
Gender (female)	1.62 (0.80, 3.28)
Symptom duration at inclusion (/month)	0.97 (0.91, 1.03)
DAS28 score (/unit)	1.25 (0.97, 1.62)
HAQ-score (/unit)	1.52 (1.00, 2.31)
Rheumatoid factor (positive)	1.40 (0.72, 2.70)
ACPA (positive)	**4.87 (2.29, 10.36)**
First DMARD failure within 6 months	**2.52 (1.16, 5.46)**

*age, gender and disease duration at inclusion adjusted HRs (95% CI)

Although not significant, there was a trend towards an association between worse disease activity at inclusion and the need to start a biologic. Furthermore, patients who failed their first DMARD due to inefficacy, within six months of starting, were more likely to need a biological later on.

Conclusion: In this cohort of patients with early IP, ACPA positive patients and those who failed their first DMARD due to inefficacy were more likely to need a biologic during follow-up. These data would support the earlier use of biologics in patients with primary non-response to their first DMARD.

Disclosure: S. M. M. Verstappen: None; **M. Lunt:** None; **D. K. Bunn:** None; **D. G. I. Scott:** None; **D. P. M. Symmons:** None.

1111

Increasing Chance of Remission in Patients with Rheumatiod Arthritis.

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Background: During the last years treatment aims in patients with rheumatoid arthritis (RA) have changed. Nowadays, achieving remission is a major goal. We therefore analyzed if the proportion of patients who achieved remission in DAS28 after several years of treatment with biologic agents changed during the last years.

Methods: The analysis was based on RA patients enrolled in the German biologics register RABBIT at start of an anti-TNF treatment. Remission rates (DAS28 $<$ 2.6) after three years of follow-up were compared between patients enrolled from 2001 to 2003 (n = 841) and those recruited from 2004 to 2006 (n = 1,290). Logistic regression was applied to compare both groups after adjustment for prognostic factors.

Results: Crude remission rates at 36 months were significantly higher in patients enrolled between 2004–2006 than in those enrolled between 2001–2003 (26% vs. 19%). Higher rates were observed especially in patients with highly active disease (DAS28 $>$ 6) at baseline (19.7% vs. 12.4 % in remission). The increase could not be explained by differences in baseline status.

The short term treatment response (DAS28 after 6 months) was the most distinct predictor for being in remission after 3 years. Additionally, male patients, younger patients, patients with better functional capacity and patients with a low disease activity at baseline had a higher chance of remission. When adjusting for these factors by multiple logistic regression the beneficial effect for patients enrolled between 2004–2006 was associated with the activity of the RA 6 months after start of treatment (Table).

Patients with an active disease 6 months after start of treatment had a higher chance of remission when they were enrolled in the later period (table). This was not due to more treatment changes in patients registered later (37% vs. 37% patients who started another biologic) but was possibly caused by more frequent use of novel biologics with different mechanisms of action (14% vs. 3%).

Table 1. Probability of remission after 3 years estimated by multiple logistic regression stratified by enrollment period and level of disease activity after 6 months of the initial treatment.

DAS28 after 6 months	n	2001–2003 remission (%)	n	2004–2006 remission (%)
≤ 3.2	217	40.3	427	38.5
> 3.2 & ≤ 4.1	180	19.6	308	25.4
> 4.1 & ≤ 5.1	200	11.0	271	18.8
> 5.1	244	3.6	284	10.0
total	841	18.3	1,290	25.0

Conclusion: The availability of more treatment options accompanied with changes in treatment strategies increases the chance for RA patients to achieve remission.

Disclosure: A. Strangfeld: None; **M. Eveslage:** None; **M. Aringer:** None; **R. Dockhorn:** None; **M. Schneider:** None; **J. Listing:** None; **A. Zink:** None.

1112

Influence of ESR on EULAR Response Rates in Patients Treated with Tocilizumab. Results from the German Biologics Register RABBIT.

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Background: Tocilizumab, a biologic agent newly approved for the treatment of rheumatoid arthritis (RA), is a human anti-interleukin (IL-)-6 receptor antibody. Clinical studies reported high response and remission rates in patients treated with this agent. Blocking the IL-6 receptor directly inhibits the production of acute-phase reactant proteins (including CRP) in hepatocytes. CRP or ESR are important components of the disease activity score (DAS) used to measure the effectiveness of a treatment.

We therefore investigated the contribution of the single components of the DAS28 to treatment response in tocilizumab treated patients in daily rheumatologic care.

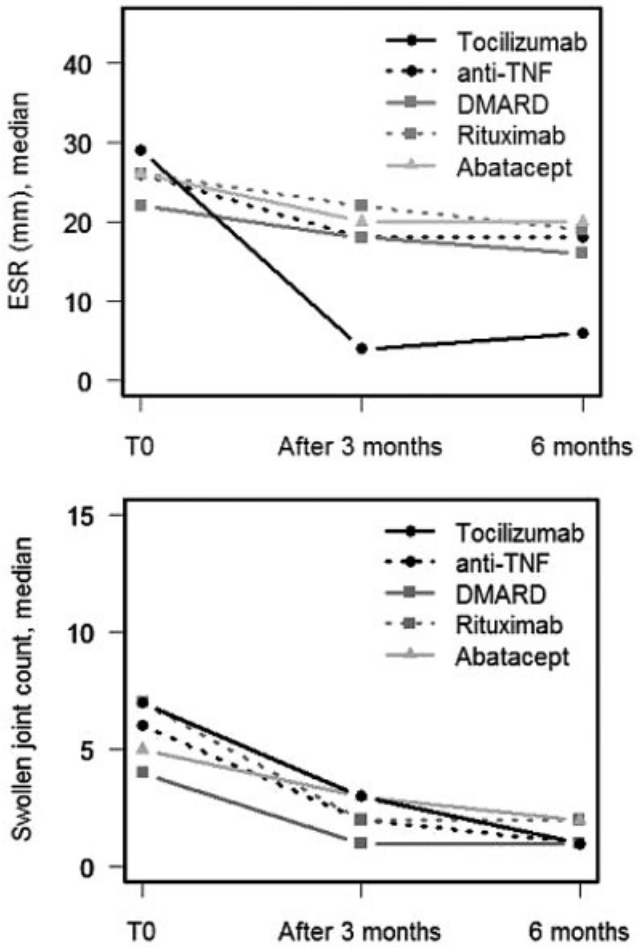
Methods: The German biologics register RABBIT is a prospective cohort study observing all licensed biologic agents applied in RA patients since 2001. In January 2009, tocilizumab was approved in Germany and patients starting this treatment were enrolled in the register. All patients included in the register will be followed up for at least 5 years with regular assessments including clinical status as well as therapy. Disease activity is measured with the DAS28 using the ESR.

Results: A total of 6,861 patients were enrolled in the register, 243 patients were treated with tocilizumab. Their mean age at start of tocilizumab was 57 years and the median disease duration 10 years.

Of 119 patients with a three months follow-up, 36% achieved a good and additional 29% a moderate EULAR response. 27% of the patients were in remission (DAS28 < 2.6). After 6 months (n = 55) the proportion of patients reaching a good EULAR response was 49%, a moderate response was reached by additional 29%. 40% of the patients were in remission.

Separating the DAS28 into its components, significant changes in swollen and tender joint counts and patient global assessment were observed in patients treated with tocilizumab. Compared to patients receiving other biologics the decrease in ESR levels was significantly higher (figures).

Conclusion: Treatment with tocilizumab improves RA in a substantial proportion of patients, response and remission rates are high. However, when considering EULAR response rates, changes in DAS28 scores or DAS28 remission rates the high impact of ESR changes on these measures has to be taken into account.



Figures. Components of the DAS28 (ESR and swollen joint count) and their change after 3 and 6 months after start of treatment with various biologic agents.

Disclosure: A. Strangfeld: None; **M. Eveslage:** None; **J. Listing:** None; **P. Herzer:** None; **A. Liebhaber:** None; **B. Krummel-Lorenz:** None; **A. Zink:** None.

1113

Joint Space Narrowing Has a Stronger Impact on Physical Function Than Joint Erosion: Results from 8-Year Longitudinal Analyses.

Desiree M. Van Der Heijde[2], Robert Landewe[3], Benoit Guerette[1], Sanjoy Roy[1], Kaushik Patra[1] and Ed C. Keystone[4]. [1]Abbott Laboratories, [2]Leiden University Medical Center, Meerssen, The Netherlands, [3]Univ Hosp Maastricht, Maastricht, The Netherlands, [4]University of Toronto, Toronto, ON, Canada

Background: Structural damage, assessed by the modified Total Sharp Score (mTSS), has been shown to be related to physical function. Thus far, it remains unclear to what extent the individual components of the mTSS contribute to long-term physical function.

Objective: To characterize the longitudinal relationship between physical function and Joint Space Narrowing (JSN) or Joint Erosion (JE) in patients with advanced RA.

Methods: DE019 was a 52-week, randomized, placebo-controlled trial for the treatment of moderate to severe advanced RA, in which patients with an inadequate response to methotrexate (MTX) were randomized to MTX, adalimumab (ADA) 20 mg every other week (eow) + MTX, or ADA 40 mg eow + MTX. Patients completing the double-blind study were eligible to receive open-label ADA 40 mg eow + MTX for an additional 7 years. This post hoc analysis evaluated the 8-year completers cohort with radiographs at baseline and years 5, 6, and 8. 28-joint Disease Activity Score (DAS28) was used to assess clinical levels of disease activity. Physical function was assessed through the Health Assessment Questionnaire (HAQ). Radiographic damage was assessed using the modified Total Sharp Score (mTSS). Longitudinal generalized linear modeling was used to characterize the dependence of the HAQ on concurrent DAS28, total mTSS, JSN, and JE

values, following adjustment for baseline age and gender and for concurrent CRP.

Results: Over time, DAS28 was linearly associated with the HAQ ($P < 0.001$). Similarly, the mTSS was significantly associated with the HAQ throughout treatment duration ($P < 0.001$). A 1 unit increase in DAS28 and a 20 unit increase in mTSS were associated with 0.22 and 0.044 increases in the HAQ, respectively. A breakdown of mTSS into the individual components revealed that JSN more strongly impacted the HAQ over time than JE, although both were significant determinants ($P < 0.001$ for both). A 20 unit increase in JSN and JE were associated with 0.1 and 0.06 increases in the HAQ, respectively. Interestingly, negative changes in mTSS trended towards lower HAQ values over time.

Conclusions: For patients with advanced disease, long-term physical functioning is associated with both the level of disease activity (DAS28) and the extent of radiographic damage (mTSS). Of the contributors to the mTSS, JSN had a greater impact on the HAQ over time than JE, suggesting that therapies with high potency for inhibiting both the progression of JSN and JE should be considered.

Disclosure: D. M. Van Der Heijde: Abbott Laboratories, 5, Amgen Inc., 5, Bristol-Myers Squibb, 5, Centocor, Inc., 5, Chugai, 5, Merck Pharmaceuticals, 5, Novartis Pharmaceuticals Corporation, 5, Pfizer Inc, 5, Roche, 5, sanofi-aventis, 5, Schering-Plou; **R. Landewe:** Abbott Laboratories, 2, 5, 8, Amgen Inc., 2, 5, 8, Bristol-Myers Squibb, 2, 5, 8, Centocor, Inc., 2, 5, 8, Pfizer Inc, 2, 5, 8, UCB, Inc., 2, 5, 8, Wyeth Pharmaceuticals, 2, 5, 8; **B. Guerette:** Abbott Laboratories, 3; **S. Roy:** Abbott Laboratories, 1, 3; **K. Patra:** Abbott Laboratories, 1, 3; **E. C. Keystone:** Abbott Laboratories, 5, Amgen Inc., 5, Bristol-Myers Squibb, 5, Pfizer Inc, 5, Roche, 5, UCB, Inc., 5.

1114

Magnetic Resonance Imaging Assessments of Patients with RA and Their Association with Clinical and Radiographic Outcomes. Paul Emery[3], Desiree M. Van Der Heijde[6], Mikkel Østergaard[5], Philip G. Conaghan[4], Mark C. Genovese[7], Ed C. Keystone[9], Roy M. Fleischmann[8], Weichun Xu[1], Stephen Xu[1], Elizabeth C. Hsia[2] and Mahboob U. Rahman[2]. [1]Centocor Research and Development, Inc., [2]Centocor Research and Development, Inc./Univ. of Pennsylvania School of Medicine, Malvern, PA, [3]Chapel Allerton Hospital, Leeds, United Kingdom, [4]Chapel Allerton Hospital, Leeds, United Kingdom, [5]Copenhagen University Hospital at Glostrup and Hvidovre, [6]Leiden University Medical Center, Meerssen, The Netherlands, [7]Stanford University, Sunnyvale, CA, [8]University of Texas SW Medical Center, Dallas, TX, [9]University of Toronto, Toronto, ON, Canada

Objective: To evaluate the relationship between changes in inflammation and structural damage detected by MRI and clinical and radiographic outcomes in RA pts.

Methods: Data from 2 large study populations were evaluated: 1) GO-BEFORE evaluated (MTX)-naïve pts with active RA and 2) GO-FORWARD evaluated pts with active RA despite MTX. In both studies, pts were randomly assigned to receive placebo(PBO)+MTX, GLM100mg+PBO, GLM50mg+MTX, or GLM100mg+MTX. GLM and PBO were administered SC q4wks. A subset of study sites capable and willing participated in MRI substudies. All pts from each site were eligible to participate in the substudies (n=318 GO-BEFORE; n=240 GO-FORWARD). MRIs of pt's dominant wrist and metacarpophalangeal joints were obtained at baseline and wks12,24,52&104. Results through wk24 are presented here. Images were scored by 2 independent expert readers blinded to image time point or sequence, pt identity, or treatment group. Readers scored synovitis(0–21), bone erosions(0–230), and bone edema(0–69) using Rheumatoid Arthritis MRI Scoring (RAMRIS) system. Preliminary assessments of relationships between RAMRIS system scores and clinical and radiographic measures were done using Spearman correlation coefficients. Disease activity was measured using 28-joint count Disease Activity Score calculated using CRP (DAS28-CRP). Structural damage was measured using the van der Heijde modification of the Sharp (vdH-S) score.

Results: Analysis results are summarized in the Table. In both studies, statistically significant correlations were observed between baseline synovitis, bone edema, and bone erosion scores and baseline vdH-S scores; strongest correlations were between baseline RAMRIS bone erosion and baseline vdH-S scores. Changes in DAS28-CRP scores at wks12&24 correlated with changes at wks 12&24, respectively, in RAMRIS synovitis, RAMRIS bone edema (wk24 only), and RAMRIS erosion scores among MTX-naïve pts in GO-BEFORE, but only with changes at wks12&24, respectively, in RAMRIS synovitis and RAMRIS bone edema scores among MTX-inadequate responders in GO-FORWARD;correlations were generally weak or moderate. Percent changes from baseline in CRP levels correlated with changes in RAMRIS synovitis and RAMRIS bone edema scores at all time points but not with changes in RAMRIS bone erosion scores. Although statistically significant in both study populations, these correlations were generally weak or moderate. Correlations observed between changes in vdH-S scores and changes in RAMRIS synovitis, RAMRIS bone edema, and RAMRIS bone erosion scores were inconsistent and weak.

Conclusion: Strong and significant correlations were observed between baseline MRI scores and baseline radiographic scores. Correlations observed between changes in RAMRIS scores and changes in clinical and radiographic measures were generally weak or moderate.

	GO-BEFORE			GO-FORWARD		
	Synovitis	Bone Edema	Bone Erosions	Synovitis	Bone Edema	Bone Erosions
Baseline RAMRIS vs:						
Baseline vdH-S	0.26 (p<0.001)	0.49 (p<0.001)	0.64 (p<0.001)	0.28 (p<0.001)	0.53 (p<0.001)	0.77 (p<0.001)
RAMRIS Δ to wk 12 vs:						
CRP %Δ to wk 4	−0.17 (p=0.010)	−0.13 (p=0.040)	−0.005 (p=0.94)	−0.23 (p=0.002)	−0.19 (p=0.007)	0.06 (p=0.39)
CRP %Δ to wk 12	−0.21 (p=0.002)	−0.19 (p=0.002)	−0.05 (p=0.45)	−0.22 (p=0.005)	−0.20 (p=0.006)	−0.04 (p=0.54)
DAS28 Δ to wk 12	0.23 (p<0.001)	0.18 (p=0.004)	0.14 (p=0.029)	0.16 (p=0.040)	0.22 (p=0.002)	0.02 (p=0.80)
DAS28 Δ to wk 24	0.92 (p=0.10)	0.96 (p=0.20)	0.93 (p=0.92)	0.89 (p=0.09)	0.92 (p=0.049)	1.04 (p=0.20)
vdH-S Δ to wk 24/28	0.08 (p=0.22)	0.14 (p=0.033)	0.05 (p=0.48)	0.16 (p=0.07)	0.10 (p=0.23)	−0.18 (p=0.027)
RAMRIS Δ to wk 24 vs:						
CRP* %Δ to wk 24	−0.20 (p=0.002)	−0.25 (p<0.001)	−0.06 (p=0.34)	−0.32 (p<0.001)	−0.22 (p=0.007)	−0.03 (p=0.69)
DAS28 Δ to wk 24	0.23 (p<0.001)	0.15 (p=0.017)	0.17 (p=0.006)	0.36 (p<0.001)	0.21 (p=0.008)	0.10 (p=0.22)
vdH-S Δ to wk 24/28	0.13 (p=0.06)	0.07 (p=0.31)	0.03 (p=0.63)	0.12 (p=0.22)	0.16 (p=0.09)	−0.06 (p=0.50)

Disclosure: P. Emery: Centocor Research and Development, Inc., 2, 9; **D. M. Van Der Heijde:** Centocor Research and Development, Inc., 2, 9; **M. Østergaard:** Centocor Research and Development, Inc., 2, 9; **P. G. Conaghan:** Centocor Research and Development, Inc., 2, 9; **M. C. Genovese:** Centocor Research and Development, Inc., 2, 9; **E. C. Keystone:** Centocor Research and Development, Inc., 2, 9; **R. M. Fleischmann:** Centocor Research and Development, Inc., 2, 9; **W. Xu:** Centocor Research and Development, Inc., 3; **S. Xu:** Centocor Research and Development, Inc., 3; **E. C. Hsia:** Centocor Research and Development, Inc., 3; **M. U. Rahman:** Centocor Research and Development, Inc., 3.

1115

Optimal Dose Prediction by Pharmacokinetic and Biomarker Response of Subcutaneous Tocilizumab Treatment – A Phase I/II Study Evaluating the Safety, Pharmacokinetics and Clinical Response in Patients with Rheumatoid Arthritis. Shuji Ohta[8], Tomomi Tsuru[5], Kimio Terao[2], Seiji Mogi[7], Midori Suzaki[4], Hitoshi Nakashima[3], Eisuke Shono[6], Eriko Tarumi[1] and Masato Imai[6]. [1]Chugai Clinical Research Center Co., Ltd, [2]Chugai Pharmaceutical Co., Ltd., Tokyo, Japan, [3]Fukuoka University, [4]Med Co LTA PS Clinic, [5]Med Co LTA PS Clinic, Fukuoka, Japan, [6]Shono Rheumatism Clinic, [7]Taga General Hospital, Hitachi, Ltd, Japan [8]Taga General Hospital, Hitachi, Ltd, Japan

Background: Interleukin-6 (IL-6) plays pathologic roles in immune-inflamatory disease as rheumatoid arthritis. Tocilizumab is a humanized monoclonal antibody which inhibits IL-6 signal transduction by binding with both soluble and membranous IL-6 receptor. It has been shown IL-6 inhibition therapy by tocilizumab is effective in RA, JIA and Castleman's disease. Previous data is established by tocilizumab by one hour infusion. Regarding with ease of use, we evaluated the safety, pharmacokinetics, biomarker response and clinical response in patients with rheumatoid arthritis using a tocilizumab new formulation for subcutaneous injection.

Objective: To evaluate the safety, pharmacokinetics and efficacy of tocilizumab subcutaneous injection.

Method: This study is an open label, multicenter, dose ascension, combined single dose (Step1) and multiple dose study (3 doses: Step2) with a 6 month extension (Step3) for two of three treatment arms and last treatment arm entered into study for 6 month multiple dose study followed by three times repeated administration. Eight, 12 and 12 patients eligibly enrolled in cohort 1, 2 and 3, respectively. And they received tocilizumab at 81 mg Q2W treatment in cohort1, 162mg Q2W in cohort2, and 162mg QW in cohort3. Total duration of treatment is 33 weeks for cohort 1and 2, and 27 weeks for cohort 3.

Result: No treatment related serious adverse event were obserbed, and there are also no serious injection site reaction.

Cmax and AUC was 4.9 μg/mL and 444 μg hr/mL at 81mg, and 10.9 μg/mL and 2300 μg hr/mL at 162mg after 1st administration.

CRP is decreased after single dose within first week for all three dose groups. However, the CRP returned back to baseline for 81 mg Q2W dose group from Week 2, 3, 5, 7 and 9 at just before the injection. After week 9, dose was switch to 81 mg QW, then mean CRP decreased slowly. At 162 mg Q2W dose level, CRP retuned to baseline at the end of week 3. Repeated administration (Step2,3) mean CRP decreased progressively going below ULN and remained over the period of this study. In the 162 mg QW group, the CRP decreased below ULN at the end of Week 1 and remained.

Eight out of 12 patients(66%) serum tocilizumab levels in 162mg Q2W group was maintained above 1 μg/mL at week2, CRP was completely normalized in these patients. The normalization of CRP indicated that tocilizumab concentration, which is capable binding of IL-6R, was sufficient to inhibit IL-6 signal.

At week 9, ACR20/50/70 response are 12.5%, 0% and 0% at 81mg Q2W, 75.0%, 16.7% and 16.7% at 162mg Q2W, At the week25, ACR20/50/70 response are 37.5%, 37.5% and 37.5% at 81mg Q2W, 83.3%, 83.3% and 58.3% at 162mg Q2W, 91.7%, 83.3% and 66.7% at 162mg QW, respectively. CDAI at the end of this study is 11.21(18.19 at baseline), 3.76(25.55 at baseline), and 2.03(27.13 at baseline) at 81mg/QW, 162mg Q2W and 162 mg QW respectively.

Conclusion: Tocilizumab subcutaneous injection is well tolerated upto 162mg QW and is associated with good clinical response both 162 mg Q2W and QW.

Disclosure: S. Ohta: None; **T. Tsuru:** None; **K. Terao:** Chugai, 3; **S. Mogi:** None; **M. Suzaki:** None; **H. Nakashima:** None; **E. Shono:** None; **E. Tarumi:** Chugai, 3; **M. Imai:** Chugai, 3.

1116

Preclinical Development of Autologous, Autoantigen-Loaded Dendritic Cells Modified with Bay11–7082 for Tolerizing Immunotherapy in Anti-Citrullinated Peptide Antibody Positive Rheumatoid Arthritis Patients Bearing the HLA-DR Shared Epitope. Sakoontalla Ramnoruth[2], Marion Brunck[2], Claire Hyde[2], Shayna Street[2], Geoffrey Strutton[1], Christelle Capini[2], Sebastien Bertin-Maghit[2], Brendan O'Sullivan[2] and Ranjeny Thomas[2]. [1]Queensland Health Pathology, [2]University of Queensland Diamantina Institute

Background: Effective antigen-specific suppression of pathogeneic T cells in rheumatoid arthritis (RA) patients might be anticipated to provide durable tolerance with low toxicity, suitable for suppression of early disease or prevention in individuals at risk. We showed previously that bone marrow derived dendritic cells modified with the irreversible short-acting NF-kB inhibitor, Bay11–7082 (Bay-DC), exposed to arthritogenic antigen, express low levels of MHC class II and costimulatory molecules and transfer antigen-specific suppression of established antigen-induced arthritis in mice, through induction of regulatory T cells. We undertook preclinical development of human autologous peripheral blood (PB) monocyte-derived Bay-DC pulsed with four SE-restricted citrullinated peptides, to establish feasibility and potential toxicity prior to a phase I trial in anti-citrullinated peptide antibody (ACPA)+ RA patients.

Methods: Under good laboratory practice conditions, we elutriated monocytes from 250 ml PB from RA patients, then generated DC in the presence of 10% human serum, GM-CSF, IL-4, and varying concentrations of Bay11–7082. We compared Bay DC and DC for surface markers and intracellular indoleamine 2,3 dioxygenase (IDO) expression by flow cytometry, the capacity to stimulate T cells in mixed lymphocyte responses, and the ratio of trypophan to kynurenine in culture medium by HPLC. We tested DC proliferation in vitro and in vivo, as well as standard cytoxicity, mutagenesis and clastogenesis assays. In vivo toxicity was tested by s.c. adoptive transfer of peptide-loaded human Bay-DC into SCID mouse recipients followed by hematology, biochemistry and organ pathology.

Results: From 9 RA patients, we elutriated an average of $10 \pm 2.5 \times 10^6$ (mean ± SEM) monocytes and generated $3 \pm 1.3 \times 10^6$ Bay-DC from 250 ml PB. Addition of Bay11–7082 dose dependently reduced expression of DC surface HLA-DR and CD86 and their capacity to stimulate allogeneic T cells. IDO expression and catabolism of tryptophan to kynurenine increased in Bay-DC after lipopolysaccharide exposure. SCID mice recipient of peptide-loaded Bay-DC showed no hematological effects or organ pathology relative to saline-treated mice after 1 week or 1 month, except a reduction in blood glucose from 7.5 to 5 umol/L.

Conclusions: Bay-DC with poor T cell costimulatory capacity and activity of the immunosuppressive enzyme IDO in response inflammatory signaling, can be feasibly generated from PB monocytes of RA patients. Transfer studies suggest Bay-DC loaded with SE-restricted citrullinated peptides have innate immune effects on glucose metabolism. A phase I trial of citrullinated antigen-specific immunotherapy using autologous Bay DC in ACPA+ RA patients is in progress to test safety, and effects on innate and adaptive immunity.

Disclosure: S. Ramnoruth: None; **M. Brunck:** None; **C. Hyde:** None; **S. Street:** None; **G. Strutton:** None; **C. Capini:** None; **S. Bertin-Maghit:** None; **B. O'Sullivan:** None; **R. Thomas:** None.

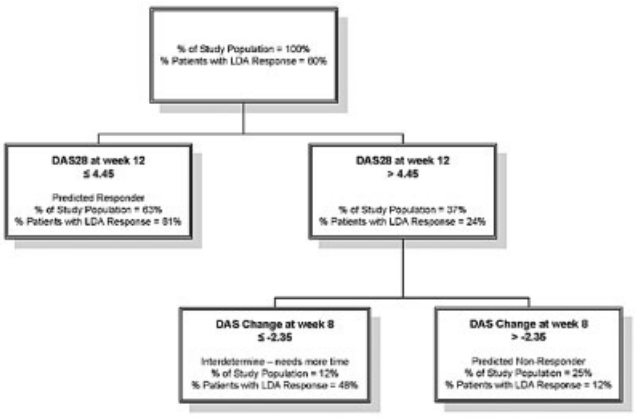
1117

Prediction of One-Year Response to Etanercept and Methotrexate in Rheumatoid Arthritis Patients in TEMPO. Jeffrey R. Curtis[4], Shuo Yang[7], Lang Chen[6], Grace S. Park[1], Bojena Bitman[2], Brian C. Wang[3], Iris Navarro-Millan[5] and Arthur Kavanaugh[8]. [1]Amgen Inc., Thousand Oaks, CA, [2]Amgen Inc., South San Francisco, CA, [3]KForce Clinical Research, South San Francisco, CA, [4]University of Alabama - Brimingham, Birmingham, AL, [5]University of Alabama at Birmingham, Vestavia, AL, [6]University of Alabama at Birmingham, Birmingham, AL, [7]University of Alabama at Birmingham, [8]University of California-San Diego, La Jolla, CA

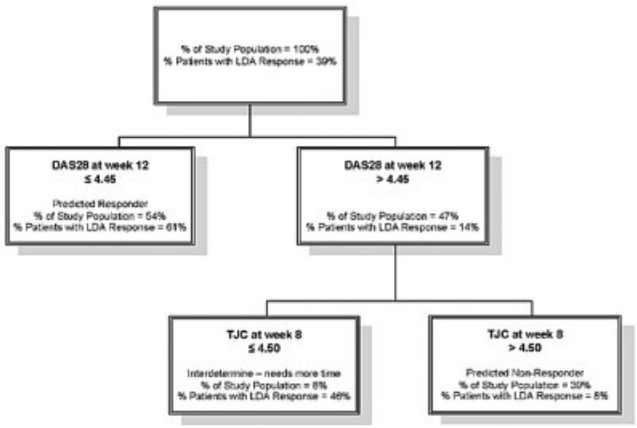
Background: The ability to predict which rheumatoid arthritis (RA) patients (pts) will respond to biologic therapy is a challenging but important endeavor. TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) data were used to evaluate moderate to severe RA pts initiating etanercept (ETN) with or without methotrexate (MTX) to derive and validate a decision tree that would predict which pts would have a good response after 1 year of therapy, determine which pts could have a treatment decision made at week (wk) 12, and identify pts who needed additional time on therapy.

Methods: Pts were included if they had disease activity scores (DAS28) at 52 (or 48) wks of therapy with either ETN 25 mg twice weekly with MTX (n = 193) or ETN alone (n = 172). Pts were classified as responders if they had low disease activity (LDA) at wk 52, i.e., DAS28 ≤ 3.2. Pts who dropped out for safety reasons were excluded. Classification and Regression Trees (CART) software [Salford Systems], which identifies variables affecting the outcome and partitions data accordingly, was used to develop and validate decision trees on clinical and demographic variables, stratified by TEMPO treatment arm. Tenfold cross-validation was used to guard against overfitting.

Results: Sixty percent (115/193) of pts in the ETN + MTX arm (Figure 1) and 39% (67/172) of pts in the ETN arm (Figure 2) achieved LDA response at wk 52. As shown in Figure 1, LDA was predicted by DAS28 at wk 12 and DAS28 change from baseline values at wk 8. Pts were categorized into 3 groups by 12 wks: 1) high-likelihood responders, such that 63% (121/193) of pts were able to be classified as responders by wk 12 with 81% accuracy (98/121 correctly classified as responders); 2) non-responders, 25% (49/193) of pts with 88% (43/49) accuracy; and 3) uncertain likelihood of response for the remaining 12% (23/193) of pts.



In the ETN only arm, results were similar (Figure 2). Response to therapy in this cohort was predicted by DAS28 at wk 12 and tender joint count at wk 8. By wk 12, 53% (92/172) of pts were able to be classified as responders, 39% of pts as non-responders (67/172), and the remaining 8% were not able to be classified well.



Conclusion: Most TEMPO pts initiating ETN with or without MTX could be classified within 12 wks of starting therapy as likely to have a good response or not at wk 52. However, approximately 10–15% of pts needed additional time on therapy to decide whether to continue ETN. This preliminarily validated decision tree needs replication and may help physicians in deciding whether to continue or change anti-TNF therapy at 12 wks.

Disclosure: J. R. Curtis: Amgen Inc., 2, Centocor, Inc., 2, 5, Corrona, 2, 5, Roche, 2, 5, 8, UCB, Inc., 5, 8; **S. Yang:** None; **L. Chen:** None; **G. S. Park:** Amgen Inc., 1, 3; **B. Bitman:** Amgen Inc., 1, 3; **B. C. Wang:** Amgen Inc., 5; **I. Navarro-Millan:** None; **A. Kavanaugh:** Amgen Inc., 2.

1118

Predictors of Response to Rituximab in Patients with Active Rheumatoid Arthritis and Inadequate Response to Anti-TNF Agents or Traditional DMARD. Javier Narvaez[4], Cesar Díaz Torné[2], Jose Miguel Ruiz[3], Maria Victoria Hernández[1], Vicens Torrente[2], Sergio Ros[3], Cesar Díaz López[2], Arturo Rodriguez de la Serna[2], Raimon Sanmartí[1] and Joan Miquel Nolla[4]. [1]Department of Rheumatology, Hospital Clinic, Barcelona, Spain, [2]Department of Rheumatology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [3]Department of Rheumatology, Hospital de Viladecans, Barcelona, Spain, [4]Department of Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain

Objective: Identifying early predictors of response to biological agents is important for both the individual patient and health economics. The aim here was to identify clinical variables that are easily assessed in clinical practice associated with a major response to rituximab (moderate-to-good EULAR response, according to DAS28 values) in patients with active rheumatoid arthritis (RA) and inadequate response to anti-TNF agents or traditional DMARD.

Methods: Rituximab (2 × 1 g, two weeks apart) was administered to 108 patients in four different Spanish centres. The primary efficacy endpoint was the percentage of patients who achieved a major response at six months. Potential predictors of a major response were identified using multivariate binary logistic regression models.

Results: Ninety-eight patients (91%) received RTX after the failure of ≥ 1 anti-TNF agent (number of previous anti-TNF agents used: 1.4 ± 0.8). Primary or secondary inefficacy, rather than development of side effects, was the reason for the anti-TNF failure in the large majority of cases (70.2%). Seven of these patients had also failed to respond to other biological agents (abatacept or tocilizumab). In ten patients (9%), RTX was administered as a first-line biological therapy due to contraindications for anti-TNF therapy.

The mean age of patients (86 women) was 58.4 ± 12.2 years and the median disease duration was 9.8 ± 9.4 years (range: 1–36). Rheumatoid factor (RF) and/or anti-CCP antibodies were positive in 84.3% of cases; only 15.7% of patients were seronegative for both antibodies. The mean number of previous DMARDs used was 2.9 ± 1.4. RTX was administered alone in 31 (28.7%) patients and in combination with one DMARD (mainly methotrexate or leflunomide) in the other 77 (71.3%) cases. The mean DAS28 score at baseline was 5.8 ± 1.1 and the mean HAQ value was 1.500 ± 0.67.

At six months of treatment 75.9% of patients achieved a major response (good: 24.1%; moderate: 51.8%). Comparing the clinical features at baseline between patients who did or did not achieve a major response, significant differences were found in RF and anti-CCP positivity, as well as in the number of failed anti-TNF agents prior to RTX.

While RTX delivers clinical benefit in seronegative patients, the presence of RF and/or anti-CCP consistently enriches clinical responses. In the multivariate analysis the only predictors of a major response were anti-CCP antibodies ($p=0.045$) and the number of previous anti-TNF agents used ($p=0.028$). Thus, patients with an anti-CCP titre > 300 were 3–4 times more likely to achieve a major EULAR response (OR: 3.38, 95% CI: 1.025 – 11.17). By contrast, those patients who had failed to respond to more than one anti-TNF agent had a 72.5% lower probability of achieving a moderate-to-good EULAR response (OR: 0.275; 95% CI: 0.087 – 0.871) than did patients who had only failed to respond to one such agent.

Conclusion: Anti-CCP titre and a lower number of previously-failed TNF blockers can help select the best candidates for RTX therapy in patients with RA.

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Proof of Concept Study for a Potent p38 MAPK Dual Action Inhibitor BMS-582949 in Subjects with RA Receiving Concomitant Methotrexate. Mark C. Genovese[6], Ling Gao[3], Jie Yin[3], Stefani Smith[3], Michael E. Weinblatt[1], Josef S. Smolen[5], Xiaoning Wang[3], Gary Schieven[3], Juan A. Garcia-Meijide[4], Robert Latek[3], Richard Pasternak[3], Sanjeev Kaul[3], Amit Roy[3], Ralph Raymond[3], Ulrich Thienel[3] and Jingsong Wang[2]. [1]Brigham & Womens Hospital, Boston, MA, [2]Bristol-Myers Squibb, Wayne, PA, [3]Bristol-Myers Squibb, [4]Hospital Clínico Universitario de Santiago, Santiago de Compostela, Spain, [5]Krankenhaus Lainz, Vienna, Austria, [6]Stanford University, Sunnyvale, CA

Background/Purpose: BMS-582949 is a potent and selective dual action inhibitor of p38 MAPK. It inhibits both p38 kinase activity and activation in cells. Previous studies showed BMS-582949 to be well tolerated in both healthy and RA subjects for up to 28 days.

Methods: This 16 week, randomized, double-blind, placebo-controlled study consisted of a 12-week treatment, and a 4-week follow-up period. One hundred and twenty one (121) subjects with active RA, with an inadequate response to MTX, were randomly assigned in a 1:1 ratio to once daily oral treatment with placebo or BMS-582949 300 mg. Efficacy, safety, PK and PD endpoints were monitored throughout the study. The ACR20 response at Day 85 was defined as the primary endpoint. Secondary endpoints were ACR50/70, ACR-N, HAQ-DI and changes in DAS28 on Day 85.

Results: Sixty and 61 subjects with RA, treated concomitantly with MTX, received BMS-582949 300 mg and placebo once daily. The proportion of BMS-582949 300 mg treated subjects (53.3%) who achieved an ACR20 response at Day 85 (Week 12) was significantly higher than the placebo group (32.8%) ($p = 0.036$). At Day 85, the mean treatment group difference for DAS28, favoring active arm, was −0.83 (95% CI: −1.29, -.036). The study also met its secondary endpoints in changes in DAS28, ACR-N and HAQ-DI scores.

Endpoints at Week 12	ACR20 (%)	ACR50 (%)	ACR70 (%)	Mean Change from Baseline in DAS28
BMS-582949 (N=60)	53	15	2	−1.81
Placebo (N=61)	33	10	7	−0.98

BMS-582949 led to a decrease in CRP, with the active treatment group having a larger median decrease in hs-CRP compared with placebo at week 12. Additional post-hoc analyses revealed that efficacy appeared to be related to exposure (Cmin) and that higher responses were observed in patients with baseline CRP levels >10 mg/L.

There were 5 discontinuations due to an AE; 2 subjects treated with BMS-582949 (diarrhea, and fatigue) and 3 subjects treated with placebo (ALT elevation, presyncope and panniculitis). No deaths were reported, and only 1 serious adverse event (SAE) of polyarthritis deterioration (placebo) was reported. Most AEs were mild to moderate in intensity. No significant increase in the frequency of subjects developing abnormal liver function tests, elevated CPK, dizziness and skin rashes was seen compared to placebo.

Conclusions: BMS-582949 300 mg significantly increased the proportion of ACR20, DAS28, and HAQ-DI responders in patients with active RA who had an inadequate response to MTX compared to placebo. BMS-582949 was safe and well tolerated in subjects with RA who were receiving concomitant therapy with MTX. The effect on biomarker (CRP) and clinical efficacy observed with this dual action p38 inhibitor indicate that this approach to

targeting the p38 MAPK pathway may be possible for the treatment of inflammatory diseases.

Disclosure: M. C. Genovese: Bristol-Myers Squibb, 2, 5; **L. Gao:** Bristol-Myers Squibb, 1, 3; **J. Yin:** Bristol-Myers Squibb, 1, 3; **S. Smith:** Bristol-Myers Squibb, 1, 3; **M. E. Weinblatt:** Bristol-Myers Squibb, 2, 5; **J. S. Smolen:** Bristol-Myers Squibb, 2, 5; **X. Wang:** Bristol-Myers Squibb, 1, 3; **G. Schieven:** Bristol-Myers Squibb, 1, 3; **J. A. Garcia-Meijide:** Bristol-Myers Squibb, 2; **R. Latek:** Bristol-Myers Squibb, 1, 3; **R. Pasternak:** Bristol-Myers Squibb, 1, 3; **S. Kaul:** Bristol-Myers Squibb, 1, 3; **A. Roy:** Bristol-Myers Squibb, 1, 3; **R. Raymond:** Bristol-Myers Squibb, 1, 3; **U. Thienel:** Bristol-Myers Squibb, 1, 3; **J. Wang:** Bristol-Myers Squibb, 1, 3.

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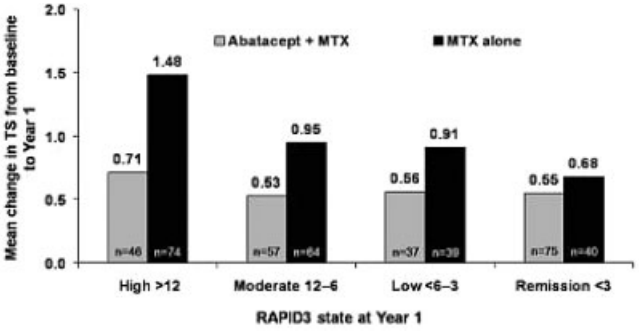
Radiographic Progression Correlates Well with Patient-Reported RAPID3 Disease Activity Levels in Methotrexate (MTX)-Naive Patients with Early Rheumatoid Arthritis (RA): Insights from the AGREE Study. Edward C. Keystone[3], Rene Westhovens[4], Diane Moniz Reed[1], Allison Covucci[1] and Alvin F. Wells[2]. [1]Bristol-Myers Squibb, Princeton, NJ, [2]Rheum & Immunotherapy Center, Oak Creek, WI, [3]University of Toronto, Toronto, ON, Canada, [4]UZ Gasthuisburg, Leuven, Leuven, Belgium

Background: Structural damage early in (RA) can translate into long-term disability; however, assessment of radiographic progression is not routinely performed in clinical practice. Consequently, a patient-derived instrument that correlates with radiographic progression would be helpful in therapeutic decision making. Here we investigate the relationship between X-ray progression and patient-derived RAPID3 disease activity, as well as physical function alone, in patients treated with abatacept (ABA) and/or MTX.

Methods: Patients with early (≤2 years) RA and poor prognostic factors were randomized (1:1) to ABA plus MTX or placebo plus MTX (MTX alone) in the double-blind Phase III AGREE study[1]. X-ray progression at Year 1 assessed by change in Genant-modified Sharp total score (TS) was a co-primary endpoint. In this *post-hoc* analysis, mean change in TS from baseline to Year 1 was analyzed by RAPID3-assessed disease activity (high >12; moderate 12–6; low <6–3; near-remission <3) and HAQ-DI score (high ≥1.5; moderate 0.8–<1.5; low 0.5–<0.8; remission <0.5) at Year 1. Data are for patients who had data available at the visits of interest (as-observed).

Results: Patients had high baseline disease activity (mean DAS28 [CRP] 6.3) and short disease duration (6.5 months); TS was 7.1, HAQ-DI was 1.7 and 86.1% of patients were seropositive for RF and anti-CCP2. In the ABA plus MTX and MTX alone groups, respectively, 215 and 217 patients had data available for the X-ray+RAPID3 analysis, and 215 and 218 had data available for the X-ray+HAQ-DI analysis. In the MTX alone arm, greater X-ray progression was seen with RAPID3-assessed high/moderate disease activity at Year 1 compared with patients in low activity or near-remission; for the ABA plus MTX arm, greater progression was seen for patients in high disease activity compared with moderate/low disease activity states (Figure). Regardless of RAPID3 state, smaller changes from baseline in TS were seen for patients treated with ABA plus MTX versus MTX alone. Similar trends were seen for HAQ-DI scores: mean TS changes for patients with high, moderate, low HAQ-DI and remission, respectively, were 0.53 (n=33) vs 1.64 (n=46), 0.69 (n=55) vs 0.92 (n=71), 0.39 (n=29) vs 0.77 (n=28), and 0.59 (n=98) vs 0.97 (n=73) for ABA plus MTX versus MTX alone.



Conclusions: Radiographic progression in patients with early RA receiving MTX showed good agreement with RAPID3 assessed disease activity state. The association between RAPID3 and radiographic progression with ABA plus MTX was not seen to the same degree, as TS change was consistently low regardless of RAPID3 driven disease activity state. Similar results were observed with HAQ-DI. The agreement observed between RAPID3 and X-ray progression in MTX patients supports the use of the RAPID3, based on patient-reported outcomes, as a guide to management of RA in routine care.

1 Westhovens R, et al. *Ann Rheum Dis* 2009;**68:**1870–7

Disclosure: E. C. Keystone: Abbott Laboratories, 2, 5, 8, Amgen Inc., 2, 5, 8, AstraZeneca, 2, Bristol-Myers Squibb, 2, 5, 8, Centocor, Inc., 2, 5, Genentech and Biogen IDEC Inc, 5, Hoffmann-La Roche, Inc., 2, 5, 8, Novartis Pharmaceuticals Corporation; **R. Westhovens:** Bristol-Myers Squibb, 5, 8, Centocor, Inc., 5, Roche, 5, Schering-Plough, 5, UCB, Inc., 2; **D. Moniz Reed:** Bristol-Myers Squibb, 1, 3; **A. Covucci:** Bristol-Myers Squibb, 1, 3; **A. F. Wells:** Bristol-Myers Squibb, 5.

1121

REGN88/SAR153191, a Fully-Human Interleukin-6 Receptor Monoclonal Antibody, Reduces Acute Phase Reactants in Patients with Rheumatoid Arthritis: Preliminary Observations from Phase 1 Studies. Allen R. Radin[1], Scott J. Mellis[1], Martine Jasson[3], Douglas Nadler[2], Pavel Belomestnov[2], Richard Wu[2], Stephanie Biedermann[2], Damir Skific[2] and Jennifer Hamilton[2]. [1]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [2]Regeneron Pharmaceuticals, Inc., [3]Sanofi-aventis, SA

Background: REGN88/SAR153191 (REGN88), a fully human IgG1 monoclonal antibody directed against the interleukin-6 receptor alpha (IL-6Rα), is being evaluated as a new therapeutic modality for rheumatoid arthritis (RA). We report the effects of REGN88 on markers of inflammation and its safety after subcutaneous (SC) administration in RA patients in phase 1 clinical trials.

Methods: Three phase 1, randomized, double-blind, placebo-controlled trials were conducted; RA patients received REGN88 or placebo (PBO) with concomitant methotrexate. Study 801 evaluated single ascending doses of 50, 100, or 200 mg REGN88 or PBO (n=15). In study 803, patients with active RA were administered parallel single doses of 50, 100, or 200 mg REGN88 or PBO (n=32). Study 802 evaluated patients with RA receiving 5 weekly or 3 biweekly doses of 50, 100, 150, 200 mg REGN88 or PBO (n=60). High-sensitivity C-reactive protein (hsCRP), serum amyloid A (SAA), erythrocyte sedimentation rate (ESR), hepcidin and interleukin-6 (IL-6) were measured to assess pharmacodynamic response. Safety and tolerability were evaluated by combining data from all 3 studies (REGN88 n=83; PBO n=24).

Results: Suppression of hsCRP, SAA, hepcidin and ESR was observed in a dose-dependent manner in REGN88 groups; at day 8, a single 200 mg dose of REGN88 was associated with median reductions of 91.7% in hsCRP, 92.5% in SAA, 66.2% in hepcidin and 33.8% in ESR. For hsCRP, reductions were observed through day 15 ($p<0.005$ vs PBO). Reductions in inflammatory markers were paralleled by increases in serum IL-6 levels that peaked at day 8 after the 200 mg dose (median increase 647%) before returning to baseline by day 22. Four patients withdrew due to adverse events; 3 on REGN88 and 1 on PBO. The most commonly reported adverse events were upper respiratory infection, increase in alanine aminotransferase (ALT) levels, and RA flare. One patient on REGN88 50 mg in Study 803 reported a serious adverse event of RA flare requiring hospitalization, as per Russian standard of care. During a maximum 16-week exposure/follow-up period, 1 patient each in REGN88 and PBO groups had a transient elevation of ALT 3–5x upper limit of normal (ULN), and 1 patient who received REGN88 had ALT >5x ULN. Also during this period, 5 patients on REGN88 and 0 on PBO had a transient decrease in neutrophil count (0.5–1.0 $\times 10^3$/uL); no patients had neutrophils <0.5 $\times 10^3$/uL. No changes in neutrophils or liver enzymes were associated with adverse clinical outcomes.

Conclusion: IL-6Rα inhibition with SC REGN88 in active RA patients resulted in dose-related reductions in hsCRP, SAA, ESR and serum hepcidin with concomitant increases in IL-6. The clinical significance of these changes has not been evaluated. SC REGN88 was well-tolerated in these patients, with no dose-limiting toxicities observed. REGN88 is being investigated in a Phase 2 program in RA and ankylosing spondylitis.

Disclosure: A. R. Radin: Regeneron Pharmaceuticals, Inc., 1, 3; **S. J. Mellis:** Regeneron Pharmaceuticals, Inc., 1, 3; **M. Jasson:** sanofi-aventis, 1, 3; **D. Nadler:** Regeneron Pharmaceuticals, Inc., 1, 3; **P. Belomestnov:** Regeneron Pharmaceuticals, Inc., 1, 3; **R. Wu:** Regeneron Pharmaceuticals, Inc., 1, 3; **S. Biedermann:** Regeneron Pharmaceuticals, Inc., 1, 3; **D. Skific:** Regeneron Pharmaceuticals, Inc., 1, 3; **J. Hamilton:** Regeneron Pharmaceuticals, Inc., 1, 3.

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Results from a Phase I Study of MLTA3698A, a Novel Anti-Lymphotoxin-a Monoclonal Antibody: Safety, Tolerability and Biologic Activity in Patients with Active Rheumatoid Arthritis. Brinda Emu[2], Diana Luca[3], Carolyn Offutt[3], Jane Grogan[3], John Davis[3], Bernadette Rojkovich[1], Marna Williams[3], Meina Tang[3] and June Lee[3]. [1]Budai Irgalmasrendi, [2]Genentech, Inc., South San Francisco, CA, [3]Genentech, Inc.

Background: Lymphotoxin (LT)-α is a cytokine transiently expressed by subsets of activated lymphocytes that are implicated in the pathogenesis of RA/autoimmunity including T-helper cells (Th1, Th17) and B cells. The biologic agent MLTA3698A is a humanized monoclonal antibody directed against the cytokine LTα, and has several distinct mechanisms of action, including blocking soluble and membrane-bound LTα from interacting with its receptors and selectively depleting subsets of activated immune cells. We report a randomized, double-blind, placebo-controlled trial designed to assess safety, tolerability, pharmacokinetics, impact on biomarkers, and preliminary evidence of biologic activity after single and multiple doses of either intravenous or subcutaneous administration of MLTA3698A in RA patients.

Methods: The first stage of the study consisted of a single dose escalation of MLTA3698A or placebo at 6 doses (0.3 IV, 1.0 IV, 1.0 SC, 3.0 IV, 3.0 SC, and 5.0 mg/kg; n=30) in patients with stable RA. The second stage of the study consisted of a multiple dose escalation phase in which patients with active RA (on stable regimen for RA, with $\geq$ 5 swollen joints, >5 tender joints and CRP $\geq$ 1.0) received 3 doses of MLTA3698A or placebo every 2 weeks (1.0 SC, 3.0 SC, or 5.0 IV mg/kg; n=35). Safety and tolerability were assessed in patients in both single and multiple dose escalation stages. CXCL-13, a downstream chemokine in LTa signaling pathway, was measured prior to and after dosing. Clinical activity endpoints were measured at multiple time points in patients in the multiple dose escalation stage.

Results: Baseline characteristics of patients who received MLTA3698A or placebo were similar with respect to demographics and RA disease status (median age of 57 years, median CRP of 1.21, and median DAS28-CRP of 4.21). The majority of adverse events were mild to moderate. There were no serious adverse events or dose-limiting toxicities in the trial. There were no serious infections or notable changes in peripheral lymphocyte subsets. Pharmacokinetic profiles were linear and clearance was independent of dose. Substantial reductions in levels of serum CXCL-13 were observed. Preliminary evidence of clinical activity was seen in the multiple dose stage as evidenced by ACR20, ACR50, and ACR70 response rates as well as reduction in DAS28CRP scores and C-reactive protein (CRP) levels.

Conclusions: Blockade of LTα pathway is a promising mechanism of action for the treatment of RA. MLTA3698A was generally well tolerated and demonstrated preliminary evidence of clinical activity.

Disclosure: B. Emu: Genentech Inc, 3, Roche, 1; **D. Luca:** Genentech Inc, 3, Roche, 1; **C. Offutt:** Genentech Inc, 3, Roche, 1; **J. Grogan:** Genentech Inc, 3, Roche, 1; **J. Davis:** Genentech Inc, 3, Roche, 1; **B. Rojkovich:** None; **M. Williams:** Genentech Inc, 3, Roche, 1; **M. Tang:** Genentech Inc, 3, Roche, 1; **J. Lee:** Genentech Inc, 3, Roche, 1.

1123

Safety of a Novel Modified-Release (MR) Prednisone Formulation: Results of the "Circadian Administration of Prednisone in Rheumatoid Arthritis" (CAPRA) Studies. Frank Buttgereit[1], Jacek Szechinski[5], Gisela Döring[6], Stephan Witte[2], Christine Knauer[3], Amy Grahn[4], Kenneth G. Saag[8] and Rieke Alten[7]. [1]Charite University Med-Berlin, Berlin, Germany, [2]Horizon Pharma GmbH, Mannheim, Germany, [3]Horizon Pharma GmbH, Mannheim, Germany, [4]Horizon Pharma, Inc., Northbrook, IL, [5]Med. Uni. Department of Rheumatology, Wroclaw, Poland, [6]Merck KGaA, [7]Schlosspark-Klinik, UnivMed, Berlin, Germany, [8]University of Alabama-Birmingham, Birmingham, AL

Background: In patients with rheumatoid arthritis (RA), nocturnal increases in proinflammatory cytokines are implicated in the typical early morning symptoms, joint stiffness and pain. Glucocorticoid (GC) chronotherapy with a novel modified-release (MR) prednisone tablet enables delivery of prednisone during the night to specifically target the nocturnal rises in inflammatory mediators and symptoms. This novel approach showed both clinically relevant reduction of morning stiffness (MS) compared to conventional, immediate-release (IR) prednisone, as well as clinically relevant improvements according to the ACR response criteria. The data here describes the safety and tolerability of low-dose prednisone chronotherapy in patients from two phase 3 clinical studies.

Methods: The CAPRA studies investigated safety and efficacy of MR prednisone in patients with RA, not adequately controlled by disease-modifying antirheumatic drug (DMARD) therapy. The CAPRA-1 study compared the novel formulation (3–10 mg/day, average of 6.8 mg/day) in 288 patients to conventional immediate release prednisone over 12 weeks, the CAPRA-2 study compared 5 mg/day MR prednisone + DMARD in 350 patients to placebo + DMARD over 12 weeks. An open-label extension of CAPRA-1 provided safety data for up to 12 months. In addition, the effect of MR prednisone on the Hypothalamus-Pituitary-Adrenal (HPA) axis was investigated in a CRH test subgroup study, as part of CAPRA-1 (62 tests in 28 patients under treatment with MR prednisone or IR prednisone). All Adverse Events (AEs) from these studies were collected by neutral questioning in a standardized manner.

Results: The incidence of serious adverse events (SAEs) and adverse events (AEs) in all treatments was low and comparable between MR prednisone and IR prednisone and comparable to the placebo arm, with more AEs related to RA signs and symptoms (arthralgia and RA flare) in the PBO arm than in the MR prednisone arm. In all studies MR prednisone was shown to be safe and well tolerated. The most frequent AEs are shown in Table 1. CRH tests in patients on treatment with MR prednisone or IR prednisone showed no evidence for a different effect on the HPA axis.

Table 1. Adverse Events occurring in ≥2% of MR Prednisone in patients of the CAPRA studies.

	CAPRA-2 (3 Months)		CAPRA-1 (3 Months)		CAPRA-1 (9 Months)
Preferred term	Prednisone MR 5mg (%) N=231	Placebo (%) N=119	Prednisone MR 3–10mg (%) N=144	Prednisone IR 3–10mg (%) N=144	Prednisone MR 3–10mg (%) N=249
Worsening of rheumatoid arthritis	6.5	9.2	7.6	9.0	14.5
Arthralgia	10.4	20.2	0.7	2.1	2.4
Nasopharyngitis	4.8	3.4	2.8	5.6	2.4
Headache	3.9	4.2	4.2	2.8	1.2
Abdominal pain upper	0.4	1.7	3.5	5.6	1.6
Bronchitis	1.3	4.2	0.7	3.5	2.4
Upper respiratory tract infection	0.4	0.8	0.7	2.1	2.8
Hypertension	2.2	0.8	2.1	2.1	<1
Back pain	1.3	0.8	<1	<1	2.8
Nausea	1.3	0.0	3.5	2.8	<1
Chest pain/discomfort	0.4	0.0	2.1	2.1	<1
Hypercholesterolemia	0.4	1.7	<1	<1	2.4
Feeling hot	0.0	0.0	<1	<1	2.0
Weight increased	0.0	0.0	<1	<1	2.8

Conclusion: Two large phase 3 clinical trials established a favorable safety profile of low-dose chronotherapy with MR prednisone. MR Prednisone has been shown to reduce duration of morning stiffness and to be more effective than placebo with regard to standard RA outcome parameters.

Disclosure: F. Buttgereit: Horizon Pharma, 2, 5, Merck Pharmaceuticals, 2, Nitec, 2, 5; **J. Szechinski:** Horizon Pharma, 9, Nitec, 9; **G. Döring:** Horizon Pharma, 5, Nitec, 5; **S. Witte:** Horizon Pharma, 3, Nitec, 3; **C. Knauer:** Horizon Pharma, 3, Nitec, 3; **A. Grahn:** Horizon Pharma, 3; **K. G. Saag:** Horizon Pharma, 5, Nitec, 5; **R. Alten:** Horizon Pharma, 5, 8, Nitec, 5, 8.

1124

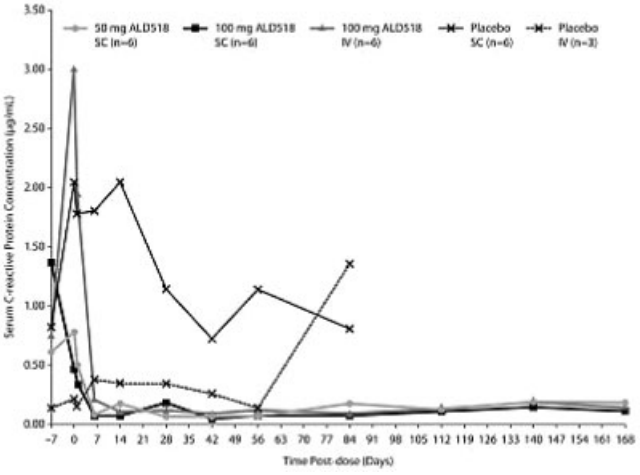
Safety, Pharmacokinetics and Pharmacodynamics of ALD518 (BMS-945429), a High-Affinity Monoclonal Antibody Directed Against Interleukin-6 (IL-6) Administered by Subcutaneous Injection: A Phase I Trial. Sepehr Shakib[2], Barbara Francis[1] and Jeffrey Smith[1]. [1]Alder Biopharmaceuticals Inc., Bothell, WA, [2]Royal Adelaide Hospital, Adelaide, Australia

Background: ALD518 (BMS-945429) is an asialated, humanized anti-IL-6 monoclonal antibody with a half-life of ~30 days. ALD518 binds to IL-6 with high affinity, preventing interaction and signalling mediated via IL-6R. Rapid and significant treatment responses have been demonstrated with intravenous (IV) ALD518 in patients with RA[1]; here we report the safety, pharmacokinetics and pharmacodynamics of subcutaneous (SC) ALD518 in healthy subjects.

Methods: In this Phase I, double-blind, placebo-controlled study, 27 subjects were randomized 2:1 to receive a single dose of ALD518 or placebo in the following groups: ALD518 50 mg SC, ALD518 100 mg SC or

ALD518 100 mg IV (n=6 active and n=3 placebo per group). The primary objective was to assess safety of SC ALD518 versus placebo over 12 weeks. Plasma concentrations of ALD518 and serum concentrations of C-reactive protein (CRP) were assessed as secondary objectives. Assessments were performed daily in Week 1 and then on Day 10, Weeks 2, 4, 6 and 8, and then monthly to Week 12. The study was unblinded at Week 12, and ALD518 subjects were monitored to Week 24.

Results: Over 24 weeks, there were no deaths or serious AEs, and no withdrawals due to AEs. Nearly all subjects (89%) experienced AEs, which were mild or moderate except one event of severe gastroenteritis in the ALD518 SC 50 mg group. Injection site reactions occurred in 5/12 ALD518 SC subjects, 1/6 placebo SC subjects and 1/3 placebo IV subjects (none were reported in ALD518 IV subjects). These were mild except one case of moderate erythema and pruritis in the ALD518 100 mg SC group. Increases in direct bilirubin and neutrophil counts below the limit of normal were more common in subjects receiving ALD518 than placebo; all were CTC Grade 1 or 2. The half life of ALD518 was similar across all groups (mean range: 30.7–33.6 days). The median T_{max} of ALD518 was longer after SC (~1 week) than after IV administration (~end of infusion). The PK of SC ALD518 was dose-proportional in terms of AUC and C_{max} at doses of 50 mg and 100 mg. Based on $AUC_{0-\infty}$ (day*μg/mL) of 237, 452 and 764 for the ALD518 50 mg SC, 100 mg SC and 100 mg IV groups, respectively, the bioavailability of ALD518 was ~60% for the SC versus IV groups. Subjects receiving ALD518 experienced rapid and sustained reductions in serum CRP (Figure).



Conclusions: In this Phase I study, the anti-IL-6 antibody ALD518 was well tolerated when administered in a single SC dose; injection site reactions were generally mild. The bioavailability of SC ALD518 was ~60% of IV ALD518, and the half life was ~30 days. Rapid and significant reductions in CRP were observed, which were sustained over 24 weeks of assessment.

Reference:
[1]Mease P, et al. *Ann Rheum Dis* 2010;**69**(Suppl3):98. Abstract OP0136

Disclosure: S. Shakib: IDT Pharmaceuticals, 5; **B. Francis:** CPR Pharma Services Pty Ltd, 1, 3, IDT Australia Ltd, 1, 3; **J. Smith:** Alder Biopharmaceuticals Inc, 1, 3.

1125

Selective Activation of Naturally Occurring Regulatory T Cells (Tregs) by the Monoclonal Antibody (mAb) BT-061. Markers of Clinical Activity and Early Phase II Results in Patients with Rheumatoid Arthritis (RA).
Anatoliy Rudnev[1], Sukanya Ragavan[6], Christina Trollmo[6], Vivianne Malmstroem[6], Christian Becker[5], Helmut Jonuleit[5], Vibeke Strand[7], Silke Aigner[1], Niklas Czeloth[1], Benjamin Daelken[1], Andre Engling[1], Helga Koch[1], Gabriele Niemann[1], Frank Osterroth[1], Christoph Uherek[1], Andrea Wartenberg-Demand[1], Olga Ershova[4], Tatiana Sotnikova[2] and Alexander Orlov-Morozov[3]. [1]Biotest AG, Dreieich, Germany, [2]Botkin Clinical Hospital, Moscow, Russian Federation, [3]City Clinical Hospital Nr. 23 n.a. Medsantrud, Moscow, Russian Federation, [4]Clinical Hospital for Emergency Medical Care, Yaroslavl, Russian Federation, [5]Johannes-Gutenberg University, Mainz, Germany, [6]Karolinska Institute, Stockholm, Sweden, [7]Stanford University, Portola Valley, CA

Naturally occurring Tregs are essential for maintaining normal immune homeostasis in healthy individuals. In patients with autoimmune diseases reduced numbers or functional impairment of Tregs has been observed. A humanized agonistic mAb, BT-061 selectively activates Tregs. It binds to a unique epitope of the CD4 molecule, leading to induction of Treg specific signaling events. While freshly isolated and resting Tregs do not inhibit T cell proliferation, pre-treatment of Tregs with BT-061 leads to suppression of CD4 and CD8 T effector cell proliferation, reduction of pro-inflammatory cytokines and a moderate increase in the anti-inflammatory cytokine TGF-beta.

To further assess the potential of BT-061 to modulate immune responses, *in vitro* studies with synovial fluid derived mononuclear cells from patients with active RA were performed. Addition of BT-061 at concentrations between 0.01 and 50 micro g/mL to isolated CD4-positive cells derived from the highly inflammatory milieu of RA synovial fluid suppressed proliferation as well as IFN-gamma production following antigen-specific stimulation.

In a Phase I/IIa trial in patients with psoriasis, a single dose of BT-061 resulted in PASI 50/75 responses for up to 90 days at doses of 0.5, 2.5, 10, 20 mg iv and 12.5, 25 mg sc. A Phase IIa, multicenter, randomized placebo-controlled trial with BT-061 monotherapy was performed in 96 patients with active RA and inadequate responses to one or more traditional DMARD despite 3 months or more of treatment. Patients were randomized to 12 treatment groups: from 1.25 – 100 mg sc, or 0.5 – 25 mg iv, once weekly for 6 weeks: 6 patients received BT-061 and 2 received placebo in each group.

Initial data analysis confirmed the clinical activity of BT-061 by ACR20/50/70 responses in a meaningful proportion of patients despite the short duration of therapy. No major safety signals were identified. Final analyses of safety and efficacy data are ongoing and will be presented.

Phase II multiple dose trials with BT-061 are underway to further evaluate the clinical benefit of BT-061 in patients with RA and psoriasis.

Disclosure: A. Rudnev: Biotest AG, 3; **S. Ragavan:** Biotest AG, 2; **C. Trollmo:** Biotest AG, 2; **V. Malmstroem:** Biotest AG, 2; **C. Becker:** Biotest AG, 2; **H. Jonuleit:** Biotest AG, 2; **V. Strand:** Biotest AG, 5; **S. Aigner:** Biotest AG, 3; **N. Czeloth:** Biotest AG, 3; **B. Daelken:** Biotest AG, 3; **A. Engling:** Biotest AG, 3; **H. Koch:** Biotest AG, 3; **G. Niemann:** Biotest AG, 3; **F. Osterroth:** Biotest AG, 3; **C. Uherek:** Biotest AG, 3; **A. Wartenberg-Demand:** Biotest AG, 3; **O. Ershova:** Biotest AG, 2; **T. Sotnikova:** Biotest AG, 2; **A. Orlov-Morozov:** Biotest AG, 2.

1126

Serum Cytokine Profile Predicts Response to Rituximab Therapy in Rheumatoid Arthritis.
Edward M. Vital[4], Richard J. Cuthbert[4], Shouvik Dass[1], Rekha Parmar[4], Andrew C. Rawstron[3], Frederique C. Ponchel[1] and Paul Emery[2]. [1]Leeds, West Yorkshire, United Kingdom, [2]Chapel Allerton Hospital, Leeds, United Kingdom, [3]Leeds Teaching Hospitals NHS Trust, Leeds, West Yorkshire, United Kingdom, [4]University of Leeds, Leeds, West Yorkshire, United Kingdom

Background: Response to B-cell depletion with rituximab in rheumatoid arthritis is variable. Several factors have been shown to have predictive value at baseline: RF and CCP status, IgG titre, circulating memory B cell numbers, synovial expression of CD79a, as well as persistence of circulating plasmablasts and synovial plasma cells after treatment. These data suggest it may be possible to select patients for therapy based on parameters indicating greater active B-cell involvement. However, parameters identified to date are not accurate and many are not suitable for routine clinical practice. We therefore studied serum cytokines that have a hypothetical role in B-cell function in RA to better understand the determinants of response, and as convenient biomarkers.

Patients and Methods: 85 patients were treated with rituximab and clinical response was evaluated at 6 months by EULAR criteria. Relapse was determined by rise in DAS28 $\geq$ 0.6. Serum was tested for BAFF (n=85 at baseline, 29 serial samples), IL6 (n=46) and IL10 (n=26) by ELISA (R&D Systems). B cell subsets were measured by 6-parameter flow cytometry using CD19, CD20, CD3, CD14, CD27 and CD38. The strength of correlations was tested by Spearman's log rank test and relationships between cytokine titres and categorical variables by either Mann Whitney U test or log transformation and Student's t test, as appropriate.

Results: Baseline Cytokines and disease activity: IL6 was correlated with CRP at baseline as expected ($R = 0.591$, $p < 0.001$) but there was no relationship of BAFF or IL-10 with DAS28 or CRP, nor any interrelationship between cytokines.

Cytokine changes after therapy: 6 months after B-cell depletion, BAFF significantly increased ($p<0.001$) and IL-6 significantly reduced ($p=0.001$) but there was no substantive or significant change in IL10. As expected, IL-6

was higher in non-responders at 6 months ($p<0.001$). Levels of each cytokine correlated between baseline and 6 months after therapy (BAFF, $R=0.735$, $p<0.001$; IL-6, $R=0.541$, $p<0.001$; IL-10, $R=0.675$, $p=0.008$).

Predictive value of baseline cytokines: Baseline DAS28, its components, and CRP/ESR did not differ between responders and non-responders. Most importantly, levels of IL-6 and BAFF were predictive of response at baseline: in responders BAFF was higher ($p=0.03$) and IL-6 was lower ($p=0.014$).

No relationship of serum cytokines with B cell depletion or repopulation: No relationship was identified between IL6, IL10 or BAFF levels at baseline or follow up and baseline B-cell number, degree of depletion at 2 or 6 weeks or rate of repopulation of any subset.

Conclusions: Serum BAFF and IL-6 titres are predictive of response to rituximab in rheumatoid arthritis and may have utility as biomarkers. However, this effect appears to be independent of B cell depletion, and the hypothesis that BAFF inhibits B cell depletion, as suggested by animal models, is not supported by these results. These relationships may differ in the synovium or other tissues.

Disclosure: E. M. Vital: GlaxoSmithKline, 5, Roche, 8; **R. J. Cuthbert:** None; **S. Dass:** Roche, 8; **R. Parmar:** None; **A. C. Rawstron:** None; **F. C. Ponchel:** None; **P. Emery:** Abbott Laboratories, 5, Roche, 5, 8, Schering-Plough, 5, Wyeth Pharmaceuticals, 5.

1127

Serum Markers Associated with Structural Damage in Methotrexate Naïve Rheumatoid Arthritis Patients Treated with MTX in Combination with Placebo or Golimumab, a Human Anti-TNFa Monoclonal Antibody. Carrie Wagner[2], Dion Chen[1], Hongtao Fan[1], Sudha Visvanathan[5], Elizabeth C. Hsia[3], Paul Emery[4], Roy M. Fleischmann[6], Michael Mack[1] and Mahboob U. Rahman[3]. [1]Centocor Research and Development, Inc., [2]Centocor Research and Development, Inc., Malvern, PA, [3]Centocor Research and Development, Inc./Univ. of Pennsylvania School of Medicine, Malvern, PA, [4]Chapel Allerton Hospital, Leeds, United Kingdom, [5]Hoffmann La Roche, [6]University of Texas SW Medical Center, Dallas, TX

Purpose: Little is known about biomarkers that are correlated with structural damage endpoints in rheumatoid arthritis (RA). The purpose of this study is to evaluate whether there are serum markers associated with structural damage in MTX naïve RA patients treated with MTX in combination with either placebo (PBO) or an anti-TNF antibody, golimumab (GLM).

Methods: In the GO-BEFORE study, 637 patients were randomly assigned in a 1:1:1:1 ratio to receive placebo (PBO) + methotrexate (MTX), GLM 100 mg+ PBO, GLM 50 mg + MTX, or GLM 100 mg + MTX. Sera were collected at wks 0, 4 and 24 from a subset of approximately 100 patients for testing select markers of inflammation and bone/cartilage metabolism and protein profiling using multi-analyte profiles (Rules Based Medicine). The baseline, absolute change and percent change from baseline to wk 4 in these markers were compared between the PBO+MTX and the combined GLM group [GLM+MTX (50 mg + 100 mg) and GLM+PBO groups] against changes in van der Heijde modified Sharp (vdh-S) score, erosion score and joint space narrowing score at wks 28 and 52 using Spearman's correlations. Significant biomarker correlations with efficacy in the GLM group relative to the PBO treatment group were evaluated using Fisher Z-transformation test.

Results: Biomarker correlations with structural damage endpoints were predominantly observed for only the PBO+MTX treatment group and very few correlations were observed with GLM treatment. With PBO+MTX treatment, only IL-1ra was observed to be repeatedly correlated with the structural damage endpoints at wks 28 and 52. However, there were a number of more consistently observed structural damage correlations in the PBO+MTX treatment group using either absolute change from baseline or percent change from baseline in biomarker levels. Absolute change or percent change from baseline markers that were repeatedly correlated with changes in structural damage endpoints at wks 28 and/or 52 included CD-40 ligand (CD40-L) and epidermal growth factor (EGF). There were repeated, but less frequent structural damage correlations with change or percent change in matrix metalloproteinase 3, MIP-1β and Col 2–3/4C long neoepitope. The only biomarker that was repeatedly correlated with structural damage endpoints in the GLM treatment group was IL-1ra.

Conclusions: Biomarker correlations with structural damage endpoints were predominantly observed in the PBO+MTX treatment group, but rarely in the GLM+MTX treatment group, likely reflecting the reduced structural damage observed following anti-TNF treatment. Change and percent change from baseline to wk 4 in levels of certain markers were repeatedly associated with structural damage endpoints at wks 28 or 52 in the PBO+MTX treatment. Markers that were repeatedly associated with structural damage measures at wks 28 and/or 52 included EGF and CD40-L. CD40-L has been reported to regulate osteoclastogenesis and EGF has been implicated in bone remodeling. Additional studies are needed to confirm whether these markers would be similarly correlated with structural damage measures in MTX-refractory patients.

Disclosure: C. Wagner: Centocor Research and Development, Inc., 3; **D. Chen:** Centocor Research and Development, Inc., 3; **H. Fan:** Centocor Research and Development, Inc., 3; **S. Visvanathan:** Hoffman La Roche, 3; **E. C. Hsia:** Centocor Research and Development, Inc., 3; **P. Emery:** Centocor Research and Development, Inc., 2, 9; **R. M. Fleischmann:** Centocor Research and Development, Inc., 2, 9; **M. Mack:** Centocor Research and Development, Inc., 3; **M. U. Rahman:** Centocor Research and Development, Inc., 3.

1128

Targeting Potassium Channels for the Treatment of Rheumatoid Arthritis. Xueyou Hu[2], Teresina Laragione[4], Liang Sun[2], Shyny Koshy[2], Karlie R. Jones[2], Frank T. Horrigan[2], Percio S. Gulko[3] and Christine Beeton[1]. [1]Baylor College of Medicine, Houston, TX, [2]Baylor College of Medicine, [3]Feinstein Institute for Medical Research, Manhasset, NY, [4]Feinstein Institute for Medical Research

Background: Activated fibroblast-like synoviocytes (FLS) in the rheumatoid arthritis (RA) synovium (RA-FLS) are major players in inflammation, synovium and bone destruction, angiogenesis, and hyperplasia. However, no currently-approved therapies specifically target these cells. Potassium channels regulate cell signaling and thus a large number of functions of non-excitable cells such as fibroblasts, lymphocytes, or astrocytes. We therefore hypothesized that targeting the potassium channels expressed by RA-FLS may represent an attractive target for the treatment of RA.

Methods: We have used four complementary methods (RT-PCR, western blot, immunocytochemistry, and patch-clamp electrophysiology) to identify the potassium channels expressed by RA-FLS isolated from 5 different patients. We next used selective blockers of KCa1.1 channels (paxilline and iberiotoxin) to probe their roles on RA-FLS proliferation, invasion, and production of cytokines, chemokines, angiogenic factors, and matrix metalloproteinases (MMPs).

Results: We have identified KCa1.1 channels (BK, Maxi-K, Slo-1) as the major potassium channels expressed by RA-FLS. Blocking KCa1.1 channels inhibited the proliferation of RA-FLS and their ability to produce vascular endothelial growth factor (VEGF), IL-8, and MMP-2 without inducing cytotoxicity or affecting the production of IL-6. In keeping with these data, blocking KCa1.1 channels also inhibited the invasion of RA-FLS in matrigel assays.

Conclusions: KCa1.1 channels play a major role in the pathogenic functions of RA-FLS. These channels are therefore attractive targets for the treatment of RA.

Disclosure: X. Hu: None; **T. Laragione:** None; **L. Sun:** None; **S. Koshy:** None; **K. R. Jones:** None; **F. T. Horrigan:** None; **P. S. Gulko:** None; **C. Beeton:** Airmid, Inc., 4, 5, Johnson & Johnson, 5, Kineta One, 4, 5.

1129

Tasocitinib (CP-690,550), an Orally Available Selective Janus Kinase Inhibitor, Exhibits Sustained Safety and Efficacy in the Treatment of Rheumatoid Arthritis over 24 Months. Carol A. Connell, Richard Riese, Susan Wood, John Bradley and Samuel H. Zwillich. Pfizer Inc

Background: Tasocitinib (CP-690,550) is an orally available, small molecule Janus kinase inhibitor that has previously demonstrated efficacy and acceptable safety in patients with active rheumatoid arthritis (RA) in randomized studies of up to 24 weeks of treatment. Here we report the safety and tolerability of tasocitinib and the durability of response beyond 24 weeks in patients with RA.

Methods: In this Phase 2/3, open label study of 1070 patients who had participated in a prior randomized study of tasocitinib (PRST), treatment was initiated with either 5 or 10 mg tasocitinib twice daily. The baseline is that of the PRST for patients who enrolled within 14 days of PRST participation; if enrollment was >14 days after PRST participation, baseline was the start of this study. The primary endpoints were laboratory safety and adverse event (AE) reports. Secondary endpoints included ACR20, ACR50 and ACR70 response rates, Disease Activity Score using the erythrocyte sedimentation rate (DAS28-4 [ESR]), and the Health Assessment Questionnaire-Disability Index (HAQ-DI). Results are reported for all patients (ALL) and stratified according to those who completed Month 12 (M12) and Month 24 (M24) visits.

Results: 1070 patients were treated for a total duration of 1295.7

patient-years; median days of treatment were 518.5 (ALL, n=1070), 655.0 (M12, n=648), and 796.0 (M24, n=207). Seventy patients discontinued from the study due to AEs. A total of 929 treatment-related AEs (TRAEs) were reported; the most frequently reported classes of events were infections and infestations (197, 18.4%), gastrointestinal disorders (109, 10.2%), and investigations [laboratory] (79, 7.4%). 188 serious AEs (SAEs) were reported, of which 48 (25.5%) were considered possibly related to treatment. The most frequently reported class of SAEs was infections (34, 18.1%, 2.62/100 patient-years of tasocitinib treatment).

Mean DAS28-4(ESR) at baseline was 6.41 (ALL); at month 12, 3.70 (ALL) and at month 24, 3.55 (ALL). ACR20, ACR50, and ACR70 percent responders were similar through month 24 in all groups, as seen in Figure 1.

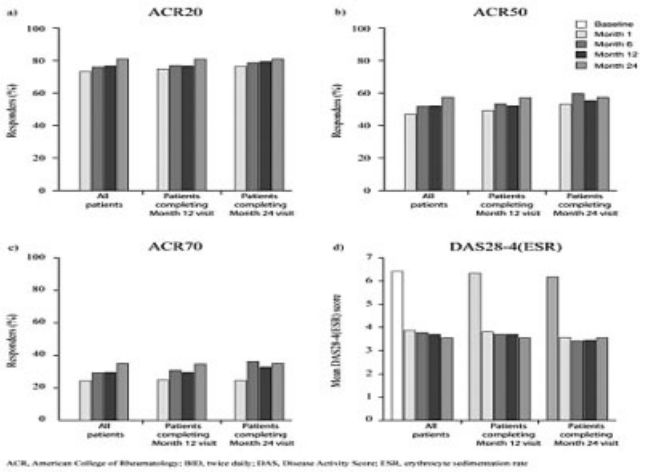


Figure 1. % responders for (a) ACR20, (b) ACR50, (c) ACR70 and (d) mean DAS28-4(ESR) score for patients initially treated with tasocitinib 5 or 10 mg BID.

Mean HAQ-DI scores were improved compared with baseline and remained consistent over time for ALL patients: 1.46 (baseline), 0.86 (Month 12), and 0.76 (Month 24) and M24 patients: 1.38 (baseline), 0.74 (Month 12), and 0.76 (Month 24).

Conclusion: Tasocitinib is effective in the long-term treatment of RA with a manageable safety profile. Efficacy is demonstrated by sustained improvement in ACR response rates, DAS28-4(ESR), and HAQ-DI over a 24-month period.

Disclosure: C. A. Connell: Pfizer Inc, 3; **R. Riese:** Pfizer Inc, 3; **S. Wood:** Pfizer Inc, 3; **J. Bradley:** Pfizer Inc, 3; **S. H. Zwillich:** Pfizer Inc, 3.

1130

The Bacterial Effector Protein YopM Reduces Bone Destruction in Rheumatoid Arthritis (RA). Jessica Bertrand[1], Christian Rüter[3], Julia Scharnert[3], Alexander Schmidt[3] and Thomas Pap[2]. [1]Institute for Experimental Musculoskeletal Medicine, Münster, Germany, [2]Institute for Experimental Musculoskeletal Medicine, [3]Institute for Infectiology ZMBE

Background: Bone marrow macrophages (BMM) are precursors of osteoclasts, which mediate the degradation of bone during rheumatoid arthritis (RA). The yersinia outer protein M (YopM) is an effector protein of Yersinia species that is able to enter host cells by membrane penetration. In the cell YopM mediates down-regulation of inflammatory responses. We investigated whether YopM has the potential to act as a "self-delivering" immune therapeutic agent by reducing the inflammation and joint destruction linked to RA.

Methods: We analysed the penetration of recombinant YopM into BMMs by confocal laserscanning microscopy and studied the effects of YopM on osteoclastogenesis using an in vitro osteoclast formation assay. To unravel the signaling pathways involved in the effects of YopM, we investigated the activation of MAP-kinases (ERK, AKT and p-38) and NF-KB signaling by Western Blot analysis. With respect to a potential in vivo application of YopM, we injected YopM intra articular and intravenous of wildtype and hTNFtg mice and monitored its distribution by fluorescence reflection imaging (FRI). Additionaly, we treated hTNFtg mice, as animal model for RA, with YopM and recorded clinical parameters (weight, grip strength and paw swelling). Finally, we analysed the destruction of bone and cartilage histologically compared to untreated hTNFtg mice and wildtype mice.

Results: As seen in confocal scanning microscopy, YopM penetrated the cell membrane of BMMs and accumulated near the nucleus. Studying the signaling pathways affected by YopM, we found that YopM reduced the TNF alpha induced activation of NF-KB by reducing the phosphorylation of IkB alpha. TNF alpha mediated phosphorylation of MAP kinases were not altered by YopM. Most interestingly, we found a strong reduction of osteoclast formation by YopM. Incubation of BMMs with YopM led to a 90% reduction in osteoclasts precursors and osteoclasts. YopM-Cy5 injected intra-articular into the knee joints of a mouse was detectable whithout a systemic distribution of YopM during a time period of 72 hours. Analysing the clinical parameters of RA in hTNFtg mice, we observed a delay of onset of paw swelling in mice treated with YopM. At histological analysis of the hind paws, we found reduced bone destruction and inflammation in YopM treated hTNFtg mice in comparison to untreated hTNFtg mice.

Conclusion: These results suggest that YopM has the potential to reduce inflammation and bone destruction in vivo. Therefore YopM may constitute a novel therapeutic principle for the treatment of RA.

Disclosure: J. Bertrand: None; **C. Rüter:** None; **J. Scharnert:** None; **A. Schmidt:** None; **T. Pap:** None.

1131

The Effects of Manzamine A on Rheumatoid Arthritis Synoviocyte Cytokine Secretion. Kyle Chong[1], Karolina Klosowska[1] and James M. Woods[2]. [1]Midwestern University, Downers Grove, IL, [2]Midwestern University

Purpose: Manzamine A (MZA) is a marine alkaloid isolated from sponges on the ocean floor known to have anti-inflammatory properties on activated macrophages. The complete synthesis of this complex compound has recently been reported. Rheumatoid Arthritis (RA) is characterized by increased production of pro-inflammatory cytokines by a variety of synovial cells found in the synovial tissue (ST) including fibroblast-like synoviocytes (FLS). We hypothesized that MZA would decrease the levels of pro-inflammatory cytokines secreted by RA cell types.

Methods: RA FLS and RA synovial tissue (ST) explants collected from patients with IRB approval were treated with MZA (10 μM, 1 μM, 0.1 μM, 0.05 μM, and 0.01 μM MZA) or vehicle control, to observe for alterations in pro-inflammatory cytokine production and to observe any cytotoxic effects. Condition media (CM), with or without IL-1β stimulation was collected at various time points. Toxicity was determined using trypan blue exclusion while cytokine levels were analyzed using antibody microarrays and ELISAs.

Results: Toxicity studies on RA FLS suggest that concentrations of 10 μM, 1.0 μM and 0.1 μM MZA had no toxic effects after 24 hours of incubation. However, after 48 and 72 hours, the 10 μM and 1.0 μM MZA concentrations appear to significantly decrease FLS viability. Using an antibody microarray, 24 hour CM with 10 μM MZA appeared to decrease the production of several pro-inflammatory mediators in both RA FLS and RA ST. Proteins decreased include monocyte chemoattractant protein (MCP)-1 (CCL2), interleukin (IL)-8 (CXCL8), growth related oncogene (Gro)-α (CXCL1), regulated on activation of normal T cell expressed and secreted (RANTES/CCL5), IL-6, and epithelial neutrophil activating peptide (ENA)-78 (CXCL5). To confirm data obtained from the cytokine microarray analysis, the level of protein expression was further examined by ELISA. At 24 hours, 10 μM, 1.0 μM and 0.1 μM MZA significantly decreased the production of MCP-1 by 57%, 37 % and 44% respectively ($n=5$; $p<0.05$). Additionally 0.1 μM MZA decreased MCP-1 by 43% at 48 hours ($n=5$; $p<0.05$). MCP-1 production, when stimulated with IL-1β, was significantly decrease with 10 μM, 1.0 μM, 0.1 μM, 0.05 μM and 0.01 μM MZA by 87%, 84%, 57%, 62%, and 67%, respectively, at 24 hours ($n=5$; $p<0.05$). RANTES production was significantly decreased with 10 μM and 1.0 μM MZA by 79% and 69%, respectively, at 24 hours, and also by 54% with 0.1 μM MZA at 72 hours ($n=5$; $p<0.05$). IL-1β stimulated RANTES production was significantly decreased with 10 μM and 1.0 μM MZA by 86% and 75%, respectively, at 24 hours, and also by 59% with 0.1 μM MZA after 72 hours ($n=5$; $p<0.05$). Also, IL-1β stimulated Gro-α production was significantly decreased by 0.01 μM MZA by 26% after 24 hours ($n=5$; $p<0.05$).

Conclusions: While some concentrations of MZA applied appeared toxic to RA FLS, we identified a number of significant effects of MZA at non-toxic concentrations and time points. Our data suggest that MZA decreases RA-associated inflammation by reducing pro-inflammatory cytokines and appears to have solid pharmacological potential to serve as a novel therapeutic in RA therapy.

Disclosure: K. Chong: None; **K. Klosowska:** None; **J. M. Woods:** None.

1132

The Hawthorne Effect, Sponsored Trials, and the Overestimation of Treatment Effectiveness. Frederick Wolfe[1] and Kaleb D. Michaud[2]. [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]Univ of Nebraska Med Ctr, Omaha, NE

Objective: Improvement in rheumatoid arthritis (RA) clinical trials is often greater than improvement seen in the clinic. But follow-up clinical trial studies by sponsors almost invariably show sustained improvement (durability of response). We investigated whether sponsored trial participation influenced study results to determine if the result of clinical trials are upwardly biased by the Hawthorne effect.

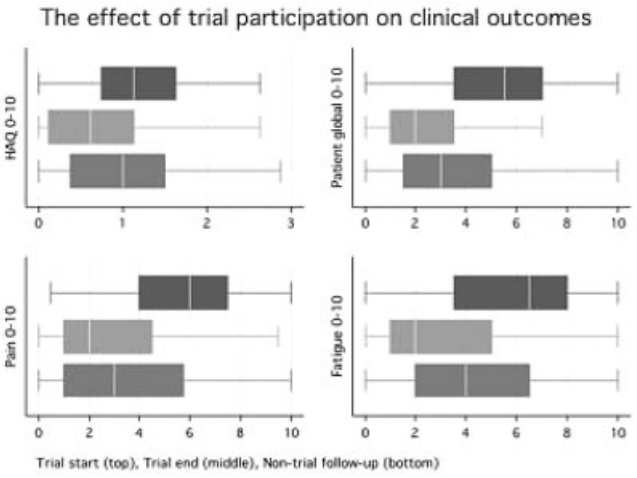
Methods: We studied 264 RA patients who completed a commercially sponsored 3-month, open label, phase 4 trial of a Food and Drug Administration approved RA treatment. We evaluated changes in the Health Assessment Questionnaire disability index (HAQ) and VAS scales for pain, patient global, and fatigue during three periods: Pretreatment in the trial, on treatment at the close of the trial, and by a trial-unrelated survey 8 months after the close of the trial, but while the patients were receiving the same treatment. The study forms were the same for the trial and post-trial assessments.

Results: The HAQ score (0–3) improved by 41.3% during the trial, but only by 16.5% when the end point was the post-trial result. Similar results for the other variables were patient global (0–10): 51.9% and 34.6%; pain (0–10) 51.7% and 39.7%; fatigue (0–10) 45.6% and 24.6%. Worsening between the trial end and the first survey assessment was: HAQ 0.29 units, pain 0.8 units, global 0.8 units, and fatigue 1.1 units. These values are documented in Table 1 and Figure 1.

Changes in Study Variables According to Study Time and Setting.

	Trial Start	*Trial end*		*Post-trial follow-up*	
Variable	Mean (SD)	Mean (SD)	Positive ES (95% CI)	Mean (SD)	Negative ES (95% CI)
ACR20 (%)		63.1			
ACR50 (%)		43.4			
ACR70 (%)		20.2			
HAQ (0–3)	1.21 (0.60)	0.71 (0.61)	0.83 (0.72, 0.95)	1.01 (0.71)	0.44 (0.60, 0.26)
Global (0–10)	5.2 (2.3)	2.5 (2.1)	1.22 (1.07, 1.38)	3.4 (2.5)	0.38 (0.49, 0.25)
Pain (0–10)	5.8 (2.3)	2.8 (2.4)	1.29 (1.12, 1.45)	3.5 (2.7)	0.30 (0.41, 0.19)
Fatigue (0–10)	5.7 (2.7)	3.1 (2.7)	0.93 (0.78, 1.09)	4.3 (2.9)	0.41 (0.54, 0.27)

Trial start: pre-treatment; trial end (6 months later); Post-trial follow-up (0.8 years later).
Differences between trial end and trial follow-up are significant at $p < 0.001$.
Positive=clinical improvement, negative=clinical worsening.
ES=Effect Size



Conclusions: Almost half of the improvement noted in the clinical trial HAQ score disappeared on entry to a non-sponsored follow-up study, and from 23%-44% of improvements in pain, patient global, and fatigue also disappeared. These changes can be attributed to the Hawthorne effect. The difference between the clinical trial HAQ and the community (clinic) HAQ is important because HAQ values are commonly used to map to utility scores and then in the calculation of cost effectiveness. If clinical trial results overstate HAQ scores, then the true effectiveness—the real functional status — is overstated. Based on our data, we hypothesize that the absolute values of RA outcome variables in clinical trials are upwardly biased, and that that treatment effect is less than observed. Our results suggest that 3rd party (non-sponsored) follow-up studies, removed from the trial assessment, can and should be used to estimate actual clinical improvement.

Disclosure: F. Wolfe: None; **K. D. Michaud:** None.

1133

The Relationship of Serum Cytokine Levels with Disease Activity Parameters and Ultrasonographic Findings in RA Patients before and after Treatment with TNF Antagonists. Nevsun Inanc[2], Atilla Bulur[2], Meryem Can[2], Onder Ergonul[1], Pamir Atagunduz[2], Sule Yavuz[2] and Haner Direskeneli[2]. [1]Marmara University Medical School, Department of Infectious Diseases, [2]Marmara University Medical School, Division of Rheumatology

Background: Although effective in most patients, response to TNF antagonists is heterogenous and unpredictable in rheumatoid arthritis (RA). Bio-markers like serum cytokine levels or imaging methods like ultrasonography (US) might be helpful in predicting response to treatment with TNF-antagonists.

Methods: Levels of IL1, IL1Ra, IL6, MCP, TNF, VEGF, IFN gamma, IL10, IL12, IL13 were measured by a Luminex multiplex technology, VEGF-R1 and ANG-1 by quantitative sandwich ELISA in 26 RA patients (72 samples) before and after TNF antagonist therapy at 3 and 6 months. Tender and swollen joint counts, ESR, CRP, DAS28, patient and physician's global assessment were recorded at each visit. US evaluation included GrayScale (0–3)(GS) and PowerDoppler (0–3)(PD) semiquantitative examination with a My Lab 70 XVG (Esaote Biomedica, Italy) equipped with 6–18 and 3–9 broad band linear transducer in 28 joints to calculate total GS and PD scores.

Results: Mean (SD) age was 49(11) and disease duration 9.7(6.2) years. Mean DAS28(SD) score was 5.3(0.6) at baseline and 3.3(1.3) at 6 months' follow-up. The number of patients in remission was 2(8%) at 3 months and 9(35%) at 6 months' visit, respectively. Although levels of all selected cytokines decreased at 6 months' visit, only the changes at levels of MCP ($p=0.009$), IL10 ($p=0.005$) and IFNgamma ($p=0.005$) reached statistical significance. IL6 levels correlated with DAS28 at all visits ($r=0.334$, $p=0.003$). The baseline levels of VEGF, TNFalpha, IL6 and IL12 were found to be predictors of remission at 6 months according to DAS28 with an AUROC of 0.64 (95% confidence interval (CI) 0.4–0.9), 0.58 (95% CI: 0.4–0.8), 0.59 (95% CI: 0.4–0.8), 0.58 (95% CI: 0.3–0.8) respectively. Total GS score decreased significantly at both 3 (12.3 ± 7.2)($p<0.001$) and 6 months' visits (9.9 ± 6.6)($p<0.001$) compared to the baseline visit (21.2 ± 15.3). Similarly total PD score changes at both 3 (7.5 ± 4.4)($p=0.001$) and 6 months' visits (5.9 ± 4.1) ($p<0.001$) differed significantly from the baseline (16.7 ± 13.5). Total GS ($r=0.402$, $p<0.001$) and PD (0.455 $p<0.001$) scores correlated with DAS28 in all visits. However, only the levels of IL6 correlated with total GS ($r=0.544$, $p=0.009$) and total PD scores ($r=0.523$, $p=0.006$) among the selected biomarkers.

Conclusion: US findings and DAS28 correlated in all visits in our study, suggesting that both clinical and imaging follow-up is useful in monitoring RA patients before and after taking TNF antagonists. Although MCP, IFNgamma and IL10 serum levels decreased significantly at 6 months, IL6 seem to be the best cytokine for follow-up, correlating both with DAS28 and US findings. Baseline levels of VEGF, TNFalpha, IL6 and IL12 might also be appropriate for the prediction of remission during TNF antagonists.

Disclosure: N. Inanc: None; **A. Bulur:** None; **M. Can:** None; **O. Ergonul:** None; **P. Atagunduz:** None; **S. Yavuz:** None; **H. Direskeneli:** None.

1134

Therapeutic Potential of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Rheumatoid Arthritis. Yanying Liu, Rong Mu, Shiyao Wang and Zhanguo Li. Peking University People's Hospital

Introduction: Rheumatoid arthritis (RA) is a T-cell-mediated systematic autoimmune disease, characterized by synovium inflammation and articular destruction. Bone marrow mesenchymal stem cells could be effective in the treatment of several autoimmune diseases. However, there has been thus far no report on umbilical cord (UC)-MSCs in the treatment of RA. Here, potent immunosuppressive effects of human UC-MSCs in RA were evaluated.

Methods: The effects of UC-MSCs on responses of FLSs and T cells in RA patients were explored. The possible molecular mechanism mediating this immunosuppressive effect of UC-MSCs was explored by addition of inhibitors to indoleamine 2,3-dioxygenase (IDO), Nitric oxide (NO), prostaglandin E2 (PGE2), transforming growth factorβ1 (TGF-β1) and interleukin 10 (IL-10). The therapeutic effects of systemic infusion of human UC-MSCs in collagen-induced arthritis (CIA) in mice model were explored.

Results: In vitro, UC-MSCs were capable of inhibiting proliferation of FLSs from RA patients, via IL-10, IDO and TGF-β1. Furthermore, the invasive behavior and IL-6 secretion of FLSs were also significantly suppressed. Albeit inducing hyporesponsiveness of T cells mediated by PGE2, TGF-β1 and NO, UC-MSCs could promote the expansion of $CD4^+$ $Foxp3^+$ regulatory T cells from RA patients. More importantly, systemic infusion of human UC-MSCs reduced the severity of CIA in mice model. Consistently, there were reduced levels of proinflammatory cytokines and chemokines (TNF-α, IL-6 and MCP-1) and increased levels of the anti-inflammatory/regulatory cytokine (IL-10) in sera of UC-MSCs treated mice. Moreover, such treatment shifted Th1/Th2 type responses and induced Tregs in CIA.

Conclusions: In conclusion, human UC-MSCs suppressed the various inflammatory effects of FLSs and T cells of RA in vitro, and attenuated the development of CIA in vivo, strongly suggesting that UC-MSCs might be a therapeutic strategy in RA.

Disclosure: Y. Liu: None; **R. Mu:** None; **S. Wang:** None; **Z. Li:** None.

1135

TRA-8 (CS-1008), a Novel Anti-Arthritic Biologic Agent That Targets Macrophages with Low Toxicity. Jun Li[1], Hui-Chen Hsu[2], PingAr Yang[2], Qi Wu[2] and John D. Mountz[1]. [1]Division of Clinical Immunology and Rheumatology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [2]Division of Clinical Immunology and Rheumatology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL

Background: Macrophages contribute to joint inflammation and destruction in both the acute and chronic phases of rheumatoid arthritis (RA). However, biologic agents that can selectively eliminate pathogenic macrophages in RA have not been identified. Death receptor 5 (DR5) is a pro-apoptotic protein, which mediates apoptosis upon binding to a novel anti-human DR5 antibody, TRA-8 (humanized, CS-1008). We have found that macrophages isolated from both synovium and peripheral blood of RA patients express DR5 and are susceptible to TRA-8 mediated killing. The purpose of this study is to use a humanized DR5 transgenic mouse to evaluate the therapeutic efficacy of TRA-8 by eliminating pathogenic macrophages in a chicken collagen II (CII)-induced arthritis (CIA) model.

Methods: A chimeric human/mouse DR5 transgenic mouse was generated using a 3kb mouse promoter/*Floxed* STOP/humanized mouse DR5 construct in which the extracellular domain of mouse DR5 was replaced by the human counterpart. Macrophages specific expression of chimeric DR5 is achieved by crossing the DR5 mice with lysozyme M-Cre mice. Arthritis was induced by AdIL-17 at day −2 plus intradermal injection of CII in CFA/IFA on day 0 and day 30. TRA-8 (0.2 mg per mouse) was administrated I.V. every 3–7 days starting on day 0 (early treatment) or on day 30 (late treatment) until mice were sacrificed 3 months after the primary CII injection. Enumeration of macrophages before and after CII injection was determined by FACS analysis. *In vivo* joint macrophage activity was quantitated using an infrared cathespin B *in vivo* imaging analysis. Clinical scoring and histologic assessments were performed to evaluate the severity of arthritis.

Results: There was a higher percentage of $CD11b^+$ macrophages in the spleen of CII immunized mice (12.08%) compared to naïve mice (2.5%). Chimeric DR5 is highly expressed on $CD11b^+$ macrophage. TRA-8 treatment resulted in 60% and 48% reduction of $CD11b^{high}$ activated macrophages isolated from the spleen for early and late TRA-8 treatment, respectively. For both early and late TRA-8 treatments, joint histopathology showed a significantly decreased severity of inflammatory cell infiltration, synovial hyperplasia, cartilage damage, and bone erosion. Immunohistochemistry staining further demonstrated a dramatically reduced $Mac\text{-}3^+$ macrophages in the synovium after TRA-8 treatment. *In vivo* live imaging of joints revealed that there was a significantly decreased macrophage activation-induced cathepsin B activity in chimeric DR5 Tg mice that received TRA-8 treatment. The arthritis clinical scores were highly correlated with the abundance of macrophages in synovium and spleen. Neither systematic toxicities nor increased incidences of infections and malignancies were found in TRA-8 treated DR5 Tg mice.

Summary: This study demonstrated that TRA-8 (CS-1008) is a novel anti-arthritic biologic agent with high safety. Importantly, since the DR5 molecule is expressed on macrophages, our results suggest that TRA-8 can be developed into a novel therapy to either prevent the onset or suppress established arthritis via elimination of macrophages.

Disclosure: J. Li: None; **H.-C. Hsu:** None; **P. Yang:** None; **Q. Wu:** None; **J. D. Mountz:** None.

1136

Treat-To-Target for the Management of Rheumatoid Arthritis: A Validation Using Patient Reported Outcomes Data from Two Phase III Clinical Trials of Golimumab. Ed C. Keystone[6], Roy M. Fleischmann[4], Chenglong Han[3], Paul Emery[2], Mark C. Genovese[5], Timothy Gathany[3], Elizabeth C. Hsia[1] and Mahboob U. Rahman[1]. [1]Centocor Research and Development, Inc./Univ. of Pennsylvania School of Medicine, Malvern, PA, [2]Chapel Allerton Hospital, Leeds, United Kingdom, [3]Johnson and Johnson Pharmaceutical Services, LLC, [4]Rheumatology Associates, Dallas, TX, [5]Stanford University, Sunnyvale, CA, [6]University of Toronto, Toronto, ON, Canada

Objectives: To assess the impact of disease remission, a treatment target in the management of rheumatoid arthritis (RA) recommended by the International Task Force, on patient reported outcomes [1].

Methods: The efficacy and safety of golimumab (GLM) were assessed in methotrexate (MTX)-naïve RA patients (GO-BEFORE, N=637), and RA patients with inadequate response to MTX (GO-FORWARD, N=444). In both trials, patients with active RA were randomly assigned to placebo (PBO) +MTX, GLM 100mg+PBO, or GLM (50 or 100mg) +MTX, q 4 weeks. Clinical remission was defined as DAS28 (ESR) <2.6. Patient reported outcomes included physical function, quality of life, fatigue, pain and work productivity as measured using instruments of Health Assessment Questionnaire (HAQ), 36-item short-form health survey (SF36 PCS and MCS), Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Pain Severity Score of Brief Pain Inventory (BPI-Pain) and a visual analogue scale of daily work productivity. An ANOVA on van der Waerden normal scores or Chi-square test were performed for between-group comparisons.

Results: At week 24, a greater proportion of patients treated with GLM+MTX achieved DAS28<2.6 compared to patients treated with PBO+MTX (22.3% vs. 11.3% in GO- BEFORE, and 21.4% vs. 6.0% in GO-FORWARD, all $p<0.01$). GLM+MTX treated-patients had a greater improvement in patient reported outcomes than patients treated with PBO+MTX. The overall distribution of SF36-PCS shifted significantly towards a distribution observed in the normal population at week 24 through 104. Compared to patients without remission, more patients in remission at week 24 achieved a normal physical function (HAQ$\leq$0.5) (75.3% vs. 27.3%), a SF-36 PCS$\geq$50 (median value of general population) (48.3%, vs. 7.6%) and a SF-36 MCS$\geq$50 (median value of general population) (66.3% vs. 40.3%), regained employability (43.5% vs. 27.6%) and achieved significant improvement in work productivity (80% vs. 28.3%) from baseline (all p-values<0.01). Greater improvements (median) in FACIT-Fatigue (week 24: 12.0 vs. 4.0) and in BPI-Pain score (week 14: 2.1 vs. 0.8) were observed among patients in remission than patients without remission.

Conclusion: This analysis indicates that controlling disease activity in patients with RA is crucial to regaining a normal life. Thus DAS28 remission may be a reasonable target in the management of RA.

Reference:

1. JS Smolen, et al: Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010 69: 631–637.

Disclosure: E. C. Keystone: Centocor Research and Development, Inc., 2, 9; **R. M. Fleischmann:** Centocor Research and Development, Inc., 2, 9; **C. Han:** Johnson and Johnson Pharmaceutical Services, LLC, 3; **P. Emery:** Centocor Research and Development, Inc., 2, 9; **M. C. Genovese:** Centocor Research and Development, Inc., 2, 9; **T. Gathany:** Centocor Research and Development, Inc., 3; **E. C. Hsia:** Centocor Research and Development, Inc., 3; **M. U. Rahman:** Centocor Research and Development, Inc., 3.

1137 WITHDRAWN

1138

Validation of an Algorithm Using Genome-Wide SNP Analysis for Prediction of Responders, Non-Responders, and Adverse Events of Tocilizumab-Treated RA Patients Using Two Population Samples from Multiple Medical Cohorts. Tsukasa Matsubara[5], Satoru Koyano[10], Keiko Funahashi[10], Takafumi Hagiwara[6], Takako Miura[5], Kosuke Okuda[5], Akira Sagawa[11], Takeo Sakurai[2], Hiroaki Matsuno[7], Tomomaro Izumihara[3], Eisuke Shono[12], Kou Katayama[4], Toyomitsu Tsuchida[13], Mitsuhiro Iwahashi[1], Tomomi Tsuru[9] and Motohiro Oribe[8]. [1]Higashi-hiroshima Memorial Hospital, Higashihiroshima, Japan, [2]Inoue Hospital, Takasaki, Japan, [3]Izumihara Rheumatic and Medical Clinic, Kagoshima, Japan, [4]Katayama Orthopedic Reumatology Clonic, Asahikawa, Japan, [5]Matsubara Mayflower Hospital, Kato, Japan, [6]Matsubara Mayflower Hospital, Kato, Japan, [7]Matsuno Clinic for Rheumatic Diseases, Toyama, Japan, [8]Oribe Rheumatism and Internal Medicine Clinic, Oita, Japan, [9]PS Clinic, Fukuoka, Japan, [10]Research Institute of Joint Diseases, Kobe, Japan, [11]Sagawa Akira Rheumatology Clinic, Sapporo, Japan, [12]Shono Rheumatology Clinic, Fukuoka, Japan, [13]Tsuchida Clinic, Chiba, Japan

Purpose: Tocilizumab, a human anti-IL-6 receptor antibody, is an effective biologic agent for inflammatory diseases such as RA. However, there is no method for prediction of responders, non-responders, and adverse events which can occur during the treatment. We established and validated an SNP algorithm for prediction of responders or non-responders, and adverse events among tocilizumab-treated RA patients by using multiple medical cohorts.

Patients and Methods: Samples were obtained from RA patients who failed to the treatment with DMARDs including MTX. The first population sample included 106 RA patients and the second included 93 patients: a total of 199 patients from 11 hospitals in different regions of Japan. The efficacy was determined by Clinical Disease Activity Index (CDAI) within 24–30 weeks after the initial treatment. The efficacy of tocilizumab was judged by the scores of CDAI (remission and low disease activity group—'responders', moderate and high disease activity group—'non-responders'). Adverse events such as leukopenia, high total cholesterol, fever, and skin manifestations were documented. Genome-wide SNP genotyping was performed by Illumina HumanHap300K chip technology. Case-control analyses between 277,141 SNPs and responsiveness or occurrence of adverse events were examined by Fisher's exact tests. We selected 10 SNPs associated with tocilizumab-responsiveness, or adverse events which were common in analyses of both the first and second population ($p < 0.02$). We then scored the relationship between each SNP and responsiveness, the estimated total score of 10 SNPs (estimated scoring in each SNP was as follows: homo allele in the majority in responders: +1 point, hetero allele: 0 point, and homo allele in the majority of non-responders: −1 point), and examined relationships between responders and non-responders, or occurrence of adverse events plus or minus, and the total score.

Results: Accuracy ((true positive+true negative)/total), specificity (true negative/(false positive+true negative)) and sensitivity (true positive/(true positive+false negative)) of the algorithm for responsiveness of tocilizumab ranged from 87–92%. For adverse events, accuracy, specificity and sensitivity of the algorithm ranged from 85–91%. It is therefore suggested that the SNP algorithm can predict responders and adverse events prior to the initiation of treatment with tocilizumab.

Conclusion: This highly accurate algorithm using SNP analysis may be useful in the prediction of responsiveness and adverse events before treatment with tocilizumab, and in this way can contribute to future tailor-made treatment with biologic agents.

Disclosure: T. Matsubara: None; **S. Koyano:** None; **K. Funahashi:** None; **T. Hagiwara:** None; **T. Miura:** None; **K. Okuda:** None; **A. Sagawa:** None; **T. Sakurai:** None; **H. Matsuno:** None; **T. Izumihara:** None; **E. Shono:** None; **K. Katayama:** None; **T. Tsuchida:** None; **M. Iwahashi:** None; **T. Tsuru:** None; **M. Oribe:** None.

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1α,25-Dihydroxyvitamin D3 Suppresses Differentiation, Maturation and Activation of Dendritic Cells from Patients with Systemic Lupus Erythematosus. Hai Jing Wu, Chak Sing Lau and Mo Yin Mok. The University of Hong Kong, Queen Mary Hospital, Hong Kong

Background: Dendritic cells (DC), professional antigen presenting cells, are believed to play a crucial role in the pathogenesis of systemic lupus erythematosus (SLE). 1α,25-Dihydroxyvitamin D3 (VitD3), in addition to its effect on bone metabolism, has been increasingly recognized to have immunomodulatory action.

Objective: To examine the effect of VitD3 on the differentiation, maturation and activation of DCs in SLE patients.

Method: CD14+ monocyte derived-DCs from SLE patients and age- and sex- matched controls were derived from growth medium cultured with IL-4 and GM-CSF. Mature DCs were induced by addition of lipopolysaccharide (LPS) and tumour necrosis factor-α (TNF-α) in the presence or absence of VitD3 (1×10−10 M) and/or dexamethasone (1×10−6 M). The expression of CD1a and co-stimulatory molecules was examined by flow cytometry. After stimulation of DCs with CD40L transfected cell line for 24h, the production of pro-inflammatory cytokines including IL-12 and IL-6, were measured by ELISA kits.

Results: 50 SLE patients and 32 normal controls were studied. VitD3 was found to suppress differentiation of monocytes into DCs with lower level of expression of CD1a for both controls ($p<0.05$) and SLE patients ($p<0.01$) compared to untreated condition. With or without dexamethasone, VitD3 inhibited up-regulation of maturation markers, including CD86, CD40 and CD83 ($p<0.05$), but not CD80 and HLA-DR (Table 1&2). In terms of pro-inflammatory cytokine production, stimulated and unstimulated DCs produced less IL-12p70 and IL-6 in SLE patients as well as controls under the effect of VitD3 with or without dexamethasone compared to pre-treatment DCs.

Conclusion: VitD3 is found to inhibit differentiation, maturation and activation of DCs in vitro in both SLE patients and controls and may be considered as immunomodulatory agent in the treatment of SLE.

Disclosure: H. J. Wu: None; **C. S. Lau:** None; **M. Y. Mok:** None.

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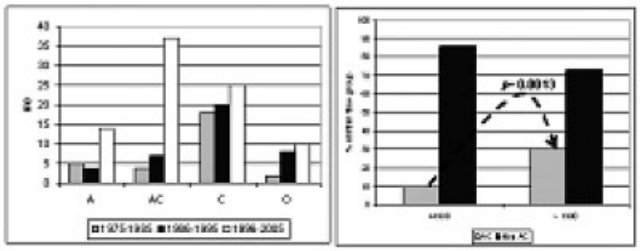
30-Year Follow-Up of Lupus Nephritis in a Single Clinic—Outcome, Serology and Ethnicity. Sara C. Croca[2], Teresa Rodrigues[1] and David A. Isenberg[3]. [1]Faculdade de Medicina de Lisboa, Laboratory of Biomathematics, Lisboa, Portugal, [2]Hospital de Santa Maria, Department of Medicine 1, Lisboa, Portugal, [3]UCL Div of Medicine, London, United Kingdom

Objectives: Although lupus nephritis (LN) represents one of the most common and potentially severe complications of systemic lupus erythematosus (SLE), there are few data on the very long-term follow up of these patients. Our aim was to characterize a LN cohort followed at a single centre for 30 years and assess its evolution over time.

Methods: Between 1975 and 2005, 156 patients were diagnosed as having LN at University College Hospital London (UCLH). We divided the cohort into 3 groups (1975–1985, 1986–1995 and 1996–2005), allowing for a minimum 5-year follow-up. The 3 groups were compared in terms of their clinical, demographic and serological characteristics, as well as disease outcome. Outcomes were defined as the 5-year mortality rate or end-stage renal disease (ESRD) development.

Results: Clinical characteristics were comparable between groups; however the proportion of Afrocaribbean (AC)-origin patients rose significantly over time accompanied by an increased prevalence of anti-ENA antibodies (ENAab). No other clinical association was found between the ENAab subgroups and ethnicity. In terms of outcome, AC-origin was associated with a poorer overall prognosis whereas no significant influence was linked to the other factors considered. The 5-year mortality rate decreased by 60% between the first and second decades and stabilised throughout the third. Disappointingly, the 5-years ESRD rate remained constant during time. An increasing number of renal transplants (RTx) was performed (n= 16, in table) with encouraging results, particularly when a living-related donor graft was used. The prognosis for the ESRD group was poorest for AC patients, with no other factors showing any influence.



Conclusions: LN is associated is a common complication of SLE associated with increased mortality and morbility, particularly among AC-origin patients. Despite encouraging results for RTX, once ESRD is established the prognosis is relatively poor and no improvement was achieved in preventing its development. Moreover, although a significant decrease in mortality was noted over the 3 decades, it has remained stable for 10 years. This result suggests that we have maximised the benefits of conventional therapies and, if further improvement is to be achieved, novel drug regimens must be considered.

Disclosure: S. C. Croca: None; **T. Rodrigues:** None; **D. A. Isenberg:** None.

1141

A Flow Cytometric Receptor Occupancy Assay Demonstrates Dose-Dependent Blockade of B7RP-1 by AMG 557 on Circulating B Cells from SLE Subjects. Barbara A. Sullivan[1], Cherie L. Green[2], Ming Zhang[1], Christina Abbott[1], Shelley Belouski[1], John Thomas[1], Kevin Gorski[1], Gerald Siu[3], James B. Chung[1] and John Ferbas[1]. [1]Amgen, Thousand Oaks, CA, [2]Amgen, Thousand Oaks, CA, [3]GlaxoSmithKline, Stevenage, United Kingdom

Background: Assessment of RO (receptor occupancy) is useful in drug development to confirm physical target coverage and support dose selection when combined with PK modeling. We describe a B7-related protein-1 (B7RP-1, B7h, ICOSL) FACS RO assay from initial experiments in SLE mouse models to validation and application to whole blood samples from subjects treated with a fully human IgG2 anti-B7RP-1 clinical candidate (AMG 557). B7RP-1 blockade in SLE is supported by the role of ICOS: B7RP-1 engagement in germinal center formation, B cell class switch recombination and antibody affinity maturation. Establishment of a correlation of B7RP-1 occupancy and efficacy with in vivo studies, including a murine lupus model, provided a rationale for incorporation of RO in an AMG 557 clinical trial.

Methods: *Preclinical*: NZB/W F1 mice were injected with 8, 1.5, or 0.3 mg/kg of 1B7-V2, 8 mg/kg mouse IgG1 isotype control or PBS once weekly for 23 weeks. RO was measured 3 months after starting treatment and just prior to the next dose; serum anti-dsDNA antibody levels were measured by ELISA as one measure of disease at 6 months. *Clinical:* Whole blood was collected from subjects in a Phase 1a single dose-escalating study of AMG 557. A four-color flow cytometric whole blood assay was constructed and validated to measure B7RP-1 on human circulating B cells. Antibody reagents directed against B7RP-1 were generated in-house according to standard procedures in mice and rats; all other antibodies were commercially available (Becton Dickinson, Inc, Immunotech S.A.).

Results: B7RP-1 RO on circulating B cells correlated with efficacy in the NZB/NZW F1 mouse model of lupus. For the clinical assay, two monoclonal antibodies from two immunization campaigns (mouse and rat) were chosen: one that competed with AMG 557 for B7RP-1 (Ab 1.64.1) and one that did not (Ab 3.7.1). These antibodies were fluorescently labeled for use in a 4-color FACS assay. The assay was validated by initially demonstrating selective inhibition of 1.64.1 binding to B cells in vitro (by AMG 557), followed by analysis of specimen stability and biological variability from ten healthy volunteers across three sequential visits. The RO assay was next implemented in the Phase 1a single dose-escalating study of AMG 557. The RO data from the clinical trial showed a reversible, dose-dependent coverage of B7RP-1 by AMG 557 in this single dose study. Moreover, measurement of receptor levels with antibody 3.7.1 indicated a dose-dependent transient rise in total B7RP-1 on circulating B cells in the treated subjects.

Conclusions: The RO assay demonstrated coverage of B7RP-1 on circulating B cells from SLE subjects after single dose administration of AMG 557 in a dose-dependent and reversible manner. Total receptor levels on the B cells increased in association with increasing occupancy in a dose dependent manner in keeping with preclinical observations in mouse studies. The relationship of receptor occupancy and pharmacodynamic effects in mouse models provides an important consideration for interpreting the RO results from the Phase 1 study and for guiding dose selection in future clinical trials of AMG 557.

Disclosure: B. A. Sullivan: Amgen Inc., 3; **C. L. Green:** Amgen Inc., 3; **M. Zhang:** Amgen Inc., 3; **C. Abbott:** Amgen Inc., 3; **S. Belouski:** Amgen Inc., 3; **J. Thomas:** Amgen Inc., 3; **K. Gorski:** Amgen Inc., 3; **G. Siu:** GlaxoSmithKline, 3; **J. B. Chung:** Amgen Inc., 3; **J. Ferbas:** Amgen Inc., 3.

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A Longitudinal Study of the Prolongation of the Corrected QT Interval in Anti-Ro/SSA Positive Adults with Systemic Lupus Erythematosus. Josiane Bourré-Tessier[3], Thao Huynh[5], Ann E. Clarke[4], Sasha R. Bernatsky[1], Lawrence Joseph[3], Patrick Belisle[3] and Christian A. Pineau[2]. [1]McGill UHC/RVH, Montreal, QC, Canada, [2]McGill Univ Health Center, Montreal, QC, Canada, [3]McGill University, [4]Montreal General Hospital, Montreal, QC, Canada, [5]Montreal General Hospital

Background: Electrocardiographic (ECG) abnormalities such as congenital heart block (CHB), bradycardia and prolongation of the corrected QT interval (QTc) are known to occur in newborns who passively acquired anti-Ro/SSA antibodies through maternal transfer. In adults, studies of the association between QTc prolongation and anti-Ro/SSA are conflicting. The goal of our study was to examine whether anti-Ro/SSA antibodies are associated with an increased risk of corrected QT (QTc) prolongation in a large systemic lupus erythematosus (SLE) cohort and to examine the stability of this relationship over a longitudinal follow-up period.

Methods: Two cross-sectional studies were conducted. Patients fulfilling ACR criteria for SLE were invited to undergo a 12-lead resting ECG between March 2002 and March 2005 in study 1, and between April 2005 and March 2006 in study 2. QTc's greater than or equal to 440msec were considered prolonged. Multivariate logistic regression models were performed to assess the association between anti-Ro/SSA and prolonged QTc. Other potentially associated factors examined included age, sex, disease duration, lupus activity (SLEDAI), damage (SLICC/ACR DI), potassium and magnesium levels and medications with the potential to prolong QTc interval (antimalarials, beta-blockers, antiarrhythmics, antibiotics, tricyclics and tetracyclics, selective serotonin reuptake inhibitors [SSRI], domperidone and human immunodeficiency virus [HIV] protease inhibitors).

Results: Study 1 included 150 subjects and study 2, 278 subjects. 118 subjects had participated in both studies, with a mean time (SD) of 505 (256) days between the 2 ECGs and of 512 (258) days between anti-Ro/SSA measurements. For these 118 subjects, most (92.4%) were female, the mean age at baseline was 45.4 years (14.2) and the mean lupus duration was 13.0 years (10.8). Mean SLEDAI was 3.3 (3.8) and median SLICC/ACR DI was 1.0 (interquartile range 0, 3). Cross-sectional analysis of prolonged QTc's on the presence of anti-Ro/SSA showed an OR (95%CI) of 12.6 (2.3–70.7) for the study 1, and of 5.1 (1.5–17.4) for the study 2. In the majority of subjects (75.4%), the anti-Ro/SSA and QTc status did not change over the observation interval. For 2 patients (1.7%), both QT and anti-Ro decreased and for one patient (0.9%), both increased. 25 patients (21.2%) changed only one of their status, and only a single participant (0.9%) had anti-Ro/SSa and QTc statuses that changed in an opposite direction (anti-Ro/SSA increased and QTc decreased).

Conclusion: The presence of anti-Ro/SSA antibodies was associated with QTc prolongation in a large SLE cohort. This cross-sectional relationship was preserved upon longitudinal follow-up. Since prolongation of the QTc is known to increase the risk of ventricular arrhythmias and sudden death, patients with anti-Ro/SSA may be exposed to a prolonged period of increased risk of cardiac events. ECG screening should be considered, so that patients

with QTc prolongation could receive appropriate counseling to avoid drugs that may put them at risk for life-threatening arrhythmias.

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Allogeneic Mesenchymal Stem Cells Transplantation in Severe and Refractory Systemic Lupus Erythematosus. Lingyun Sun[1], Dandan Wang[1], Huayong Zhang[1], Jun Liang[1], Xuebing Feng[1] and Yayi Hou[2]. [1]Department of Rheumatology and Immunology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, [2]Immunology Laboratory, Nanjing University Medical School

Objective: To assess the long-term efficacy and safety of allogenic bone marrow (BM) or umbilical cord (UC) mesenchymal stem cells transplantation (MSCT) for patients with severe and refractory systemic lupus erythematosus (SLE).

Methods: A single-arm trial involved 82 SLE patients, aged from 12 to 56 years old, average disease duration was 44 months. 24 patients were infused once with BM MSC, 50 patients received once UC MSC, while the other 8 patients received both MSC twicely. Allogeneic MSC were administered $\geq 1.0\times10^6$/body weight(KG)intravenously. BM MSC were aspirated from related healthy donors and expanded in vitro, and UC MSC were obtained from Stem Cell Center of Jiangsu Province of China. The clinical manifestations and laboratory parameters were compared pre- and post-MSCT, with a mean follow-up of 16.5 months (range, 3 to 36 months). Side effects were monitored all the time during and post-MSCT.

Results: Complete remission (CR) of disease activity (SLEDAI less than 3 and prednisone dose≤10mg/d) was seen in 9/41 (22%) patients 1 year post-MSCT and up to 9/16 (56%) and 3/5 (60%) at 2 and 3 years point respectively. Probability of disease relapse (DR) or unresponsive to MSCT (SLEDAI increased ≥3 and an increase in prednisone or immunosuppressive drug) was 8/41 (20%) at 1 year and 4/16 (25%) at 2 years visit. Of 5 patients completed 3 years visit, 2 of which with DR, and both were unresponsive to a second MSCT. The other 6 patients, who received second MSCT, reached to complete or partial remission. Significant improvements in SLEDAI score were examined 3 months (9.4±0.5) post-MSCT (n=82, $p<0.01$ *vs* pre-MSCT 14.0±0.6), and further decline in 1 and 2 years visit (4.9±0.4 *vs* 14.1±0.6, n=41 in 1 year, 3.6±0.6 *vs* 18.4±1.5, n=16 in 2 years, $p<0.01$). SLEDAI score <3 in 3 patients at 3 years visit. Amelioration of lupus nephritis was identified by the obvious decline of 24-hour proteinuria in 3 (1771±157mg *vs* 2799±152mg, n=64, $p<0.05$) and 6 months (1353±153mg *vs* 2584±179mg, n=31, $p<0.05$) visit, with further decline at 1 year visit (945±177mg *vs* 2045±112mg, n=20, $p<0.05$), and for 11 patients completed 2 years visit (989±289mg, $p<0.05$). Serology index showed serum albumin and complement C3 increased combined with decline of serum autoimmune antibodies. In addition, of 22 patients with moderate to severe hematological disorders, haematoglobin and/or platelet count reached to almost normal levels post-MSCT. Furthermore, 4 patients had central nervous system involvement (seizures, cerebralgia) with improvement and no relapsed post-MSCT. Significant improvements of glomerular filtration rate were found for 3 patients 12, 12, 20 months after MSCT respectively (from 65.23, 71.86, 23.45 ml/min to 94.45, 100.07, 69.82 ml/min). There was no difference in efficacy between BM and UC MSCT. Four patients died 5, 6, 6, 10 months post-MSCT respectively, due to uncontrolled infection or disease relapse. No transplant related mortality or any significant toxicity was observed and overall 3 years survival rate was 95% (78/82).

Conclusion: Allogeneic MSCT is safe and results in amelioration of disease activity. These data provide a foundation for conducting BM or UC MSCT for severe and treatment-refractory SLE.

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Analysis of the Use of Rituximab in the Treatment of Lupus Nephritis. Sara C. Croca[1] and David A. Isenberg[2]. [1]Hospital de Santa Maria, Department of Medicine 1, Lisbon, Portugal, [2]UCL Div of Medicine, London, United Kingdom

Background: Lupus nephritis (LN) represents one of the most common and potentially severe complications of systemic lupus erythematosus (SLE). Classical serological markers of disease activity include the erythrocyte sedimentation rate (ESR) and the levels of anti-dsDNA antibodies and C3. Other serological markers with potential prognostic value such as the anti-ENA antibodies (ENAab) have also been studied. As traditional therapies show their limitations in achieving rapid disease control and damage prevention, novel treatment approaches have emerged. Rituximab (RTX) is an anti-CD20 monoclonal antibody that has been widely reported to be effective in treating renal disease flares. Our published data (Lu et al, Arthritis Rheum 2009) indicates that clinical benefit is related to the period of B-cell depletion. In this study we have analysed this period in detail, trying to determine if there are correlations to standard lupus tests and ethnicity.

Methods: Between July 2001 and December 2009, 40 LN patients were treated with RTX at the University College Hospital London (UCLH). A minimum follow-up of 12 months was required for this study ($n=38$). Patients were assessed at baseline and at 6 months after RTX in terms of serological and renal profile. Response to treatment was defined as an absolute CD19 count < 0.005 and values above this were considered evidence of repopulation.

Results: Following the first RTX cycle, 89.47% ($n=34$) were successfully depleted (CD19< 0.005). After 6 months, only 32.35% ($n=11$) of these remained depleted. When comparing the depleted *vs.* the repopulated group, no differences were found in terms of the classical disease activity markers (ESR, anti-dsDNA and C3). Other serological markers such as the anti-C1q antibodies, ENAab and anti-cardiolipin antibodies also showed no association with depletion status. However, analysis of the ENAab subgroups showed that anti-Sm negative patients tend to remain depleted at 6 months. The baseline proteinuria and serum creatinine level also failed to influence response. In terms of ethnicity, Afro-caribbean origin patients were more likely to have repopulated at 6 months.

Conclusions: In the last 10 years, RTX has progressively shown its potential as an effective drug in the treatment of SLE flares. However, its use in the context of LN is not as well documented. Despite the limitations imposed by the small size of our sample, a few interesting results have emerged. Renal disease background and classical disease activity markers did not predict response to treatment. Other serological markers such anti-C1q antibodies, anticardiolipine antibodies and ENAab status are also irrelevant. However, anti-Sm positive patients seem to be more likely to repopulate. In addition, AC patients tend to have higher rates of repopulation. Thus, classical serological markers are of no use in predicting response to RTX, apart from anti-Sm antibodies which may be associated with earlier repopulation. Finding predictors of response is important in order to select the patients more likely to respond and identify those with a probable shorter term response allowing for closer monitoring.

Disclosure: S. C. Croca: None; **D. A. Isenberg:** None.

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Anti-Mullerian Hormone in Systemic Lupus Erythematodes – Is Fertility Affected? Joerg C. Henes[1], Melanie Henes[4], Tanja Fehm[4], Diethelm Wallwiener[4], Lothar Kanz[2], Ina Koetter[2] and Barbara Lawrenz[3]. [1]Department for Internal Medicine II; University Hospital Tuebingen, Tuebingen, Germany, [2]Department for Internal Medicine II; University Hospital Tuebingen, Germany, [3]Department of Gynecology and Obstetrics; University Hospital of Tuebingen, Germany, [4]Department of Gynecology and Obstetrics; University Hospital Tuebingen, Germany

Introduction: Systemic lupus erythematodes (SLE) usually manifests in women during their childbearing age. Women with SLE have a lower number of births compared to healthy controls although fertility is considered not to be reduced. Anti-Mullerian hormone is expressed in granulosa cells of growing follicles, reflects the size of the primordial follicle pool and therefore is used to assess fertility potential.

Method: Serum samples of 40 patients with SLE without previous cytotoxic – especially cyclophosphamid – treatment and 40 age matched, healthy controls were collected. All patients gave written informed consent and filled out a questionnaire on menstrual irregularities, lifestyle, pregnancy outcomes and contraception. AMH was quantified using a standard ELISA with standard value 1–8μg/l; values $< 1\mu$g/l defined as reduced, $< 0{,}4\mu$g/l as severely reduced fertility. Systemic lupus erythematosus disease activity index (SLEDAI) and European Consensus Lupus Activity Measurement (ECLAM) were used for clinical disease activity assessment.

Results: Median age was 29,5 (20–39) years. Disease activity was low to moderate with a median SLEDAI of 2 (0–17) and ECLAM of 1,75 (0–5). The median AMH level was 1,7 (0,01 – 15μg/l) and thus lower compared to historic control groups with 2,1 and 2,3 (1). In 30% (12 patients) AMH level

was below 1μg/l and in 6 even < 0,4μ/l. 8 patients were pregnant at the time of sample acquisition and patients had an average of 0,55 children.

Discussion: This is the first study to examine AMH levels in women with SLE. Lupus patients seem to have a reduced ovarian reserve and a reduced period of reproduction. As cytotoxic therapy is still standard for some SLE manifestations this data has an impact on fertility preservation strategies. Ovary protection during cytotoxic treatment is even more important in SLE patients.

Literature:

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Belimumab, a BLyS-Specific Inhibitor, Significantly Reduced Autoantibodies, Normalized Low Complement, and Reduced Selected B-Cell Populations in Patients with Seropositive Systemic Lupus Erythematosus (SLE): The Phase 3 BLISS Studies.

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Purpose: To assess the effects of belimumab on biomarkers, and B- and T-cell populations in patients with seropositive SLE.

Methods: In 2 randomized, double-blind, placebo-controlled phase 3 studies (BLISS-52, NCT00424476; and BLISS-76, NCT00410384),1684 seropositive (ANA ≥1:80 and/or anti-dsDNA ≥30 IU/mL) SLE patients with SELENA-SLEDAI ≥6 on stable standard-of-care (SOC) therapy ≥30 d received belimumab 1 or 10 mg/kg, or placebo, plus SOC, on d 0, 14, and 28, then q28d for 48 wk in BLISS-52 and 72 wk in BLISS-76. Immunoglobulin (Ig), complement (C), and autoantibodies (anti-dsDNA, ANA, anti-Sm, anti-CL, anti-ribosomal P) were evaluated. In addition, B- and T-cell subsets were evaluated in BLISS-76.

Results: Overall, belimumab treatment reduced autoimmune antibody titers and promoted conversion from antibody seropositive to seronegative status (table). More patients treated with belimumab converted from positive to negative for anti-dsDNA, anti-Sm, anti-ribosomal P, and aCL-IgG compared with placebo. Belimumab-treated patients had significantly greater increases in C3 and C4 levels with a dose response; patients receiving 10 mg/kg had significantly greater increases at every visit through wk 52 and a greater % achieved normalized levels (table). Normalization of hypergammaglobulinemia (≥16.2 g/L) occurred in significantly more patients in the 2 belimumab groups vs placebo (49.2% vs 19.7%; table). Belimumab significantly reduced various circulating B-cell subsets, but not T-cell subsets. Reductions in naïve B-cells and short-lived plasma cells ($CD20^{-}/27^{BRIGHT}$), as well as the SLE B-cell subset ($CD19^{+}/27^{BRIGHT}/38^{BRIGHT}$), were observed as early as wk 8 with the 10-mg/kg dose. Memory B-cells increased ~100% by wk 8 and gradually decreased toward baseline levels through wk 52. A modest expansion of T-cell subsets was observed at wk 52, but this is considered to be a secondary effect of the B-cell reductions.

Conclusions: In these phase 3 studies, belimumab treatment led to rapid, significant, and sustained reductions in autoantibodies, and normalization of C3, C4, and hypergammaglobulinemia compared with placebo. These findings, and the selective reduction of B-cell and short-lived plasma cell subsets, are all consistent with the mechanism of action of belimumab.

Table. Biomarker Data at Wk 52

	SOC + Placebo n=562	SOC + Belimumab 1 mg/kg n=559	SOC + Belimumab 10 mg/kg n=563
Autoantibodies shift from positive at baseline to negative at wk 52			
Anti-dsDNA[a]			
Positive patients, median % change	−10.2	−36.6*	−40.8*
Positive to negative	19/280 (6.8%)	47/314 (15.0%)***	50/313 (16.0%)***
Negative to positive	14/143 (9.8%)	9/134 (6.7%)	4/134 (3.0%)*
Anti-Sm[b]			
Positive patients, median % change	−29.6	−39.1**	−53.6*
Positive to negative	22/120 (18.3%)	32/125 (25.6%)	42/131 (32.1%)*
aCL IgG[c]			
Positive patients, median % change	−22.7	−30.8*	−32.1*
Positive to negative	34/85 (40.0%)	63/96 (65.6%)***	48/86 (55.8%)*
Anti-ribosomal P[d]			
Positive patients, median % change	−8.2	−35.7**	−54.0*
Positive to negative	16/74 (21.6%)	25/69 (36.2%)	31/60 (51.7%)***
Normalization of low complement at wk 52			
C3[e]	**n=176**	**n=193**	**n=202**
Median % change	2.2%	14.7%*	17.0%*
% normalized	30/176 (17.0%)	51/193 (26.4%)*	77/202 (38.1%)*
C4[f]	**n=218**	**n=246**	**n=259**
Median % change	12.9%	37.5%*	50.0%*
% normalized	40/218 (18.3%)	86/246 (35.0%)*	115/259 (44.4%)*
Ig at wk 52			
IgG	**n=424**	**n=447**	**n=448**
Median % change from baseline	−2.5%	−13.8%*	−15.3%*
% normalized	38/193 (19.7%)	91/185 (49.2%)*	97/197 (49.2%)*
B-cell, median % change at wk 52	**n=275**	**n=271**	**n=273**
CD20+	−9.17%	−46.1%*	−46.1%*
CD20+/69+ activated	−15.8%	−40.5%	−45.1%*
CD20+/27+ memory	0.0%	50.0%*	35.3%*
CD20+/27− naïve	−8.9%	−66.7%*	−69.6%*
$CD20-/27^{BRIGHT}$ plasma	−1.2%	−11.3%	−35.4%**
CD20−/138+ plasma	−0.3%	−21.6%	−34.9%**
CD20+/138+ plasmacytoid	−14.4%	−50.6%***	−64.4%*
$CD19+/27^{BRIGHT}/38^{BRIGHT}$	6.1%	−23.7%	−38.5%***
T-cell, median % change at wk 52	**n=275**	**n=271**	**n=273**
CD3+/4+	−2.6%	15.1%***	9.5%*
CD3+/8+	−3.2%	10.0%***	10.8%**
CD3+	−4.2%	11.8%***	11.9%**
CD4/CD8R	1.9%	3.9%	3.7%

[a]Anti-dsDNA; positive (≥30 IU/mL), negative (<30 IU/mL); [b]anti-Sm: positive (≥15 U/mL), negative (<15 U/mL); [c]aCL IgG: positive (≥10 GPL U/mL), negative (<10 GPL U/mL); [d]anti-ribosomal P: positive (>25 EU/mL), negative (≤25 EU/mL); [e]C3: normal/high (≥900 mg/L), low (<900 mg/L); [f]C4: normal/low (≤16 mg/dL), high (>16 mg/dL).
*p < 0.05, **p < 0.01, ***p < 0.001, *p<0.0001.

Disclosure: W. Stohl: Human Genome Sciences, Inc., 2, 9; **F. Hiepe:** GlaxoSmithKline, 5, Human Genome Sciences, Inc., 9; **M. Thomas:** Human Genome Sciences, Inc., 9; **M. A. Scheinberg:** Human Genome Sciences, Inc., 9; **A. E. Clarke:** GlaxoSmithKline, 5, Human Genome Sciences, Inc., 9; **C. Aranow:** Human Genome Sciences, Inc., 9; **R. Jimenez:** Human Genome Sciences, Inc., 2, 5, 9; **F. Wellborne:** Human Genome Sciences, Inc., 9; **C. Abud-Mendoza:** Human Genome Sciences, Inc., 9; **D. Hough:** Human Genome Sciences, Inc., 1, 3; **L. Pineda:** Human Genome Sciences, Inc., 1, 3; **T. S. Migone:** Human Genome Sciences, Inc., 1, 3; **W. Freimuth:** Human Genome Sciences, Inc., 1, 3; **W. W. Chatham:** Human Genome Sciences, Inc., 2, 9; **on Behalf of the BLISS-52 and -76 Study Group:** None.

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Comparison of Serum Free Light Chains, Interferon and Interleukins as Biomarkers of Disease Activity in Systemic Lupus Erythematosus (SLE).

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Background: SLE may affect any organ and is associated with significant morbidity and mortality. Other than DsDNA in the context of Lupus nephritis, studies thus far exploring a biomarker for disease flare have been equivocal. We previously reported superior utility of serum free light Chains (FLC) compared to DsDNA and IgG as biomarkers for disease activity in SLE. We also reported that Total FLC (TFLC) elevation was greater in SLE as compared to rheumatoid arthritis, and that its association with disease

activity was stronger in SLE than rheumatoid arthritis. There have been studies by other authors showing association of Interleukin-6 (IL-6), Interleukin-10 (IL-10) and Interferonα (IFN-α) with SLE disease activity. Herein, we compare the utility of total FLC with IL-6, IL-10 and IFN- α for disease activity in SLE.

Aims: To determine the association of (1)serum TFLC with IL-6, IL-10 and IFN-α (2)to compare their association of disease activity, demographic variables (age. gender and ethnicity), immunosuppressive agents and ACR criteria.

Methods: This is a cross-sectional study of 134 SLE patients (ACR criteria) recruited from a University Center from 2008–2010. PGA and SLEDAI were assessed by the same physician. Adjusted SLEDAI was calculated by deleting DsDNA and complement items from the SLEDAI. Serum was tested for TFLC (The Binding Site U.K), IL-6, IL-10 and IFN-α. Chart review was done for demographics, clinical and serological characteristics and treatment. Statistical analysis performed included correlation analysis, Mann Whitney test.

Results: Mean age of the patients was 43$\pm$12 yrs; females composed 91% of the study group; African American 50%, Caucasians 24%,Hispanic 16%. PGA (Mean$\pm$SD, Median) was 0.5$\pm$0.6, 0, while SLEDAI was 4$\pm$4, 2. Forty eight percent patients were on prednisone. The (mean$\pm$SD, median) values were: TLC (58$\pm$64, 43), IL-6 (6$\pm$7, 4), IL-10 (16$\pm$20, 13) and IFN-α (21$\pm$39, 4). TFLC was correlated with IFN-α (r=0.37, p=0.0001) and IL-6 (r=0.25, p=0.009). IFN-α correlated with IL-6 (r=0.20, p=0.05).

TFLC showed a moderate correlation with PGA (r=0.39, p=0.002), SLEDAI (r=0.35, p=0.001) and adjusted SLEDAI (r=0.34, p=0.005). IL-10 was moderately associated with adjusted SLEDAI (r=0.32, p=0.02). IL-6 weakly correlated with SLEDAI (r=0.23, p=0.04) but not with adjusted SLEDAI. IFN-α was not associated with either of them.

IFN-α correlated with age (r=0.22, p=0.02), while IL-6 correlated with height (r=0.22, p=0.04). TFLC, IFN- α and IL-6 showed correlation with ethnicity. TFLC correlated with use of prednisone (r=0.30, p=0.001) while IFN-α correlated with use of methotrexate (r=0.20, p=0.04).

Conclusion: Serum TFLC is moderately correlated with PGA and adjusted SLEDAI. Strength of TFLC association with adjusted SLEDAI is greater than observed with IL-10. Longitudinal studies to determine if changes in disease activity result in changes in TFLC are now indicated.

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Coronary Calcification in SLE: Comparison with Multi-Ethnic Study of Atherosclerosis (MESA). Adnan N. Kiani[3], Wendy Post[4], Moyses Szklo[2], Joan M. Bathon[4], Laurence S. Magder[6], Russell Tracy[8], Pamela Schreiner[7], Daniel O'Leary[5] and Michelle A. Petri[1]. [1]Timonium, MD, [2]Johns Hopkins University, Department of Epidemiology, [3]Johns Hopkins University, School of Medicine, Baltimore, MD, [4]Johns Hopkins University, School of Medicine, [5]Tufts University, [6]University of Maryland, [7]University of Minnesota, [8]University of Vermont

Objectives: Women with lupus (SLE) have been demonstrated to have a marked increase in risk for myocardial infarction compared with the general population. CT coronary artery calcium (CAC) is a measure of subclinical atherosclerosis associated with risk for cardiovascular (CV) events in women with SLE. The purpose of this study was to determine whether the prevalence of CAC is higher in female SLE patients compared with the participants in the Multi-Ethnic Study of Atherosclerosis (MESA) who were free of CV events and SLE at the baseline exam.

Methods: CAC was measured in 88 female SLE patients enrolled in the Lupus Atherosclerosis Prevention Study (LAPS) and 583 female MESA controls from the Baltimore Field Center aged $\geq$ 45 years without evidence of clinical cardiovascular disease. Poisson regression with robust variance estimation was used to estimate the ratio of CAC prevalence between SLE and MESA controls, controlling for demographic and CV risk factors.

Results: Mean ages were 53.8 (SD=7.1) years (SLE) and 63.3 (SD=10.1) (MESA). 28 percent of SLE and 55 percent of controls were African-American. Sixty percent of SLE and forty seven percent of MESA controls had coronary calcification. In all age groups, SLE patients had a higher prevalence of CAC than MESA controls (Table1).

Table 1. Proportion (%) with coronary artery calcium (>0), by study group and age

Age Group	SLE Patients (n=88)	MESA Controls (n=583)
45–54	33/57 (58%)	31/144 (22%)
55–64	13/22 (59%)	52/144 (36%)
65–74	5/7 (71%)	120/211 (57%)
75+	2/2 (100%)	70/84 (83%)

After controlling for age, ethnicity, diabetes, hypertension, hyperlipidemia, smoking, education, and BMI, SLE patients had a significantly higher prevalence of CAC than controls (Prevalence Ratio 1.8 (1.5, 2.3)) (Table 2).

Table 2. Association between predictors and presence of coronary calcium based on a multivariable prevalence-ratio regression model.

Variable	Prevalence Ratio (95% CI)	P-value
SLE patients vs. MESA controls	1.8 (1.4, 2.3)	<0.0001
Age (per 10 years of life)	1.5 (1.4, 1.6)	<0.0001
Caucasian vs. NonCaucasian	1.3 (1.1, 1.5)	0.0013
Diabetes	1.2 (1.0, 1.5)	0.042
Total cholesterol >200 mg/dl	1.0 (0.9, 1.2)	0.65
Hypertension	1.2 (1.0, 1.4)	0.020
Ever smoked	1.3 (1.2, 1.5)	0.0001
BMI 25–29 vs. <25	1.0 (0.9, 1.3)	0.67
BMI 30+ vs. <25	1.1 (0.9, 1.4)	0.24

Conclusion: SLE is associated with a greater prevalence of CAC in women than MESA controls even after adjusting for traditional cardiovascular risk factors. We previously demonstrated that inflammatory markers and degree of disease activity are not associated with CAC in SLE. Future studies are needed to determine the etiology of increased subclinical atherosclerosis in this population.

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Decrease in Complement (C3) Levels during Systemic Lupus Erythematosus Pregnancy Is Associated with Higher Rates of Pre-Eclampsia. Aisha Lateef[2], Laurence S. Magder[3] and Michelle A. Petri[1]. [1]Johns Hopkins Lupus Center, School of Medicine, Johns Hopkins University, Timonium, MD, [2]National University Health System, Singapore, Singapore, [3]University of Maryland Medical School, Baltimore, MD

Objective: To determine the changes in complement (C3 and C4) levels during pregnancy in women with systemic lupus erythematosus (SLE), and to evaluate the association between these changes and adverse pregnancy outcomes.

Methods We reviewed all pregnancies in a cohort of SLE patients who were observed prospectively from 1987 to 2009. Four hundred and twenty nine pregnancies were recorded in 352 women. We calculated the mean value of C3 and C4 during the first and second halves of the pregnancy. The change in C3 and C4 was evaluated by subtracting the mean C3 and C4 during the first half from the mean C3 and C4 during the second half of pregnancy. This analysis is based on 296 pregnancies, with both a first-half and second-half value of C3 and C4.

We investigated if pregnancy outcomes, including miscarriage, pre-eclampsia, gestational age, birth weight, pre-term birth and intra-uterine growth restriction(IUGR) were associated with the change in C3 and C4 levels during pregnancy.

Results: C3 levels increased (greater than 3 point rise) during the second half of pregnancy in 211 (71%), decreased (greater than 3 point drop) in 50 (17%) and remained stable in 35 (12%) of pregnancies. C4 levels increased (greater than 1 point rise) in 115 (39%), decreased (greater than 1 point drop) in 93 (31%) and remained stable in 88 (30%) of pregnancies.

Pre-eclampsia was noted in 12 out of 50 (26%) pregnancies where C3 levels decreased during pregnancy. In contrast, only 15 out of 211 (7%) pregnancies were complicated by pre-eclampsia if the C3 levels increased during pregnancy. The difference reached statistical significance (p <0.01), after adjusting for age, race, use of steroids, plaquenil and immunosuppressants. There was a trend towards lower gestational age at birth, (35.9 weeks in group with lower C3 versus 37.0 weeks with higher C3 in second half of pregnancy), but the difference was not statistically significant (p=0.16). Miscarriages, pre-term births, IUGR and birth weight were similar among the different groups (Table). No significant differences in pregnancy outcomes were noted among groups with increased or decreased C4 levels during pregnancy.

Conclusion: Complement levels generally rise during normal pregnancies. Similarly, SLE pregnancies with stable disease tend to have higher levels of complement during pregnancy. In our cohort, 71% of the pregnancies had

a rise in C3 levels, while only 17% had a decline.Decreasing C3 levels during pregnancy were predictive of a higher rate of pre-eclampsia, compared to stable or rising C3 levels. The risk of pre-eclampsia is higher in SLE pregnancies, occurring in 22–30% of pregnancies, compared to 5–7% of normal pregnancies. Earlier studies have suggested renal disease, thrombocytopenia and anti-phospholipid antibodies to be the predictors of pre-eclampsia in SLE. Our study suggests that a declining trend of C3 level is another risk factor for pre-eclampsia.

	Number (%) with the outcome, by change in C3			
Outcome	Decrease in C3 more than 3 points (n=50)	Change of 3 or fewer points (n=35)	Increase in C3 more than 3 points (n=211)	P-value
Miscarriage	3 (6%)	4 (11%)	3 (1%)	Too few
Preterm	16 (37%)	9 (28%)	70 (35%)	.34
Pre-eclampsia	12 (26%)	1 (3%)	15 (7%)	.0061
IUGR	4 (9%)	2 (6%)	13 (6%)	.82
OLIGO	6 (14%)	2 (6%)	21 (10%)	.55

Disclosure: A. Lateef: None; **L. S. Magder:** None; **M. A. Petri:** None.

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Dendritic Cells and Regulatory T CD4+CD25^{Bright} in Pregnant Patients with Systemic Lupus Erythematosus. Luis J. Jara[1], Griselda Teresa Romero-Sánchez[1], Laura A. Montiel-Cervantes[1], Gabriela Medina[1], Polita Cruz-Cruz[2], Jorge Vela-Ojeda[1], Rafael Arias-Flores[1], Olga Vera-Lastra[1] and Miguel A. Saavedra Salinas[1]. [1]Hospital de Especialidades Centro Medico La Raza, IMSS, Mexico City, DF, Mexico, [2]Hospital de Gineco-Obstetricia No.3, Centro Medico La Raza, IMSS, Mexico City, DF, Mexico

Introduction: During pregnancy, dendritic cells (DC) participate in the shift from T-helper 1 (Th1) to T-helper 2 (Th2) activity. Myeloid DC induce Th1 cell differentiation, and plasmacytoid DC induce Th2 cell differentiation. On the other hand, CD4+ CD25^{bright} + FOXP3+ T regulatory cells (Treg cells) are CD4+ T cells with suppressive properties. An inadequate expression of Treg cells is associated with obstetric complications. Therefore, Treg/DC maintain maternal-fetal tolerance. However, their role in systemic lupus erythematosus (SLE) and pregnancy remains unknown.

Objective: To analyze the changes of DC and Treg cells in the peripheral blood of pregnant SLE patients in comparison with normal pregnancy. To correlate these alterations with clinical activity and maternal-fetal complications of SLE patients.

Material and Methods: Fifty pregnant, 25 with SLE (mean age 26.6+−6 years), and 25 pregnant healthy as controls (mean age 27.8+−5 years) were enrolled in the study. The majority of SLE patients were treated with low doses of prednisone (96%) and chloroquine (68 %). Mononuclear cells of peripheral blood were obtained during pregnancy (each trimester) and postpartum. The subtypes of DC and Treg cells from whole blood samples were analyzed as previously described. A total of 100 microlitres of whole blood was incubated with 20 microlitres of monoclonal specific antibodies: For DC Lin1-FITC, CD123-PE, HLADR-PERCP, CD11C-APC for determination of CD1(Myeloid DC), and CD2 (plasmacytoid DC). For Treg: FoxP3, CD4 PerPC, CD25 APC. The antibodies and cells were incubated for 25 min at room temperature in a dark room. Labeled cells were analyzed with the program Cell Quest pro, using FACSCalibur BD flow cytometer. We used SLAM-M modified to measured SLE activity during pregnancy. Statistic analysis: Mann-Whitney U test, Spearman correlation, and logistic regression.

Results: Fetal loss (2), pre-eclampsia (2), and abortion (2) were observed in SLE patients. No maternal-fetal complications were observed in controls. During pregnancy, decrease tendencies of percentages of CD1, and Treg were observed in SLE patients vs controls: CD1, 35.2+−42 vs 58.3+ −44 ($p<0.06$), and Treg, 53.9+ −56 vs 89.8+ −133 ($p<0.2$), with a significant decrease of CD2, 9.9+−8 vs 26.6+−25 ($p< 0.003$), respectively. In postpartum, a significant decrease of CD1 was observed in SLE patients: pregnancy SLE, 40.2+−35 vs postpartum SLE, 17.7+−17 ($p< 0.05$) without significant differences in CD2 and Treg. A direct correlation between CD1 and CD2 ($r=0.58$, $p< 0.001$), CD1 and Treg ($r=0.65$, $p< 0.0001$), and CD2 and Treg ($r= 0.27$, $p<0.05$) was found in SLE patients. In normal controls we did not observed a correlation among subpopulations of CD, and Treg. We did not observe a direct correlation among CD1, CD2, and Treg with SLAM-M in SLE patients.

Conclusions: The significant decrease of CD2 during pregnancy, and CD1 in postpartum of SLE patients, with positive correlation among CD1, CD2, and Treg without correlations with SLE activity may reflect the immunological and subclinical activity of SLE. These alterations may be associated with maternal-fetal complications observed in these patients despite of treatment.

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Distinctions in the ISN/RPS 2003 Subclasses of Class IV Lupus Nephritis. Suhail Hameed[2], Kun Chen[2], Surya Seshan[3] and Michael D. Lockshin[1]. [1]Hosp for Spec Surgery, Cornell, New York, NY, [2]Hospital for Special Surgery, Cornell, New York, NY, [3]Weill Cornell Medical Center

Purpose: We hypothesized that the ISN/RPS 2003 classification subclasses of Class IV Lupus Nephritis (LN) better correlate with respect to clinical, morphological and prognostic distinctions. The distinction between the subclass IV-Segmental (IV-S) and IV-Global (IV-G) has been the subject of a few prior studies without a consensus in conclusions. Whether this distinction between IV-S and IV-G will be retained in future iterations of ISN/RPS classification will depend on how distinct these subclasses prove to be.

Methods: This is a single institution retrospective study comparing the ISN/RPS 2003 Class IV LN subclasses. 95 SLE patients who had biopsy diagnosed Class IV LN from 1990 to 2007 and had clinical follow-up at our institutions were included.

All renal biopsies were reclassified according to the ISN/RPS 2003 LN classification by a single renal pathologist. Relevant clinical data was collected from the medical records of the subjects. The investigators were blinded to the histopathologic and clinical data of the subjects until all data collection was complete. A comparison of IV-S and IV-G with respect to clinical, morphological and pre-defined outcome measures was made. Independent samples t-test for means, Fischer's exact test and Kaplan-Meier survival curves were performed for statistical analysis.

Results: Out of the 95 Class IV LN patients, there were 58 G (61%) and 37 S (39%). Overall, there were 82.8% females and 17.2% males with 16.7% Caucasians, 30.8% African Americans, 34.6% Hispanics and 17.9% Asians. 53.7% had Medicaid and 46.3% had private medical insurance.

The mean duration of follow-up since renal biopsy was 93.79 months and mean duration of SLE at diagnosis of lupus nephritis was 50.30 months. The mean age at diagnosis of SLE was 22.13 years and mean age at diagnosis of LN was 26.42 years. Significant clinical and histopathologic distinctions in ISN/RPS 2003 subclasses of Class IV LN were noted as shown in figure 1.

Figure 1. Shows significant clinical and histopathologic distinctions in ISN/RPS 2003 Subclasses of Class IV LN

Clinical Distinctions	ISN/RPS 2003 Class IV LN Subclass		
Mean baseline clinical characteristics	Segmental	Global	p-value
Hematocrit (%)	31.90	29.59	0.057
Lymphocyte (%)	13.12	20.59	0.001
Neutrophil (%)	79.93	71.20	0.001
Serum abumin (G/dl)	2.72	2.49	0.034
Urine protein (gm/24hr)	3.44	4.78	0.055
C3 (mg/dL)	62.26	47.42	0.003

Histopathologic Distinctions	ISN/RPS 2003 Class IV LN Subclass		
Histopathologic characteristics (% Present)	Segmental	Global	p-value
Segmental Cellular Proliferation	91.9	6.9	<0.001
Global Cellular Proliferation	2.7	94.8	<0.001
Segmental Glomerulosclerosis	45.9	13.8	0.001
Global Glomerulosclerosis	45.9	29.3	0.099
Fibrous Crescerts	43.2	22.4	0.032
Interstitial Fibrosis	64.9	43.1	0.038
Tubular Atrophy	67.6	50.0	0.092
Wire Loops	27.0	81.0	<0.001
Hyaline Thrombi	2.7	41.4	<0.001

Activity and Chronicity Distinctions	ISN/RPS 2003 Class IV LN Subclass		
Mean Activity and Chronicity Indices Scores	Segmental	Global	p-value
Activity Index	8.22	10.55	0.004
Chronicity Index	3.43	1.83	0.001

Subclass G had hypocomplementemia, hypoalbuminemia, increased proteinuria, hyaline thrombi, wire loops and higher activity index, implying an immune complex etiopathogenesis. Subclass S had higher hematocrit, relative lymphopenia and neutrophilia, higher chronicity, glomerulosclerosis and fibrosis suggesting more of a pauci-immune and relapsing process. Subclasses S and G had similar outcomes and there was no statistically significant difference in any of the pre-defined outcome measures including remission, relapse, doubling of serum creatinine, ESRD and death.

Conclusion: S and G are clinically and morphologically distinct subclasses of Class IV LN suggesting different underlying pathogenetic mechanisms. Currently the 2003 ISN/RPS classification does not distinguish the prognosis of subclass S from G. Therapeutic advances targeting the different pathogenetic mechanisms for these subclasses, might yield a change in their prognosis.

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Does Smoking Influence Disease Manifestations and Disease Severity in Systemic Lupus Erythematosus? Nayef Al Ghanim[2], Aqeel Ghanem[2], Ebrahim Nahar[1], John M. Esdaile[2] and Diane Lacaille[2]. [1]Mubarak Al Kabeer Hospital, Vancouver, BC, Canada, [2]University of British Columbia, Vancouver, BC, Canada

Objective: Several studies have established that smoking is a risk factor for Systemic Lupus Erythematous (SLE). However, few studies have evaluated whether smoking influences disease manifestations or disease activity and severity.

The objective of our study was to evaluate whether smoking is associated with differences in pattern of organ involvement and with greater disease severity, as measured by the SLICC.

Method: A retrospective medical chart review was conducted between 2002 and 2005 of all SLE patients seen since 1990 from eight rheumatology practices. All patients included met the 1982 ACR criteria for SLE. Data were extracted on: demographics, SLE duration, SLE treatment, SLICC, and organ involvement using predefined criteria derived from the SLAM, and current smoking status at baseline (ie time of first rheumatologist visit). Smokers and non-smokers were compared using Chi-square for categorical variables and Student t-test for continuous variables. To take into account the multiple comparisons tested, we considered $p < 0.01$ as statistically significant. SLICC score, because of its skewed distribution, was analyzed as a binary variable with a cut off of 2 (i.e. values of 0 or 1 vs. values of 2 or greater). Multivariable binary logistic regression analysis was performed with SLICC score as the dependent variable, controlling for SLE duration, age, gender, and ethnicity.

Results: Our sample included 306 patients, 52 were smokers and 254 non-smokers (92% women, mean (SD) age 43.3 (12.9) years, disease duration 12.2 (8.8) years). No significant differences were observed in the pattern of organ involvement between smokers and non-smokers (Table 1). A trend was observed with smokers having increased frequency of antiphospholipid syndrome (APLS) compared to non-smokers (31.4% vs 16.9%, respectively. $p = 0.03$). However, it did not reach statistical significance at the preselected level of $p < 0.01$. No difference was observed in the medications received for SLE, such as glucocorticosteroids or immunosuppressant medications (data not shown). After adjusting for age, gender, disease duration and ethnicity, the likelihood of severe disease, as measured by SLICC >= 2, was not increased in smokers compared to non-smokers (OR: 1.18, 95% CI: 0.56–2.46).

Conclusion: In our sample of SLE patients, there was no association between smoking and the pattern of organ involvement or disease severity measured by SLICC.

Organ involvement	Non - smokers (n=254)	Smokers (n=52)	p value
Mucocutaneous	216 (85%)	47 (92%)	0.26
MSK	228 (90%)	46 (90%)	1
Renal	89 (36%)	12 (25%)	0.13
CNS	140 (55%)	30 (59%)	0.64
Hematological	220 (87%)	38 (75%)	0.03
APLS	43 (17%)	16 (31%)	0.03
Pulmonary	85 (34%)	23 (45%)	0.14
Cardiac	52 (21%)	8 (16%)	0.56
GI	8 (3%)	1 (2%)	1

Abbreviations: MSK: Musculoskeletal; CNS: Central Nervous System; APLS: Antiphospholipid syndrome; GI: Gastrointestinal

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Early Treatment with Rituximab (RTX) in Newly Diagnosed Systemic Lupus Erythematosus (SLE) Patients: A Steroid Sparing Regimen. Amara N. Ezeonyeji[2] and David A. Isenberg[1]. [1]UCL Div of Medicine, Room 331, 3rd Floor, London, United Kingdom, [2]University College London Hospital NHS Trust, London, United Kingdom

Introduction: The efficacy of a RTX as induction therapy enabling long-term steroid therapy reduction or withdrawal has recently been reported in patients with lupus nephritis by Pepper et al.[1] We describe a RTX/Azathiaprine (AZA) based steroid sparing regimen given in 9 newly diagnosed mostly non-renal patients with SLE.

Patients and Methods: Nine female patients fulfilling at least 4 of the revised ACR criteria for the diagnosis of SLE were treated. Mean age at time of B cell depletion therapy was 39 years, Mean duration of symptoms prior to treatment was 16.5 months (range 4–96). Eight were treated with two intra-venous (iv) infusions of RTX (1000mg) and methylprednsiolone (2 × 100mg) and one iv 750mg infusion of cyclophosphamide (CYC). One patient received 375mg/m^2 equivalence RTX over 3 weeks with CYC. Post treatment all patients received AZA and any steroid treatment rapidly weaned [table 1]. The British Isles Lupus Assessment Group (BILAG) disease activity index was used for both individual organ system assessment and as a global index. The patients full blood count, serum creatinine (Cr), serum C3, immunoglobulin G (IgG), erythrocyte sedimentation rate (ESR), anti-dsDNA and circulating B lymphocytes (CD19+) count were tested at baseline, 1, 3, 6 and 12 months post treatment.

Table 1. Patient characteristics: prednisolone; pred, weeks; wks

Patient	Disease manifestation at baseline	Therapy pre-RTX	Therapy post-RTX
1	Headache, rash, pleurisy, proteinuria	Pred 30 mg ↓ over 8 weeks for flare	Pred 40 mg ↓ over 4 wks
2	Rash, lymphadenopathy, angioedema, fevers, ↑ anti-dsDNA, lymphopenia, ↓ C3	Depomedrone 120mg i.m.	Pred 20mg ↓ over 8 wks at 2 months for flare
3	Rash, headache, alopecia, aicca symptoms, ↓ C3, lymphopenia,	None	None
4*	Rash, headache, thrombocytopenia, anaemia, proteinuria ↑ anti-dsDNA, lymphopenia, ↓ C3	AZA (stopped) & Pred 2.5 mg Pred 30mg ↓ over 2 wks for thrombocytopenia	Pred 60mg ↓ over 8 wks
5	Rash, livido reticularis, serositis, oral ulcers, proteinuria, ↑ anti-dsDNA, lymphopenia, ↓ C3.	Pred 40mg stat	Pred 40mg ↓ over 12 wks AZA
6	Polyarthritis, ↑ anti-dsDNA, lymphopenia, ↓ C3	Pred 7.5mg for 2 wks	AZA
7	Skin rash, raynauds, alopecia, pleurisy, ↑ anti-dsDNA, lymphopenia.	Pred 7.5mg for 12 wks	AZA
8	Rash, alopecia, raynands, arthralgia, ↓ C3	None	AZA
9	Polyarthritis, ↑ anti-dsDNA, lymphopenia	AZA for colitis	AZA

Results: All patients achieved B cell depletion (CD 19 < 0.005 $\times 10^9$/l. at 1 month). Patient 3 re-populated at 6 months but did not flare. The mean BILAG global score fell from 12.1 (SD 8.6) (n=9) at baseline to 7.4 (SD 4.7) (n=7) at 1 month, 3.9 (SD 2.3) (n=7) at 3 months, 3.5(SD 1.3) (n=4) at 6 months, and 1.5 (SD 0.7) (n=2) at 1 year. Patients 7 achieved improvement of BILAG grades A→D for mucocutaneous manifestations by 3 months and patient 2 and 8 by one year although patient 2 had a musculoskeletal flare at 2 months requiring steroid treatment. No patient developed any major sustained deterioration i.e. new A or D→B scores. Manifestations such as rash, arthritis, fever, thrombocytopenia and pleurisy responded well. Mean ESR fell from 76 to 32.9 at 1 month (n=9). Anti-dsDNA antibody levels fell by >50% in 3 patients. Serum C3 level did not change significantly except for patient 7 where it rose from 0.4 to 1.04 (NR 0.8 to 1.8g/l) by 3 months. Cr was stable throughout. In patient 1 and 5, urine protein: creatinine ratio (PCR) was stable at 6 and 3 months respectively although patient 5 required a renal biopsy as the PCR was 236 mg/mmol at 3 months. PCR fell from 104 to 15 mg/mmol by 1 month in patient 4. Mean total serum IgG fell modestly from 20.3 to 13.8 g/l.

Adverse Events: Treatment was safe and well tolerated. There were no adverse events on follow up.

Conclusions: A RTX/AZA protocol as a steroid sparing regimen is safe and effective in newly diagnosed patients with SLE.

References:

(1) Pepper R, et al Nephrol Dial Transplant. 2009 12:3717–23.

Disclosure: A. N. Ezeonyeji: None; **D. A. Isenberg:** Roche, 9.

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Evidence of Peripheral B Cell Depletion in Subjects with Controlled Systemic Lupus Erythematosus (SLE) Following Subcutaneous Administration of SBI-087. Roy M. Fleischmann[3], Stanley B. Cohen[7], Patricia Pardo[4], Marianne L. Shaw[1], Megan E. B. Clowse[2], Kyri Dunussi-Joannopoulos[6], Indranil Bhattacharya[6], Sudhakar T. Sridharan[5], Annette Diehl[6] and Ian Gourley[6]. [1]Altoona Center for Clinical Research, Duncansville, PA, [2]Duke University, Durham, NC, [3]Metroplex Clinical Research Center, Dallas, TX, [4]Miami Research Associates, [5]Pfizer Inc, Collegeville, PA, [6]Pfizer Inc, [7]Rheumatology Associates, Dallas, TX

Background: Preclinical data have shown a critical role of B cells in murine SLE models. Positive results from several open-label trials with CD20+ depleting agents and other B cell directed therapies support targeting B cells in human SLE. There have been two negative controlled studies of rituximab in SLE; however methodologic issues may have contributed to these results. SMIP™ biologics are disulfide bonded single chain polypeptides comprising binding, hinge, and effector domains designed to meet predetermined therapeutic specifications for diseases such as SLE. SBI-087 is a humanized SMIP biologic directed against the CD20 antigen located on B cells. SBI-087 is structurally different from rituximab, and has shown enhanced B cell depleting activity in the blood, bone marrow, and lymph nodes in cynomolgus monkeys. SBI-087 is being developed for subcutaneous (SC) administration that will eliminate the need for intravenous (IV) infusions and premedication with IV corticosteroids.

Objectives: To examine the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of ascending single doses of SBI-087 in subjects with controlled SLE.

Methods: Twenty-four subjects (23 females) received a single IV (0.5 mg/kg) or SC (25, 75, or 200 mg) dose of SBI-087 in this phase 1 open-label study. Each cohort contained 6 subjects. Blood was drawn for PK, PD (CD19+ B cells using a high-sensitivity assay), immunogenicity, and clinical safety assessments. Follow-up of subjects and data acquisition are ongoing.

Results: B cell depletion has been observed in the IV and all SC cohorts. Between wks 2 and 4, one subject in the 25 mg SC cohort, 5 subjects in the 75 mg SC cohort, and 4 subjects in the 200 mg SC cohort achieved B cell depletion to <5 cells/uL. 2 subjects in the 75 mg SC cohort and 1 subject in the 200 mg SC cohort achieved complete B cell depletion to the lower limit of quantitation (0.3 cells/uL) between wks 2 and 4. The 75 mg dose depleted peripheral blood B cell levels in all subjects to below 20 cells/uL by wk 4. SBI-087 has been generally well tolerated. Treatment-emergent adverse events (AEs) in more than 1 subject were upper respiratory tract infection, back pain, diarrhea, headache, fatigue, anxiety, chills, flushing, muscle spasms, nasopharyngitis, pain in extremities, and somnolence. Serious AEs included pregnancy, ankle fracture, spinal stenosis, diverticular perforation, and urinary tract infection. Chills occurred in 2 subjects after administration of 25 mg SC, and were abrogated in the 75 mg SC cohort with a day-of-treatment oral steroid regimen. 2 subjects in the 200 mg SC cohort had moderate flushing on the day of injection that was self-limiting. Injection site reactions have not been seen in any subject. Immunoglobulin levels have remained within normal limits in all subjects.

Conclusions: SBI-087 given as a single SC dose with a day-of-treatment oral steroid regimen appears to be generally well tolerated with an acceptable safety profile. B cell depletion has been observed in all SC cohorts dosed to date. Data from later timepoints for the 200 mg SC cohort will be necessary to fully explore the exposure/B cell response relationship and to select doses for future studies in SLE.

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Fibroblast Growth Factor (FGF23) Serum Levels in Juvenile Onset Systemic Lupus Erythematosus (JSLE): A Potential Link with Renal Involvement. Fernanda Falcini[1], Laura Masi[2], Serena Capannini[1], Francesco Franceschelli[2], Gigliola Leoncini[2], Valentina Denaro[1], La Torre Francesco[3], Giuseppina Calcagno[3], Marco Matucci Cerinic[1] and Maria Luisa Brandi[2]. [1]Dpt of BioMedicine, Rheumatology Section, Transition Unit, University of Florence, [2]Dpt of Internal Medicine, Metabolic Bone Diseases Unit, University of Florence, Florence, [3]Dpt of Paediatrics, Rheumatology Unit, University of Messina, Messina, Italy

Background: Phosphatonins are involved in phosphate homeostasis, Vitamin D metabolism, and bone mineralization. FGF23, the master phosphatonin, acts through FGFr1 present in kidney, vessels and heart; its levels are high in chronic renal disease, and association between FGF23 levels and high death a part of other risk factors has been reported. JSLE is associated with high risk of atherosclerosis and cardiovascular disease. Endothelial dysfunction, by autoantibodies, ICC and cytokines play a role in vascular injury.

Objectives: 1.To evaluate the serum level of intact FGF23 in JSLE pts. 2.To correlate FGF23 values to lipid profile, renal function, renal biopsy, and cardiac data.

Patients and Methods: 53 consecutive pts (46 F 7 M, mean age at diagnosis 13.3±5.6) with SLE onset before 18 yrs entered the study. 12/53 had renal disease (GN) at onset while 13/53 developed GN signs over time. Steroids were the first drug in all pts, then hydroxychloroquine, AZA, CyA, and MMF while antiCD20 was applied to 3 pts. At study entry, the disease was controlled by hydroxychloroquine in 28/53, while in 25/53 with low dose prednisone, MMF or AZA; 1 pts developed renal failure and went on dialysis. All pts with GN were biopsied 6 mths from renal manifestations onset: 4 WHO IIA, 6 IIB, 10 III, 5 IV. 35 sex and age matched subjects acted as controls. Serum intact FGF23 levels were measured with an ELISA assay (Immunotopics Inc. San Clemente, CA, USA).

Results: FGF23 serum levels resulted higher in JSLE pts than in controls (t-student:67.1±40SD *vs* 5±3.2SD pg/ml). By Mann-Whitney U Test; GN pts had FGF23 values higher than those without (45.3±20 *vs* 13,77±9.2 SD pg/ml; p=0.0001). By Ancova analysis pts with severe disease (WHO III-IV) had higher levels than patients with biopsies WHO IIA-IIB (52,5±21 and 58,5±15 pg/ml respectively vs 13.7±9 and 35±10 pg/ml p=0.004). No significant correlation was found among serum FGF23 levels, lipid profile and cardiac function. A trend characterized by an inverse correlation between FGF23 and HDL was found (r−0.07;p=n.s.).

Conclusion: Serum FGF23 levels are higher in JSLE pts and seem to correlate with renal damage. FGF23 serum values should be a helpful biomarker for assessing the risk of renal damage, and helpful in pts with early kidney disease in whom FGF23 levels firstly increase. Data in a larger cohort of pts are needed to define the role of FGF23 in renal disease of JSLE pts.

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Fracture Risk Assessment and Prevalence of Low Bone Mass in Canadian Females Living with Systemic Lupus Erythematosus (SLE). Jennifer J. Lee[6], Angela M. Cheung[6], Ellie Aghdassi[6], Stacey Morrison[6], Valentina Peeva[6], Carolyn Neville[1], Sarah Hewitt[4], Janet E. Pope[3], Deborah DaCosta[2] and Paul R. Fortin[5]. [1]McGill University, Montreal, QC, Canada, [2]McGill University, [3]St Joseph Health Care London, London, ON, Canada, [4]St. Joseph's Health Care, [5]University Health Network, Toronto, ON, Canada, [6]University Health Network

Background: Systemic Lupus Erythematosus (SLE) is an autoimmune disease with many complications. SLE patients are at risk of osteoporosis (OP) and fractures due to the disease and/or long-term steroid use.

Objective: To estimate in SLE females: 1) low bone mass prevalence and 2) fracture probability in those over the age of 40 using the Fracture Risk Assessment Tool (FRAX).

Methods: 271 SLE females with no OP fracture history were enrolled from 3 Canadian centres. Demographic data including age, SLE duration, body mass index (BMI), smoking status, OP risk factors, and medications were collected. Bone mineral density (BMD) of the lumbar spine, hip, and femoral neck were determined using DEXA. OP was defined as t-scores <−2.5 for those >50 years, and low bone mass as z-scores <−2 for those

<50. For those >40, the 10 year probabilities of a major OP event (FRAX Major) and hip fracture (FRAX Hip) were calculated using age, sex, BMI, past fractures, family history, smoking, alcohol, presence of rheumatoid arthritis, steroid use and femoral neck BMD. Risks high enough to warrant pharmacological treatments are >20% for FRAX Major and >3% for FRAX Hip.

Results: Subjects had a mean (SD) age of 43.8 (13.1) years, SLE duration of 11.6 (10.4) years, BMI (kg/m^2) of 26.3 (6.3), 57% consumed alcohol, 44% were smokers, 38% were postmenopausal, 28% had a prior fracture, 24% were on steroids >7.5 mg, and 41% were on steroids for at least 3 months. Calcium and vitamin D were used by 48% and 39% respectively. There was a significant correlation between BMD of the femoral neck ($r=-0.26$, $p=0.001$) and hip ($r=-0.35$, $p<0.01$) with the duration of steroid use.

In females ≥50 years (32.8%), the mean t-scores of the spine, hip, and femoral neck were −0.73, −0.52, −0.78 respectively. OP was diagnosed overall in 4.8%, and in 11.5%, 4.2%, and 5.7% in spine, hip, and femoral neck respectively.

In females <50 (67.2%), the mean z-scores of the spine, hip, and femoral neck were −0.22, 0.11, and −0.19 respectively. Low bone mass was at the spine, hip, and femoral neck in 52.7%, 39%, and 2.8% of the participants.

Overall, there was no difference in BMDs based on calcium and vitamin D intake. However, spine BMD was significantly lower in those who took steroids longer than 3 months [1.1 (0.1) vs. 1.0 (0.1), $p=0.006$].

Of those ≥40 (63.5%), the mean FRAX Major was 10.2% (6.3) and FRAX Hip was 1.8% (3.3). FRAX Major ≥20% was seen in 7% (n=12) of whom only half were on OP treatment. FRAX Hip ≥3% was noted in 15.8% (n=27) where 2/3 were on treatment. OP treatment was given to 22% and 16.7% of females who had low FRAX Major (<20%) and FRAX Hip (<3%) scores respectively. FRAX Major correlated significantly with: steroid duration ($r=0.31$, $p=0.03$) and age ($r=0.21$, $p=0.01$). Similarly, FRAX Hip correlated significantly with: steroid duration ($r=0.32$, $p=0.03$), age ($r=0.23$, $p=0.01$), and SLE duration ($r=0.20$, $p=0.01$).

Conclusion: Low bone mass is prevalent in SLE females without prior OP fractures. This is important for females <50 years, where routine BMD monitoring is not currently part of standard care. FRAX scores may provide additional insight to the level of risk and identify those who may benefit from OP treatments. This may help reduce future morbidity and mortality.

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Immunosuppression in the Treatment of Systemic Lupus Erythematosus Associated Pulmonary Arterial Hypertension: Improvement in Functional and Exercise Capacity. Judith Ashouri[2], Yon Sung[2], Roham Zamanian[2] and Lorinda Chung[1]. [1]Stanford Univ Medical Center, Palo Alto, CA, [2]Stanford University School of Medicine

Purpose: Accumulating evidence suggests that autoimmunity and inflammation are important in the pathogenesis of systemic lupus erythematosus associated pulmonary arterial hypertension (SLE-APAH). Several case reports and series have described improvement in dyspnea, exercise capacity, and hemodynamics with aggressive immunosuppression (IMM), both alone and in combination with PAH-specific therapies. We aimed to assess the effects of IMM in combination with PAH-specific therapies on the clinical outcomes of SLE-APAH patients followed at our center.

Methods: We identified 13 patients from Stanford's PAH database diagnosed with PAH by right heart catheterization between 1999–2009. All patients fulfilled ACR criteria for a diagnosis of SLE based on medical record review, and patients who fulfilled ACR criteria for another connective tissue disease were excluded. All patients received PAH-specific therapies according to standard of care. Patients who underwent aggressive IMM for a minimum of 8 months between the baseline and follow-up evaluations were compared with those receiving PAH-specific therapies alone. Cumulative probability of freedom from worsening New York Heart Association functional class (FC) was calculated using the Kaplan-Meier estimator, and compared using the log-rank test. Follow-up time was calculated from the time of the baseline evaluation. The mean changes in clinical parameters were compared between the IMM and non-immunosuppression (non-IMM) groups using Student's t-test.

Results: All patients were female, 69% Asian, 15% white, with a mean age of 38±9 years and mean SLE disease duration at PAH diagnosis of 5.6±6.1 years. 46% had a history of renal disease, 46% had Raynaud's, and 38% a history of serositis. 100% were ANA+, 85% anti-dsDNA+, 71% anti-RNP+, 40% anti-Smith+, and 29% antiphospholipid antibody+. 4 (30%) patients were treated with aggressive IMM (3 with high dose steroids and mycophenolate mofetil, 1 with hematopoietic stem cell transplant) during a mean follow-up time of 14.8±4.3 months. At baseline, there were no significant differences in demographics, SLE clinical features or autoantibodies in patients treated with or without IMM, except for increased prevalence of oral ulcers in the IMM group (23% vs. 8%, $p=.02$). Baseline PAH disease duration (9±15 vs. 35±42 months), hemodynamics (mean right atrial pressure 11.3±6.1 vs. 7.5±4.9 mmHg, mean pulmonary arterial pressure 46±12.7 vs. 51.3±16.1 mmHg, cardiac index 2.6±0.7 vs. 2.3±0.6, peripheral vascular resistance 10.1±2 vs. 12.4±6.1 WU), FC (3.3±0.5 vs. 2.7±0.9), 6 minute walk distance (6MWD, 276±168 vs. 397±177 m), and PAH-specific therapies did not differ significantly between the IMM and non-IMM groups. At follow-up, hemodynamics and PAH-specific therapies did not differ between the groups. No patients in the IMM group had worsened FC compared with 22% and 45% at 1- and 3-years in the non-IMM group ($p=.2$). Mean improvements in FC (−2±1 vs. 0±1, $p=.01$) and 6MWD (+206±46 vs. +52±200 m, $p=.054$) were higher in the IMM group.

Conclusion: Immunosuppression in addition to PAH-specific therapies may improve functional and exercise capacity in patients with SLE-APAH.

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Immunosuppressive Drugs for Systemic Lupus in the Michigan Lupus Cohort: Increased Requirement for Cyclophosphamide and Mycophenolate Mofetil in Men. Emily E. Lewis[3], Emily Crooks[4], Zhichao Sun[4], Patricia C. Cagnoli[3], Tania Gonzalez-Rivera[4], Mariana J. Kaplan[3], Wendy Marder[2], Panduranga Rao[4], Emily C. Somers[1] and W. Joseph McCune[3]. [1]U of Michigan Health System, Ann Arbor, MI, [2]Univ of Michigan, Ann Arbor, MI, [3]University of Michigan, Ann Arbor, MI, [4]University of Michigan

Purpose: Male lupus patients have been reported to have more aggressive disease, including more rapid accrual of damage, and increased mortality when compared to females. We examined sex differences in the use of immunosuppressive agents to treat systemic lupus erythematosus (SLE), hypothesizing that first line drugs for severe lupus, cyclophosphamide (CYC) and/or mycophenolate mofetil (MMF), are more frequently prescribed for men than women, reflecting more severe disease activity in men.

Methods: An extensive retrospective chart review was conducted on the records of 764 patients, including 91 men and 673 women, enrolled in the Michigan Lupus Cohort (MLC) from 2000 – present, to determine the frequency of administration of immunosuppressive drugs. The evaluation included all University of Michigan electronic records spanning 1992 – present, in addition to any available outside records. Chart review confirmed that patients satisfied ≥4 ACR criteria for SLE. An electronic medical search engine (EMERSE) was used to scan patient records for use of immunosuppressive drugs; all records were then carefully assessed to confirm that the immunosuppressive was prescribed to treat SLE. The use of CYC, MMF, azathioprine (AZA), and/or methotrexate (MTX) was then recorded if the drug was prescribed to treat SLE and the patient began treatment.

Results: Of the 764 patients enrolled, the majority of patients received treatment with at least one immunosuppressive drug including 81.3% of men and 72.1% of women. CYC was used by 52.7% men vs. 37.7% women ($p=0.006$). MMF was used by 69.2% of men vs. 51.1% of women ($p=0.001$). In contrast, AZA was used by 36.3% of men vs. 41.8% of women, and MTX was used by 16.5% of men vs. 26.6% of women ($p=0.0375$). Approximately 75% of men in the MLC received at least one first line drug as treatment for their SLE.

IMS Medications	Female n=673	Male n=91	P - value
CYC	254 (37.7)	48 (52.7)	0.0060
MMF	344 (51.1)	63 (69.2)	0.0012
CYC or MMF	388 (57.7)	68 (74.7)	0.0018
AZA	281 (41.8)	33 (36.3)	NS
MTX	179 (26.6)	15 (16.5)	0.0375
None	188 (27.9)	17 (18.7)	NS

( )=percent

Conclusions: There is a highly significant increase in the proportions of men who receive first line drugs for severe lupus, cyclophophamide and

mycophenolate mofetil, compared with women. These data highlight the importance of fully characterizing pathogenic mechanisms contributing to the increased severity of lupus in men vs. women.

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Increased Recruitment of Brain Activation within the Hippocampus in SLE Patients as Shown by Functional MRI May Be a Compensatory Mechanism To Cope with Memory Impairment. Daphna Paran[3], Ifat Glikmann-Johnston[2], Talma Hendler[2], Irena Litinsky[3], Eli Vakil[1], Dan Caspi[3] and Irit Shapira-Lichter[2]. [1]Department of Psychology and Gonda Multidisciplinary Brain Research Center, Bar-Ilan University, [2]Functional Brain Center, Wohl Institute for Advanced Imaging, Tel-Aviv Sourasky Medical Center, [3]Rheumatology Department, Tel-Aviv Soursky Medical Center

Objectives: The hippocampus has been shown to have a major role in memory processes. Atrophy of the hippocampus has been correlated to cognitive impairment in SLE and other diseases. This study aimed to assess neural correlates of memory impairment within the hippocampus in SLE patients by functional MRI.

Methods: Twelve female SLE patients (mean age: 30±5.9 years; mean education: 14.6±1.7 years; disease duration 9.5±3.4 yrs; SLE disease activity index 6.3±6.4; SLICC damage index: 0.9±1.0) without clinically overt NPSLE and 11 female healthy controls (mean age: 29.8±6.8 years; mean education: 15.1±1.3 years) underwent fMRI testing using an auditory verbal memory test. The paradigm consisted of three blocks of verbal encoding and repeated free recall steps followed by a recognition test. During retrieval blocks subjects indicated by pressing a key when a word was recalled or recognized. Brain activation patterns were evaluated within the hippocampus in both groups using this paradigm. Hippocampal volume was measured using Brain Voyager QX.

Results: Free recall was impaired in SLE patients as compared with healthy subjects ($p<0.05$). Among SLE patients, learning was correlated with hippocampal responsiveness to the encoding task, reflected in the percent signal change in activation from baseline to each of the encoding blocks (EB) (left hippocampus: EB1: $r=0.38$, $p<0.05$; EB2: $r=0.39$, $p<0.05$; EB3: $r=0.4$, $p<0.05$; right hippocampus: EB1: $r=0.4$, $p<0.05$; EB2: $r=0.36$, $p<0.05$; EB3: $r=0.37$, $p< 0.05$). No such correlation was seen in the healthy controls. Furthermore, greater activations were evident within both the right and left hippocampus in SLE patients compared to controls during the encoding, free recall and recognition tests. The left hippocampus was significantly smaller in SLE patients as compared to controls ($p<0.05$), however there was no correlation between hippocampal volume and learning abilities (i.e. number of learned words).

Conclusions: SLE patients demonstrated memory difficulties along with greater activity in the hippocampus as compared to healthy controls. This increased activity correlated with learning performance. These findings suggest that increased brain activation within the hippocampus during learning in SLE patients, may reflect compensatory mechanisms required to overcome impaired memory and learning abilities and cope with memory tasks.

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1160

Inhibition of Complement Activation by Heparins but Not Fondaparinux on Alternative, Mannose/Mannan Binding Lectin (MBL) and Classical Pathways in Active SLE with Low C3/C4. Andrea A. Ramirez[1], Ankur A. Kamdar[2] and Barry L. Myones[1]. [1]Baylor College of Medicine/ Texas Children's Hospital, Houston, TX, [2]University of Texas Medical School at Houston, Houston, TX

Background: Activation of 1 or more of the complement cascades has been implicated in disease pathogenesis in several autoimmune disease processes including SLE and antiphospholipid antibody syndrome (APS). Low molecular weight heparins (LMWH) have been used to treat thrombosis, microangiopathic processes and anecdotally in the therapy of giant coronary aneurysms in Kawasaki Disease. Unfractionated heparin (UFH) and LMWH have also been implicated in classical pathway complement inhibition in APS. We have previously demonstrated complement inhibition only at supra-pharmacologic levels of heparin (5 to 10x the accepted therapeutic cutoff).

Purpose: Evaluate the effect of UFH, LMWH, and a factor Xa inhibitor (fondaparinux) on cell membrane-associated classical (CP), MBL, and alternative pathway (AP) activation *in vitro* utilizing serum with normal and very low C3/C4 (simulating active SLE).

Methods: AP hemolytic assay was modified to 100% lysis. Unsensitized rabbit erythrocytes (RaE) (direct activator of human AP) @1.25 $\times 10^8$ in GVB/MgEGTA (blocks CP activation by calcium chelation) were utilized per tube. Sheep erythrocytes (ShE) were sensitized with mannan by CrCl3 incubation in MBL assay (GVB/Ca++/Mg++). ShE were sensitized with hemolysin (anti-ShE IgM) in CP hemolytic assay. Varying doses of UFH or enoxaparin (0.5–10 IU/ml final concentration) or fondaparinux (1.25 – 6.25 mg/ml) were added to normal human serum (C3 120–140 mg/dL; C4 >15 mg/dL) and active/inactive SLE (C3 25–50 mg/dL; C4 0–10 mg/dL) as complement sources. (C3/C4 ascertained by Mancini immunodiffusion; C4 allotyping performed on test sera). Mixtures were incubated up to 30 minutes @37°C. Supernatants were read at OD541 and expressed as % lysis against controls.

Results: Escalating doses of enoxaparin or UFH (up to 20 IU/ml) resulted in increased % inhibition of complement-mediated RaE or ShE lysis (1mg enoxaparin ~100 IU anti-Factor-Xa activity) whereas fondaparinux had no appreciable inhibition of lysis in control or patient serum. A small % inhibition (<20%) of membrane-associated complement activation was noted at anti-factor-Xa activity levels achievable with standard therapeutic anticoagulant regimens of UFH or LMWH, but LMWH > UHF achieved inhibition at higher (>2 IU/ml) dosing levels for CP > AP components for both controls and SLE patients with normal C3/C4 (only 50–70% even at 5 IU/ml). Sera with higher C3/C4 (>140 mg/dL; >20 mg/dL) were much harder to inhibit. Sera with limited C3 /C4 levels (<30 mg/dL; <5 mg/dL) resulted in significantly more inhibition of complement-mediated RaE or ShE lysis at lower dosing levels of UFH or LMWH (1 to 2 IU/ml).

Conclusions: UFH and LMWH inhibit membrane-associated complement activation via all 3 pathways *in vitro* while fondaparinux, a factor Xa inhibitor, had no effect. Anticoagulation effects were again discordant from complement inhibitory effects in controls and SLE patients with normal C3/C4 levels. Active SLE sera with very low C3/C4 levels resulted in inhibition by heparins at 1.5 to 2 IU/ml dosing levels (lower bleeding risk). These data suggest heparins as an additional therapeutic modality in very active SLE patients with limited complement supply.

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Long-Term Outcome of Autologous Hematopoietic Stem Cell Transplantation (AutoHSCT) Using Lymphoablative Conditioning in Treatment-Resistant Systemic Lupus Erythematosus. Gabor G. Illei[11], Sarfaraz A. Hasni[7], Nikolay P. Nikolov[1], Francis Hakim[2], Susan Leitman[2], James Balow[9], Howard Austin[4], Juan Gea-Banacloche[2], Unsong Oh[10], Jeanie Odom[2], Donna Hardwick[8], Claude Sportes[2], Ronald Gress[2], Steven Pavletic[2], Cheryl Yarboro[6], Paolo Muraro[5] and Peter Lipsky[3]. [1]Bldg. 22, Room 3335, HFD-570, Silver Spring, MD, [2]National Cancer Institute, [3]National Institue of Arthritis, Musculoskelatal and Skin Diseases, [4]National Institue of Dibetes, Digestive and Kidney DIseases, [5]National Institue of Neurological Diseases and Stroke, [6]National Institute of Arthritis, Musculoskelatal and Skin Diseases, [7]National Institute of Arthritis, Musculoskelatal and Skin Diseases, Bethesda, MD, [8]National Institute of Arthritis, Musculoskeletal and Skin Diseases, [9]National Institute of Diabetes, Digestive and Kidney Diseases, [10]National Institute of Neurological Disroders and Stroke, [11]NIDCR, NIH #10 1N114, Bethesda, MD

Background: Despite improvements in the outcomes of SLE patients with major organ involvement, treatment failure and relapse continue to affect significant proportion of patients. In this pilot study we tested if intensive lymphoablation followed by autoHSCT can lead to sustained, complete, treatment-free remission in severe, recalcitrant SLE and whether this approach fundamentally changes abnormal immune response.

Methods: Patients were enrolled with active SLE despite prior treatment with IV cyclophosphamide (CYC). Of the 8 patients treated, 2 had transverse myelitis, 1 retinal vasculitis and 5 WHO Class IV nephritis. Stem cell mobilization regimen consisted of 2,000 mg/m^2 CYC, 750 mg/m^2 rituximab (RTX) and G-CSF. Conditioning regimen consisted of 750 mg/m^2 RTX, 4.8 g/m^2 CYC and 120 mg/m^2 fludarabine, followed by CD34+ selected stem cell infusion and G-CSF.

All immunosuppressive medications and hydroxychloroquine (HCQ)

were stopped at the start of mobilization and steroids were rapidly tapered off after the transplant. Clinical response was evaluated by organ specific response criteria. Disease activity indices (SLEDAI and SLAM) were used to assess overall lupus activity. The primary endpoint was complete response (CR) at 24 months defined as no lupus activity and no treatment for lupus (including HCQ and steroids).

Results: Among the 8 patients, there were 2 early deaths (one from diffuse alveolar damage, one from mycobacterial meningoencephalitis). One patient had lupus flare (retinal vasculitis responding to corticosteroids) 6 months post-transplant. Five patients were tapered off corticosteroids, achieved CR criteria within 6 months of transplant and SLEDAI scores of 0. One of these patients had SLE relapse 18 months post-transplant which responded to standard treatments, whereas 4 continue to be in CR beyond 4 (n=2) to 5 years (n=2). The reconstituted immune system of long-term responders showed a significant shift from a phenotype dominated by memory and activated effector T and B cells at baseline to a predominantly naïve phenotype post-transplant. In contrast, the patient who flared had an early recurrence of memory B cells and circulating plasma cells preceeding the flare.

Conclusions: Our data indicate that lymphoablative autoHSCT leads to sustained (over 5 years) clinical and serologic remission, without the use of any maintenance therapy in a subset of otherwise recalcitrant SLE patients. This clinical benefit is associated with marked normalization of the immune repertoire. Reducing the intensity of conditioning and/or exclusion of patients with multiple organ dysfunction may decrease short term toxicity and would make this approach an acceptable alternative for the treatment of severe SLE.

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Microembolic Signals Detected by Transcranial Doppler Ultrasound Corresponds to Persistence of Foramen Ovale in Neuropsychiatric Lupus with Brain MRI Abnormalities.

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Background: Magnetic resonance imaging (MRI) abnormalities, as small punctuate hyperintense lesions in subcortical and periventricular brain white matter areas (WMHL) are a frequent but not specific finding in systemic lupus erythematosus (SLE) patients with and without neuropsychiatric (NP) involvement. Their pathogenesis is not fully understood yet, being recurrent cerebral micro-embolism - detectable through transcranial Doppler ultrasound (TCD) - one of the hypothesized mechanism. In general population micro-embolic signals (MES) may be detected with a reported frequency of about 15 % often due to the persistence of foramen ovale.

Aim: To assess the frequency of microembolic signals (MES) by using transcranial Doppler (TCD) ultrasound in SLE patients with and without brain MRI abnormalities.

Methods: A TCD registration to detect MES from the middle cerebral artery was carried out accordingly to a local standardized protocol in 21 SLE patients (mean age of 42,2 years, range 32–55) with and without NP involvement lupus, after exclusion of aortic and/or carotid atheromatous disease. In all patients brain magnetic resonance imaging (MRI) and trans-esophageal echocardiography were performed. Patients were stratified in two groups, with and without MRI WMHL and compared. Antiphospholipids antibodies (APL) and lupus anticoagulant (LA) status were checked too.

Results: MES were detected in a total of 11 patients (52,3%), 4 APL/LA+ and 7 APL/LA-, 9 out of 15 patients (60 %) with abnormal MRI and history of NP SLE had MES compared with 2 out of 6 patients (33.3 %) with normal MRI (1 NPSLE and 5 without NP involvement). No correlations between MES and APL or LA were found. The persistence of foramen ovale was confirmed in almost all case of MES detection. However with abnormal MRI only one case did not show persistence of foramen ovale.

Conclusion: Compared with what has been reported in general population, MES is a frequent finding in SLE patients irrespective of their previous history of NP involvement and more prevalent in patients with MRI abnormalities compared with patients with normal MRI. These finding either suggest caution in the interpretation of MRI pictures and a careful evaluation of MES in patients with MRI abnormalities which should be included in the work-up of SLE patients prompting further investigations for micro-embolic sources (i.e. carotid plaques and/or right-left shunt due to the persistence of foramen ovale).

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Multivariate Analysis of Vitamin D Insufficiency and Deficiency in SLE: The SOLD (Systemic Lupus Associates of Low Vitamin D) Project.

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Purpose: Vitamin D is an important immunomodulator in animal models of autoimmune diseases. In humans, in addition to its role in bone health, it may be important in the prevention of diabetes, cardiovascular disease, and certain cancers. We explored clinical and laboratory associates of Vitamin D insufficiency (<32 ng/mL) and deficiency (<15 ng/mL) in SLE.

Methods: 810 SLE patients (mean age 44.94, 49.54% Caucasian, 40.36% African-American, 92.07% female) were included. 25 OH Vitamin D was measured from July 20, 2009 to April 22, 2010.

Results: Univariate analyses suggested that age, ethnicity, hypertension, diabetes, physician global assessment of SLE activity (PGA), urine protein/creatinine ratio (>0.5), systolic blood pressure, cholesterol, and obesity were associated with both Vitamin D insufficiency and Vitamin D deficiency.

Table 1. Association between various factors and deficiency/insufficiency of Vit D in patients with SLE based on a multivariable logistic regression model

Variable		Odds Ratio (95% CI) with Vit D Deficiency	P-Value	Odds Ratio (95% CI) with Vit D Insufficiency	P-Value
Age	18–30	1.00 (reference)		1.00 (reference)	
	31–49	0.83 (0.47; 1.47)	0.524	1.20 (0.77; 1.85)	0.419
	50+	0.40 (0.21; 0.78)	0.007	0.63 (0.39; 0.99)	0.048
Race	White	1.00 (reference)		1.00 (reference)	
	Black	5.92 (3.76; 9.33)	0.001	2.18 (1.57; 3.04)	0.001
	Other	1.89 (0.80; 4.51)	0.149	1.22 (0.68; 2.18)	0.501
Urine Pr/Cr Ratio	<0.5	1.00 (reference)		1.00 (reference)	
	>=0.5	1.01 (0.54; 1.91)	0.967	1.71 (0.90; 3.24)	0.102
BMI	<=30	1.00 (reference)		1.00 (reference)	
	>30	1.85 (1.23; 2.78)	0.003	2.51 (1.79; 3.53)	0.001
Cholesterol	<=200	1.00 (reference)		1.00 (reference)	
	>200	1.43 (0.93; 2.21)	0.102	1.79 (1.26; 2.55)	0.001
Systolic BP	<140	1.00 (reference)		1.00 (reference)	
	>=140	1.60 (0.97; 2.63)	0.065	1.60 (1.02; 2.51)	0.039
Diabetes	No	1.00 (reference)		1.00 (reference)	
	Yes	2.05 (1.13; 3.69)	0.017	1.49 (0.85; 2.61)	0.165

However, in the best multivariate logistical regression model (see table 1), age, ethnicity, and obesity remained statistically significant, but urine protein/creatinine ratio did not. In the best multivariate linear regression model (see table 2), urine protein/creatinine ratio was significantly associated with Vitamin D levels.

Table 2. Association between various factors and Vit D levels in patients with SLE based on a multivariate linear regression model

Variable	Effect on Mean Vit D	P-value
Age (per year)	0.11 ± 0.04	0.005
Race (Black vs White)	−6.32 ± 1.04	0.001
Systolic BP (per mmHg)	−0.09 ± 0.03	0.004
Diabetes	−2.43 ± 1.71	0.156
Urine Pr/Cr Ratio	−1.55 ± 0.78	0.047
BMI	−0.29 ± 0.07	0.001
Cholesterol (per mg/dL)	−0.04 ± 0.01	0.001

Conclusion: Younger age, African-American ethnicity and obesity are associated with both Vitamin D insufficiency and deficiency, after adjustment for other variables, in multiple variable models. The apparent association with disease activity in univariate analyses did not remain in multiple variable models. The association with urine protein/creatinine ratio, however, did remain in the multivariate linear regression model. This suggests that Vitamin D deficiency may play a role in renal lupus.

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Network Analysis of Associations between Serum Interferon Alpha, Serology, and Clinical Features in Systemic Lupus Erythematosus in a Large Multi-Ancestral Cohort. Corinna E. Weckerle[6], Beverly S. Franek[7], Jennifer Kelly[2], Marissa Kumabe[7], Rachel Mikolaitis[5], Stephanie Green[7], Gail R. Bruner[3], Tammy O. Utset[6], Meenakshi Jolly[4], Judith A. James[1], John B. Harley[8] and Timothy B. Niewold[9]. [1]Oklahoma Med Research Foundation, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, [3]Oklahoma Medical Rsrch, Oklahoma City, OK, [4]Rush University Med Ctr, Chicago, IL, [5]Rush University Med Ctr, [6]Univ of Chicago Med Ctr, Chicago, IL, [7]Univ of Chicago Med Ctr, [8]Univ of OK Hlth Sci Ctr, Oklahoma City, OK, [9]University of Chicago, Chicago, IL

Background: Interferon-alpha (IFN-α) is a primary pathogenic factor in systemic lupus erythematosus (SLE), and high IFN-α levels may be associated with particular clinical manifestations. The prevalence of individual clinical and serologic features differs significantly by ancestry. We used logistic regression modeling to establish the network of associations between clinical and serologic manifestations and serum IFN-α in SLE patients from multiple ancestral backgrounds.

Methods: We analyzed the presence or absence of ACR clinical criteria for SLE, autoantibodies, and high serum IFN-α in 1089 SLE patients (387 African-American, 186 Hispanic-American, and 516 European-American). Iterative multivariate logistic regression was performed in each background separately to establish associations between variables, and network diagrams were constructed illustrating associations that were significant following Bonferroni correction.

Results: We found 14 unique associations forming network maps of relatively sparse density in each background. Of those, only 7 associations were shared by more than one ancestral background. Network maps of the interactions between clinical criteria were different in different ancestral backgrounds. In contrast, associations between autoantibodies and IFN-α were very similar in different backgrounds. In all backgrounds, high IFN-α was associated with presence of anti-Ro and anti-dsDNA antibodies (p-values 4.6×10^{-18} and 2.9×10^{-16} respectively). IFN-α and serology were not associated with ACR clinical features in these multivariate models.

Conclusions: Serum IFN-α was strongly and consistently associated with serology, and not independently associated with clinical features in SLE. Our study suggests that IFN-α may be more relevant to humoral tolerance and initial disease pathogenesis than ongoing late clinical disease manifestations.

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Peripheral Neuropathy in Patients with Systemic Lupus Erythematosus. Brandusa Florica[2], Jiandong Su[1], Ellie Aghdassi[1], Dafna D. Gladman[1], Murray B. Urowitz[1] and Paul R. Fortin[1]. [1]University Health Network, [2]University of Toronto, Toronto, ON, Canada

Background: Peripheral neuropathy (PN) is a common feature of neuropsychiatric syndromes in Systemic Lupus Erythematosus (SLE) that can affect the quality of life of these patients. Currently the studies describing the clinical features of SLE patients with PN are scarce.

Objective: To determine in SLE patients: 1) the prevalence, the clinical course of PN and the impact on quality of life, 2) the clinical features and sub-classes of PN, and 3) whether there is an association between PN and any other clinical feature.

Methods: Patients who met at least 4 of the ACR classification criteria and met the ACR case definition criteria for peripheral neurological SLE were selected from the database registry of the University of Toronto Lupus Clinic. Chart review was performed to confirm clinical findings, determine the contributing factors and outcome of PN. PN found to be due to non-SLE causes were analyzed but kept in a separate group than SLE-related PN. Demographic data including age, gender and SLE duration, as well as SLE related clinical and investigational data at the time of the first appearance of PN were extracted by chart review. Disease activity and damage were assessed by SLE- Disease Activity Index (SLEDAI-2K) and SLICC Damage Index (SDI) at the time of the first appearance of PN. Quality of life was determined using the SF-36 questionnaire and scored for the physical (PCS) and mental (MCS) component summary scores. Data were analyzed using SAS statistical program.

Results: Out of 1520 patients in the database, 210 (14%) with a mean (SD) ACR criteria of 5.7 (2.0) met the inclusion criteria. Subjects had mean (SD) for age of 44 (14.4) years and SLE duration of 9.2 years (10.2); median (IQR) for SLEDAI of 6.0 (IQR: 2.0, 12.0) and SDI of 1.0 (IQR: 0.0, 2.0); and 86.6% were female. Among patients, 66.9% had at least one SLE-related or possible SLE-related PN including mononeuritis multiplex (14.2%), sensory PN (27%) and mononeuropathy (25.8% including cranial neuropathy in 7.4%). Asymmetric presentation was most common (62.8%), and distal weakness occurred in 31.8% of patients. Peroneal nerve (61.4%), sural nerve (51.8%) and median nerve (40.9%) were frequently involved. Associated SLE features were: 85% arthritis, 69.3% rash, 47.8% CNS involvement. ANA titer of 1:320 or higher was significantly more prevalent in patients with SLE-related PN than non-SLE related PN (43.5% vs. 21.4%; p=0.028). EMG/NCS was performed in 67.7% of patients and indicated axonal neuropathy in 76.8% and demyelination in 18.3% of patients. Treatment included oral steroid in 85.4%, cyclophosphamide in 19.3% and pulse steroids in 7.9 % of patients. Chart review completed in 130 of the patients, showed that 67.7% of patients improved and 28.4% had no response to treatment, within a mean (SD) follow up period of 5.4 (7.6) years. SF-36 PCS was low in those with PN with a mean (SD) of 35.8 (10.7).

Conclusion: PN is relatively prevalent in SLE, may occur at any time after SLE diagnosis and with different presentations. This manifestation of SLE has a big impact on patient's quality of life.

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Predictors of Mortality in Diffuse Alveolar Haemorrhage (DAH) Associated with Systemic Lupus Erythematosus. Marco U. Martínez-Martínez[2], Eufrates Hernández-Núñez[3], Enrique Cuevas-Orta[3], Ricardo Moreno-Valdés[3], Martin Saldaña-Barnad[3], Martin Magaña-Aquino[3], Juan C. Rizo-Rodríguez[2] and Carlos Abud-Mendoza[1]. [1]Rheumatology Unit, Hospital Central and Faculty of Medicine, University of San Luis Potosí, San Luis Potosi, Mexico, [2]Rheumatology Unit, Hospital Central and Faculty of Medicine, University of San Luis Potosí (México), [3]Rheumatology Unit, Hospital Central and Faculty of Medicine, University of San Luis Potosí (Mexico)

Objectives: Evaluation of clinical, demographic and treatment-associated mortality factors in patients with DAH associated with SLE.

Methods: Clinical, laboratory test, SLEDAI-2K, predictors of mortality (APACHE II) and different treatments including cyclophosphamide, methylprednisolone and rituximab were evaluated in SLE patients who were diagnosed with DAH, to determine potential association with factors that could be predictive of mortality.

Results: Twenty nine episodes of DAH in 22 SLE patients were included (one patient with 4 episodes, 4 patients with two episodes (7 recurrences)), 15 died. Mean age was 25.1 years and 1.5 years of SLE evolution with haemoglobin drop 3.4 g/dl. In 4 of 22 patients, the DAH diagnosis was confirmed by autopsy. Six episodes were in patients under 18 years of age (2 patients with recurrence). DAH was the initial manifestation of SLE in 10 patients. Of the 22 patients, 17 were women and 22/29 DAH episodes. Through evaluation of all included factors, only thrombocytopenia, renal failure, requirement for mechanical ventilation and high APACHE II were associated with higher mortality. In 3 patients mycoses were diagnosed, all died. There is benefit using cyclophosphamide in selected patients (not statistically differences). Table 1 show the main characteristics evaluated in the 29 episodes.

Table 1. Characteristics evaluated at admission.

	All (mean ± SD)	Alive (mean)	Deceased (mean)	p
hsCRP (*)	9.9 ± 8.1	7.3	12.4	0.137
Leukocytes (†)	10.8 ± 8.9	10.4	11.1	0.832
Lymphocytes (†)‡	0.72 (0.1–4.6)	0.98	0.54	0.252
Haemoglobin (§)	6.9 ± 1.7	7.0	6.8	0.772
Platelets (†)‡	162 (4–496)	224	144	0.055
Creatinine (*)‡	1.2 (0.3–31.9)	0.79	2.54	0.016
GFR (‖)	73.4 ± 51.9	104.1	42.9	0.001
SLEDAI-2K	17.1 ± 7.5	15.9	18.3	0.416
APACHE II	18.4 ± 6.1	15.7	21.1	0.015
Renal failure (%)	41.4	6.9	34.5	0.004
Haemodialysis (%)	27.6	6.9	20.7	0.215
MV (%)	72.4	24.1	48.3	0.014
Cyclophosphamide (%)	58.6	34.5	24.1	0.176

(*): mg/dl, (†): × 10^3/mm^3, ‡ Median (minimum-maximum), (§): g/dl, (‖): ml/min/1.73 m^2, SD: standard deviation, hsCRP: high sensitivity C reactive protein, GFR: Glomerular filtration rate, SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000, APACHE II: Acute Physiology And Chronic Health Evaluation. MV: Mechanical ventilation

Conclusions: Mortality of DAH associated with SLE has continued being high in spite of intensive treatment. Thrombocytopenia, renal failure, requirement of mechanical ventilation and high APACHE II are factors associated with higher mortality. Cyclophosphamide would be useful to diminish mortality related to DAH associated with SLE. Patients should receive therapy against prevalent and opportunistic infectious agents.

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Prefrontal Lobe Volume Could Reveal Working Memory Function in Patients with System Lupus Erythematosus. Yongfei Fang[2], Haitao Lii[1], Qinghua Zou[3] and Yun Lin[1]. [1]Department of Radiology, Southwest Hospital, Third Military Medical University, Chongqing, China, [2]Department of Rheumatology, Southwest Hospital, Third Military Medical University, Chongqing, China, [3]Department of Rheumatology, Southwest Hospital, Third Military Medical University, Chongqing, China

Background: As a disease found with multiple organ involvement, cerebral atrophy in systemic lupus erythematosus has been reported by recent studies. The aim of the current study is i) to localize cerebral areas affected by SLE, and ii) to find any clinical index significantly correlated with cerebral atrophy.

Methods: 45 patients with SLE and 30 age, gender and education matched healthy controls were included, patients first underwent a working memory test named Paced Visual Serial Adding Test (PVSAT) and then scanned in a 3.0 Tesla MRI scanner for whole brain by 3D MPRAGE sequence. Images were process by Statistical Parametric Mapping (SPM8) software using a voxel based morphometry (VBM) through a newly improved Diffeomorphic Anatomical Regstration Through Exponentiated Lie algebra (DARTEL) approach, which mainly included segmenting brain images into grey matter, white matter and cerebral spinal fluid; estimating the deformations that best align the images together by iteratively registering the segmented images with their average, and generating spatially normalised and smoothed Jacobian scaled grey matter images, by using the deformations estimated in the previous step; and finally a two sample t test to depict cerebral areas of SLE patients with significant atrophy compared with controls. Then SLEDAI score, duration of disease, daily corticosteroid dosage and working memory test results were correlated with individual volume of these atrophied areas.

Results: diffuse grey matter atrophy was found in patients with SLE, mainly involved with prefrontal, temporal lobe, and cerebellum. By extracting individual volume of these cerebral areas, prefrontal lobe volume was positively correlated with test score of working memory test, and whole brain volume was negatively correlated with disease duration. No other clinical indexes were found to be in significant correlation with cerebral atrophy of SLE.

Conclusion: in consistence with previous researches, diffuse grey matter atrophy was found in patients with SLE. Further more, correlation between cognitive impairment and prefrontal lobe atrophy was discovered, indicating that i) cognitive impairment in SLE could be reflected by individual prefrontal lobe volume; ii) prefrontal lobe volume may be served as an marker of cognitive function in SLE. Nevertheless, negative correlation between disease duration and whole brain volume demonstrated a significant and chronic impact of SLE on human brain. However, as such results were generated based on a limited number of subjects, further research is required to depict the insights of the profile in the future.

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Preliminary Results: Baseline Nutritional Vitamin D Level Does Not Predict Progression of Subclinical Atherosclerosis in Women with SLE. Apinya Lertratanakul[2], Peggy Wu[2], Alan R. Dyer[2], Craig Langman[1], William Pearce[2], Kim Sutton-Tyrrell[4], George Kondos[3], Daniel Edmundowicz[4], James Carr[2] and Rosalind Ramsey-Goldman[2]. [1]Childrens Memorial Hospital, Chicago, IL, [2]Northwestern University, Chicago, IL, [3]University of Illinois, Chicago, IL, [4]University of Pittsburgh, Pittsburgh, PA

Background: CV events and subclinical atherosclerosis are increased in women with SLE. Low levels of 25(OH)D have been associated with disease activity and cardiovascular (CV) risk factors in SLE. CV events and subclinical atherosclerosis are increased in women with SLE.

Objective: Determine if baseline 25(OH)D level predicts progression of subclinical atherosclerosis in women with SLE.

Methods: Demographic, traditional CV risk factors, disease activity (SLEDAI) and severity (ACR/SLICC-DI), medications and imaging to assess subclinical atherosclerosis by carotid B-mode ultrasound to measure carotid plaque index (PI), intima-media thickness (IMT) and electron beam or multidimensional computed tomography to measure coronary artery calcification (CAC), and aortic calcification (AC) were measured at baseline and 3 yrs later in the Study of Lupus Vascular and Bone Long-Term Endpoints (SOLVABLE). Abnormal PI, CAC, and AC were defined as PI≥1, CAC>10 and AC>100. Progression at 3y was defined as abnormal and an increase in PI, CAC>10 and AC>100 with an increase of >10% in CAC and AC. Hypertension (HTN) was defined as SBP≥140 or DBP≥90 or on treatment. Regression models investigated the relationship between PI, CAC, AC, and IMT and traditional CV risk factors, SLEDAI and ACR/SLICC-DI as well as baseline 25(OH)D (adjusted for age, race, & season) and progression of each imaging marker.

Results: In 118 women, mean±SD age, disease duration, SLEDAI, ACR/SLICC-DI, and 25(OH)D levels at baseline were 44.3±9.6 yrs, 12.6±8.8, 3.6±3.2, 1.7±1.7 and 28.2±11.6 ng/mL, respectively. Preliminary imaging data at baseline and 3y followup were available on 118 women for IMT and PI, 91 with CAC, and 56 with AC. The frequency at baseline (#, %) of abnormal PI, CAC, and AC was 45 (38%), 21(23%), and 16 (29%), respectively. The frequency of progression at 3y followup (#, %) of PI, CAC, and AC was 34 (29%), 23 (25%), and 24 (61%), respectively. 13, 5, and 9 patients progressed from normal to abnormal at 3y followup visit for PI, CAC, and AC, respectively. The mean (SD) for IMT at baseline and 3y followup was 0.61 (0.12) and 0.64 (0.15), respectively. IMT change was associated with triglycerides (p=0.035, β=0.019,95% CI 0.001–0.037). PI, AC, and CAC progression were associated with HTN (p=0.045,OR=3.96,95% CI 1.14–18.41), (p=0.038,OR=2.91,95% CI 1.09–8.30), (p=0.017,OR=3.59,95% CI 1.32–10.98), respectively. AC and CAC progression were associated with ACR/SLICC-DI (p=0.003, OR=1.61,95% CI 1.20–2.26), (p=0.002, OR=1.63,95% CI 1.22–2.25). CAC progression was also associated with fibrinogen (p=0.039,OR=1.64,95% CI 1.03–2.70).

Vitamin D and Progression of PI, CAC, AC, and IMT

Imaging Type	Adjusted vitamin D model β	OR	95% CI	p
PI		0.73	0.33,1.48	0.40
CAC		0.95	0.51,1.74	0.88
AC		1.18	0.62,2.26	0.62
IMT	−0.02		−0.04,0.002	0.08

Conclusion: These preliminary results suggest that baseline 25(OH)D levels did not predict progression of PI, CAC, AC, or IMT over 3 yrs in women with SLE. However, traditional CV risk factors and SLE-related markers may be important in predicting progression of vascular bed abnormalities.

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Progression of Carotid Atherosclerosis and Its Determinants in Lupus Patients. Rosa Weiss Telles[3], Cristina Costa Duarte Lanna[3], Tulio Pinho Navarro[3], Adriano Jose Souza[1], Rodrigo Citton Padilha Reis[4], Fabiana Lemos Sousa[2], Luciana Andrade Rodrigues[3] and Antonio Luiz Ribeiro[3]. [1]Clinica Radiologica CONRAD, Brazil, [2]Hospital das Clinicas, Universidade Federal de Minas Gerais, Brazil, [3]School of Medicine - Universidade Federal de Minas Gerais - Brazil, [4]Statistics Department - Universidade Federal de Minas Gerais - Brazil

Objective: to determine the rate and risk factors of carotid atherosclerosis progression in patients with Systemic Lupus Erythematosus (SLE)

Patients and Methods: carotid intima-media thickness (IMT) and plaque were obtained by ultrasound at an interval of 39(37–42) months in 157 lupus patients out of 181 patients initially included in a prospective study. Progression of atherosclerosis was defined by either an increase of common carotid IMT>0.15mm or a higher plaque score. Traditional risk factors for coronary heart disease (CHD) and SLE-related factors were assessed longitudinally. Poisson regression was used to assess the predictors of atherosclerosis progression, given robust relative risk (CI95%) for each independent variable.

Results: The cohort was 96.2% female, 75.8% non-white, with a median (IR) age at baseline of 38(29–46) years. Median (IR) age at lupus diagnosis and disease duration was 27.3(21.5–34.7) years and 7.72 (4.31–11.44) years, respectively. A common carotid IMT increase of 0.06(−0.01–0.14)mm was detected, with a mean annual increase of 0.018(−0.003–0.015)mm. Forty three patients (27.4%) had progressive atherosclerosis: nine(5.7%) had higher plaque score, 31(19.7%) increase in IMT>0.15mm and 3(1.9%) both. Univariate determinants of atherosclerosis progression were age at baseline (p=0.017), SLE duration (p=0.004) and triglycerides level (p=0.024). Nephrotic proteinuria (p=0.063) and the use of prednisone for a longer period (p=0.056) were more frequent in patients with progression, although not statistically significant. Multivariate determinants of atherosclerosis progression were duration of SLE (p=0.007; RR=1.06 CI95%=1.03–1.10) and nephrotic proteinuria (p=0.021; RR=4.22 CI95%=2.18–8.15). Traditional risk factors for CHD were not independently related to atherosclerosis progression.

Conclusion: Atherosclerosis progresses in a substantial number of young SLE patients during short-term follow up. SLE-related risk factors were associated with IMT and plaque progression after controlling for the traditional risk factors for CHD.

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Regional Brain Diffusion Abnormalities in Systemic Lupus Erythematosus. Simone Appenzeller[3], Leticia Rittner[4], Gabriel Leonard[1], Martin Vielleux[2], Bruce Pike[1] and Ann Clarke[1]. [1]McGill University, Canada, [2]McGill University, Canada [3]State University of Campinas, Brazil, [4]State University of Campinas, Brazil

Objective: To determine regional brain diffusion abnormalities and to evaluate the relationship between diffusion parameters [fraction anisotropy (FA) and mean diffusivity (MD)] and cognitive impairment and mood disorders in systemic lupus erythematosus (SLE).

Method: We screened consecutive female SLE patients followed in a longitudinal cohort between 2007/2008. We excluded patients with any factors associated with cerebral atrophy or vasculopathy [i.e., age ≥ 50 years, hypertension, renal insufficiency, transient ischemic attack or stroke, scleroderma features, diabetes, drug abuse, or malignancy] or not educated primarily in English or French. Healthy age-matched women were selected as controls. All underwent a standardized neuropsychological evaluation assessing the following: simple attention, complex attention, memory, visuospatial processing, language, reasoning/problem solving, psychomotor speed, and executive functions. Individual results were converted into standard scores and compared to normative data. Subjects with a total score in any of the 8 domains ≤2 SD below the normative value were considered impaired. Mood disorders were determined by Becks Depression and Becks Anxiety Inventory (BDI and BAI). Magnetic resonance imaging (MRI) was performed on a Siemens 3 Tesla scanner and volumetric T1, T2 and PD weighted images were used for automatic segmentation of the brain. Diffusion images were acquired in 63 directions (b=1000s/mm2; TR=10900ms; TE=105ms; FOV=256mm). Brain regions of interest (ROI) were overlaid to the diffusion images acquired and FA and MD were calculated for each structure. The FA and MD values were compared between groups using the t-test. Correlation between cognitive impairment, mood disorders and FA and MD was assessed through the Pearson correlation.

Results: Twenty-seven patients (mean age 34.08, SD 8.85) and ten controls (mean age 33, SD 8.3) were included. We observed significantly lower FA and higher MD in SLE when compared to controls in the following white matter structures: bilateral frontal lobe (p=0.01), right temporal lobe (p=0.031), bilateral parietal lobe (p=0.02), in addition to bilateral amigdala (p=0.005) and the thalamus (p=0.01). No difference between diffusion parameters were observed in the hippocampus, left frontal lobe, occipital lobes, cerebellum, corpus callosum, caudate, putamen and parahippocampal region. FA and MD of the amigdalacorrelated with the severity of anxiety (r=0.7; p=0.001) and FA and MD of the frontal lobe with cognitive impairment (r=0.56; p=0.03).

Conclusion: Diffusion abnormalities are not uniform in SLE patients. Increased MD and reduced FA, indicating reduction in myelination and axonal damage were observed in frontal, temporal, parietal white matter and in the amigdala. The severity of anxiety and the presence of cognitive impairment correlated with axonal damage in the amigdala and in the frontal lobe white matter. Diffusion parameters can be used to evaluate SLE patients with central nervous system manifestations and visually normal MRIs.

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Renal Biopsy in Systemic Lupus Erithematosus Patients with Low Levels of Proteinuria. Esther Rodriguez, Julio Sánchez, Eva Salgado, Isabel Mateo, María Galindo and Patricia E. Carreira. Rheumatology Department, Hospital 12 de Octubre, Madrid, Spain

Objective: To evaluate the need of performing renal biopsy in SLE patients with low levels of proteinuria.

Patients and Methods: From 443 patients included in our SLE data base (1974–2009), 150 with biopsy proven lupus nephritis were selected. Demographic (sex, age at onset and diagnosis, death), clinical (type of nephritis, proteinuria, urinary casts, creatinine, aDNA, complement, high blood pressure –HBP-), treatment and outcome (renal failure, relapse, death) data, had been previously included in the data base, or were obtained from the charts. In patients with proteinuria <1 g/d, relationship between clinical data and renal histology, and risk factors for relapse and renal failure were analyzed. Clinical and outcome data were compared between patients with proteinuria lower and higher than 1 g/d. Chi square, Student t test and binary logistic regression were used for statistics.

Results: Out of 150 patients, 42 (29%; 39 f, 3 m; age 30±14 a) had proteinuria <1g/d. Ten patients (24%) did not have renal symptoms, 15 (37%) presented HBP, 8 (19%, all with HBP) creatinine elevation, 9 (21%) granular casts, 26 (62%) aDNA and 36 (86%) low complement levels. Renal biopsies showed: minimal changes 1 (2%), mesangial GN 18 (43%), focal proliferative GN 7 (17%), diffuse proliferative GN 12 (29%) and membranous GN 4 (9%). No correlation between clinical characteristics and histological findings were found. One patient did not receive any treatment, 19 received only glucocorticoids, 15 cyclophosphamide, 6 azathioprine and 1 mophetil mycophenolate. Thirty seven (97%) responded well to therapy (28 complete and 9 partial response). After 14±8 years of follow up, 8 patients relapsed, 6 developed renal failure and 6 died. Presence of proliferative/membranous GN was a risk factor for relapse in this group (p<0.0001). Renal failure in patients with low levels of proteinuria was related to the presence of HBP (p<0.001) and creatinine elevation (p=0.006). Compared to 107 patients with higher proteinuria levels, these had more frequently diffuse proliferative GN (p=0.007) and more relapses (p=0.03). Both groups developed renal failure with similar frequency.

Conclusions: More than half SLE patients with low proteinuria levels present severe disease on renal biopsy. Although they present less diffuse proliferative GN and renal relapses than patients with higher proteinuria, may develop renal failure with the same frequency. Our results support the convenience of performing renal biopsy and careful follow-up to patients with low proteinuria levels, especially if HBP and/or creatinine elevation are present.

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Safety Profile of Belimumab, a BLyS-Specific Inhibitor, in Patients with Active Systemic Lupus Erythematosus (SLE): Pooled Data from Phase 2 and 3 Studies. D. J. Wallace[1], S. Navarra[12], A. Gallacher[2], R. Gúzman[10], M. Thomas[7], R. A. Furie[8], O. Zamani[9], R. A. Levy[4], R. van Vollenhoven[11], S. Cooper[6], Z. J. Zhong[5], W. Freimuth[6], L. Pineda[6], R. Cervera[3] and for the BLISS-52 and -76 and LBSL02/99 Study Groups. [1]Cedars-Sinai/UCLA, Los Angeles, CA, [2]Hospital Británico de Buenos Aires, Argentina, [3]Hospital Clinic, Barcelona, Spain, [4]Hospital Universitário Pedro Ernesto, Rio de Janeiro, Brazil, [5]Human Genome Sciences, Inc, Rockville, MD, [6]Human Genome Sciences, Inc, Rockville, MD, [7]Kerala Institute of Medical Sciences, Kerala, India, [8]North Shore LIJ Health System, Lake Success, NY, [9]Rheumazentrum Favoriten, Wien, Austria, [10]SaludCoop, Bogotá, Colombia, [11]The Karolinska Institute, Stockholm, Sweden, [12]University of Santo Tomas Hospital, Manila, Philippines

Purpose: To provide phase 2 and 3 clinical trial safety data on belimumab in SLE patients.

Methods: Safety data were evaluated in 2133 patients with seropositive SLE from 1 phase 2 (LBSL02; N=449; NCT00071487) and 2 phase 3 (BLISS-52; N=865; NCT00424476; and BLISS-76; N=819; NCT00410384), multicenter, double-blind, placebo-controlled studies of belimumab (1 and 10 mg/kg in all studies, plus 4 mg/kg in phase 2 only). Belimumab or placebo was infused over 1–2 h on d 0, 14, and 28, and q28d thereafter, for 48 or 72 wk. All patients received SLE standard of care (SOC), including various combinations of corticosteroids, antimalarials, and immunosuppressants. Clinical and laboratory findings were monitored at every scheduled visit and adverse events (AEs) were reported as they occurred. All 3 studies had a 52-wk placebo-controlled phase; only BLISS-76 had a controlled phase to wk 76. Pooled data of belimumab 1 and 10 mg/kg were compared with placebo. Since the 4-mg/kg dose was not used in the phase 3 studies and can only be appropriately evaluated within LBSL02, it was not included in the table.

Results: There were no remarkable differences between the belimumab 1- and 10-mg/kg, and placebo groups when AEs were categorized by severity, seriousness, or whether they resulted in discontinuation of study agent. Rates of different AEs are shown in table. Rates of infections were numerically slightly higher in the belimumab groups, while rates of serious and/or severe infections were comparable across all groups. Rates of infections of special interest (using a composite definition for each), such as sepsis, cellulitis, herpes, fungal, and respiratory infections, were comparable among all treatment groups. Rates of infusion reactions were numerically slightly higher in the belimumab groups. There were no reports of malignancy, death, or serious hypersensitivity/infusion reactions with the 4-mg/kg dose during the double-blind period. The rate of malignancy, excluding nonmelanoma skin cancers, per 100 patient-y in patients exposed to belimumab was similar to the rate in SLE patients reported by Bernatsky et al (2005). The safety profile of the 4-mg/kg dose was comparable to those of the 1- and 10-mg/kg doses, and placebo in LBSL02.

Conclusions: Overall, belimumab plus SOC therapy was generally well tolerated, with a safety profile comparable to placebo plus SOC.

Table. Integrated Safety Data of 52-Wk Double-Blind Phase

		SOC + Belimumab	
	SOC + Placebo (n=675)	1 mg/kg (n=673)	10 mg/kg (n=674)
% patients with ≥ 1:			
AE in general	92.4	93.0	92.7
AE resulting in discontinuation	7.1	6.2	6.7
Serious and/or severe AE	21.5	23.0	22.6
AE infections in general	66.7	71.0	69.9
AE infection resulting in discontinuation	1.0	0.7	0.6
Serious and/or severe AE infection	6.7	7.3	5.9
AE infections of special interest			
Cellulitis	6.4	8.2	6.4
Sepsis	0.4	0.6	0.7
Fungal	3.3	3.0	2.5
Herpes viral	8.0	7.6	6.5
All respiratory	48.4	50.8	51.9
Lower respiratory	8.6	11.3	12.0
Possible opportunistic	0	0	0.3[a]
All Infusion/hypersensitivity reactions, %	14.7	16.6	16.8
Hypersensitivity reactions	0.1	1.3	0.4
Infusion/hypersensitivity reactions resulting in discontinuation, %	0.3	0.6	1.0
Hypersensitivity reactions resulting in discontinuation	0	0.3	0.3
Serious and/or severe infusion/ hypersensitivity reactions, %	0.6	1.2	1.2
Serious and/or severe hypersensitivity reactions	0	0.3	0.3
Death, %	0.4	0.7	0.9
Malignant neoplasm, %	0.3	0.6	0.4
Solid organ	0.1	0.6	0
Nonmelanoma skin	0.1	0	0.4
Hematologic/plasma cell	0	0	0

All malignancies[b] excluding non-melanoma skin cancers vs historical data

	Background[c] N=9547	All Belimumab Doses[c] N=1955	Belimumab: Background Ratio
Patient y	76,948	3507	
Patients with events, n (%)	410 (4.3)	17 (0.9)	
Rate/100 patient-y (95% CI)	0.53 (0.48, 0.59)	0.48 (0.28, 0.78)	0.91 (0.52, 1.47)

[a]1 report of Acinetobacter bacteremia and 1 of disseminated cytomegaloviral infection; [b]Bernatsky S et al. *Arthritis Rheum.* 2005;52:1481–90; [c]includes all studies: phases 1–3, and long-term, open-label, continuation trials as of 12/31/09.
CI, confidence interval.

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1173

Second Renal Biopsy in Proliferative Lupus Nephritis. Alberto Allievi[2], Ana Malvar Perrin[2], Bruno Lococo[2], Mariac Cristina Basta[2], Paola Pirruccio[2], Sebastian Andres Muñoz[2], Alejandra Quevedo[2], Bernarda Fazzini[2], Valeria Alberton[2] and Alejandro Iotti[1]. [1]Hospital Britanico, Ciudad Autonoma de Buenos Aires, Argentina, [2]Hospital Juan A Fernandez, Ciudad Autonoma de Buenos Aires, Argentina

Background: Renal biopsy is one of the main diagnostic tools in lupus nephritis. Disease activity and prognosis can be established through a systematic light microscopic and indirect immunofluorescence analysis of renal tissue. Ultrasonographic guided biopsy has made the collection of renal tissue a common and safe procedure in clinical nephrology. Frequently only clinical parameters are used to evaluate therapeutic response. Correlation between clinical response and histopathology is not always present.

Purpose: To compare the predictive value of clinical and histopathological criteria after six month of induction therapy in diffuse proliferative lupus nephritis at two years.

Methods: thirty three SLE patients with diffuse proliferative lupus nephritis were evaluated prospectively between august 2002 and september 2007. A second renal biopsy was performed after induction treatment with six pulses of cyclophosphamide in 29 patients and sodium mycophenolate in four patients. All patients completed 2 years of maintenance treatment. Responders were treated with azathioprine. We compared between clinical parameters and second renal biopsy findings as predictors of clinical outcome after 24 months. Renal biopsies were evaluated by two experienced renal pathologists blinded to clinical data. The ISN/RPS 2003 classification was used. Serum creatinine levels and 24 hr proteinuria were compared with the second biopsy histopathological findings as predictors of clinical outcome after 24 months. Patients were categorized according to their response to treatment. Those patients with complete or partial response were defined as responders. Clinical response was based on increase or decrease of 24 hs proteinuria and creatinine. Histological response was assesses according to the activity and chronicity index. The increase of both parameters was considered no response, the disparity of both was apartial response and the improvement of both parameters was considered response.

Results: Thirty three patients were assessed according to the protocol. We

have biopsy results for all of them and they have been followed for 2 years. Seven patients presented membranous glomerulopathy in the second renal biopsy, 6/7 had good clinical evolution two years later. 19/26 patients with good clinical response after induction treatment were in low concordance with clinical evolution two years after (46.15 %; Spearman's: 0.1785, Kappa: 0.13). Second renal biopsy performed after induction treatment revealed information more accurate about two years clinical evolution with concordance of 73.08 % (Spearman's: 0.57, Kappa: 0,50, p<0,001).

Conclusions: In our experience, membranous nephropathy in the second renal biopsy was coincidental with good clinical evolution. Second renal biopsy revealed more accurate information than clinical evolution.

Disclosure: A. Allievi: None; **A. Malvar Perrin:** None; **B. Lococo:** None; **M. C. Basta:** None; **P. Pirruccio:** None; **S. A. Muñoz:** None; **A. Quevedo:** None; **B. Fazzini:** None; **V. Alberton:** None; **A. Iotti:** None.

1174

Seroprevalence of NMO-IgG (Anti-Aquaporin 4 Antibodies) in Patients with Neuropsychiatric Systemic Lupus Erythematosus. Jakub Zavada[4], Petra Nytrova[1], Klaus-Peter Wandinger[2], Svobodova Radka[4], Ivana Putova[4], Dana Tegzova[4] and Jiri Vencovsky[3]. [1]Department of Neurology, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Czech Republic, [2]Institute of Experimental Immunology, Euroimmun, Lübeck, Germany, [3]Institute of Rheumatology, Prague, Czech Republic, [4]Institute of Rheumatology and First Faculty of Medicine, Charles University in Prague, Czech Republic

Background: Neuropsychiatric manifestations are present in up to 60% of patients with systemic lupus erythematosus (SLE) with psychosis, seizures, headaches and cerebrovascular accidents being most common. However, transverse myelitis has also been described in aproximately 1–2% of SLE patients. Neuromyelitis optica (NMO) is an inflammatory demyelinating disease (syndrome) of the central nervous system (CNS), characterized by sequential or concomitant attacks of transverse myelitis (TM) and optic neuritis (ON), and has occasionally been reported in conjunction with SLE. The distinction between myelitis associated with NMO-IgG and myelitis of another etiology may be difficult but crucial for futher treatment and prognosis of the involved patients. The serum autoantibody NMO-IgG (anti-aquaporin 4 antibody) is considered to be a sensitive and specific marker for NMO. The antigenic target of these antibodies is aquaporin-4 (AQP4), the most abundant water channel in the CNS. Although the prevalence of NMO-IgG antibodies was examined in minor cohorts of patients with established SLE, only one very recent study reported data on SLE patients with established neuropsychiatric involvement. That is why we decided to evaluate the NMO-IgG seroprevalence in another larger cohort of patients with diagnosed neuropsychiatric lupus (NPSLE).

Patients and Methods: We have retrospectively studied NMO-IgG (anti-AQP4 Ab) in sera of 50 patients with NPSLE. All of the patients fulfilled the American College of Rheumatology (ACR) criteria for SLE and suffered from neuropsychiatric involvement as defined by the ACR nomenclature for NPSLE. Only one of them was treated for TM. ON was not documented in this strictly defined cohort. NMO-IgG (anti-AQP4 Ab) has been tested by indirect immunofluorescence on AQP-4 transfected HEK cells

Summary of the Results: Only one of the examined sera (in the patient with TM who has not fulfilled the criteria for NMO) has been positive for NMO-IgG (anti-AQP4 Ab). None of the remaining 49 NPSLE patients without documented concomittant ON or TM has been found to be seropositive for NMO-IgG (anti-AQP4 Ab) antibodies.

Conclusion: These findings support the notion that NMO-IgG (anti-AQP4 Ab) could play a role in the pathogenesis of some cases of TM and/or ON. NMO-IgG (anti-AQP4 Ab) are not detectable in NPSLE patients without TM and/or ON. However, in patients with SLE and concomitant ON/TM, it is very useful to assess the NMO-IgG (anti-AQP4 Ab) in serum due to selection of a suitable treatment regimen.

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1175

Serum Free Light Chains and Disease Activity in Systemic Lupus Erythematosus. Meenakshi Jolly[1], Rohit Aggarwal[4], Rachel Mikolaitis[3], Joel A. Block[2] and Winston Sequeira[1]. [1]Rush University Medical Center, Chicago, IL, [2]Rush University Medical Center, Chicago, IL, [3]Rush University Medical Center, [4]University of Pittsburgh Medical Center, Pittsburgh, PA

Purpose: We previously reported the superiority of using Total Free Light Chains (TFLC) as a biomarker of disease activity as compared to high sensitivity DsDNA and IgG in 75 patients with Systemic Lupus Erythematosus (SLE). Herein we report our experience with the use of TFLC in 205 SLE patients as a biomarker for disease activity.

Methods: 211 consecutive consenting SLE patients attending an outpatient Rheumatology clinic at a University Hospital were enrolled. Disease activity was assessed using physician global assessments (PGA) and Selena-SLEDAI. Adjusted SLEDAI (adjSLEDAI= SLEDAI – [C3C4 and Ds-DNA score]) was obtained. Serum FLC (Kappa (κ), Lambda (λ) and total FLC ($\kappa + \lambda$)) was measured using nephelometry (Binding site, UK). Additional data on DsDNA (positivity {n=182} and titres {n=171}) and complement (C3 & C4 abnormality {n=171} and titres {109}) were available from the same blood sample. Spearman correlation was used to correlate total FLC, DsDNA positivity, titre, Complement abnormality and titre with PGA, SLEDAI and adjusted SLEDAI. Mann-Whitney or Kruskall Wallis test was used to compare continuous data.

Results: The mean age was 42±13 yrs. African American 45%, Caucasian 30%, Hispanic 12%, Asian 10% and Others 4%. PGA and SLEDAI were (mean± SD, median) 0.7± 0.8, 0.5 and 4.2 ±4.3, 2 respectively. Fifty six percent were taking prednisone. The TFLC values (mean± SD, median) were 62.5 ± 69.8, 44.3. Correlations are tabulated below.

Table 1. Correlation between markers and disease activity.

	TFLC	DsDNA abnormality	DsDNA titre	Complement abnormality	C3 titre	C4 titre
PGA	0.39 (P=0.0001)	0.39 (P=0.0001)	0.34 (P=0.0001)	−0.14 (P=0.07)	−0.24 (P=0.01)	−0.14 (P=0.16)
SLEDAI	0.44 (P=0.0001)	0.49 (P=0.0001)	0.47 (P=0.0001)	−0.13 (P=0.16)	−0.41 (P=0.0001)	−0.23 (P=0.03)
Adj-SLEDAI	0.39 (P=0.0001)	0.23 (P=0.03)	0.211 (P=0.05)	−0.08 (P=0.45)	−0.15 (P=0.22)	−0.12 (P=0.31)

Conclusions: TFLC is correlated with disease activity, even after removing DsDNA and complement information from the disease activity score. Its correlation with adjusted SLEDAI is the strongest as compared to DsDNA positivity, titres, complement abnormality or complement titres. These data suggest that TFLC may serve as a potential biomarker for SLE, especially in the patients who lack DsDNA antibodies. Longitudinal studies are now indicated.

Disclosure: M. Jolly: The Binding Site, 2; **R. Aggarwal:** The Binding Site, 2; **R. Mikolaitis:** None; **J. A. Block:** The Binding Site, 2; **W. Sequeira:** The Binding Site, 2.

1176

Shrinking Lung Syndrome Is Associated with Pleuritis. David Allen[3], Zoheir Bshouty[3], Mellissa Moyen[3], David B. Robinson[3], Christine A. Peschken[1], Carol A. Hitchon[3], Hani S. El-Gabalawy[2] and Shikha Mittoo[1]. [1]Univ of Manitoba, Winnipeg, MB, Canada, [2]University of Manitoba, Winnipeg, MB, Canada, [3]University of Manitoba, Winnipeg, MB, Canada

Background: Shrinking lung syndrome (SLS) is a form of pulmonary damage in systemic lupus erythematosus (SLE) characterized by unexplained dyspnea, small lung volumes and restrictive lung physiology with or without diaphragmatic elevation. The pathophysiology of SLS is incompletely understood but is associated with significant morbidity and may require escalation of therapy to avoid fulminant respiratory failure. Pleuritis has been reported in 30–60% of patients with SLS. We set out to determine the frequency of SLS in patients with SLE and if pleuritis is associated with SLS.

Methods: Consecutive patients ≥ 18 years of age who met American College of Rheumatology (ACR) criteria for SLE were enrolled. Demographics, disease duration, smoking status, body-mass index (BMI), self-reported dyspnea, pleuritic chest pain (CP), autoantibodies and measures of disease activity; SLE Activity Measure (SLAM), cumulative organ damage (Systemic Lupus International Collaborating Clinics damage index (SDI), ACR criteria modified to exclude pulmonary variables (mACR) were recorded. All

patients underwent pulmonary function testing (PFTs) and chest imaging (X-ray or CT scan).

Pleuritis was defined as serositis by ACR criteria, relying on the presence of CP, a rub or a history of pleural effusion on chest X-ray. At enrollment, SLS was defined as a forced vital capacity (FVC) or total lung capacity (TLC) <80% predicted without evidence of interstitial/pleural disease on imaging or myositis/myalgia causing impairment.

Univariate and multivariate logistic regression was used to determine factors associated with SLS and the relationship between pleuritis and SLS. Results are reported as mean ± SD unless stated otherwise.

Results: One hundred patients (94% women, 81% Caucasian) with an age at diagnosis of 33.8 ± 13.8 years, disease duration of 13.2 ± 9.2 years, had a mACR of 5.5 ± 1.2, total SDI of 1.2 ± 1.2, and total SLAM of 7.1 ± 3.6. Fifty-four of 99 reported ≥ 1 respiratory symptom; 52/99 had dyspnea and 26/99 had CP. Thirty-four had SLS; 23/33 had dyspnea and 13/33 had CP. Dyspnea and CP was more common in those with SLS [n=25/34 (71%) vs n=27/65 (42%), p=0.006] and [n=15/34 (43%) vs n=11/64 (17%), p=0.007].

Thirty-five patients had pleuritis. SLS was more common among those with pleuritis compared to those without, [26/34 (57%) vs. 14/65 (22%), (p<0.0001)]. As well, disease duration (p=0.05), self-reported dyspnea (p=0.02), anti-RNP (p=0.001), anti-Sm (p=0.002), and mACR (p=0.02) were significantly associated with SLS. However, age at diagnosis, BMI, pCP, ethnicity, smoking status, SDI, SLAM and anti-dsDNA, anti-Ro, and anti-La, were not associated with SLS.

In multivariate analysis controlling for pleuritis, disease duration, self-reported dyspnea, mACR, presence of anti-RNP and Sm antibodies, only pleuritis remained associated with SLS [OR= 3.6, 95% CI of 1.3–10.1, p=0.02].

Conclusions: SLS was a frequent finding in this unselected cohort, occurring in 57% of patients and pleuritis was significantly associated with SLS. This suggests that pleural disease may be important in the etiology of SLS. Further, the presence of pleural disease in patients with SLE should result in an assessment for SLS.

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The Metabolic Syndrome in Systemic Lupus Erythematosus: More Than the Sum of Its Parts? Ben Parker[3], Yasmeen Ahmad[4], Joanna Shelmerdine[1], Sahena Haque[2] and Ian N. Bruce[1]. [1]Manchester, United Kingdom, [2]Manchester, United Kingdom, [3]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom, [4]Manchester Royal Infirmary, Manchester, United Kingdom

Purpose: The metabolic syndrome (MetS) is a clustering of metabolic abnormalities in individuals with increased adiposity and is associated with an increased risk of developing diabetes and coronary heart disease (CHD). The prevalence of the MetS is increased in SLE although rates of obesity are not. Therefore lupus-specific factors and inflammatory disease may be an important contributor to the metabolic derangements observed in those SLE patients with the MetS. The aim of this study is to determine those disease characteristics associated with the presence of the MetS and to investigate whether the MetS is associated with the presence of carotid plaque in patients with SLE.

Methods: Caucasian women with SLE were assessed in a cross-sectional observational study. Disease activity (SLEDAI), disease damage (SLICC-DI) and clinical characteristics were determined. The MetS was defined according to the 2009 Consensus Statement from the IDF and partners. All patients underwent B-mode ultrasound of the common carotid and proximal internal and external carotid arteries to detect plaque. Mutivariate logistic regression was performed to determine the association between disease characteristics and the MetS, and the presence of carotid plaque and the MetS.

Results: 200 women with SLE were assessed of whom 30% fulfilled the criteria for the MetS. Those meeting the MetS definition were older (median (IQR) age 53 (46, 59) years vs. 46.5 (41, 53) years, p = 0.001) and had a longer disease duration (median (IQR) 14 (6–22) years vs. 7 (4–16) years, p = 0.002) than those who did not. In a multivariate model the presence of the MetS was associated with age, disease duration and low C3 but not with average steroid dose.

Table 1. Lupus Features associated with the MetS

Variable	Age-Adjusted OR (95% CI)
Low C3	8.46 (1.25, 57.0))
Age	1.06 (1.01, 1.10)
Disease duration	1.05 (1.01, 1.09)
Steroids Ever	2.46 (0.69, 8.72)
Azathioprine Ever	2.06 (0.89, 4.75)
SLICC	1.35 (0.99, 1.85)
Renal Disease Ever	1.89 (0.63, 5.66)
Average Steroid Dose (6 months)	1.03 (0.97, 1.11)

Carotid plaque was present in 42% of SLE patients with the MetS compared to 23.5 % of patients without (p = 0.01). Overall, the MetS was not independently associated with the presence of carotid plaque (OR 1.7 (95% CI 0.8, 3.4). However, fulfilling IDF criteria for high blood pressure and hypertriglyceridaemia (OR 2.9 (1.3, 6.3) and 2.2 (1.1, 4.4) respectively) were both associated with the presence of carotid plaque.

Conclusions: The MetS is more prevalent with increasing age in SLE. Low complement and disease duration were independently associated with the presence of the MetS in SLE suggesting a role for inflammatory activity in contributing to the syndrome. The MetS was not associated with the presence of carotid plaque overall, although individual criteria were. Therefore a CHD risk assessment strategy attending to these individual risk factors would appear a more important way to modify CHD risk in patients with SLE.

Disclosure: B. Parker: None; **Y. Ahmad:** None; **J. Shelmerdine:** None; **S. Haque:** None; **I. N. Bruce:** None.

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The Prevalence of Liver Abnormalities in Patients with Systemic Lupus Erythematosus. Darryl Huang[2], Ellie Aghdassi[2], Jiandong Su[2] and Paul R. Fortin[1]. [1]Toronto Western Hospital, Toronto, ON, Canada, [2]University Health Network, Division of Rheumatology, Toronto, ON, Canada

Studies reporting on liver involvement in Systemic Lupus Erythematosus (SLE) are limited, often focused on liver transaminases and without inclusion of imaging procedures and/or liver biopsies. Furthermore, the etiology for the abnormal transaminases has not been investigated. This study determined in SLE patients: 1) the prevalence of abnormal liver function tests (LFTs) and whether further investigations were done; 2) the differences in SLE-related and/or metabolic factors in patients with and without abnormal LFTs. Patients who met at least 4 of the ACR classification criteria for SLE and had 1.5 times the upper limit for AST or ALT on two visits within a 2-year period were selected from the database registry of the University of Toronto Lupus Clinic. Demographic, and laboratory data at the time of the first appearance of LFTs abnormality were extracted from these patients as well as the age, gender and SLE duration matched controls who had normal LFTs. Disease activity and damage were assessed by SLE- Disease Activity Index (SLEDAI) and SLICC Damage Index (SDI). Chart review was performed to determine the contributing factors to these liver abnormalities. Data were analyzed using SPSS statistical program. Out of 1533 patients in the database, 135 (8.8%) with a mean (SD) ACR of 6.4 (1.5) met the inclusion criteria. The subjects had mean (SD): age of 40.1 (13.7) years, BMI of 25.9 (5.8) kg/m2, SLEDAI of 6.4 (5.4), SDI of 1.5 (1.8) and 83% were female. Among patients, 65% were Caucasian; 23% smoked; 30% consumed alcohol, 61% had hypertension, 7% had previous cardiovascular involvement and 68% had other autoimmune disorders. Medication profile of the two year period preceding the first abnormal LFT included: prednisone (67% of patients) with a mean (SD) dose of 12.1 (15.3) mg; antimalarial (63%), immunosuppressants (61%), statins (16%), hormone replacement therapy (13%) and anticoagulants (13%). Laboratory findings were normal for CBC, blood glucose and lipid profile except for serum triglycerides that was elevated (2.10 ± 2.04 mg/dl). The mean (SD) levels for AST and ALT were 73 (67) and 88 (79) respectively. Chart review completed in 60 of the patients, showed that only 12 patients were further evaluated by a Hepatologist, 30 had an abdominal ultrasound (US) (15 fatty liver, 3 fibrosis, 11 with suspected drug-induced hepatitis), and only 3 had a liver biopsy. However, only 15 of the US were done specifically for liver investigation. In the nested case control study of 134 matched subjects, cases had higher prevalence of: hypertension (60% VS. 46%, p=0.02); antiphospholipid syndrome (9% VS. 2% p=0.02); and immunosuppressants use (60% VS. 37%, p<0.001), especially azathioprine (39% VS. 22%, p<0.01) and methotrexate (22% VS. 10%, p<0.01) compared to controls. Although, BMI, SLEDAI and SDI were similar, blood biochemistry showed a significantly lower IgM (1.2 (0.7) vs 1.5 (1.0), p=0.03) and higher triglycerides (2.1 (2.1) vs 1.7 (1.2), p=0.05) among cases compared to the controls. Factors associated with the metabolic syndrome, such as obesity, insulin resistance, and hypertension, as well as side-effects of the drugs used in the treatment of SLE may contribute to liver abnormalities in SLE.

Disclosure: D. Huang: None; **E. Aghdassi:** None; **J. Su:** None; **P. R. Fortin:** None.

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Undertreatment of Active Disease May Increase Mortality in Lupus Patients with End Stage Renal Disease. Anna R. Broder[2] and Chaim Putterman[1]. [1]Albert Einstein College of Med, Bronx, NY, [2]Montefiore Medical Ctr, Bronx, NY

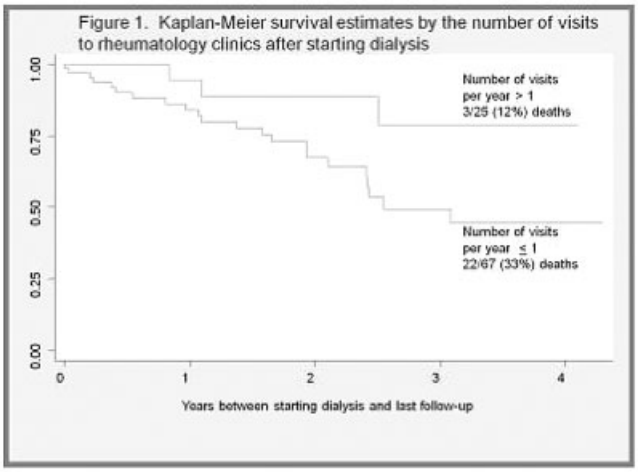
Background: Earlier studies have concluded that SLE becomes quiescent once end stage renal disease (ESRD) develops. However, more recent publications and our clinical experience suggest that SLE can remain active even in patients undergoing dialysis. SLE patients with ESRD receiving chronic dialysis may not be followed as closely by the rheumatologists, and, therefore, active SLE is underdiagnosed and undertreated.

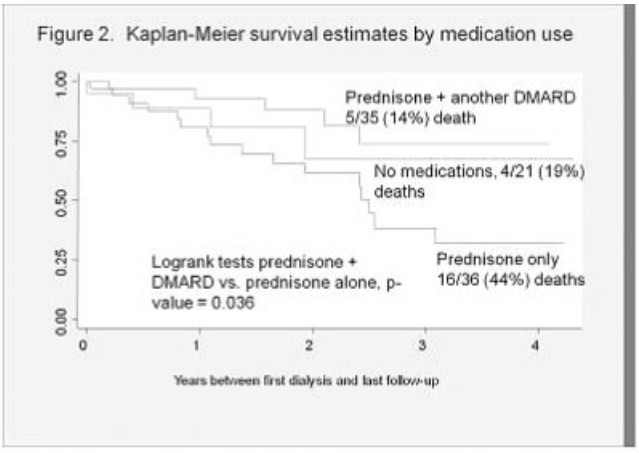
Methods: We identified all patients over 18 years old with SLE who started dialysis between 2000 and 2010 at a large urban tertiary care center. Mortality data was obtained using in-hospital records and Social Security Death Index database.

The number of rheumatology clinic visits was analyzed as 1 or more visits per year ("frequent") or between 0 to 1 visits per year ("infrequent"). Time to event was defined as the number of years from the start of dialysis to the last follow-up date.

Results: We identified 92 ESRD/SLE on dialysis, 79 women and 13 men, mean age 48 (±16) years. The median duration between first dialysis and last follow-up was 1.6 years IQR (0.5, 2.5). Twenty of these patients (22%) died during follow-up from various causes includin infections, GI or CNS hemorrhage, status epilepticus, and heart failure. ESRD/SLE patients seen frequently by rheumatologists were younger compared with patients followed infrequently (35 years old (28, 43) vs. 51 years old (41, 58)). The 2 groups were similar in terms of race/ethnicity and duration of follow-up.

The results of survival analysis are shown in Figures 1 and 2.





ESRD/SLE patients followed frequently in rheumatology clinics at our center had significantly lower mortality rates compared with patients followed infrequently, 3/25 (12%) vs. 22/67 (33%), log rank p-value =0.039; HR 0.24, 95% CI (0.07, 0.83), p=0.041 adjusted for age and the number of rheumatology visits before they began dialysis. Moreover, ESRD/SLE patients treated with prednisone alone had higher mortality rates compared with prednisone in combination with hydroxychloroquine, mycophenolate mofetil, or azathioprine, 16/36 (44%) vs. 5/35 (14%), logrank p = 0.036; adjusted HR 0.36, 95% CI (0.13, 1.0), p=0.05. We did did account for medication doses. Differential selection, misclassification, and medication compliance may have affected the results in this retrospective analysis.

Conclusions: Treatment with prednisone alone in ESRD/SLE patients may be associated with higher mortality rates compared to prednisone in combination with other DMARDS. Active disease in SLE patients on dialysis may be unrecognized and undertreated leading to increased mortality.

Disclosure: A. R. Broder: None; **C. Putterman:** None.

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Vitamin D Levels Are Positively Associated with Complement among Patients with SLE. Michelle A. Petri[1], Kayode Jibril Bello[2], Hong Fang[2] and Laurence Magder[3]. [1]Timonium, MD, [2]Johns Hopkins University School of Medicine, [3]University of Maryland School of Medicine

Purpose: Vitamin D deficiency is common in SLE. Vitamin D deficiency has been associated with diabetes mellitus, cardiovascular disease, and certain forms of cancer; all represent outcomes increased in SLE patients. In murine SLE models, Vitamin D is an immunomodulator. We investigated whether Vitamin D levels were associated with disease activity in patients who took vitamin D supplements for vitamin D deficiency.

Methods: As part of routine clinical care, 478 SLE patients were determined to have low levels of 25 OH Vitamin D (<32 ng/mL). 50,000 units Vitamin D was then given weekly for 12 weeks, with Ca/D 200 units twice daily. One physician measured the physician's global assessment (PGA) and SLEDAI at all visits. Linear regression models were used to estimate the association between change in vitamin D and change in various measues of disease activity. The dependent variables analyzed in the models were change in PGA, change in SLEDAI, change in Urine Protein/Creatinine Ratio, change in C3, change in C4, and change in anti-dsDNA. The independent variable was change in Vit D. Generalized estimating equations were used to account for the repeated observations from the same patients.

Results: The SLE patients were 91.7% female, mean age 44.9, 53.9% Caucasian, 38.3% African-American, 7.8% other ethnicity. At baseline, the mean PGA (0–3 VAS) was 0.6 ± 0.6 and mean SLEDAI was 2.0 ± 2.8. The mean 25 OH Vit D at baseline was 29.3 ± 14.4 and at 3 months was 35.9 ± 14.9.

Table 1. Effect of change in Vit D on disease activity by univariate analysis

	Estimated change in variable per 10 units increase in Vit D	P-Value
PGA	0.002 ± 0.012	0.9004
SLEDAI	0.029 ± 0.051	0.5680
Urine Pr/Cr Ratio	−0.009 ± 0.011	0.4124
C3	1.739 ± 0.542	0.0013
C4	0.315 ± 0.118	0.0076
Anti-dsDNA	2.281 ± 1.978	0.2487

Vit D levels were not associated with PGA, SLEDAI, urine protein/Creatinine ratio, but were associated with an improvement in C3 and C4.

Conclusion: Change of Vitamin D levels in this outpatient SLE population were neutral in terms of clinical disease activity. Further followup of this population will allow us to determine if there are delayed clinical effects. However, there was a statistically significant effect on both C3 and C4. The effect on C3 might have clinical implications in that low C3 is known to be associated with SLE renal disease and increases the risk of flare. This analysis cannot address the effects of "super" supplementation, since no attempt was made to achieve 25 OH Vit D levels higher than 40 ng/mL. However, the data suggest that clinical trials to achieve higher levels of 25 OH Vit D are indicated.

Disclosure: M. A. Petri: None; **K. J. Bello:** None; **H. Fang:** None; **L. Magder:** None.

1181

Acute Flares of Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) Are Sometimes Associated with Spikes of Interferon-alpha Activity in the CSF. Elisabet Svenungsson[2], Clio P. Mavragani[1], Liisa Hopia[3], Mohsen Khademi[3], Anna Laveskog[2], Mary K. Crow[1] and Magnus Andersson[2]. [1]Hospital for Special Surgery, New York, NY, [2]Karolinska Institutet, Stockholm, Sweden, [3]Karolinska Institutet, Sweden

Background: Neuropsychiatric involvement in Systemic Lupus Erythematosus (NPSLE) is a serious complication affecting a large proportion of systemic lupus erythematosus (SLE) patients. Diagnosis and treatment is a challenge as no specific biomarker/investigation for NPSLE is available. Enhanced interferon-alpha (IFN-a) activity has been identified as an important ethiopathogenic factor in SLE, and a previous study reported that IFN-a contributes to NPSLE. We investigated IFN-a activity in the systemic and intrathecal compartments of patients with acute and chronic symptoms of NPSLE.

Methods: 59 NPSLE patients, who fulfilled the ACR 1982 revised criteria for SLE, were evaluated clinically. Lumbar puncture and magnetic resonance imaging (MRI, n=56) was performed. All presented with one or several NPSLE manifestations as defined by the ACR NPSLE case definitions. The majority (n= 49) had chronic NPSLE symptoms but 10 were investigated during acute NPSLE flares. Paired blood and cerebrospinal fluid (CSF) samples were collected from patients and controls (15 Multiple Sclerosis (MS) patients, 22 patients with other neurological diseases (OND)). IFN-a activity was measured as a score with a functional cell reporter assay. mRNA expression of IFN-a was determined in peripheral blood and CSF mononuclear cells (PBMC, CSF-MC) in 39 patients and in a different set of controls (MS=34, OND=24).

Results: On a group level there were no differences between SLE patients and controls with respect to IFN-a activity or IFN-a mRNA expression in PBMCs or CSF-MCs, but IFN-a scores were higher in acute than in chronic NPSLE cases ($p=0.007$). A few patients, but no controls, had very high levels of IFN-a activity in CSF and blood. 4/10 acute vs. 5/49 chronic NPSLE patients had high (>+2SD) IFN-a activity in the CSF ($p=0.02$). A similar trend was observed in blood where 5/10 with acute vs. 5/49 with chronic NPSLE had high IFN-a scores ($p=0.07$). There was no corresponding increase in mRNA expression in CSF-MCs or PBMCs. Two patients had very high mRNA expression in CSF-MCs. One of these patients had an acute NPSLE flare. There was no specific NPSLE symptom (mood disorder, headache, cognitive dysfunction, seizures or previous infarction), CSF aberration or MRI finding, which was convincingly associated with high IFN-a activity or high expression of IFN-a mRNA.

Conclusion: Our results indicate that IFN-a activity in the CSF is high in some patients with NPSLE and is often associated with acute NPSLE symptoms. As a group, patients with chronic NPSLE had similar IFN-a activity in CSF and blood to controls. IFN-a activity may be of diagnostic potential in patients with SLE who present with acute neurological symptoms.

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1182

Allogeneic Mesenchymal Stem Cells Inhibited OAZ Expression in Patients with Systemic Lupus Erythematosus. Xuebing Feng[1], Rongliang Li[2], Jing Huang[2], Dandan Wang[2], Xiaolei Ma[2], Betty P. Tsao[3] and Lingyun Sun[2]. [1]Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China, [2]Affiliated Drum Tower Hospital of Nanjing University Medical School, [3]UCLA School of Medicine, Los Angeles, CA

Objective: Allogeneic mesenchymal stem cell transplantation (MSCT) has been applied to successfully treat patients with refractory systemic lupus erythematosus (SLE) (Sun et al A & R, 2010). However, the underlying mechanism is still unclear. Recently we have shown Olf1/EBF associated zinc finger protein (OAZ), a novel lupus susceptibility gene, involves in the production of antinuclear antibody (ANA) that is partly through the regulation of ID genes. This study is to explore whether allogeneic MSCT helps down-regulate elevated OAZ expression in SLE patients.

Methods: Study protocol was approved by the hospital's Ethics Committee. MSCs were isolated and expanded from bone marrow of 5 SLE patients and 6 healthy subjects. After culturing for 3 passages, MSCs were harvested and mRNA levels of OAZ and ID1, ID3, two downstream genes of OAZ, were measured by qRT-PCR. MSCs expanded from umbilical cord (9 cases) or bone marrow cells (1 case) of healthy donors were infused once to 10 refractory SLE patients at 10^6cells/kg of body weight. Peripheral blood cells (PBLs) were collected before and one week as well as four weeks after MSCT, and transcript levels of OAZ and IDs were measured. Concurrently, serum levels of IL-10, IL-12, IL-21, CCL2 and ANA were tested by ELISA. Relationships between gene expressions and cytokine levels as well as ANA values were analyzed. Data were shown as mean +/− SEM.

Results: Compared to PBLs, MSC expression of OAZ transcripts was 150 and 110 times higher in SLE patients and normal controls, respectively. OAZ expressions of MSCs in SLE patients were elevated compared to those in normal subjects ($p = 0.03$), but expressions of ID1 and ID3 were not different. Ten SLE patients (9 female and 1 male, 32.2 ± 3.7 years old) who accepted MSCT had decreased OAZ expressions in PBLs by 42.6% ±17.1% one week after MSCT compared to those before MSCT ($p < 0.05$) with concomitant reduction in disease activity (SLEDAI score was 14.9 ± 0.6 before MSCT, 13.0 ± 0.5 one week later) which continued to drop further four weeks after the transplant (a reduction of 37.6% ±12.4% compared to those at one week, $p < 0.05$). Peripheral gene expressions of ID1 and ID3 were also significantly down-regulated after MSCT ($p < 0.05$). Four weeks after MSCT, serum levels of IL-10, IL-21 and ANA were significantly decreased ($p < 0.05$ in all), while CCL2 level was elevated ($p < 0.05$) compared to the baseline levels. Compared to the value before MSCT, inhibited peripheral OAZ expression four weeks after MSCT was inversely correlated with reduced IL-21 levels ($r = -0.88$, $p < 0.05$) and ANA values ($r = -0.91$, $p < 0.01$) but positively correlated with increased CCL2 levels ($r = 0.92$, $p < 0.01$).

Conclusion: OAZ is highly expressed in MSCs from SLE patients. Allogeneic MSCT helps down-regulate OAZ expression and its downstream components, which may account for the ameliorated SLE disease activity. The differential expressions of ID1 and ID3 in peripheral blood cells but not MSCs support that MSCs could exert their roles through the regulation of other cells types.

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1183

Analysis of Vascular Endothelium from Female Systemic Lupus Erythematosus (SLE) Patients Identifies an Interferon Signature That Correlates with Disease Activity. Diana Goldenberg[3], Mikhail Olferiev[3], Duygu Onat[1], Danieli Andrade[3], Mary K. Crow[3], Paolo C. Colombo[1] and Jane E. Salmon[2]. [1]Columbia University College of Physicians and Surgeons, New York, NY, [2]Hospital for Special Surgery, New York, NY, [3]Hospital for Special Surgery, New York, NY

Background: Accelerated atherosclerosis has emerged as a significant threat to the health of patients with systemic lupus erythematosus (SLE). Endothelial dysfunction represents an important precursor to the development of atherosclerosis. The type I interferons likely influence the relationship between endothelial dysfunction and vascular health in lupus patients. To study the pathogenesis of endothelial dysfunction in SLE, we utilized a novel, minimally-invasive approach to sample venous endothelial cells (ECs) and perform gene expression profiling.

Methods: Venous endothelial cells were sampled from 11 adult SLE patients and 10 healthy controls. ECs were collected from arm veins using endovascular wires. ECs were purified; amplified RNA was hybridized with Affymetrix HG-U133 2.0. Samples were normalized to the baseline median level according to the RMA algorithm. Data was analyzed using GeneSpring GX 11 software. Student T test analysis for multiple samples was performed. Differentially expressed genes with >2.0 fold expression and $p<0.05$ were selected. SLE disease activity was assessed by SLEDAI at the time of endothelial sampling. The interferon score was determined using the mean of the normalized expression values for IFIT1, IFIT3, MX2 and OAS2. To simulate our in vivo findings and to determine whether SLE serum could directly alter endothelial cell gene profiles, we cultured HUVECs with sera from SLE patients and healthy controls and assessed their capacity to induce interferon-inducible genes, IFIT1, IFI44 and MX1 using Real-time quantitative polymerase chain reaction.

Results: Eleven (8 females, 3 males) adult SLE patients meeting American College of Rheumatology criteria for SLE and 10 age-matched controls

were studied. Their mean age was 32.2 ± 10.2 yrs, mean SLEDAI score was 6.82; range 0–20. Ten age-matched healthy subjects were studied. A total of 2013 known genes were differentially expressed (FC ≥2, p<0.05) between all SLE patients and controls while 183 known genes were differentially expressed (FC ≥2, p<0.05) between female SLE patients and matched controls. IFIT1 and IFIT3 were upregulated in the 11 SLE patients compared with controls. In female SLE patients the interferon signature was particularly robust: IFIT1, IFIT3, MX2 and OAS2 were upregulated. The interferon score correlated significantly with SLEDAI in female patients (R=0.75, p = 0.04). Similar to the results of our in vivo venous endothelial samples, HUVECs cultured with sera from SLE patients showed increased expression of the interferon inducible genes compared with those exposed to sera from control patients (109.1 ± 41.42 vs 0.04 ± 0.01).

Conclusions: Microarray analysis of primary venous endothelial cells distinguished SLE patients from healthy controls based on the expression of interferon-inducible genes. In the 8 female SLE patients, SLE disease activity correlated with the interferon score. These results support the possibility that interferon contributes to the pathogenesis of endothelial dysfunction in SLE patients.

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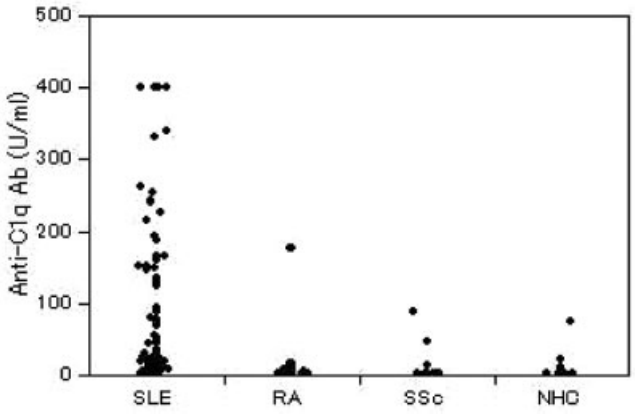
1184

Anti-C1q Antibodies Are Associated with Global Activity of Systemic Lupus Erythematosus, but Not Specifically with Nephritis. Yuko Okamoto[1], Yasuhiro Katsumata[5], Yasushi Kawaguchi[2], Kohei Miyake[5], Manabu Kawamoto[5], Kae Takagi[5], Takahisa Gono[5], Sayumi Baba[5], Yuko Ota[5], Masako Hara[4] and Hisashi Yamanaka[3]. [1]Tokyo Women's Medical University, Tokyo, Japan, [2]Tokyo Women's Medical University, Tokyo, Japan, [3]Tokyo Women's Medical University, Shinjuku-ku, Tokyo, Japan, [4]Tokyo Women's Medical University, Kamakura Kanagawa, Japan, [5]Tokyo Women's Medical University

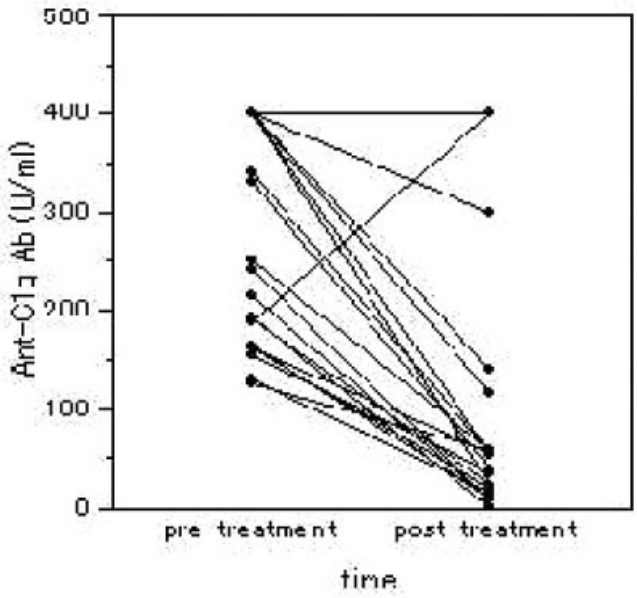
Purpose: Antibodies against complement C1q (anti-C1q Abs) are frequently found in patients with autoimmune diseases such as systemic lupus erythematosus (SLE). It has been reported that they correlate with the occurrence and activity of nephritis and cutaneous vasculitis in SLE. Additionally, their pathogenic role in SLE, such as direct link with apoptosis, has been suggested. However, the significance of anti-C1q Abs in SLE has not been fully characterized. This study was conducted to investigate associations between anti-C1q Abs and clinical and serological parameters of SLE.

Methods: Anti-C1q Abs were measured using ELISA kit (BÜHLMANN Laboratories AG, Schönenbuch, Switzerland) in sera of 126 consecutive active SLE patients who were admitted to our university hospital from 2007 through 2009. Sera of patients with high-titer anti-C1q Abs at initial evaluation were re-evaluated when their disease ameliorated (n = 20). Sera of patients with other autoimmune diseases and normal healthy controls were also assessed (n = 20 in each control group). Associations between anti-C1q Abs and clinical and serological parameters of SLE were statistically analyzed.

Results: The titers and the positivity rate of anti-C1q Abs were significantly higher in patients with active SLE than in patients with rheumatoid arthritis, systemic sclerosis, or normal healthy controls ($p < 0.0001$ in all comparisons).



Anti-C1q Abs were detected in sera of active SLE patients with various manifestations, which yields sensitivity of 63% and specificity of 90%. Inconsistent with previous reports with fewer samples, the titers or the positivity rate of anti-C1q Abs were not associated with active lupus nephritis (n = 23; $p = 0.75$ and 1.00, respectively). However, the titers of anti-C1q Abs were mildly correlated with the values of SLEDAI, anti-dsDNA Abs, C3, C4 and CH50 ($p < 0.0001$ in all comparisons). In addition, the titers of anti-C1q Abs significantly decreased in accordance with clinical amelioration by treatment in the cases with high-titer anti-C1q Abs at initial evaluation (median decrement 85%; $p = 0.0008$).



Conclusions: These findings indicate that anti-C1q Abs are associated with global activity of SLE, but not specifically with active lupus nephritis. Moreover, anti-C1q Ab might be useful as a surrogate marker of SLE in cases with this antibody.

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Biomarkers of Oxidative Stress, mTOR Activation, and Treg Depletion Correlate with Disease Activity in Patients with Systemic Lupus Erythematosus. Zhiwei Lai[1], Adam Bartos[1], Tiffany Tekarico[1], Robert Hanczko[1], Gabriella Miklossy[1], Brandon Clair[1], John Jimah[1], Lisa Francis[1], Hajra Tily[1], Ricardo Garcia[1], Maha Dawood[1], David R. Fernandez[1], Paul E. Phillips[2], Ioana Coman[1] and Andras Perl[3]. [1]SUNY, [2]SUNY-Upstate Medical Univ, Syracuse, NY, [3]Upstate Medical Univ, Syracuse, NY

Purpose: Systemic lupus erythematosus (SLE) patients' T cells exhibit persistent elevation of the mitochondrial transmembrane potential ($\Delta\Psi m$) or mitochondrial hyperpolarization (MHP) which predisposes to pro-inflammatory death via necrosis. Persistent MHP has been attributed to the depletion of reduced glutathione (GSH) and increased production of nitric oxide (NO) and reactive oxygen intermediates (ROI). Here, we evaluated metabolic checkpoints of mitochondrial dysfunction as biomarkers of disease activity in patients with SLE.

Patients and Methods: 34 female SLE patients and 34 female healthy controls were studied. 24 patients with stable disease were enrolled in double-blind placebo-controlled treatment trial with N-acetylcysteine (NAC; ClinicalTrials.gov identifier: NCT00775476). 10 patients with uncontrolled disease due to lack of efficacy or tolerance to current medications were enrolled in prospective treatment trial with rapamycin (RAPA; NCT00779194). SLE disease activity was assessed by using the British Isles Lupus Assessment Group (BILAG) and SLE Disease Activity Index (SLEDAI). Peripheral blood lymphocytes (PBL) and untouched T cells (using Dynal negative T-cell isolation kit) were freshly isolated on the same morning from patients and controls matched for ethnicity and age within 10 years and investigated in parallel for $\Delta\Psi m$, mitochondrial mass, glutathione, NO and

ROI production, cytosolic ([Ca2+]c) and mitochondrial calcium levels ([Ca2+]m), and T and B cell subset distribution by flow cytometry after 24 with or without CD3/CD28 co-stimulation. mTOR activity was assessed through the phosphorylation of its substrates by western blot. Spearman's correlation coefficients rho and the two-tailed significance levels were estimated in SPSS version 17.

Results: SLEDAI (8.6 +/− 1.2) and BILAG (24.6 +/−1.8) of 24 patients enrolled in the NAC trial were exceeded by the SLEDAI (16.5 +/− 2.9; p = 0.004) and BILAG (33.0 +/− 4.4; p = 0.04) scores of 10 patients enrolled in the RAPA trial. MHP, increased mitochondrial mass, increased [Ca2+]c, and increased NO production were detected in all T cell subsets irrespective of disease activity. mTOR activity was increased in negatively isolated T cells. Foxp3 expression was reduced CD4+/CD25+ Treg cells. [Ca2+]c was also increased in CD19+ B cells. Across all patients, individual total SLEDAI scores best correlated with glutathione depletion (p=0.002) and ROI elevation in T cells (p=0.008). Within SLEDAI components, anti-DNA titers were correlated with increased [Ca2+]m in CD3+/CD4+, CD3+/CD4-/CD8- (p < 0.008) but not in CD3+/CD8+ T cells. Leukopenia was correlated with diminished CD4+/CD25+ T cells (p=0.003).

Conclusion: While mitochondrial dysfunction is detectable in lupus T cells irrespective of disease activity, oxidative stress characterized by the depletion of GSH and increased ROI production as well as activation of mTOR and Treg depletion may represent biomarkers of disease activity in patients with SLE.

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CD138 RNA Can Be Detected in the Circulation of Patients with Systemic Lupus and Correlated to Other Factors Suggestive of Plasma Cell Activation. Ming Chen[3], Joy G. Hutcheson[2], Stan Kamp[2], Danny Walker[2] and Joan T. Merrill[1]. [1]Oklahoma Med Research Foundation, Oklahoma City, OK, [2]OMRF, Oklahoma City, OK, [3]OMRF, Allen, TX

Background: Plasma cells are key components in models of SLE pathogenesis, but are sequestered from easy analysis in humans, being rare and difficult to detect in peripheral blood. We hypothesized that quantification of CD138 RNA by real time PCR of peripheral blood leukocytes might provide a sensitive marker for activation of the plasma cell compartment.

Methods: The following measurements were performed on blood samples from 102 patients with SLE: CD138 RNA by RTPCR, BLyS (BAFF) RNA and protein by RTPCR and ELISA, and immune complexes (CIC/C1Q) by ELISA. Routine blood testing and clinical information were also recorded.

Results: CD138 RNA was detectable in most patient samples. Samples were divided into two groups: Group A was comprised of 39 patients with higher levels of CD138 (5–28 copies/5ng). Group B included 61 patients with CD138 < 5 copies/5 ng. There were no differences in age (median 46 vs 47), gender (% female 89.5 vs 91.3) or ethnicity (% CAUC/AFR/ASIAN 63/26/11 Group A and 61/21/18 Group B). Compared to group B, Group A had greater prevalence of anti-dsDNA (28% vs 6.5%, p=0.008), and C3 below normal (25.6% vs 5.0%, p=0.007). Group A trended to higher levels of immune complexes (median 417 ng/ml vs 189, p=ns) as well as increased BLyS protein (median 3333 ng/ml vs 2805, p=ns) and BLys RNA (median 529 copies/5ng vs 421, p=ns). Levels of CD138 did not impact on disease activity by SLEDAI or BILAG, although CIC were increased in patients with SLEDAI >/= 6 vs those with lower scores (median 1580.7ng/ml vs 132.6, p=0.009) as were levels of BLyS protein (median 3927ng/ml vs 2742, p=0.042). An exploratory multivariate analysis was performed, considering the possibility that circulating CD138 reflects increased global plasma cell activity, which might contribute to autoantibody formation and complement consumption systemically. C3 levels were chosen as the dependent variable by virtue of being the furthest downstream of the elements studied. After adjusting for several potentially confounding factors, CD138 maintained a strong, independent effect on C3 levels (see table).

Variables With Potential Impact on Complement C3

Independent Variables	Univariate p value	Multivariate p value
Anti-dsDNA	<0.001	0.008
CIC/C1Q	ns	ns
CD138 RNA	<0.001	0.005
BlyS protein	0.014	0.059
BlyS RNA	0.022	0.056

Conclusions: CD138 can be measured in peripheral blood from lupus patients and may be related to meaningful upstream B Cell stimulants (such as BLyS) as well as downstream effects of plasma cell activation, including anti-dsDNA antibodies and complement consumption. Since some biologic agents in development are expected to have more impact on plasma cells than others, studies of the few that enter the circulation could provide predictive biomarkers for treatment selection.

Disclosure: M. Chen: None; **J. G. Hutcheson:** None; **S. Kamp:** None; **D. Walker:** None; **J. T. Merrill:** None.

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Characterisation of Lipid Order in Lymphocyte Subsets from Patients with Systemic Lupus Erythematosus (SLE). Laura Miguel[2], Chrissie Lim[2], David A. Isenberg[1] and Elizabeth C. Jury[2]. [1]UCL Div of Medicine, London, United Kingdom, [2]University College London, London, United Kingdom

Membrane lipid microdomains (lipid rafts) enriched with cholesterol and glycosphingolipid are thought to play an important role in lymphocyte function by forming areas of high lipid order that facilitate the activation process. Patients with SLE have defects in T and B cell receptor-mediated activation pathways involving altered expression and membrane localisation of key intracellular signalling molecules. However, the precise role that lipid rafts play in these abnormalities is not fully understood.

Here, using a new probe, di-4-ANEPPDHQ, to define lipid microdomains, we were able to distinguish areas of high lipid order (lipid rafts) and disorder (non-rafts) in the membrane of T and B lymphocytes from patients with SLE (n=79) compared with healthy volunteers (n=44), and patients with Sjorgrens Syndrome (SS) (9) or rheumatoid arthritis (RA) (n=15) as controls. Lipid order was quantified by calculating a generalized polarization (GP) value from mean fluorescence intensity emissions at 570nm and 630nm using a LSRII flow cytometer. Plasma membrane lipid order was related to naive, memory, regulatory and activated phenotypes using a range of T and B cell surface markers and flow cytometry. In addition membrane lipid order was related to levels of membrane and serum cholesterol, triglycerides, HDL and LDL.

The results revealed that lymphocytes from healthy controls had three distinct populations with relative High, Intermediate and Low membrane lipid order. The majority of T cells had high membrane order, whereas B lymphocytes had an expanded Intermediate order population. Patients with SLE and RA had significantly reduced lymphocyte membrane order compared with healthy controls (p=0.001), except for patients with inactive SLE on prednisolone therapy who had lymphocytes of higher overall order than healthy controls (p=0.01). No significant differences were observed in patients with SS compared with healthy volunteers.

Phenotyping showed that in both healthy and patient samples T cells with High lipid order were predominantly naive and responder cells whilst Low order T cells were associated with activated, regulatory and effector memory phenotypes. Immature B cells tended to be associated with Low membrane order. These results correspond with the increased frequency of activated, regulatory and memory T cells in patients with autoimmune disease. Interestingly, in healthy volunteers, the serum cholesterol:HDL ratio showed a positive correlation with plasma membrane lipid order (p=0.05). However, this relationship was lost in patients with SLE, regardless of therapy, who had increased serum LDL and reduced serum HDL resulting in high cholesterol:HDL ratios.

In conclusion, the correlation between immune phenotype and membrane lipid order supports an important role for lipid microdomains in modulating adaptive immune responses and the contribution of dyslipidaemia to immunopathology. The results support the need for further investigation to define the relationship between serum cholesterol and plasma membrane microdomains in lymphocytes from healthy volunteers compared to patients with autoimmune rheumatic disease.

Disclosure: L. Miguel: None; **C. Lim:** None; **D. A. Isenberg:** None; **E. C. Jury:** None.

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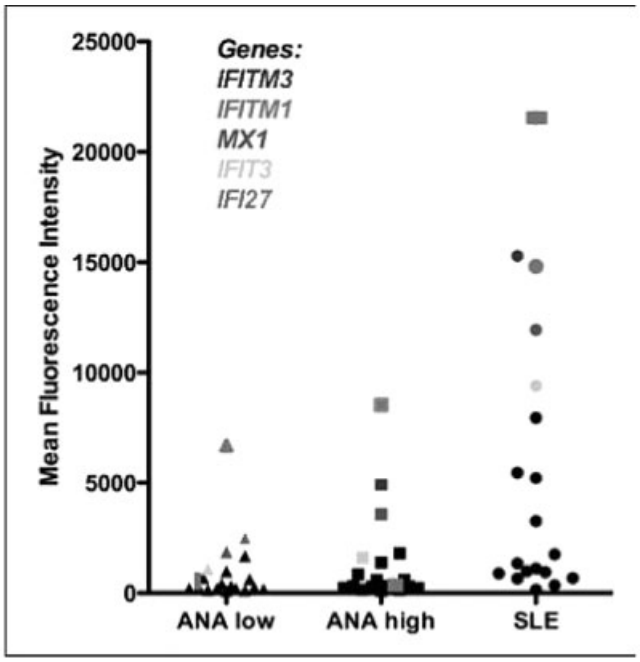
Correlates of ANA Positivity in Healthy Individuals. David R. Karp[2], Quan-Zhen Li[2], Valerie K. Branch[2], Jiexia Quan[3] and Nancy J. Olsen[1]. [1]Univ of TX Southwestern Med Ctr, Dallas, TX, [2]UT Southwestern Med Ctr, Dallas, TX, [3]UT Southwestern Med Ctr., Dallas, TX

The significance of ANA positivity that is observed in up to 25% of the population is unknown. We sought to determine demographic, immunologic and gene expression correlates of elevated ANA values in healthy controls (HC) to provide insights into when this might signal elevated risk for development of autoimmune disease. ANA was measured by ELISA in serum samples from 1159 individuals in the Dallas Regional Autoimmune Disease Registry (DRADR) and autoantibodies in the ENA panel were quantitated by a Luminex-based assay. CCP measurements utlized ELISA. More detailed studies were carried out on a subset of HC with high ANA (N=18) or low ANA (N=18) and SLE patients (N=14) matched for gender and age. A slide-based array was used to measure approximately 100 autoantibodies in IgG and IgM classes. Gene expression profiles were measured in these individuals using RNA isolated from whole blood and analyzed on the Illumina Human-6 V3 Bead Chip. Elevated ANA levels in the HCs were strongly correlated with female gender ($P=0.033$) but not with age ($R^2=0.01$). CCP autoantibodies did not show gender dimorphism in HC or autoimmune individuals, indicating that female gender is not a risk factor for all autoantibodies. Autoantigen arrays identified 12 autoantibodies with SLE-comparable levels in ANA high but not ANA low HC. Of these, 6 (50%) were directed against antigens associated with autoimmune skin disorders (MMP-1, nidogen-1, laminin 5, $\alpha6\beta4$ integrin, desmoglein4, plectin-1) or other autoimmune diseases (dsDNA, aggrecan, thyroglobulin, liver cytosol type-1). A total of 95 genes were significantly ($P<0.01$) dysregulated in ANA high vs ANA low HC, and the vast majority (90) were upregulated in the ANA low group. The highest upregulated gene in ANA high HC was TGM2 which encodes transglutaminase2, a celiac disease autoantigen. Some gene components of the Type I IFN signature were elevated in the ANA high group (MX1, IFITM3, IFITM1, IFIT3) while others, notably IFI27, were only elevated in SLE (Figure).



The findings suggest that early lupus-like autoimmunity might begin in the skin and that some ANA positivity may herald development of other autoimmune diseases. Identification of gene and protein patterns along with ANA and demographic features has potential to predict risk of lupus and other autoimmune diseases in normal individuals.

Disclosure: D. R. Karp: None; **Q.-Z. Li:** None; **V. K. Branch:** None; **J. Quan:** None; **N. J. Olsen:** None.

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Dysfunctional, Pro-Inflammatory High Density Lipoproteins Directly Influence Monocyte PDGFRβ Transcript Levels, TNFα Secretion, and Chemotaxis. Brian J. Skaggs[1], Bevra H. Hahn[4], Lori Sahakian[2], Jennifer M. Grossman[3] and Maureen A. McMahon[1]. [1]UCLA School of Medicine, Los Angeles, CA, [2]UCLA School of Medicine, [3]University of California Los Angeles, Sherman Oaks, CA, [4]University of California Los Angeles School of Medicine, Los Angeles, CA

Statement of Purpose: Accelerated atherosclerosis is a major co-morbid condition of women with SLE. Dysfunctional, pro-inflammatory HDL (piHDL), found in half of SLE patients, increase the risk for carotid artery plaque 16-fold. Because monocytes are intimately involved in lipid regulation and are the main immune cell involved in atherosclerosis initiation, we hypothesized that piHDL might directly influence monocyte gene expression and function.

Methods: Peripheral blood monocytes isolated from 54 SLE patients were stratified into three groups: 1) carotid artery plaque+piHDL+ 2) plaque neg-piHDL+ and 3) plaque neg-piHDL neg (n=18/group). Transcript levels of 84 atherosclerosis-specific genes were examined by real-time PCR-based gene arrays. RNA from the human monocyte cell line THP-1 was examined by real-time PCR after 4 hr treatment with 20 μg/ml of either subject-isolated normal, anti-inflammatory HDL (nHDL) or piHDL. THP-1 secretion of TNFα was measured by ELISA after concurrent treatment with lipids and either 1) a peptide mimetic of an anti-inflammatory HDL-associated protein (apoJ) that converts piHDL to nHDL or 2) imatinib (Gleevec), a small molecule platelet-derived growth factor receptor β (PDGFRβ) inhibitor. THP-1 chemotaxis after 2 hr treatment with lipids and inhibitors (as described above) was also examined.

Summary. PDGFRβ was upregulated in primary monocytes from plaque+piHDL+ patients versus monocytes from the other two groups (3.4 fold, $p<0.01$ versus plaque neg-piHDL neg; 2.5 fold, $p=0.02$ versus plaque neg-piHDL+) and in THP-1 monocytes treated in vitro with piHDL compared to normal HDL (2.8 fold, $p=0.03$). TNFα transcript levels were significantly upregulated in primary monocytes from both piHDL+ groups. THP-1 cells treated with piHDL (vs. nHDL) secreted significantly greater amounts of TNFα and exhibited greater migration to chemotactic signals. TNFα levels and increased chemotactic responses were both reduced to normal after apoJ-mimetic peptide or imatinib treatment.

Conclusions: Dysfunctional piHDL has profound pro-inflammatory effects on human monocytes. These effects can be neutralized by blocking the PDGFRβ receptor. Therefore, piHDL directly influences monocyte biology and could promote accelerated atherosclerosis in SLE patients Imatinib or an apoJ-mimetic peptide could be used as targeted therapy in piHDL+ SLE subjects at risk of atherosclerosis as determined by the presence of plasma piHDL.

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Dysregulation of the Microvascular as Assessed by Expression of Protective and Injury Associated Markers Is Reflected in the Non-Lesional Non-Sunexposed Skin of Patients with Lupus Nephritis. Peter M. Izmirly[1], Shane Meehan[2], Sherry X. Xu[2], Anca D. Askanase[1], Joan T. Merrill[3], Jill P. Buyon[1] and Robert M. Clancy[4]. [1]NYU School of Medicine, New York, NY, [2]NYU School of Medicine, [3]Oklahoma Med Research Foundation, Oklahoma City, OK, [4]Tisch Hospital 4–407, New York, NY

Purpose: Coagulation is one of the first pathways to be elicited by vascular injury, and its activation is followed by proinflammatory phenomena, in part due to loss of the anti-inflammatory activity of both the Protein C pathway and membrane Endothelial Protein C receptor (mEPCR). It has been recently demonstrated that mEPCR is highly expressed in the cortical peritubular capillaries of kidneys from patients (pts) with active lupus nephritis compared to normal human kidney. Profound upregulation of mEPCR was observed even in areas absent tubulointerstitial damage. This study addressed the hypothesis that changes in the microvasculature extend beyond the clinically targeted organ and that dysregulation is a fundamental characteristic of SLE.

Methods: The study included SLE pts in whom renal disease was considered active as assessed by proteinuria and urinary sediment. Renal biopsies were performed in all pts. Thirty skin biopsies from non-lesional non-sunexposed skin (buttocks) were obtained in 26 pts (23 females, 3 males)

and five healthy controls (4 females, 1 male). The paraffin skin sections were individually stained with specific antibodies against mEPCR and adiponectin (protective markers), ICAM-1 (proinflammatory) and CD31 (pan endothelial marker). Immunohistochemistry (IHC) was scored by counting peroxidase-brown labeled blood vessels (10–20 microns in diameter) without knowledge of the clinical information associated with the biopsy. The number of blood vessels with an intensity of at least 1+ were quantitatively scored with ranges 1–12. To account for the number of blood vessels per slide, the CD31 count had to be 12 to be included in the analysis.

Results: The 28 renal biopsies comprised the following ISN/RPS classifications: 4 Class III, 7 Class IV, 8 Class V, I Class VI, 3 Class III/V, 3 Class IV/V. Nineteen percent of the pts had a GFR <60 (mean GFR, 82 ml/min). Abnormal laboratory values for complement and anti-dsDNA antibodies were reported in 72% and 75% of pts, respectively. Nephrotic range proteinuria was present in 37%. For IHC skin assessments of the controls, the mean score for mEPCR was 1 (highest 2), ICAM-1 was 4 (highest 7) and adiponectin was 1 (highest 2). In 17/25 (68%) of the SLE non-lesional non-sun exposed skin sections, mEPCR was expressed above the highest control. In 16/30 (53%) ICAM-1 staining exceeded 7. In contrast, only 6/25 (19%) expressed adiponectin above 2. For each specific stain there were no apparent differences between biopsy class, degree of proteinuria, presence of anti dsDNA or low complement levels. However, pts with mEPCR staining above 2 had higher GFR measurements than those with staining < 2 (88 ml/min ± 31 versus 53 ± 32, p= 0.0168). In contrast, GFR was unrelated to ICAM-1 and adiponectin expression.

Conclusion: These data are consistent with the notion that there is widespread activation of the microvasculature. The capacity of endothelial cells to utilize anticoagulation pathways is not restricted to the kidney and expression of mEPCR in the microcirculation likely represents an attempt to limit microvascular inflammation in kidney and skin.

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1191

Evidence of N-methyl-D-aspartate Receptor (NMDAR) Expression on Primary Human Endothelial Cells. Cagri Yildirim-Toruner[3], Paola Mina-Osario[2] and Betty Diamond[1]. [1]Feinstein Institute for Medical Research, Manhasset, NY, [2]Feinstein Institute for Medical Research, [3]Morgan Stanley Children's Hospital of NewYork- Presbyterian Columbia University Medical Center, Feinstein Institute for Medical Research, New York, NY

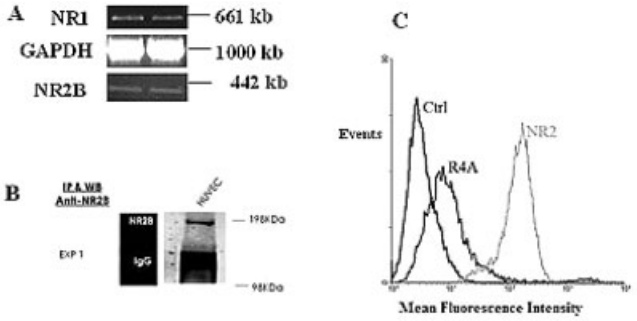
Background: A subset of anti-DNA antibodies has been implicated in neuropsychiatric lupus. These antibodies bind NMDARs and mediate excitotoxic neuronal death, but cause no appreciate neuronal damage when present in the circulation unless there is a breakdown in the blood-brain barrier (BBB). Thus, the BBB is the limiting step for the onset of neurotoxicity. Identifying the mechanisms of antibody transfer through the BBB has important prophylactic and therapeutic implications. It has recently been proposed that anti-NMDAR antibodies modify the permeability of BBB, but presence of NMDARs on BBB is controversial. In order to address this controversy, we studied two different human endothelial cells (EC) considered as in-vitro models of human BBB, Human Umbilical Vein Endothelial cells (HUVEC) and human brain microvascular endothelial cells (HBMEC), to determine the presence of the NMDAR in EC.

Methods: After HUVEC cells were grown to confluency, total RNA was isolated with the RNeasy RNA isolation kit (Qiagen) and reverse-transcribed by using the iScript RT-PCR System (BioRad). Resulting cDNA was amplified with NR1 and NR2B primers. PCR amplicons were visualized in a 1% agarose gel.

For immunoprecipitation, cells were trypsinized, lysed with and then centrifuged at 14,000 rpm. The supernatants were incubated overnight with 2 μg/ml of a polyclonal anti-NR2B antibody. The lysates were then incubated for 1h at 4°C with protein-A agarose. The beads were pelleted by a short centrifugation, washed several times and resuspended in Laemli sample buffer. Then immunoprecipitates were separated by PAGE under non-denaturing conditions.

HUVEC were grown to confluency on gelatin-coated culture dishes. After trypsinization, cells were fixed in 1% PFA, permeabilized in Triton-X100 0.1%/PBS for 10 min, washed and incubated with the indicated antibodies or an isotype control for 1 hour at 4°C followed by a PE-conjugated secondary antibody for 30 min at 4°C. Cells were subsequently analyzed in a FACS-Calibur flow cytometer.

Results: Human endothelial cells express NMDAR and bind anti-DNA/NMDAR cross-reactive antibodies RT-PCR experiments demonstate the expression of NMDAR subunits, NR1 and NR2B, are expressed in HUVEC **(Fig1A)**. We were also able to immunoprecipitate the NR2B subunit of NMDAR from total cell lysates of HUVEC (**Fig1B**). Finally, the anti-NMDAR antibody R4A and two human anti-NMDAR antibodies (clone E2 and G11) bound to HUVEC and HBMEC as determined by flow cytometry (**Fig1C**).



Conclusion: NMDARs are expressed in in-vitro models of human BBB. The demonstrated physical interaction of these anti-NMDAR antibodies with NMDAR raises the possibility of a role for the antibodies in modulating the permeability of BBB through antibody- receptor interaction in the pathogenesis neuropsychiatric lupus. Functional and expression assays are ongoing to elucidate the role of anti-NMDAR antibodies on BBB.

Disclosure: C. Yildirim-Toruner: None; **P. Mina-Osario:** None; **B. Diamond:** None.

1192

Expession of B Cell Subsets in SLE Pregnancy: Correlation with Preterm Birth. Megan E. B. Clowse[1], Sara Sparks[2], Sallie Allgood[2], Mark Lanasa[2] and David S. Pisetsky[3]. [1]Duke Univ Med, Durham, NC, [2]Duke University, Durham, NC, [3]Duke University Medical Ctr, Durham, NC

Background: Pregnancy demands significant shifts in immunologic function to maintain tolerance to the fetus. Women with systemic lupus erythematosus (SLE), particularly active SLE, have a several-fold higher rate of preterm birth and miscarriage compared to healthy women, suggesting that immune systems changes in SLE affect maternal-fetal tolerance and thereby promote pregnancy complications. To investigate this possibility, we tested whether alterations in the B cell compartment associated with SLE (increased plasmablasts and plasma cells and decrease naïve B cells) are associated with SLE activity and pregnancy outcomes.

Methods: Pregnant women with rheumatologic disease were consecutively enrolled in a prospective cohort. Disease activity using the SLE pregnancy disease activity index (SLEPDAI), and blood for autoantibody levels and peripheral blood mononuclear cells were collected in the first trimester, at a mid-pregnancy visit (between 20–26 weeks gestation) and at least 6 weeks post-partum. Flow cytometry was performed and data analyzed using Flowjo. Plasmablasts were identified as CD27++, CD38++, and IgD- cells. Plasma cells, memory B cells, and naive B cells were delineated based on the degree of CD27 positivity. T tests and Fisher's exact test were used to determine statistical significance.

Results: The cohort included 25 pregnant women: 19 with SLE and 6 with rheumatoid arthritis (RA). Extractable nuclear antigens were identified in 68% and the anti-dsDNA antibody was positive in 42% of the women with SLE. Five women had active disease, determined by a SLEPDAI ≥8. Three of the SLE pregnancies resulted in a pregnancy loss. Of the live births, 37% of SLE pregnancies were delivered preterm (<37 weeks gestation). All of the RA pregnancies resulted in a live birth at term.

Pregnant women with RA had a higher percentage of naive B cells than women with SLE both at mid-pregnancy (RA 88% vs SLE 80%, p=0.07) and post-partum (RA 88% vs SLE 80%, p=0.007). Women with a positive anti-dsDNA antibody had a higher percentage of plasmablasts (p=0.03), plasma cells (p=0.07), and memory B cells (p=0.08), but fewer naive B cells (p=0.09) than other women with SLE. Compared to values post-partum, in the 1st trimester women with SLE had a trend toward fewer lymphocytes, a higher percentage of B cells, fewer memory B cells and more naive B cells (see Table).

Table. Comparison of B cell subsets for pregnant women with SLE.

	1st trimester	Post-partum	P-value
Total white blood cell count	6.7×10^9 cells/mm^2	6.3×10^9 cells/mm^2	0.65
Lymphocyte count	1.5×10^9 cells/mm^2	2.2×10^9 cells/mm^2	0.07
B cells (% of lymphocytes)	5.3%	3.3%	0.09
Memory B cells (% of B cells)	9.5%	12%	0.07
Naïve B cells (% of B cells)	85%	80%	0.03
Plasma cells (% of B cells)	0.56%	0.69%	0.89
Plasmablasts (% of B cells)	0.55%	0.53%	0.67

The week of delivery correlated negatively with the percentage of plasmablasts in the 1st trimester ($r -0.7$, $p=0.02$) and trended towards a negative correlation with plasma cells ($r -0.5$, $p=0.07$). SLE activity and pregnancy loss were not correlated with any B cell subset.

Conclusion: Women with SLE have altered B cell homeostasis in the 1st trimester which may reflect the immunologic changes of pregnancy that allow fetal tolerance. In women with SLE, increased numbers of plasmablasts in the first trimester were associated with preterm delivery.

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Increased Male Fetal Loss and Fewer Male Siblings in a Cohort of Systemic Lupus Erythematosus Families. Rachna Aggarwal[1] and Robert H. Scofield[2]. [1]OUHSC, [2]OUHSC, OMRF, VA

Purpose: A sex bias has been found absent in sibships of non-female predominant diseases like diabetes. We undertook this study to enhance our understanding of sex ratios in live sibships and lost fetuses in a large cohort of Systemic lupus erythematosus (SLE).

Methods: Families were collected through the Lupus Family Registry and Repository. All patients met atleast four of the 1982 ACR classification criteria for SLE. All families had atleast one member with SLE. Collective sibling gender data were obtained for the SLE cohort studied. Spontaneous miscarriage and abortion information was assessed, when self-reported, on a standard questionnaire filled by the patient. Male to female sex ratios were calculated.

Results: Collectively, 282 SLE affected male patients had 314 male siblings and 415 female siblings. The 2296 SLE affected female patients had 3113 male siblings and 3772 female siblings. Thus the ratio of male to female siblings= $(314+3113) / (3772+415) = 0.82$. SLE affected females reported 36 events of male fetal loss and 20 events of female fetal loss. Thus, ratio of male to female fetal loss was found to be 1.8:1.

Conclusions: There is a trival explanation for too few male siblings in this cohort. Sibships with lots of girls are more likely to have SLE because of the excess girls with SLE and, therefore are more likely to be included in the study. So, to correct for the ascertainment bias, we left out the SLE patients. Even when doing this, the male/female ratio is 0.8 and live births and fetal loss is nearly twice more common in males. The most parsimonious and perhaps the only explanation is a gene on X where a mutation or allele is lethal for males in utero and gives girls risk for SLE as we have discussed. This means this gene should be on the maternal X chromosome of patients in families where the sibship containing the SLE patient has excess girls and/or there are reports of male fetal loss.

Disclosure: R. Aggarwal: None; **R. H. Scofield:** None.

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Low Levels of Atheroprotective Natural IgM Antibodies Against Phosphorylcholine and Increased Prevalence of Vulnerable Atherosclerotic Plaques in Patients with SLE. Cristina Anania[2], Thomas Gustafsson[2], Xiang Hua[2], Jun Su[2], Mikael Heimbürger[1], Tomas Jogestrand[2] and Johan Frostegård[2]. [1]Abbot, [2]Karolinska Institutet

Background: We recently reported that natural antibodies against phosphorylcholine (anti-PC) are negatively associated with atherosclerosis and cardiovascular disease (CVD) in the general population: low IgM anti-PC levels predict increased risk of CVD and high levels protect against increase in atherosclerosis over time. We have determined two potential mechanisms: anti-inflammatory effects of anti-PC (inhibiting inflammatory phospholipids which are implicated in both atherosclerosis and RA) and decreased uptake of oxidized lipids in macrophages. According to our hypothesis, an immune deficient state – low levels of anti-PC –predispose to chronic inflammatory diseases. We here study atherosclerosis as determined by carotid ultrasound in systemic lupus erythematosus (SLE) and the role of traditional and non-traditional risk factors for atherosclerosis and CVD.

Methods: One hundred fourteen patient with SLE were compared with one hundred twenty two age- and sex matched population-based controls. Common carotid intima-media thickness (IMT), calculated intima-media area (cIMa) and plaque occurrence were determined by B-mode ultrasound as a surrogate measure of atherosclerosis. Plaques were graded according to echogenicity and grouped as 1–4, with 1 being echoluscent, and considered most vulnerable. Osteoporosis was studied by DXA and anti-PC by ELISA.

Results: IMT and cIMa did not differ significantly between groups. However, plaques were more often found in SLE patients ($p=0.029$). Age, LDL and IgM anti-PC (lowest tertile) were independently associated with plaque occurrence in SLE. Further, in the left carotid arteries echoluscent plaques (grade 1) were more prevalent in SLE as compared to controls $p<0.016$).

Triglycerides, insulin resistance (determined by homeostasis model assessment of insulin resistance) hypertension, and C-reactive protein (CRP) were increased in SLE ($p<0.01$) while smoking, LDL and HDL did not differ between groups. Low levels of anti-PC IgM (lowest tertile) were more common in SLE patients than in controls ($p=0.0022$). Osteoporosis was more prevalent in the hip in SLE-patients as compared to controls ($p<0.05$) but not otherwise. 18.4% of SLE patients and 1.6% of controls ($p<0.01$) exhibited a history of CVD (myocardial infarction, angina, heart valve disease, stroke or claudication).

Conclusion: Plaque occurrence and the frequency of vulnerable plaques in the carotid arteries are increased in SLE. Anti-PC could be a novel risk marker also with a therapeutic potential in SLE.

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Presence of HMGB1 (High Mobility Group Box 1) and Antibodies to HMGB1 in Systemic Lupus Erythematosus (SLE). Deena Abdulahad, Johanna Westra, Pieter Limburg, Cees Kallenberg and Marc Bijl. UMCG

Background: Apoptotic cells accumulate in SLE and are considered to play an important role in the pathogenesis. High mobility Group box 1 is a non-histone nuclear protein, that can be secreted actively by inflammatory cells, and is released passively from apoptotic and necrotic cells where it may act as an autoantigen and as a pro-inflammatory mediator. There is increasing evidence that HMGB1 contributes to the pathogenesis of chronic inflammatory and auto-immune diseases. Indeed, presence of HMGB1 in serum of mice with SLE has been reported in the serum of lupus mice.

Objectives: In this study we determined levels of HMGB1 and anti-HMGB1 in SLE patients compared to healthy controls (HC).Also their relation with clinical and biochemical parameters was assessed.

Methods: The study population consisted of 69 SLE patients and 35 age and sex matched HC. Of the 69 SLE patients 35 were visiting the outpatient clinic and randomly chosen. The other 34 patients were selected for active disease and paired samples of these patients were selected during inactive phase of the disease. Eighteen of 34 patients had renal involvement and remaining 16 patients had other organ involvement. HMGB1 levels were measured with a Western blot and anti-HMGB1 levels were measured with an in-house developed ELISA using recombinant HMGB1 as antigen. Clinical and biochemical parameters of all patients were assessed routinely.

Results: HMGB1 levels in all SLE patients were significantly increased compared to HC. HMGB1 levels were relatively more increased in patients with renal involvement compared to non renal patients. HMGB1 levels were correlated with disease activity, as determined by SLEDAI. HMGB1 levels were correlated with anti-dsDNA levels and showed a negative correlation with C3. Anti-HMGB1 levels were significantly increased in all SLE patients compared to HC and were correlated to HMGB1 levels in all SLE patients.

Conclusions: In SLE patients serum HMGB1 levels are significantly increased, in particular in patients with renal involvement, and are related to disease activity. Furthermore, in SLE patients increased levels of anti-HMGB1 antibodies were detected. Whether HMGB1, and HMGB1-anti-HMGB1 immune complexes play a role in the pathogenesis of SLE, in particular in patients with renal involvement needs to be established.

Disclosure: D. Abdulahad: None; **J. Westra:** None; **P. Limburg:** None; **C. Kallenberg:** None; **M. Bijl:** None.

1196

Reversal of CD3+/CD4+/CD25+/Foxp3+ Treg Depletion in Active SLE Patients with Rapamycin. Zhiwei Lai[1], Tiffany N. Telarico[1], Adam Bartos[1], Gabriella Miklossy[1], Robert Hanczko[1], John Jimah[1], Brandon Clair[1], Lisa Francis[1], Hajra Tily[1], Ricardo Garcia[1], Paul E. Phillips[2], Irene Ramos[1] and Andras Perl[3]. [1]SUNY, [2]SUNY-Upstate Medical Univ, Syracuse, NY, [3]Upstate Medical Univ, Syracuse, NY

Purpose: Activation and death pathway selection of T cells are regulated via the mitochondrial transmembrane potential ($\Delta\Psi m$). Systemic lupus erythematosus (SLE) patients' T cells exhibit persistent $\Delta\Psi m$ elevation or mitochondrial hyperpolarization (MHP) and ATP depletion which predispose them to pro-inflammatory death via necrosis. Here, we examined the role of the mammalian target of rapamycin (mTOR), which serves as a sensor of MHP, in activation and death signal processing of lupus T cells.

Patients and Methods: 34 female SLE patients and 34 female healthy controls were studied. 24 patients with stable disease were enrolled in double-blind placebo-controlled treatment trial with N-acetylcysteine (NAC; ClinicalTrials.gov identifier: NCT00775476) and only baseline values were evaluated. 10 patients with uncontrolled disease due to lack of efficacy or tolerance to current medications were enrolled in prospective treatment trial with rapamycin (RAPA; NCT00779194) and both pre and post-treatment data were evaluated. SLE disease activity was assessed by using the British Isles Lupus Assessment Group (BILAG) and SLE Disease Activity Index (SLEDAI). Peripheral blood lymphocytes and untouched T cells (using Dynal negative T-cell isolation kit) were freshly isolated on the same morning from patients and controls matched for ethnicity and age within 10 years and investigated in parallel for $\Delta\Psi m$, mitochondrial mass, glutathione, production of nitric oxide (NO) and reactive oxygen intermediates (ROI), cytosolic ([Ca2+]c) and mitochondrial calcium levels ([Ca2+]m), and T and B cell subset distribution by flow cytometry and for mTOR activity by western blot.

Results: SLEDAI (8.6 +/− 1.2) and BILAG (24.6 +/− 1.8) of 24 patients enrolled in the NAC trial were exceeded by the SLEDAI (16.5 +/− 2.9; p = 0.004) and BILAG (33.0 +/− 4.4; p = 0.04) scores of 10 patients enrolled in the RAPA trial. MHP and mitochondrial mass were elevated, most robustly in CD3+/CD4-/CD8- cells (1.6- to 2-fold) both among NAC and RAPA study patients. The prevalence of annexin V+/propidium iodide+ necrotic cells was only increased in RAPA patients. Likewise, the prevalence of Foxp3+ cells within the CD4+/CD25+ compartment was only reduced in RAPA patients (37.05 +/− 3.0 %) relative to controls (48.37 +/− 2.5 %; p = 0.0014). mTOR activity, as measured by the accumulation of pS6 protein, was increased > 1.5-fold in CD3+ T cells (p=0.012) and CD19+ B cells (p=0.006) in RAPA patients. Relative to healthy controls (3.18 ± 0.39%), the frequency of Foxp3+/CD4+/CD25+ cells was reduced in RAPA patients (1.70 ± 0.42%; p=0.021) prior to RAPA treatment. In vivo treatment with RAPA increased the frequency of Tregs from 1.50 ± 0.45% to 2.8 ± 0.59% (p=0.040) while the SLEDAI scores were reduced in 5 SLE patients from 22.4 ± 5.7 to 16.7 ± 2.8 (p=0.017).

Conclusion: While mitochondrial dysfunction was detectable in lupus T cells irrespective of disease activity, predisposition to necrosis and Treg depletion were confined to "RAPA" patients with high disease activity. The data identify the in vivo expansion of Tregs as a potential mechanism of action that may contribute to the therapeutic efficacy of RAPA in SLE.

Disclosure: Z. Lai: None; **T. N. Telarico:** None; **A. Bartos:** None; **G. Miklossy:** None; **R. Hanczko:** None; **J. Jimah:** None; **B. Clair:** None; **L. Francis:** None; **H. Tily:** None; **R. Garcia:** None; **P. E. Phillips:** None; **I. Ramos:** None; **A. Perl:** None.

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Strong Viral Associations among Filipinos with Systemic Lupus Erythematosus. Evan Glenn Vista[6], Michael H. Weisman[3], Mariko L. Ishimori[1], Jourdan Anderson[5], Robelle Tanangunan[8], Noga Gal[2], John B. Harley[7], Guthridge Joel[5], Sandra Navarra[8] and Judith A. James[4]. [1]Cedars Sinai Medical Center, Los Angeles, CA, [2]Cedars-Sinai, [3]Cedars-Sinai Medical Center, Los Angeles, CA, [4]Oklahoma Med Research Foundation, Oklahoma City, OK, [5]Oklahoma Medical Research Foundation, [6]Oklahoma Medical Research Foundation, Oklahoma City, OK, [7]Univ of OK Hlth Sci Ctr, Oklahoma City, OK, [8]University of Santo Tomas Hospital

Background: Specific environmental determinants could determine development of SLE among susceptible individuals. Among potential viral environmental agents, the ubiquitous Epstein Barr virus (EBV) has been associated with SLE through seroprevalent exposure in pediatric and adult populations, viral DNA association, increased viral loads in the peripheral blood of SLE patients and increased evidence of viral reactivation. SLE patients have also been shown to have abnormal humoral and T cell responses against EBV. Filipinos, compared to other populations, could have potential major differences in terms of genetic risk, environmental exposure and disease causation brought about by their location as an archipelago separated from other Asian nations and a strong history of racial admixture.

Methods: Filipinos with written and informed consent belonging to the University of Santo Tomas Hospital lupus cohort and fulfilling the 1997 American College of Rheumatology criteria (ACR) for SLE (233 cases) along with 544 unaffected first degree relatives (FDRs) and 220 unrelated controls were studied. Sera were tested for seroconversion to EBV, Cytomegalovirus (CMV) and Herpes simplex viruses (HSV1 and HSV2) by standardized ELISAs for IgG responses to EBV early antigen (EA), EBV viral capsid antigen (VCA), EBNA1, CMV immediate early antigen, HSV-1 (strain F) and HSV-2 (strain G). Correlation statistics (Fisher's exact test, student's t-test, and one-way ANOVA) were done to determine associations between patients and their controls and FDRs.

Results: Filipino patients have significantly higher seroconversion for EBV EA (92.3%), EBV VCA (99.6%), CMV (94.4%), HSV1 (87.5%) and HSV2 (79.4%). Seroconversion against EBV-EA (a measure of reactivation) was dramatically higher in SLE patients compared to controls (92.3% vs 40.4%; OR=17.6, p <0.0001) or compared to FDRs (92.3% vs 49.4%; OR=12.2, p< 0.0001). For VCA, the cases have higher seroconversion than controls (OR 7.62, p 0.03). The cases have higher seroconversion for CMV than controls (OR 4.85, p<0.0001). Higher seroconversion for HSV1 was also seen for cases than controls (OR 7.2, P< 0.0001). Lastly, the cases have higher seroconversion for HSV2 compared among controls (OR 7.9, p <0.0001) and FDRs (OR 2.17, p <0.0001). Significantly higher antibody titers were seen for all viruses among the cases compared to controls and FDRs (p <0.0001).

Conclusions: This study shows strong viral associations among Filipinos with SLE by the significantly higher seroconversion for EBV-EA, EBV-VCA, CMV, HSV1 and 2. Exposure to these environmental determinants could predispose Filipinos with high susceptibility in developing clinical disease.

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TNFα Expression in Peripheral Blood Mononuclear Cells of Cutaneous Lupus & Dermatomyositis Patients. Adam S. Nabatian[2], Maria Wysocka[4], Muhammad M. Bashir[1] and Victoria P. Werth[3]. [1]Philadelphia VAMC, University of Pennsylvania, [2]UMDNJ-Robert Wood Johnson Medical School, Philadelphia VAMC, University of Pennsylvania, [3]University of Pennsylvania, Philadelphia, PA, [4]University of Pennsylvania

Background: There has been data published regarding TNFα in skin lesions and serum of patients with cutaneous lupus erythematosus (CLE) and dermatomyositis (DM). TNFα is increased in lesional skin of patients with discoid lupus erythematosus (DLE), subacute cutaneous lupus erythematosus (SCLE), and DM compared to controls. TNFα has been measured in sera from patients with systemic lupus erythematosus (SLE), DLE, SCLE, and DM and is elevated in patients with SLE, DLE, SCLE, but not DM. In vitro production of TNFα by unstimulated peripheral blood mononuclear cell (PBMCs) from juvenile DM patients was measured and it was found that PBMCs from children who had disease course ≥36 months produced more TNFα compared to PBMCs from juvenile DM patients who had disease <36 months. Since there has been minimal data published on TNFα expression in PBMCs of CLE and DM patients, the purpose of our experiments was to evaluate TNFα production in PBMCs of DLE, SCLE, tumid lupus erythematosus (TLE), and DM patients.

Methods: PBMCs were separated from heparanized venous blood of 21 DLE, 10 SCLE, 10 TLE, and 18 DM patients and 18 healthy controls. A subset of these cells were placed in culture and an ELISA was performed to measure TNFα protein levels. In another subset, Real-Time-PCR was performed to measure TNFα and ADAM17 (TACE) transcription. Lastly, flow cytometry was performed on another subset of cells to determine which cell type is secreting TNFα.

Summary of the Results: The transcription of TNFα and ADAM17 and the TNFα protein production in DLE patients (55.9±11.1, 5.3±0.46, 31.6±8.9 pg/mL, respectively), but not SCLE (15.8±0.9, 2.4±0.3, 5.5±1.2 pg/mL), TLE (8.9±1.2, 3.7±1.0, 4.3±0.8 pg/mL), or DM, (11.6±2.7, 1.4±0.2, 2.0 ±0.2 pg/mL) was significantly greater than controls (3.2±0.7,

2.1±0.09, 1.5±0.37pg/mL, respectively) ($P < 0.001$). TNFα was predominately produced from monocytes and myeloid dendritic cells (mDCs). There was a significantly greater percentage of cells with TNFα intracellular staining in mDCs of DLE (28.5±7.1) ($P < 0.01$) and DM (21.6±4.1) ($P < 0.05$) patients when compared to controls (3.14±1.7). The mean fluorescence intensity of both monocytes (1569.8±485.8) and mDCs (1,044.5±185.4) from DLE patients was significantly greater ($P < 0.05$) when compared to healthy controls (470.9±82.6 and 293.6±138.1, respectively). Lastly, the total number of both monocytes (11.8±1.5%) ($P < 0.001$) and mDCs (1.14±0.4%) ($P < 0.01$) was significantly greater in DLE patients compared to healthy controls (5.2±1.1% and 0.37±0.09%). The total number of monocytes was also significantly greater in DLE patients (11.8±1.5%) compared to DM patients (6.5±2.8) ($P < 0.01$).

Conclusion: TNFα may be critically important in the induction and development of DLE as these patients have significantly greater TNFα transcription and protein production. Myeloid DCs and monocytes may also have a greater role in the pathogenesis of DLE than was previously believed.

Disclosure: A. S. Nabatian: None; **M. Wysocka:** None; **M. M. Bashir:** None; **V. P. Werth:** None.

1199

Type I IFN Signature in Pregnant Patients with Lupus. Danieli Andrade[3], Gloria C. Koo[3], Patricia Redecha[3], Kyriakos A. Kirou[3], Mimi Kim[1], Mary K. Crow[3] and Jane E. Salmon[2]. [1]Albert Einstein College of Medicine, New York, NY, [2]Hospital for Special Surgery, New York, NY, [3]Hospital for Special Surgery, New York, NY

Purpose: The cytokine milieu in SLE pregnancy is skewed towards a tolerant anti-infammatory state. Type I interferon (IFN) pathway is activated in many SLE patients and is associated with increased disease activity. That IFN-α has anti-angiogenic effects raises the possibility that it may be deleterious for pregnancy. We hypothesized that an IFN type I signature in pregnant lupus patients would be suppressed and if present, it would correlate with poor pregnancy outcomes.

Methods: We performed a nested case-control study of SLE patients in the PROMISSE Study- **P**redictors of Pr**e**gnancy **O**utcome: Bio**m**arkers **I**n Antiphospholipid Antibody **S**yndrome and **S**ystemic Lupus **E**rythematosus. Exclusions were: prednisone >20mg, proteinuria >1gm/24 hr and creatinine >1.2 mg/dl. Subjects were evaluated and blood collected monthly beginning at <12 wks' gestation. Poor pregnancy outcome was defined as: fetal death >12 wks (n=3); placental insufficiency or preeclampsia (PE) (n=9), severe IUGR (n=4) or disease activity (n=2). Each of 18 patients with SLE and poor pregnancy outcomes (SLE/outcome) were matched 1:1:1 by age and ethnicity to an SLE patient with an uncomplicated pregnancy (SLE/no outcome) and a pregnant healthy control (HC). A total of 324 samples prospectively collected during pregnancy were tested. Serum samples from the 3 matched pregnancies were assayed simultaneously for IFN-α activity using a reporter cell assay (WISH assay) based on expression of IFN-regulated genes (MX1, IFIT1 and IF144). Data were compared between disease groups at each gestational time window with an ANOVA model. To examine the influence of PE in type I IFN signature in patients without autoimmune disease, we analyzed a second group of samples collected through pregnancy in 6 patients who developed PE and 6 controls with uncomplicated pregnancies.

Results: Type I IFN signature was present throughout pregnancy in SLE patients compared to controls. Type I IFN score was higher in SLE patients without poor outcomes compared to controls (29.4 ± 14.73 vs 16.2 ± 6.71,18 pairs of patients, 230 samples, p=0.03) and it trended to be higher in SLE patients with poor outcomes compared to controls (38.4 ± 21.68 vs 16.2 ± 6.71, n= 18 pairs of patients, 209 samples, p=0.06). The two SLE groups did not differ significantly with respect to IFN signature. Mean SLEPDAI scores at enrollment were also not different between SLE with or without poor outcomes (4.1±3.4 vs. 2.1±2.9, respectively. SLE patients with PE showed a trend for increase in Type I IFN signature compared to non-autoimmune patients with PE, respectively. (55.13 ± 145 vs 8.93 ± 6.10, p= 0.09). In the non-autoimmune patients, the IFN signature did not differ between patients with and without PE (8.60 ± 6.36 vs 9.82 ± 2.52, p=0.91).

Conclusions: Pregnancy does not abrogate the IFN signature in lupus patients. PE, in and of itself, is not associated with increase in type I IFN signature. The onset of proteinuria and increased blood pressure in pregnancy that is accompanied by a high Type I IFN score is suggestive of SLE flare rather than PE. Elevated type I IFN may help distinguish SLE from PE in pregnant patients.

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Vitamin D and Vascular Stiffness in Patients with Systemic Lupus Erythematosus. John A. Reynolds[3], Sahena Haque[4], Jacqueline L. Berry[4], Lee-Suan Teh[2], Pauline Ho[1], Rachel Gorodkin[1] and Ian N. Bruce[4]. [1]Central Manchester University Hospitals NHS Foundation Trust, [2]East Lancashire Hospitals NHS Trust, [3]University of Manchester, Manchester, United Kingdom, [4]University of Manchester

Background: Vitamin D deficiency is highly prevalent amongst patients with systemic lupus erythematosus (SLE) and is associated with increased disease activity. Low vitamin D levels are associated with increased cardiovascular events in the general population. We hypothesised that in patients with SLE, lower vitamin D levels would be associated with increased vascular stiffness (measured by aortic pulse-wave velocity, aPWV), and subclinical atherosclerosis (carotid intima-media thickness (cIMT) and plaque presence).

Methods: Patients with SLE who fulfilled 4 or more ACR 1997 criteria were recruited from regional outpatient clinics. Clinical assessment and serum collection occurred between Jan 2007 and Jan 2009. Serum 25-hydroxyvitamin D (25(OH)D) was measured by ELISA and 25(OH)D deficiency was defined as <20ng/ml. Aortic pulse-wave velocity was measured (Micro Medical PWV) and cIMT and plaque measured using B-mode Doppler ultrasound.

Results: We studied 75 female patients with SLE with a median (IQR) age and disease duration of 53 (46, 60) and 16 (8, 27) years respectively. Thirty three (52%) of patients had inactive disease (SLEDAI score=0). The median (IQR) serum 25(OH)D was 19.7 (15.1, 29.6) ng/ml, and 39 (52%) of subjects were vitamin D deficient.

Vitamin D levels were significantly lower (median [IQR] 12.88 [12.0, 16.2] ng/ml) in patients with the most active disease (SLEDAI score ≥75th centile) compared to less active disease (20.5 [16.5, 30.8] ng/ml) (p=0.0187).

Serum 25(OH)D was significantly associated with increased aPWV (p=0.010), but not carotid plaque presence (p=0.205) or cIMT (p=0.571). The association with aPWV remained significant after adjustment for traditional CVD risk factors (age, systolic blood pressure, smoking, body mass index (BMI) and season sample taken) (p=0.04), but this association did not remain following adjustment for lupus disease activity (p=0.16).

Table. Serum 25(OH)D and subclinical markers of cardiovascular disease

	Unadjusted 25(OH)D Model				Adjusted 25(OH)D Model 1[1]				Adjusted 25(OH)D Model 2[c]			
Marker	**β**	**OR**	**95% CI**	**p**	**β**	**OR**	**95% CI**	**p**	**β**	**OR**	**95% CI**	**p**
Aortic pulse wave velocity*	−0.022		−0.04, −0.01	0.010	−0.028		−0.06, −0.00	0.048	−0.020		−0.03, 0.01	0.175
Carotid plaque presence#		1.03	0.96, 1.08	0.206		0.99	0.90, 1.09	0.860		1.00	0.91, 1.11	0.928
Carotid intima-medial thickness*		1.02	0.96, 1.07	0.571		0.99	0.92, 1.07	0.889		0.95	0.85, 1.07	0.402

β = β coefficient, CR=odds ratio, 95% CI=95% confidence interval, p=p-value
* linear regression model of log(aPVW)
# logistic regression model
c logistic regression model cIMT above upper quartile
1 Adjusted for age, season (summer or winter), body mass index (BMI), systolic blood pressure, pack-years smoking, disease duration
2 As model 1 plus disease activity score (SLEDAI)

Discussion: Vitamin D deficiency was highly prevalent within our study population. Lower levels of 25(OH)D were associated with increased vascular stiffness, but not cIMT or plaque presence. This association may be mediated by increased disease activity, and prospective studies are now required to determine whether treatment of vitamin D deficiency can modify CVD risk in patients with SLE.

Disclosure: J. A. Reynolds: None; **S. Haque:** None; **J. L. Berry:** None; **L.-S. Teh:** None; **P. Ho:** None; **R. Gorodkin:** None; **I. N. Bruce:** None.

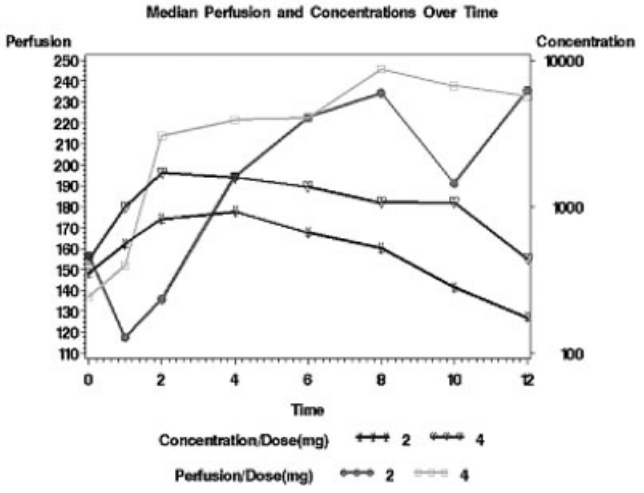
1201

A Pilot Study To Evaluate Digital Perfusion in Scleroderma Patients Treated with Oral Treprostinil. Ami A. Shah[2], Laura K. Hummers[2], Kristan D. Rollins[4], Susan Walker[4], Mike Wade[4], Cynthia Anderson[3], Robert Wise[3], Francesco Boin[2] and Fredrick M. Wigley[1]. [1]Johns Hopkins University, Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD, [3]Johns Hopkins University, [4]United Therapeutics

Background: Raynaud's phenomenon and a small vessel obliterative vasculopathy in scleroderma frequently lead to ischemic digital ulcers (DU). Previous studies have demonstrated a therapeutic effect of intravenous prostacyclin analogs for ischemic DU, but oral prostacyclin analogs have had limited success. During a Phase I pharmacokinetic (PK) trial of an oral treprostinil formulation, we sought to quantify changes in perfusion as assessed by laser Doppler imaging (LDI) and to determine whether improvements in perfusion correlated with drug concentration.

Methods: Ten patients with scleroderma and a history of recent or active ischemic DU were enrolled into the study. All subjects received oral treprostinil and titrated the dose up to 4mg twice daily (BID) as tolerated over 6–8 weeks. Assessments were performed when subjects achieved the 2mg and 4mg (or maximally tolerated) doses. Subjects who did not reach a dose of 2 mg BID during the study had assessments performed only at the end of study visit. Eight serial measures of digital perfusion and drug concentration were obtained at each of the 2 study visits. Repeated measures analyses using random effects models were performed using perfusion and skin temperature as dependent variables of interest and perfusion obtained at drug trough, log-transformed drug concentration, visit number, individual timepoints of Doppler assessment at each PK visit, and left/right hand as potential explanatory variables. Covariates with p-values <0.15 were retained in the statistical model.

Results: Ten subjects with a mean age of 44.3 years and mean scleroderma disease duration of 12.2 years were studied. Seventy percent had limited cutaneous scleroderma. Nine subjects tolerated the 2mg BID dose by the first PK visit, and 6 subjects tolerated the 4mg BID dose by the 2nd PK visit. Two subjects completed the study at 0.5mg BID and 1mg BID, respectively. Subjects experienced transient adverse effects typical of prostacyclin therapy: headache, jaw pain, photosensitivity, fatigue, leg pain, nausea, emesis, diarrhea, abdominal bloating, and flushing.



Perfusion was positively associated with log-transformed plasma concentration at the 4mg visit (but not the 2mg visit), after adjusting for the individual time points of Doppler assessment at each PK visit ($p=0.015$). Digital skin temperature was positively associated with log-transformed plasma concentration at the 4mg visit (but not the 2mg visit), after adjusting for the individual time points of Doppler assessment at each PK visit ($p=0.013$).

Conclusions: An increase in digital perfusion was observed with increased treprostinil blood concentrations, suggesting a dose-response relationship. Further investigation with a larger sample size and a control population is needed to confirm this association, to correct for individual subjects' natural perfusion variations, and to evaluate for dose effects.

Disclosure: A. A. Shah: United Therapeutics, 2; **L. K. Hummers:** United Therapeutics, 2; **K. D. Rollins:** United Therapeutics, 1, 3; **S. Walker:** United Therapeutics, 1, 3; **M. Wade:** United Therapeutics, 1, 3; **C. Anderson:** None; **R. Wise:** None; **F. Boin:** None; **F. M. Wigley:** United Therapeutics, 2.

1202

An Analysis of Agreement of Guidelines for Management in SSc from a Large Database (CSRG: Canadian Scleroderma Research Group). Janet E. Pope[3], Sarah Harding[4], Sarit Khimdas[4], Ash Bonner[2], Murray Baron[1] and The CSRG. [1]Jewish General Hospital, Montreal, QC, Canada, [2]McMaster University, [3]St Joseph Health Care London, London, ON, Canada, [4]University of Western Ontario

Objective: We determined congruence with recently published guidelines from EULAR/EUSTAR, for SSc investigations and treatment practices within the Canadian Scleroderma Research Group (CSRG)

Methods: Investigations and medication use for SSc complications were obtained from SSc patients in the CSRG to determine adherence to guidelines.

Results: The CSRG database of 938 SSc patients demonstrated that annual echocardiograms for PAH screening were done in 86.5%; for PAH treatment one quarter were receiving warfarin which has no recommendations, all diagnosed with PAH Class III/IV were on PAH specific treatment (9% of total CSRG patients had PAH). For Raynaud's: 47% were on calcium channel blockers and some sites used PDE5 inhibitors more than others. Iloprost is not approved in Canada, so its use for severe RP and digital ulcers was low. In the guidelines it is recommended that all SSc patients with GERD be recommended for PPIs. In the CSRG database, PPIs were used in 86%, and one quarter with GI symptoms were on prokinetic drugs. In those with SRC ever: 77% were on current ACE inhibitors, one third were on dialysis and 10% had received kidney transplants. It is recommended that ACE inhibitors not be discontinued post SRC. 19% of MRSS >10 were on methotrexate whereas only 3% were using D-penicillamine which was not recommended in the guidelines. In severe ILD, there was significant variability in use of cyclophosphamide. There was also variation between centers with >50 patients for treatment for inflammatory arthritis (with hydroxychloroquine and D-penicillamine). The rate of ordering some investigations such as HRCT was different at some centers, but obtaining echocardiograms annual did not differ and was at a rate of $>90\%$.

Eular guideline	Medication	% of CSRG patients
Raynaud's phenomenon		
1. Calcium channel blockers should be considered for first-line therapy for SSc-related RP and intravenous iloprost, or other available i.v. prostanoids, should be considered for severe SSc-related RP.	Calcium channel blockers	47.3
	Iloprost	0.3
Digital ulcers (active)		
2. Intravenous prostanoids, (particularly iv iloprost) should be considered for the treatment of active digital ulcers.	Iloprost	<1%
3. Bosentan should be considered in treatment of diffuse SSc patients with multiple DU, after failure of CCBs and, usually, prostanoid therapy.	Bosentan	9.2
PAH		
4. Bosentan should be strongly considered in the treatment SSc-related PAH.	Bosentan	19
5. Sitaxentan may be considered in treatment of SSc-related PAH.	Sitaxentan	11.9
6. Sildenafil may be considered in treatment of SSc-related PAH.	PDE5 inhibitors	14.3
7. Intravenous epoprostenol should be considered for the treatment of severe SSc-related PAH.	Epoprostenol	6
Skin involvement (mRSS>10)		
8. Methotrexate may be considered in the treatment of skin involvement in early diffuse SSc.	Methotrexate	18.8
ILD		
9. Cyclophosphamide should be considered in the treatment of SSc-related ILD.	Cyclophosphamide)	16.2
Renal crisis		
10. Angiotensin converting enzyme inhibitors should be used in the treatment of scleroderma renal crisis.	ACE inhibitors	77.1
Gastrointestinal involvement		
12. Proton pump inhibitors should be used for prevention of SSc-related GERD, esophageal ulcers and strictures.	PPIs (GERD)	85.5
13. Prokinetic agents should be used for the management of SSc-related symptomatic motility disturbances (dysphagia, GERD, delayed gastric emptying, bloating, pseudoobstruction, etc.)	Promotility agents (GERD)	24.6
	Promotility agents (delayed gastric emptying)	27.8
	Promotility agents (pseudo-obstruction)	40.3
	Promotility agents	26.8

Treatment and investigation practice frequency and variation among centers with n>50

	Centre						
N=640	A N=52 Frequency (%)	B N=65 Frequency (%)	C N=86 Frequency (%)	D N=98 Frequency (%)	E N=154 Frequency (%)	F N=185 Frequency (%)	P-value
Raynaud's phenomenon							
N (%) with RP	52 (100)	65 (100)	86 (100)	91 (94.8)	152 (100)	183 (98.9)	0.002
Calcium Channel Blocker	25 (48.1)	25 (38.5)	41 (47.7)	50 (54.9)	62 (40.8)	85 (46.4)	.280
Iloprost	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)	.678
PDE5 Inhibitors	5 (9.6)	2 (3.1)	1 (1.2)	0 (0)	8 (5.3)	6 (3.3)	.036
Digital ulcers (DU) (ever)							
N (%) with DU ever	28 (53.8)	31 (47.7)	56 (65.1)	47 (48.0)	56 (36.4)	60 (32.4)	0.000
Calcium Channel Blocker	15 (53.6)	11 (35.5)	28 (50)	28 (59.6)	28 (50.0)	39 (65.0)	.131
Bosentan	2 (7.1)	3 (9.7)	2 (3.6)	1 (2.1)	2 (3.6)	4 (6.7)	.650
Skin involvement (MRSS>10)							
N (%) with MRSS>10	21 (40.4)	42 (64.6)	54 (62.8)	47 (48.0)	76 (49.4)	88 (47.6)	0.020
Corticosteroids	3 (14.3)	8 (19.0)	8 (14.8)	15 (31.9)	16 (21.3)	23 (26.1)	0.299
D-penicillamine	0 (0)	1 (2.4)	6 (11.1)	0 (0)	1 (1.3)	1 (1.1)	0.004
Methotrexate	2 (9.5)	9 (21.4)	8 (14.8)	8 (17.0)	6 (8.0)	15 (17.0)	0.387
Cyclophosphamide	3 (14.3)	0 (0)	1 (1.9)	5 (10.6)	3 (4.0)	8 (9.1)	0.062
Dysphagia							
N (%) with dysphagia	31 (59.6)	41 (63.1)	55 (64.0)	54 (55.1)	94 (61.0)	94 (50.8)	0.236
Esophageal Dilatation	7 (22.6)	11 (26.8)	8 (14.5)	12 (22.6)	35 (37.2)	4 (4.3)	0.000
Inflammatory arthritis							
N (%) with inflammatory arthritis	19 (37.3)	23 (35.4)	71 (83.5)	42 (44.7)	32 (21.2)	39 (21.1)	0.000
Methotrexate	1 (5.3)	7 (30.4)	10 (14.1)	9 (21.4)	4 (12.5)	8 (20.5)	0.259
Hydroxychloroquine	5 (26.3)	0 (0)	10 (14.1)	11 (26.2)	7 (21.9)	13 (33.3)	0.023
D-penicillamine	0 (0)	0 (0)	7 (9.9)	0 (0)	0 (0)	0 (0)	0.008
Corticosteroids	4 (21.1)	8 (34.8)	10 (14.1)	16 (38.1)	6 (18.8)	13 (33.3)	0.039
Inflammatory myositis							
N (%) with inflammatory myositis	3 (5.9)	11 (17.2)	42 (50.6)	11 (11.7)	6 (3.9)	18 (10.1)	0.000
Methotrexate	1 (33.3)	4 (36.4)	8 (19.0)	2 (18.2)	1 (16.7)	5 (27.8)	0.826
PAH							
N (%) with PAH	1 (2.2)	2 (3.3)	1 (1.3)	4 (4.2)	10 (7.4)	24 (14.4)	0.001
ILD							
N % with ILD	13 (25.0)	28 (44.4)	36 (43.4)	35 (36.1)	38 (25.5)	83 (45.4)	0.001
Corticosteroids	3 (23.1)	7 (25.0)	4 (11.1)	12 (34.3)	11 (28.9)	25 (30.1)	0.284
Cyclophosphamide	4 (30.8)	1 (3.6)	2 (5.6)	3 (8.6)	1 (2.6)	10 (12.0)	0.037
Axathioprine	2 (15.4)	6 (21.4)	4 (11.1)	2 (5.7)	3 (7.9)	2 (2.4)	0.037

* P-values measure variation among centers

Conclusions: Although the guidelines were not published until after our standard of care was established, the SSc experts were mostly practicing in accordance with EULAR/EUSTAR recommendations. Methotrexate use for skin was only 19% for current use, but we did not study ever use so it may have been higher if studied in that way. CSRG practices were generally comparable to recently published guidelines; however, use of iloprost for digital ulcers and severe RP differed from guidelines as this drug is not approved in Canada. The CSRG adherence is a 'best case' scenario as these are centers with an interest in SSc and queries for non-adherence to recommended tests occur in the database. The adherence to EULAR/EUSTAR SSc guidelines in general rheumatology practice is likely far less than in SSc centers.

Disclosure: J. E. Pope: None; **S. Harding:** None; **S. Khimdas:** None; **A. Bonner:** None; **M. Baron:** None; **The CSRG:** None.

1203

Are SSc Experts Doing What They Should Do? An Analysis of Practice Variability in Large SSc Centers within the Canadian Scleroderma Research Group (CSRG) Shows Practice Differences. Sarah Harding[4], Sarit Khimdas[4], A. Bonner[2], Murray Baron[1] and Janet E. Pope[3], [1]Jewish General Hospital, Montreal, QC, Canada, [2]McMaster University, [3]St Joseph Health Care London, London, ON, Canada, [4]University of Western Ontario

Objective: There is currently no consensus on best practice in SSc. To determine if variability in treatment and investigations exists, practices among Canadian Scleroderma Research Group (CSRG) centers were compared.

Methods: Prospective clinical and demographic data from adult SSc patients are collected annually from 15 CSRG treatment centers. Laboratory parameters, self-reported socio-demographic questionnaires, current and past medications and disease outcome measures are recorded. For centers with >50 patients enrolled, treatment practices were analyzed to determine practice variability.

Results: Data from 640 of 938 patients within the CSRG database met inclusion criteria, where 87% were female, the mean ± SEM age was 55.3 ± 0.5; 49% had limited SSc and 48% had diffuse SSc (and 3% uncharacterized). Several investigation and treatment practices were inconsistent among 6 centers including proportion receiving PDE5 inhibitors for Raynaud's phenomenon (p=0.036); cyclophosphamide (p=0.037) and azathioprine (p=0.037) for treatment of ILD; hydroxychloroquine (p=0.023), D-penicillamine (p=0.008), and steroids (p=0.039) for inflammatory arthritis; hyperalimentation (p=0.000) and esophageal dilatations (p=0.000) among centers analyzed. Where negative trails exists, there were differences in use of D-penicillamine (although infrequent) for MRSS >10 (p=0.004), Between site performing of: chest X-rays (72–98%,p=0.000), HRCTs (11–41%,p=0.000) and ECGs (75–98%p=0.000) were different. Annual echocardiograms (91–100%, p=0.2) and PFTs (85–97%, p=0.17) were usually performed annually and did not vary among sites.

Treatment and investigation practice frequency and variation among centers with n>50

	Center						
N=640	A N=52 Frequency (%)	B N=65 Frequency (%)	C N=86 Frequency (%)	D N=98 Frequency (%)	E N=154 Frequency (%)	F N=185 Frequency (%)	P-value
Raynaud's phenomenon							
N (%) with RP	52 (100)	65 (100)	86 (100)	91 (94.8)	152 (100)	183 (98.9)	0.002
Calcium Channel Blocker	25 (48.1)	25 (38.5)	41 (47.7)	50 (54.9)	62 (40.8)	85 (46.4)	.280
Iloprost	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)	.678
PDE5 Inhibitors	5 (9.6)	2 (3.1)	1 (1.2)	0 (0)	8 (5.3)	6 (3.3)	.036
Digital ulcers (DU) (ever)							
N (%) with DU ever	28 (53.8)	31 (47.7)	56 (65.1)	47 (48.0)	56 (36.4)	60 (32.4)	0.000
Calcium Channel Blocker	15 (53.6)	11 (35.5)	28 (50)	28 (59.6)	28 (50.0)	39 (65.0)	.131
Bosentan	2 (7.1)	3 (9.7)	2 (3.6)	1 (2.1)	2 (3.6)	4 (6.7)	.650
Skin involvement (MRSS>10)							
N (%) with MRSS>10	21 (40.4)	42 (64.6)	54 (62.8)	47 (48.0)	76 (49.4)	88 (47.6)	0.020
Corticosteroids	3 (14.3)	8 (19.0)	8 (14.8)	15 (31.9)	16 (21.3)	23 (26.1)	0.299
D-penicillamine	0 (0)	1 (2.4)	6 (11.1)	0 (0)	1 (1.3)	1 (1.1)	0.004
Methotrexate	2 (9.5)	9 (21.4)	8 (14.8)	8 (17.0)	6 (8.0)	15 (17.0)	0.387
Cyclophosphamide	3 (14.3)	0 (0)	1 (1.9)	5 (10.6)	3 (4.0)	8 (9.1)	0.062
Dysphagia							
N (%) with dysphagia	31 (59.6)	41 (63.1)	55 (64.0)	54 (55.1)	94 (61.0)	94 (50.8)	0.236
Esophageal Dilatation	7 (22.6)	11 (26.8)	8 (14.5)	12 (22.6)	35 (37.2)	4 (4.3)	0.000
Inflammatory arthritis							
N (%) with inflammatory arthritis	19 (37.3)	23 (35.4)	71 (83.5)	42 (44.7)	32 (21.2)	39 (21.1)	0.000
Methotrexate	1 (5.3)	7 (30.4)	10 (14.1)	9 (21.4)	4 (12.5)	8 (20.5)	0.259
Hydroxychloroquine	5 (26.3)	0 (0)	10 (14.1)	11 (26.2)	7 (21.9)	13 (33.3)	0.023
D-penicillamine	0 (0)	0 (0)	7 (9.9)	0 (0)	0 (0)	0 (0)	0.008
NSAIDs	9 (47.4)	5 (21.7)	26 (36.6)	21 (50.0)	15 (46.9)	12 (30.8)	0.174
Corticosteroids	4 (21.1)	8 (34.8)	10 (14.1)	16 (38.1)	6 (18.8)	13 (33.3)	0.039
Renal crisis ever							
N (%) with renal crisis ever	3 (5.8)	3 (4.6)	6 (7.0)	5 (5.2)	12 (7.9)	8 (4.3)	0.787
ACE inhibitor	2 (66.7)	2 (66.7)	5 (83.3)	5 (100.0)	7 (58.3)	7 (87.5)	0.463
PAH							
N (%) with PAH	1 (2.2)	2 (3.3)	1 (1.3)	4 (4.2)	10 (7.4)	24 (14.4)	0.001
Bosentan	1 (100.0)	1 (50.0)	0 (0)	1 (25.0)	2 (20.0)	4 (16.7)	0.383
Sitaxentan	0 (0)	1 (50.0)	0 (0)	0 (0)	1 (10.0)	7 (29.2)	0.516
Warfarin	1 (100.0)	0 (0)	0 (0)	1 (25.0)	2 (20.0)	5 (20.8)	0.476
PDE5 Inhibitors	1 (100.0)	1 (50.0)	0 (0)	0 (0)	3 (30.0)	3 (12.5)	0.150
ILD with FVC<70%							

* P-values measure variation among centres

Conclusions: There is site variation in SSc with respect to investigations and management among CSRG centers suggesting a need for a standardized approach to the investigation and treatment of SSc. One would speculate that more variability would occur between rheumatologists who did not have a critical mass of SSc and were not given reminders of annual tests to be performed (ex. echocardiograms) as we looked only at practices within a database.

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1204

Assessing Health Status in Patients with Systemic Sclerosis: Construct Validity of the Karnofsky Performance Status Score. Christelle Nguyen[2], Alice Bérezné[2], François Rannou[3], Caroline Mestre-Stanislas[2], Sandrine Morell-Dubois[1], Loïc Guillevin[2], Serge Poiraudeau[3] and Luc Mouthon[2]. [1]Universite Lille 2; Service de Medecine Interne; Centre de Reference Pour la Sclerodermie Systemique; Hopital Claude Huriez; Lille; France, [2]Universite Paris Descartes; Faculte de Medecine Paris Descartes; Pole de Medecine Interne, Centre de Reference Pour les Vascularites Necrosantes et la Sclerodermie Systemique; Hopital Cochin; Assistance Publique-Hopitaux de Paris (AP-HP); [3]Universite Paris Descartes; Faculte de Medecine Paris Descartes; Service de Medecine Physique et Readaptation; Hopital Cochin AP-HP; Inserm, Institut Federatif de Recherche sur le Handicap, Paris

Purpose: Systemic sclerosis (SSc) is a connective-tissue disease, responsible for skin, tendon, joint, and vessel damage, which can ultimately lead to disability, compromised health-related quality of life and poor health status. However, available instruments assessing global, patient's perceived and location-specific disabilities do not specifically survey patient global health status. An example of a score that surveys global health status is the Karnofsky Performance Status (KPS) score. Previous data support the use of the KPS score to predict outcome in SSc. Nevertheless, before considering the KPS score as a suitable outcome measure in SSc, its relevance should be definitely established. Therefore, we aimed to assess the construct validity of the KPS score in the assessment of health status in patients with SSc, by determining its convergent and divergent validity.

Methods: Three-hundred-and-sixty-two SSc patients fulfilling the American College of Rheumatology and/or the Leroy and Medsger criteria were assessed for visceral involvement, handicap and health-related quality of life (HRQoL). Global health status was evaluated by the KPS score. KPS score convergent and divergent validities were assessed using the Spearman's rank correlation coefficient.

Results: Mean age and disease duration at the time of evaluation were 55.7 (13.3) and 9.6 (7.9) years, respectively. Thirty-three (9.3%) patients had limited SSc, 179 (50.7%) limited cutaneous SSc, and 141 (39.8%) diffuse cutaneous SSc. Mean total score of the KPS score was 77.6 (11.7). The KPS score had fair convergent validity with disease duration ($r=-0.361$), dyspnea (NYHA classification, $r=-0.308$), perceived handicap as assessed by McMaster-Toronto Arthritis Patient Preference Disability Questionnaire ($r=-0.479$) and global disability as assessed by the Health-Assessment Questionnaire (HAQ, $r=-0.337$), and no correlation with hand-located disability as assessed by the Cochin Hand Functional Scale ($r=-0.278$), mouth-located disability as assessed by the Mouth Handicap In Systemic Sclerosis Scale ($r=-0.003$), anxiety and depression symptoms as assessed by the Hospital Anxiety and Depression Scale ($r=-0.053$), aesthetic impairment assessed on an 11-point scale ($r=-0.071$), and HRQoL as assessed by SF-36 mental and physical component scores ($r=0.064$ and $r=0.168$, respectively).

Conclusion: For assessing global health status in patients with SSc, the KPS score has acceptable construct validity. The weak correlation between KPS score and previously validated outcome measures in SSc suggests that the KPS score adds useful information for assessing the global health status in patients with SSc and that it may be a suitable instrument for daily practice or clinical trials in SSc.

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1205

Association of Gastrointestinal Involvement and Depressive Symptoms in Patients with Systemic Sclerosis. Vijay Bodukam[1], Ron D. Hays[2], Paul Maranian[2], Daniel E. Furst[2], James R. Seibold[3], Ann Impens[4], Maureen D. Mayes[5], Philip J. Clements[2] and Dinesh Khanna[2]. [1]Interfaith Medical Center, Brooklyn, Los Angeles, CA, [2]UCLA, [3]Univ of Connecticut, [4]University of MIchigan, [5]University of Texas Houston

Background: Systemic sclerosis-associated gastrointestinal tract involvement (SSc-GIT) is an important predictor of depressive symptoms. UCLA Scleroderma Clinical trial Consortium Gastrointestinal tract 2.0 (UCLA SCTC GIT 2.0) is a 34 item instrument that captures GIT symptom severity and impact on quality of life. This instrument is feasible, reliable and valid. It has seven scales—reflux, distension/bloating, diarrhea, fecal soilage, constipation, emotional well-being and social functioning and a total GIT score.

Objective: To assess 1) whether there is an association between depressed mood with GI symptoms as assessed by the UCLA SCTC GIT 2.0 instrument, and 2) to explore which GI specific symptom scales are associated with depressed mood in patients with SSc.

Methods: 152 patients with SSc completed the UCLA SCTC GIT 2.0 and the Center for Epidemiologic Studies Short Depression scale (CES-D 10; 0–30). Patients were divided into depressed (CES-D $\geq$ 10) or non-depressed group (CES-D $<$ 10) and compared using t-test or Chi-Square test. Multiple linear regression was used to determine associations between GI scales and depressed mood (CES-D).

Results: Study participants were 84% female, 78% Caucasian and 40% had depressed mood (CES-D10 $\geq$ 10). Patients with depressed mood had statistically worse GI scale scores (except fecal soilage) and worse total GIT score ($P<0.05$). In the multivariable model, reflux and constipation scales were independently associated with worse CES-D scores ($P=0.01$ to 0.06)

Conclusion: SSc-GIT involvement is associated with depressed mood. Reflux and constipation scales of UCLA-SCTC GIT 2.0 were independently associated with CES-D. Future studies should assess if treatment of GIT symptoms will improve depressed mood in patients with SSc-GIT.

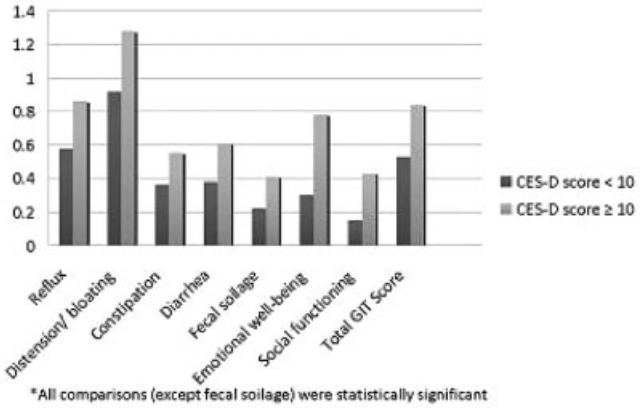

Figure. UCLA SCTC GIT 2.0 scale scores in patients with and without depressed mood.

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1206

Bone Mineral Density and Body Composition in Systemic Sclerosis: A Case-Control Study. Chi Chiu Mok, Ling Yin Ho, Chi Hung To and Kwok Man Ma. Tuen Mun Hospital

Background: Whether bone mineral density (BMD) is lower in patients with systemic sclerosis (SSc) than age-matched population is controversial. We conducted a case-control study on BMD and body composition (BC) in a group of southern Chinese patients with SSc.

Method: Consecutive patients who fulfilled the ACR criteria for SSc were invited for this cross-sectional study on BMD and BC (fat and lean mass), which was measured by dual energy X-ray absorptiometry (DXA) scan (Hologic, Belford USA). Exclusion criteria were: (1) Age $<$18 years; (2) Presence of other underlying rheumatic diseases (overlap syndrome); (3) Informed consent could not be obtained. An equal number of age and gender matched healthy controls were also recruited for the same measurements.

Results: 46 patients with SSc and 46 controls were studied. The mean age of patients at the time of DXA study was 48.4 ± 9.7 years. The mean duration of SSc since diagnosis was 5.5 ± 3.2 years. Thirteen (28%) patients had diffuse SSc while the others had limited SSc. Only 2 (4%) patients were currently receiving bisphosphonates. According to the World Health Organization (WHO) criteria, 5 (11%) patients with SSc had osteoporosis (T score ≤-2.5) at the hip and 16 patients (35%) had osteoporosis at the lumbar spine. 61% and 30%, respectively, of the patients had osteopenia at the hip and spine (T score between -1 and -2.5). One patient (2%) had vertebral fractures on radiological screening but no patients had a personal history of non-vertebral fractures. The body mass index (BMI) of patients with SSc was significantly lower than that of controls (20.9 ± 3.2 vs 26.1 ± 2.4kg/m^2; $p<0.001$). After adjustment for age, BMI and other risk factors for osteoporosis by ANCOVA, BMD of the total hip (0.778 ± 0.135 vs 0.838 ± 0.106g/m^2; $p=0.02$) and femoral neck (0.671 ± 0.127 vs 0.721 ± 0.106g/m^2; $p=0.04$) were significantly lower in patients with SSc than that of normal controls. The BMD of the lumbar spine (L2–4) was lower in SSc patients (0.903 ± 0.167 vs 0.944 ± 0.135g/m^2; $p=0.19$) but the difference was not statistically significant. The total bone mineral content (BMC) (1.73 ± 0.34 vs 1.85 ± 0.24g; $p=0.04$), fat mass (15.15 ± 5.34 vs 17.34 ± 4.09kg; $p=0.04$), lean mass (31.58 ± 4.61 vs 34.66 ± 3.95kg; $p=0.002$) were significantly lower in patients with SSc than controls. Among patients with SSc, linear regression analysis revealed that the whole body lean mass correlated positively with hip BMD ($p=0.02$), but age correlated negatively with BMD at the hip ($p=0.004$), after adjustment for sex, major organ complications and other common risk factors for osteoporosis. On the other hand, both lean mass and fat mass correlated positively with spinal BMD ($p<0.05$), whereas increasing age correlated with a significantly lower BMD at the lumbar spine ($p<0.001$).

Conclusions: Patients with SSc have significantly lower BMD at the hip than age-matched healthy controls, which is probably contributed by a significantly lower body lean mass.

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1207

Clinical Significance of Defined ANCA Positivity in Systemic Sclerosis. Emma C. Derrett-Smith[2], Svetlana Nihtyanova[2], Jennifer Parker[1], Christopher Bunn[1], Aine Burns[1], Mark A. Little[1] and Christopher P. Denton[3]. [1]Centre for Immunology, Royal Free Campus, UCL Medical School, London, [2]Centre for Rheumatology and Connective Tissue Diseases, Royal Free Campus, UCL Medical School, London, [3]Royal Free Hospital, London, United Kingdom

Purpose: While an atypical ANCA is reported in 20–30% of patients who have systemic sclerosis (SSc), this is not usually clinically significant. Conversely, patients with systemic sclerosis who have confirmed ANCA positivity with either myeloperoxidase (MPO) or proteinase-3 (PR3) antibodies on ELISA and clinical vasculitis are rarely reported in the literature. We have interrogated our database of patients with SSc who also have listed a clear clinical or histological diagnosis of vasculitis to look for the prevalence of overlap disease with ANCA-associated vasculitis (AAV) and whether these patients have altered disease features.

Methods: We examined a clinical database of 2200 patients with either limited or diffuse cutaneous SSc. Patients who had a clear clinical or histological diagnosis of vasculitis of any description had their serology investigations reviewed and repeated if possible to look for ANCA positivity with either MPO or PR3 reactivity. The clinical features, serology and histology of those patients who had both SSc and AAV were examined in detail.

Results: From our SSc cohort, 35 patients (1.6%) had a current or previous history of vasculitis, in whom the distribution of antibodies characteristically associated with the SSc features of their disease was comparable to those previously published from our cohort. For example, 20% were anti-centromere positive, 20% anti-topoisomerase-1 positive and 6% anti-fibrillarin antibody positive. Of these 35 patients, 8 (0.4% of total cohort) were either anti-MPO or anti-PR3 antibody positive. Both patients from the 35 who carried anti-fibrillarin antibodies, usually associated with overlap disease and increased incidence of renal and cardiac complications, were ANCA positive. No patients with vasculitis and anti-centromere antibodies were ANCA positive. Of the 8 ANCA positive patients, 7 had limited cutaneous SSc and anti-MPO antibodies and one had diffuse disease with anti-PR3 antibodies. The latter patient had clinical features of microscopic polyangiitis with renal, neurological and skin involvement. None of the MPO positive patients had granulomatous disease. All but one had glomerulonephritis, and 6 had pulmonary fibrosis.

Conclusions: SSc in overlap with ANCA-associated vasculitis is rare, and clinical features are more mixed than when either of these two conditions occurs separately. From our database, anti-fibrillarin antibodies may be more associated with overlap AAV than the other scleroderma-specific antibodies.

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1208

Cognitive Impairment in Systemic Sclerosis. Neslihan Yilmaz[2], Aynur Mollahasanoglu[1], Meryem Can[2], Müge Koçak[1], Nese Tuncer[1], Nevsun Inanç[2] and Sule Yavuz[2]. [1]Marmara University, Faculty of Medicine, Neurology Department, Istanbul, Turkey, [2]Marmara University, Faculty of Medicine, Rheumatology Department, Istanbul, Turkey

Background and Aim: Systemic sclerosis (SSc) is a connective tissue disorder that is characterized by microvascular damage and tissue fibrosis. Although nervous system involvement is unusual in SSc, cerebral hypoperfusion has been shown in imaging studies. Here, we aimed to evaluate cognitive functions in SSc patients who had no previous or current history of neurological involvement.

Methods: Thirty-one scleroderma patients (24 limited SSc, 4 diffuse SSc, 3 overlap) were examined. Fifteen rheumatoid arthritis patients (RA) and 20 healthy subjects(HC) were selected as aged and sex matched controls. To evaluate of different areas of cognition six neuropsychological tests was performed.

Results: Five out of 6 test scores including Wechsler Memory Scale digit span (WMS), Wisconsin card sorting test(WSCT),Stroop color-word interference test,Controlled oral word association tes(COWAT), California verbal learning test (CVLT) were different among the groups ($p<0.005$). WSCT categories completed test (HC vs SSc and RA vs SSc, $p<0.0001$), WSCT perseverative responses (HC vs SSc, $p<0.0001$; RA vs SSc, $p=0.005$), WSCT percentage perseverative errors (HC vs SSc, $p<0.0001$; RA vs SSc, $p=0.003$), WSCT percentage conceptual level responses (HC vs SSc, $p<0.0001$; RA vs SSc, $p= 0.001$) and CVLT perseveration (HC vs SSc, $p<0.0001$; RA vs SSc, $p=0.001$) test scores were significantly impaired in Ssc patients compared to both RA patients and HC subjects.

Table 1. Neuropsychological performances of SSC and RA patients vs healthy controls

	HC	RA	SSc
WSCT categories completed test	6 ± 0.0	5.6 ± 0.7	3.9 ± 1.2 □
WSCT perseverative responses	14.6 ± 7.8	21.7 ± 12.2	36.5 ± 17.5 □
WSCT percentage perseverative errors (%)	13.1 ± 4.5	16.3 ± 6.6	25.0 ± 10.2 □
WSCT percentage conceptual level responses (%)	73.5 ± 6.5	66.9 ± 13.5	47.4 ± 16.6 □
CVLT perseveration	1.7 ± 1.7	2.2 ± 1.3	4.58 ± 2.4 □

Kruskal Wallis test $p<0.0001$, Post hoc analysis; □ vs RA and HC $p<0.005$

On the other hand, WMS, Stroop test, COWAT and CVLT scores were found to be impaired in both SSc and RA patients compared to healthy controls ($p<0.005$).

Conclusion: This is the first extensive study showing cognitive impairment in SSc patients. WSCT might be considered a useful tool for detection of cognitive dysfunction in SSc patients.

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1209

Coronary Artery Calcification in Systemic Sclerosis: There Was No Difference between SSc and Healthy Control Groups. Young-Eun Park[2], Seong-Hu Park[2], Seung-Hoon Baek[2], Jun-Hee Lee[2], Joung-Wook Lee[2], Geun-Tae Kim[2], Yeon-Ju Jeong[3], Su-Yeon Choi[4], Wan-Hee Yoo[1] and Sung-Il Kim[2]. [1]Chonbuk National University Medical School, Jeonju, Jeonbuk, South Korea, [2]Department of Internal Medicine, School of Medicine, Pusan National University, Busan, South Korea, [3]Department of Radiology, School of Medicine, Pusan National University, Busan, South Korea, [4]Seoul National University Hospital Healthcare System Gangnam Center, Seoul, South Korea

Background: Several systemic autoimmune diseases are associated with an increased prevalence of coronary artery disease. In systemic sclerosis (SSc), microvascular abnormality is well recognized, but previous studies about macrovascular disease including coronary artery disease showed conflicting results. Measurement of coronary calcification score (CCS) by a multi-detector computed tomography (MDCT) is an accurate and non-invasive method to detect coronary atherosclerosis, and the high level of CCS can predict coronary events.

Objective: To investigate the CCS in patients with SSc by using MDCT and to evaluate the risk of coronary artery disease.

Methods: We investigated the clinical and laboratory characteristics in patients with SSc (41 patients, all were women, mean 50 years, 22 with limited and 19 with diffuse type). The CCS was measured by MDCT and the risk of coronary events were evaluated by CCS and Framingham risk score (FRS). We selected sex and age-matching controls (123 controls) among the historical healty control group in South Korea, who were scanned by same CT scanner with our group, and analysed data statistically between SSc and control groups. We also assessed whether disease specific factors of SSc were correlated with CCS.

Results: The mean CCS of SSc was not significantly increased compared with healthy control (7.0 ± 26.3 vs 5.5 ± 41.2, $p=0.829$). The frequency of CCS>0 was not significantly different between SSc and control groups (17% vs 13%, $p=0.339$) (figure 1). There was also no difference in coronary

calcification between SSc and control groups after correction for the confounders high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, fasting glucose, body mass index and waist measurement. The CCS had no significant correlations with disease specific factors. The FRS was evaluated in 36 patients, all patients were categorized into low-risk group (FRS<10%).

Statistics of coronary calcification scores in 41 patients with systemic sclerosis

	CCS, Mean ± SD	CCS>0, no. (%)
Control (n=123)	5.5 ± 41.2	16 (13.0)
SSc-total (n=41)	7.0 ± 26.3	7 (17.1)
p-value	0.829	0.339
SSc-limited (n=22)	12.0 ± 35.3	5 (22.7)
SSc-diffuse (n=19)	1.1 ± 3.2	2 (11.2)
p-value	0.161	0.217

Conclusion: These results imply that the risk of coronary events due to coronary atherosclerosis might not be high in patients with SSc.

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1210

CXCL4, a Novel Marker for Systemic Sclerosis That Clearly Correlates with the Clinical Hallmarks and Pathological Events. Timothy Ruben Radstake[3], Lenny van Bon[2], Jasper Broen[2], Romy Beatriz-Christmann[1], Alsya Affandi[1], Madelon Vonk[2], Mike York[1], Cindy Collins[1], Mark Wenink[2], Roger Hesselstrand[7], Dirk Wuttge[7], Sandeep Agarwal[6], John Reveille[6], Joost Drenth[2], Jaqueline de Graaf[2], Martin Den Heijer[2], Cees Kallenberg[5], Marc Bijl[4], Wim van den Berg[2], Joosten Leo[2], Waander van Heerde[2], Piet van Riel[2] and Robert Lafyatis[1]. [1]Boston Medical Center, [2]Radboud University Nijmegen Medical Center, [3]Radboud University Nijmegen Medical Center/Boston Medical Center, Nijmegen, The Netherlands, [4]University Hospital Groninge, [5]University Hospital Groningen, [6]University Hospital Houston, TX, [7]University Hospital Lund, Sweden

Background: Despite recent advances in our understanding of systemic sclerosis (SSc) many patients still suffer from progressive disease leading to severe complications and premature death. Currently predictors for disease phenotype and prognosis are lacking.

Methods: We exploited proteome-wide analysis (SELDI-TOF) of secreted proteome from plasmacytoid dendritic cells (pDCs) from clinically well-defined groups of SSc patients (n = 214) to study the differential expression of proteins between SSc subsets. We confirmed the presence of the most predominant protein CXCL4 by ELISA in the supernatant and plasma of SSc patients in comparison with healthy individuals (n=129) and other autoimmune (SLE, n = 109), auto-inflammatory (AS, n = 93) and fibrosing (liver fibrosis, n = 93) clinical conditions. Using SSc phenotypic data including the presence of autoantibodies, skin- and lung fibrosis and pulmonary arterial hypertension (PAH) we examined the potential correlation between these clinical hallmarks and circulating CXCL4 levels. Finally, we studied the direct effects of CXCL4 on skin fibroblasts and HUVEC by investigating COMP expression and secretion of endothelin-1, respectively.

Results: Circulating pDCs were found at higher frequencies in SSc patients but did not spontaneously produce higher levels of IFNa compared to controls. Proteome-wide analysis of SSc pDC supernatants revealed the chemokine CXCL4 as the most abundant protein detected, seen predominantly in patients having early diffuse disease. Validation using ELISA confirmed this observation and also showed that circulating CXCL4 levels were significantly higher in SSc patients compared to controls and other conditions such as SLE, AS and liver fibrosis. CXCL4 levels were higher in diffuse SSc compared with limited SSc but showed by far the highest levels in those patients having early diffuse SSc. CXCL4 levels correlated well with the extent of skin fibrosis and the presence of lung fibrosis and PAH. These correlations could be explained by the ability of CXCL4 to induce myofibroblast transformation of skin fibroblasts and the secretion of endothelin-1 by human endothelial cells (HUVEC).

Conclusion: The anti-angiogenic chemokine CXCL4 is highly expressed in SSc patients and correlates well with the clinical hallmarks of SSc skin- and lung fibrosis and PAH and therefore provides a novel biomarker for SSc phenotype but also other fibrosing diseases.

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1211

Determinants of Work Disability in Patients with Systemic Sclerosis: A Longitudinal Study of the GENISOS Cohort. Roozbeh Sharif[2], Maureen D. Mayes[8], Perry M. Nicassio[1], Emilio B. Gonzalez[6], Hilda T. Draeger[5], Terry A. McNearney[7], Deepthi K. Nair[3], John D. Reveille[4], Frank C. Arnett[9] and Shervin Assassi[2]. [1]Department of Psychiatry, University of California, Los Angeles, CA, [2]Division of Rheumatology and Immunogenetics, University of Texas Health Science Center at Houston, Houston, TX, [3]Division of Rheumatology and Immunogenetics, University of Texas Health Science Center at Houston, Houston, TX, [4]Univ Texas Health Sci Ctr, Houston, TX, [5]University of Texas Health Science Center at San Antonio, San Antonio, TX, [6]University of Texas Medical Branch at Galveston, Galveston, TX, [7]University of Texas Medical Branch at Galveston, TX, [8]University of Texas-Houston, Houston, TX, [9]UT Medical School, Houston, TX

Background: Systemic sclerosis (SSc) is associated with substantial morbidity and mortality. SSc can have profoundly detrimental impact on the patients' personal and professional life. There are no published data on the prevalence of the work disability (WD) in patients with SSc in the United States, nor longitudinal studies examining long-term predictors of WD in general. The goal of this study was to determine the prevalence and correlates of WD at enrollment and to investigate the longitudinal determinants of WD in the patients enrolled in the Genetic versus Environment in Scleroderma Outcome Study (GENISOS) cohort.

Methods: Patients were subdivided into three groups based on their employment status at enrollment: work disabled, working, and retired or homemakers. The latter group was excluded from further analysis. Utilizing logistic regression analysis with a forward hierarchical variable selection strategy, we evaluated the independent socio-demographic, clinical, and quality of life measure correlates of WD at enrollment. Furthermore, patients working at enrollment were included in the longitudinal study. We used a Cox regression proportional Hazard's model with a similar variable selection strategy to determine the predictors of WD on follow up visits. All quality of life measures demonstrated adequate internal consistency reliability in the current study.

Results: At the time of analysis, 284 patients with mean age of 48.7 (±13.2) years were enrolled in the GENISOS cohort. There were 237 (83.5%) female; 133 (46.8%) Caucasian, 83 (28.9%) Hispanic, 58 (20.4%) African American, and 10 (3.5%) from other ethnic groups. Overall; 162 (57.0%) patients had diffuse cutaneous involvement; the disease duration at enrollment was 2.5 (±1.6) years. Patients were followed for 3.9 (±3.6) years; in 1438 consecutive visits. At entry; 124 patients (43.7%) were WD, 131 (46.1%) working, and 29 (10.2%) retired or homemakers. In a multivariate regression model, older age (p=0.012), educational level below associate degree (p<0.001), higher Fatigue Severity Score (p=0.045), lower SF-36 physical component scores (p<0.001) and lower % predicted FVC (p=0.009) were independently associated with WD at the cross sectional level.

At mean follow-up of 4.4 (±3.8) years (range up to 12 years) of those working at baseline, 96 (73.3%) were still working while 35 (26.7%) became disabled. Using multivariate Cox regression analysis, lower coping skills as measured by higher IBQ scores (p=0.004), lower % predicted DLCO (p=0.047), and the presence of joint contractures in small joints (p=0.004) were the independent predictors of WD on follow up visits.

Conclusion: Socio-demographic, lung involvement, fatigue severity, and SF-36 physical component scores were the strongest independent correlates of WD in patients with SSc at early stages of the disease. Whereas small joint contracture, lung involvement, and higher IBQ scores, reflecting lower coping skills are the main predictors of the WD at the later stages of the disease.

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1212

Developing a Disease Activity and Therapeutic Response Index in Connective Tissue Disease Related Interstitial Lung Disease (CTD-ILD): Rationale, Aims, Design and Results from Tier 0, the Pre-Delphi Exercise. Lesley Ann Saketkoo[4], Dörte Huscher[2], Dinesh Khanna[12], Paul F. Dellaripa[1], Kevin Flaherty[15], Eric L. Matteson[5], Chester V. Oddis[16], Kristine Phillips[14], David Pittrow[3], Athol Wells[8], Christopher P. Denton[9], Oliver Distler[11], Otylia M. Kowal-Bielecka[6], Vibeke Strand[10], Kevin K. Brown[7] and James R. Seibold[13]. [1]Brigham & Womens Hospital, Boston, MA, [2]German Rheumatism Research Centre - Berlin, Germany, [3]Institute of Clinical Pharmacology, Medical Faculty, University of Dresden, Germany, [4]Louisiana State University Health Sciences Center - New Orleans, LA, [5]Mayo Clinic, Rochester, MN, [6]Medical University of Bialystok, Poland, [7]National Jewish Health, Denver, CO, [8]Royal Brompton Hospital and National Heart and Lung Institute, London, United Kingdom, [9]Royal Free Hospital, London, United Kingdom, [10]Stanford University; Palo Alto, Portola Valley, CA, [11]University Hospital Zurich, Switzerland, [12]University of California Los Angeles, [13]University of Connecticut Health Center, Farmington, CT, [14]University of Michigan, Ann Arbor, MI, [15]University of Michigan, Ann Arbor, [16]University of Pittsburgh, PA

Background: There are currently no licensed therapies for interstitial lung disease (ILD). There is no consensus on measures of disease activity or therapeutic responsiveness, thus hampering effective drug development and regulatory evaluation of candidate therapies. We present the first phase of a multi-tiered investigation to identify consensus on provisional criteria to measure disease activity and therapeutic response in CTD-ILD and Idiopathic Pulmonary Fibrosis (IPF).

Methods: A multi-disciplinary steering committee (authors) engaged in extensive literature review and agreed upon the following methodology: Pulmonary, rheumatology and cardiology specialists with ILD expertise were identified by literature review, task force membership in international societies and peer recommendation. Each was invited to participate in a 3-Tier Delphi project with a preceding 'Tier 0' exercise. The goal of 'Tier 0' was to engage the participants in a brainstorming exercise to identify *qualities that are important to measure* ('domains') in CTD-ILD and IPF and '*instruments'* to measure these domains. The goal of contrasting CTD-ILD and IPF is to distinguish similarities and differences between these entities. Additionally, suggestions of positive and negative instruments were collected for specific CTD-ILD disease groups. Data was collected via a custom designed secure web-site. Participants typed their additions into a 'sparse' framework of 12 sample 'domains' with 12 sample 'instruments'. The steering committee initially participated in a series of individual exercises followed by a group effort to limit redundancy and identify the broadest spectrum of reasonable domains that would appropriately accommodate the diversity of 'instruments' or 'outcome measures' suggested by the participants.

Results: 98% of invited experts participated. 137 pulmonary, 102 rheumatology and 4 cardiology specialists participated from 32 countries representing 6 continents. 74% and 69% of participants considered 'ILD' and 'rheumatologic lung disease' respectively to be their primary fields of investigation. 133 domains were suggested and after review resulted in the 23 domains listed below. More than 6700 instruments were proposed and later reduced to 616.

Table 1. Final 23 Preliminary Domains From Tier 0 of the Delphi Process

Survival	Mental Health
Biomarkers	Sleep
Imaging	Global Assessment
Lung Physiology/Function	Health Related Quality of Life
Lung Parenchyma	Functionality
Lung Vascular	Participation
Cardiac Function	Employment
Composite Scores	Extra-Pulmonary/CTD Features
Gastroesophogeal Reflux	Medication
Cough	Co-Morbidities
Dyspnea	Barriers to Care
Fatigue	

Discussion: This is the first known multi-disciplinary effort to assess domains and instruments in the study of CTD ILD – which is essential in a field devoid of meaningful outcome measures and with many candidate therapies on the horizon. The high response rate of this comprehensive, multi-disciplinary, international effort reflects both the need for a systematic approach to ILD and the collective interest in establishing criteria for this group of diseases. The overall results are very promising and reflect the innate complexities of the spectrum of ILD, thus creating a robust platform for next phases of this consensus study.

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1213

Development of a Limited Scleroderma Cutaneous Activity and Damage Index. Lorinda Chung[1], Daniel E. Furst[5], Paul Maranian[3], Kait Arefiev[2], Jeffrey Zwerner[2], Dinesh Khanna[4], Victoria P. Werth[6] and David Fiorentino[2]. [1]Stanford Univ Medical Center, Palo Alto, CA, [2]Stanford Univ Medical Center, [3]UCLA Medical School, [4]University of California Los Angeles, Los Angeles, CA, [5]University of California Los Angeles Medical School, Los Angeles, CA, [6]University of Pennsylvania, Philadelphia, PA

Purpose: Most clinical trials for skin disease in systemic sclerosis patients have excluded patients with the limited cutaneous subtype (lcSSc) due to the lack of a robust measure of cutaneous disease in these patients. We sought to develop and partially validate a novel cutaneous index for patients with lcSSc.

Methods: We developed the Limited Scleroderma Cutaneous Activity and Damage Index (L-SCADI) based on an extensive literature review and input from 11 SSc experts (6 rheumatologists and 5 dermatologists) providing face and content validity. Following a 30 minute training session, 6 physicians (2 rheumatologists and 4 dermatologists) used the L-SCADI to score the severity of skin disease in 12 lcSSc patients. To assess construct validity, physicians completed visual analogue scales (VAS) to score global assessment of cutaneous activity and damage (PGA-a and PGA-d), and patients completed a VAS global assessment of skin disease (PtGA), the Health Assessment Questionnaire Disability Index, the Dermatology Life Quality Index, and the Short-Form-36 (SF-36). Inter-rater reliability was assessed using intraclass correlation coefficient (ICC) in a 2-way random model. After scoring every patient once, each physician scored at least one patient a second time to assess intra-rater reliability.

Results: All 12 patients were female, 83% Caucasian, with mean disease duration from first non-Raynaud's symptom of 11.9 ± 9.6 years (5 with ≤ 6 years, 7 with > 6 years). Mean time to complete the L-SCADI was 6.9 ± 1.5 min. Mean activity (0–63), damage (0–53), and total (0–116) scores were 10.7 ± 6.3, 7.0 ± 5.2, and 17.7 ± 9.1, where 0=no disease. L-SCADI activity and damage scores were highly correlated with PGA-a and PGA-d (rho=0.77 (p=0.004) for activity, 0.8 (p=0.002) for damage). L-SCADI activity was moderately correlated with PtGA (rho=0.6, p=0.04), while L-SCADI damage was highly negatively correlated with the SF-36 Physical Component Summary score (rho=−0.92, p=0.0001). The inter-rater reliability for PGA-a and PGA-d was modest (ICC 0.34 and 0.43), while the consistency among raters for the L-SCADI activity, damage, and total scores was moderate (ICC 0.52, 0.58, 0.55). The ICC for L-SCADI total improved to 0.62 after excluding edema. Mean time between repeat assessments was 50.2 ± 34.7 min. Intra-rater reliability for PGA-a was not significant, but was excellent for PGA-d (ICC 0.89). Intra-rater reliability for L-SCADI activity was moderate (ICC 0.57), while the damage and total scores had much higher correlations (ICC 0.86 and 0.69).

Conclusions: The L-SCADI is easy to perform and has reasonable construct validity. Inter- and intra-rater reliability for the L-SCADI activity score is moderate, but better than the PGA-a, with much greater intra-rater agreement for the assessment of disease damage. The variability in physician assessments suggests that more extensive training prior to use of the L-SCADI is essential, and further development of the scale is necessary.

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1214

Effect of Selective and Dual Endothelin Receptor Antagonists (ERAs) on SSc and Control Endothelial Cells Apoptosis. Yongqing Wang, Omar R. Kahaly and Bashar Kahaleh. University of Toledo, Toledo, OH

Objectives: microvascular endothelial cells (MVEC) apoptosis is a critical event in the pathogenesis of SSc vascular disease. Endothelin 1 (ET) signaling in MVEC favors cell survival and antagonizes apoptotic signals. In this study we examined the effects of selective and non-selective ERAs on ET mediated resistance to apoptosis.

Methods: MVEC apoptosis was induced by oxidative stress or by growth factor withdrawal (GFW) and was assessed by flow cytometry, caspase-3 activity and cell viability. We tested the selective and non-selective ERAs: PD145065 a dual ERA, BQ 788 a selective B, and the selective type A ERAs FR139317 and Ambrisentan. We also investigated the effects of si-RNA knockdown of EDNRA, B or A&B mRNAs on MVEC apoptosis. Finally, a focused apoptosis gene expression microarray was utilized to investigate the effect of ET and ERAs on MVEC apoptotic gene expression profile.

Results: significant upregulation of both type A and B- ET receptors in SSc-MVEC was noted, particularly the A receptors. SSc- MVEC apoptotic responses to oxidation or GFW were significantly higher in SSc than in control cells. The addition of ET resulted in a significant, albeit incomplete, reversal of MVEC apoptosis, particularly in control cells. The addition of ERAs alone did not alter the level of apoptotic responses. Selective type A-ERAs maintained ET antiapoptotic effects, while selective type B-ERA and dual-ERAs completely blocked the antiapoptotic effect of ET. ET effects were also blocked when selective A-ERAs concentrations were increased beyond the concentrations associated with selectivity of the tested agent. To confirm the conclusion that signaling through type B receptor mediates ET protective effects, we performed si-RNA knock down experiments. Type A receptor mRNA knock down had no effect on ET protective effect, while type B receptor knock down and the combined A&B mRNAs knock down completely abolished ET antiapoptotic effects. Next, we performed focused apoptosis microarray gene expression profiling of MVEC after GFW and the effects of ET and ERAs on gene expression were examined. GFW induced an upregulation of the pro-apoptotic gene *BAX* expression and the addition of ET inhibited *BAX* expression. Selective type A-ERA maintained ET induced downregulation of *BAX* while the nonselective ERAs and selective type B-ERA prevented ET effect on *BAX* expression.

Conclusions: · Oxidation and growth factor withdrawal induced MVEC apoptosis is prevented by ET.

· ET antiapoptotic effects are mediated by inhibition of *BAX* gene expression.

· Selective A-ERAs preserve ET anti-apoptotic effects, while the dual and selective B-ERAs negate ET protective effect.

· Therapeutic strategies utilizing selective A-ERAs may be superior to the non-selective approaches from a vascular prospective.

Disclosure: Y. Wang: None; **O. R. Kahaly:** None; **B. Kahaleh:** None.

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Findings in Ocular Examination of Patients with Systemic Sclerosis. Niki Tsifetaki[3], Charalampos Papagoras[3], Contantinos A. Paschides[1] and Alexandros A. Drosos[2]. [1]Department of Ophthalmology, Medical School, University of Ioannina, Ioannina, Greece, [2]Ioannina Medical School, Ioannina, Greece, [3]Rheumatology Clinic, Department of Internal Medicine, Medical School, University of Ioannina, Ioannina, Greece

Background: Systemic sclerosis (SSc) is characterized by vascular dysfunction (Raynaud's phenomenon, pulmonary hypertension), while patients often complain for dry symptoms. Eye examination provides information on both exocrine function and vascular integrity.

Objectives: To seek for evidence of vascular dysfunction and sicca syndrome in a cohort of SSc patients.

Methods: Patients with SSc, underwent ophthalmologic screening for dry eyes [Schirmer's test (ST), Break-up time (BUT), Rose Bengal stain (RBS)]. For comparison age and sex-matched healthy controls underwent similar testing. A patient or control was considered to have xerophthalmia, if at least 2 out of 3 tests were positive (ST$<$5 mm after 5 min, BUT $<$10 sec, RBS suggestive of dry keratopathy grade $>$3+). Patients were also surveyed for symptoms of xerostomia by means of a questionnaire and screened for antinuclear antibody (ANA) positivity and type. Those with strong evidence of Sjögren's syndrome (SS) underwent minor salivary gland biopsy. Finally, a random subset of patients underwent full ophthalmologic examination, including fundoscopy and fluorangiography.

Results: Seventy-two SSc patients (65 females, 7 males, mean age 53.4$\pm$14.8 years) and 72 matched controls were screened for dry eyes. Twenty-four SSc patients were positive for xerophthalmia (33.3%), compared to only 11 controls (15.3%) ($p<0.05$). Further, 38 (52.3%) SSc patients reported xerostomia, while 21 (29.2%) complained for both dry eyes and mouth. Only 31 (43%) of SSc patients were completely free of dry symptoms and signs. Among patients with xerophthalmia 87.5% reported dry mouth, 95.8% were ANA-positive, 45.8% had anti-Scl-70, 33.3% had anticentromere, 8.3% anti-U_1RNP, 25% anti-Ro and 12.5% anti-La antibodies. The corresponding values for SSc patients without dry eyes were 35.4% for dry mouth, 97.9% for ANA and 45.8, 18.8, 16.7, 35.4 and 2.1% for the ANA subtypes. Minor salivary gland biopsy was undertaken in 14 patients and was suggestive of SS in 9. Overall 9 (12.5%) patients had SS based on sicca symptoms, positive ophthalmologic tests and positive anti-Ro/La antibodies or biopsy, fulfilling the American-European consensus criteria for SS. Finally, 29 patients underwent anterior segment examination, fundoscopy and fluorangiography. Blepharitis was the most common clinical abnormality in 11 (37.9%) patients, followed by pinguecula in 6 (20.7%). In fundoscopy and fluorangiography retina was normal in 19 (65.5%) patients. The most common abnormality was maculopathy and pigmented epithelium impairment in 6 (20.7%) patients suggestive of vascular damage of the choroidal layer. Other findings were drusen in 3 (10.3%) patients, a peripheral aneurysm in one patient and a nevus in another. While all patients had Raynaud's phenomenon, no major retinal arterial abnormalities were detected.

Conclusion: Objective signs of xerophthalmia are encountered in 1/3 of SSc patients and are usually associated with symptoms of dry mouth. Full-blown SSj may be found in 1 every 8 SSc patients. There seems to be a sparing of retinal arteries in contrast to choroidal vessels in SSc.

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1216

Genetic and Clinical Correlates of Anti-Fibrillarin (U3-RNP) Auto-Antibodies in African Americans with Systemic Sclerosis. Roozbeh Sharif[2], Marvin J. Fritzler[4], John D. Reveille[3], Shervin Assassi[1], Maureen D. Mayes[5] and Frank C. Arnett[6]. [1]Univ of Texas Health Science, Houston, TX, [2]Univ of Texas Health Science Center at Houston, Houston, TX, [3]Univ Texas Health Sci Ctr, Houston, TX, [4]University of Calgary, Calgary, AB, Canada, [5]University of Texas-Houston, Houston, TX, [6]UT Medical School, Houston, TX

Background: Previous studies have suggested that anti-fibrillarin (U3-RNP) autoantibodies (AFA) are specific for systemic sclerosis (SSc) and occur more frequently in African Americans (AA) and men. A better prognosis in AAs with AFA also has been reported. The aim of this study was to investigate the associations of clinical features and human leukocyte antigen (HLA) class II alleles among AFA positive AAs with SSc and compare it with the AFA negative AA patients and unaffected AA controls.

Methods: Between 1990 and 2010, 74 AA patients were enrolled in the ongoing observational cohort studies of AA patients, at our institution. Genetic characteristics, autoantibody profile, and clinical manifestations were examined. AFAs were determined by immunoprecipitation of the full length radiolabeled recombinant protein. HLA class-II (DRB1, DQA1, and DQB1) alleles were oligotyped or sequenced in AA patients (n=74) and AA controls (n=263). We used chi-square, Fisher's exact test, and student's t-test for comparative studies. We compared allelic frequencies between AFA positive (n=30) and negative (n=44) AAs, and subsequently with unaffected AA normal controls.

Results: The mean age of AA patients with SSc was 47.7 ($\pm$13.4) years. Sixty one (61; 82.4%) were female and 52 (70.2%) had diffuse disease. There were no significant differences in gender and disease type (diffuse versus limited SSc). There were no significant differences in gastrointestinal, cardiac, and renal SSc between patients with and without AFA. Significant results are described in Table 1.

Conclusions: These findings imply a strong association between *HLA-DRB1*08, DRB1*0804, DRB1* 1302, DQB1*0301* and having two of three *DQB1* alleles HLA-*DQB1*0301, 0602,* and *0604* with AFA in AA patients with SSc. This subset of SSc patients had less musculoskeletal involvement and secondary Sjögren's disease.

	Comparison between AFA positive (n=30) and AFA negative patients (n=44)		Comparison between AFA positive and unaffected AA controls (n=263)	
	P-value	OR (CI)	*P-value*	OR (CI)
DRB1*08	0.031	3.35 (1.10, 10.22)	<0.001	5.67 (2.50, 12.90)
DRB1*0804	NS*		<0.001	5.81 (2.37, 14.25)
DRB1*1302	NS*		0.007	4.39 (2.28, 9.36)
DQA1*01	NS*		0.003	0.27 (0.11, 0.66)
DQB1*0301	NS*		0.012	2.90 (1.18, 7.38)
DQB1*0301/0602/0604†	0.008	4.39 (1.45, 13.31)	0.002	3.69 (1.60, 8.49)
Arthritis	0.005	0.13 (0.01, 0.69)	N/A	
Joint contractures	0.036	0.34 (0.11, 1.04)	N/A	
Myositis	0.044	N/A	N/A	
Loss of digital pulp	0.011	0.27 (0.08, 0.85)	N/A	
Sclerodactyly	0.032	N/A	N/A	
Sjögren's syndrome	0.024	0.22 (0.04, 0.99)	N/A	

* NS: not significant; †having two or more of these alleles

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Impact of Systemic Sclerosis on Occupational and Professional Activity with Attention to Patients with Digital Ulcers. Alice Berezne[3], Raphaele Seror[2], Sandrine Morell-Dubois[1], Christelle Nguyen[4], Eric Hachulla[1], Loic Guillevin[4] and Luc Mouthon[4]. [1]Service de Medecine Interne, Centre de Reference Pour la Sclerodermie Systemique, Hôpital Claude Huriez, Universite Lille 2, Lille, France, Metropolitan, [2]Université Paris Descartes, Faculté de Médicine, Pôle de Médecine Interne, Centre de Reference Pour les Vascularites Necrosantes et la Sclerodermie Systemique, Hôpital Cochin, Assistance Publique-Hopitau, [3]Universite Paris Descartes, Faculte de Medicine, Pôle de Medecine Interne, Centre de Reference Pour les Vascularites Necrosantes et la Sclerodermie Systemique, Hôpital Cochin, Assistance Publique-Hôpitaux de Paris, Paris, Fra, [4]Universite Paris Descartes, Faculte de Medicine, Pole de Medecine Interne, Centre de Reference Pour les Vascularites Necrosantes et la Sclerodermie Systemique, Hopital Cochin, Assistance Publique-Hopitaux de Paris (AP-HP), Paris, France, Metro

Objective: To evaluate the impact of systemic sclerosis (SSc) and digital ulcers (Dus) on daily living and professional activities.

Methods: We prospectively evaluated 189 SSc patients for employment status and handicap during meetings of the French patients association (n=86; 45.5%) or during hospitalisation (n=103; 54.5%).

Results: Seventy eight patients (43.6%) had diffuse SSc. The mean (±SD) age was 54±13 years and disease duration 9.3±8.4 years at the time of evaluation. Sixty patients (31.7%) had at least one DU. Global disability, hand disability and anxiety, respectively assessed using health assessment questionnaire (1.12±0.79 vs 1.39±0.84, P=0.001), Cochin hand function scale (20.2±18.3 vs 27.8±19.1, p<0.0001) and Hospital Anxiety Scale (9.9±5 vs 8.5±4,2, p=0.04) were significantly higher in patients with Dus than in others. Most patients reported a limitation in daily activities related to SSc, as assessed by a daily activity limitation scale (score 4.4±2.9) and an increased need for help in the home. Patients reported needing 4±13.5 hours per month of paid household help related to SSc and 1.5±10 hours per month related to Dus, with significant differences between patients with or without Dus (p=0.004). Among the 113 patients in the workforce, 67 (59.3%) were employed; 42 (37.2%) in were full-time employment, 36 (31.8%) received full disability pension, and 27 (23.9%) were on sick leave, with no difference between patients with or without Dus.

Conclusion: SSc has a significant impact on activities of daily living and work disability. Disability and the need for external home help are increased for those with Dus.

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1218

Is Surfactant D or CC-Chemokine Ligand 18 Biomarkers for Interstitial Lung Disease in Systemic Sclerosis? Shervin Assassi[2], Julio Charles[3], Frank C. Arnett[7], Roozbeh Sharif[2], Robert E. Lasky[3], Emilio B. Gonzalez[5], Hilda T. Draeger[4], Terry A. McNearney[1], Sandeep K. Agarwal[2], Ramana V. Gutala[3], Rosa M. Estrada-Y-Martin[3] and Maureen D. Mayes[6]. [1]Eli Lilly and Co, Indianapolis, IN, [2]Univ of Texas Health Science Center at Houston, TX, [3]Univ of Texas Health Science Center at Houston, [4]Univ of Texas Health Science Center at San Antonio, San Antonio, TX, [5]Univ of Texas Medical Branch Galveston, TX, [6]University of Texas-Houston, TX, [7]UT Medical School, Houston, TX

Objective: Previous studies have indicated that surfactant D (SP-D) levels correlate with the presence of interstitial lung disease (ILD) in patients with systemic sclerosis (SSc).

CC-chemokine ligand 18 (CCL18) is a chemokine produced by activated macrophages that upregulates collagen production in lung fibroblasts. Previous studies have suggested that CCL18 predicts the change in forced vital capacity (FVC) in patients with idiopathic pulmonary fibrosis.

Our goal was to investigate the predictive significance of SP-D and CCL18 for the decline rate in FVC over time in a large prospective cohort of SSc patients.

Methods: SP-D and CCL18 levels were determined in 266 SSc patients and 100 age, ethnicity and gender matched unaffected controls using commercially available ELISA kits. The SSc plasma samples were collected at the initial visit of the Genetics versus Environment in Scleroderma Outcome Study (GENISOS), an observational cohort of patients with early SSc. Pulmonary function tests (PFT) were obtained at the initial visit and annually thereafter. The primary outcome was FVC expressed as a percentage of predicted value. First, the protein levels between patients and controls were compared by t-test. Subsequently, the correlation of protein levels with the FVC at the enrollment visit was investigated by linear regression. Finally, a generalized linear mixed model with the sequentially obtained FVCs as the outcome variable was utilized for the longitudinal analysis. The predictive value of SP-D and CCL-18 for the decline rate in FVC was investigated by the interaction term between the protein levels and follow up time. The protein levels were examined as continuous variable as well as a dichotomized variable according to the 95th percentile level in controls.

Results: The average disease duration at enrollment was 2.5 years. 156 patients (59%) had diffuse cutaneous involvement. The mean follow up time in the study was 3.8 years. 926 FVC measurements belonging to 244 patients fulfilled the American Thoracic Society criteria and were included in the analysis.

SP-D levels were significantly higher in SSc patients than controls (p=0.001, mean difference= 643.9, CI= 256–1031.8). Furthermore, the SP-D level correlated with the FVC levels at enrollment (p=0.008, R^2=0.033). However, the SP-D did not predict the decline rate in FVC over time (p=0.649). Similarly, the dichotomized value of SP-D (based on 95th percentile in controls) did not predict the rate of decline in FVC (p=0.195).

CCL18 levels did not differ significantly between patients and controls (p=0.212, mean difference=7.4, CI= − 4.3– 19.1). The CCL18 did not correlate with the FVC at enrollment (p=0.21). Furthermore, CCL18 did not predict the decline rate in FVC over time as a continuous or dichotomized variable (p=0.439 and p=0.212, respectively).

A repeat analysis after adjustment for smoking status showed similar results for both proteins.

Conclusion: Although SP-D correlates with the concomitantly obtained FVC levels, it is not useful as a predictive biomarker for the decline rate in FVC. On the other hand, CCL18 correlates neither with the concomitantly obtained FVC nor with its progression over time in SSc.

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Longitudinal Fatigue Severity Scale Scores Correlate with Modifiable Psychosocial Variables in Early Systemic Sclerosis. Astrud Lorraine Leyva[3], Shervin Assassi[1], Maureen D. Mayes[6], Deepthi K. Nair[1], Michael Fischbach[2], Roozbeh Sharif[1], John D. Reveille[5], Emilio B. Gonzalez[3] and Terry A. McNearney[4]. [1]Univ of Texas Health Science Center Houston, TX, [2]Univ of Texas Health Science Center San Antonio, TX, [3]Univ of Texas Medical Branch, Galveston, TX, [4]Univ of Texas Medical Branch; Currently at Eli Lilly and Co, Indianapolis, IN, [5]Univ Texas Health Sci Ctr, Houston, TX, [6]University of Texas-Houston, TX

Purpose: Fatigue is a major complication of Systemic Sclerosis (SSc). Longitudinal studies examining the baseline predictors of fatigue in SSc have not been reported previously. We analyzed the association of the baseline demographic, clinical and self-reported psychometric variables with longitudinally obtained Fatigue Severity Scale (FSS) scores to identify potentially modifiable factors to improve fatigue severity in SSc.

Methods: FSS scores in 266 patients enrolled in the Genetics versus Environment in Scleroderma Outcomes Study (GENISOS) were examined. GENISOS is a large multi-center, prospective observational cohort of patients with early SSc (disease duration $\leq$ 5 years at enrollment). The association of baseline variables with sequentially obtained FSS was investigated in a generalized linear mixed model. A comprehensive list of baseline variables including demographic characteristics, disease type, autoantibody status, pulmonary function test parameters and psychometric measures were examined. Initially a univariate analysis was conducted, followed by a multivariate analysis utilizing a hierarchical forward variable selection strategy. Internal consistency of the psychometric variables including the FSS was assessed and validated with Cronbach's alpha computation.

Results: The mean age was 48.6 years, 83% of patients were female and 47% of patients were Caucasian. Fifty-nine percent had diffuse cutaneous involvement. The mean follow up time was 3.8 years, ranging up to 11.4 years. The average baseline FSS score was 4.7 $\pm$ 0.96, comparable to scores reported in systemic lupus erythematosus and multiple sclerosis patients. A total of 1090 FSS measurements obtained during the enrollment time were studied for the longitudinal analysis. The FSS did not show a consistent trend for change over time ($p=0.221$). Although a number of baseline variables were associated with longitudinally obtained FSS, only coping skills as measured by the Illness Behavior Questionnaire ($p<0.001$), Short Form-36 physical component summary ($p<0.001$), shortness of breath-visual analogue scale ($p=0.011$) and Gastrointestinal Medsger Severity Index ($p=0.025$) were independent predictors of FSS in the multivariable model.

Conclusions: Longitudinal FSS scores were strongly associated with perceived physical functioning and coping patterns of illness behavior. Our results emphasize the importance of potentially modifiable psychosocial factors in treatment of fatigue. For example, an interventional strategy targeting coping mechanisms in SSc patients may directly improve fatigue severity. Consideration of specific psychosocial and behavioral support may have more impact in managing fatigue severity than currently available traditional or pharmacologic interventions.

Disclosure: A. L. Leyva: None; **S. Assassi:** None; **M. D. Mayes:** None; **D. K. Nair:** None; **M. Fischbach:** None; **R. Sharif:** None; **J. D. Reveille:** None; **E. B. Gonzalez:** None; **T. A. McNearney:** None.

1220

Loss of Microvascular Response to Central Nervous Impulses to Finger Pulp in Systemic Sclerosis. Tone Kristin Bergersen[2], Anna-Maria Hoffmann-Vold[1], Oivind Midtvet[2], Jan Tore Gran[2], Cato Mork[2] and Karin Toska[3]. [1]Oslo University Hospital, Oslo, Nydalen, Norway, [2]Oslo University Hospital, Oslo, Norway, [3]University of Oslo, Blindern, Norway

Thickening and fibrosis of digital skin with recurrent digital ulcera are major problems in systemic sclerosis (SSc). Probably, digital ulcera are caused by damage of the microvascular bed (1). Typically, the fingers are more severely affected than the proximal parts of the palm. Blood flow in skin of hands is mainly controlled by the arteriovenous anastomoses (AVAs) located in the palm and nailbeds (2). The vasomotion of the AVAs is controlled by the CNS and is synchronous in all skin areas. We have studied the vasomotor activity in skin of fingers and thenar region in SSc.

Laser Doppler flux (Moor instruments, England) from finger pulp and thenar region were simultaneously recorded together with ipsilateral radial artery blood velocities (ultrasound Doppler, SD100, Vingmed, Norway) and mean arterial blood pressure (Finapres) in 11 patients and in 11 aged matched healthy subjects. The subjects were resting on a bench in thermoneutral condition for 30 min before a 15 min continuous recording was obtained.

The mean duration of SSc was 7.3 yrs (range 2–15 yrs), mean age 55 yrs (range 45–67 yrs). Eight of the patients had previous history of digital ulcera, but none had ongoing ulcera. All patients had Raynauds phenomenon and disturbed microvascular architecture visualized by nailfold capillaroscopy. The blood velocity in the radial artery in both groups showed the typical large fluctuations caused by synchronous opening and closing of the AVAs (2) (Fig. 1A). In the control group, fluctuations in thenar flux and finger pulp flux were closely correlated to the velocity fluctuations in the radial artery (Table 1). In the SSc group, there was also a close correlation between the thenar flux and the velocity fluctuations in the radial artery (Fig 1A and B, Table 1). However, the simultaneous finger pulp flux was statistically significantly less correlated to the velocity in radial artery than the thenar flux (Table 1). Furthermore, in some patients, a positive correlation was seen between finger pulp flux and short-time variability in MAP (Fig. 1 C and D).

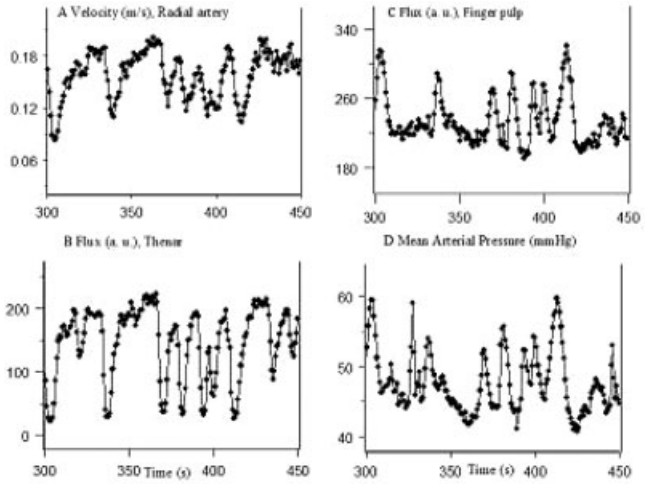

Figure 1. Simultaneous blood velocity, flux and MAP in a patient with SSc.

Table 1.

	SSc		Control group	
	median r	94% CI	median r	94% CI
finger pulp flux - radial artery	0.27	−0.15, 0.67	0.87	0.73, 0.96
thenar flux - radial artery	0.77	0.65, 0.86	0.90	0.87, 0.94
Wilcoxon sign test, p	0.016		0.81	

r= correlation coefficient, CI=Confidence Interval, significance level $p<0.05$

In conclusion, the pattern of bursts of efferent sympathetic impulses to skin AVAs is probably unchanged in SSc. However, the AVAs in the SSc finger do have an attenuated response to impulses from the CNS. A positive correlation between perfusion of finger tip and short-time variability in MAP suggest a passive vascular bed where blood flow variations is a result of variations in MAP.

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1221

Lower Education as a Proxy for Socioeconomic Status Is?Not Associated with Poor Outcomes in Systemic Sclerosis (SSc): Data from a Large SSc Cohort (Canadian Scleroderma Research Group). Samah Mansour[4], Ashley Bonner[2], Murray Baron[1], Janet E. Pope[3] and The CSRG. [1]Jewish General Hospital, Montreal, QC, Canada, [2]McMaster University, [3]St Joseph Health Care London, London, ON, Canada, [4]University of Western Ontario

Background: In SLE, socioeconomic status (SES) has a large effect on outcomes such as renal failure. It is unknown what the effect of SES is on outcomes in SSc. SES is often measured by income and education. In SSc, in general, highest education would be attained often decades prior to disease onset whereas current income could be low due to SSc and thus would confound interpretation of effect of SES on SSc. SES can modify outcomes

by altering timing of access to care, access to medications, and adherence. Lower SES may be a surrogate for other health related behaviors that can impact outcome.

Methods: The Canadian Scleroderma Research Group (CSRG) collects detailed data annually on more than 1000 SSc patients including income, education level, antibodies, organ involvement, medications and survival. For measuring SES we used education: did not complete high school (<HS) or completed high school (HS). We could not use income for SES as poor outcome would be associated with lower income if it caused work disability. Linear regressions were used to assess the education effect on disease outcome as measured by severity score, global physician scores and survival (time from onset of scleroderma till death). Logistic regressions were done to detect any effect of education on mortality, presence of Class III pulmonary artery hypertension (PAH), interstitial lung disease (ILD) [total lung capacity (TLC) less or more than 70%], renal failure (serum creatinine level less or more than 150 umol/L). Data were subdivided into limited and diffuse cutaneous SSc and by disease duration.

Results: The study included 1145 patients. Eighty six percent of the patients were females (986 females) and 14 % were males (159 males). Their mean age was 55.4 years. About 27.6% of them did not complete high school while 72.4% completed high school. In table (1), linear regressions did not show any statistically significant association between education level and severity score, global physician severity score, global physician activity score, global physician damage score and survival (p = 0.94, 0.63, 0.89, 0.78, and 0.60 respectively). Moreover in table (2), logistic regressions did not show any statistically significant association between education level and ILD, PAH, renal failure and mortality. The odds ratio and its confidence interval were 0.87 (0.45, 1.72), 1.09 (0.72, 1.66), 0.66 (0.32, 1.36) and 0.61 (0.37, 1.02) respectively. Education was not predictive of worse outcomes of scleroderma containing usual risk factors (Gender, age, ESR, Hb, ANA and SCL70).

Conclusions: Unlike SLE which has younger onset, in SSc education is not associated with worse outcomes when adjusting for usual risk factors.

Disclosure: S. Mansour: None; **A. Bonner:** None; **M. Baron:** None; **J. E. Pope:** None; **The CSRG:** None.

1222

Open Label Trial of Oral Treprostinil in Patients with Systemic Sclerosis and History of Digital Ulcers: Multiple Dose Pharmacokinetics and Tolerability. Elena Schiopu[6], Laura K. Hummers[2], Ami A. Shah[2], Susan Walker[4], Kristine Phillips[6], James R. Seibold[5], Fredrick M. Wigley[1] and Kristan Rollins[3]. [1]Johns Hopkins University, Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD, [3]United Therapeutics, RTP, NC, [4]United Therapeutics, [5]University of Conneticut, Farmington, CT, [6]University of Michigan, Ann Arbor, MI

Purpose: Fibrotic vasculopathy leading to endothelial dysfunction is the hallmark of scleroderma (SSc) and is the underlying cause of clinical complications including Raynaud's phenomenon, digital ulcers, pulmonary hypertension and renal crisis. Treprostinil diethanolamine (TDE) is an innovative salt form of the prostacyclin analog treprostinil for oral delivery as a sustained-release (SR) osmotic tablet for twice-daily dosing. Prior studies have demonstrated a therapeutic effect of IV prostacyclin analogs for ischemic DU, but oral prostacyclin analogs have had limited success. The lack of sustained plasma concentrations, particularly with immediate release oral prostacyclin analogs, may have limited the ability of prostanoids to produce sustained benefits in earlier studies. The objective of this study was to evaluate the disposition of TDE SR in patients with systemic sclerosis with peripheral vascular complications.

Methods: Patients with SSc and evidence of peripheral vaso-occlusive disease (defined as presence or history of an active digital ulcer within the past 6 months) participated in this study. Subjects with PAH were excluded. All subjects received oral treprostinil and the dose was titrated, based on tolerability, up to a target dose of 4 mg BID (or maximum dose tolerated by patients), in 0.25 mg increments approximately every 48 hours over eight weeks. Pharmacokinetic assessments were performed when subjects achieved a 2 mg and 4 mg BID (or maximally tolerated at end of study) dose. Eight blood samples were obtained over 12 hrs following dose administration and plasma concentrations of treprostinil quantified by liquid chromatography/mass spectrometry. Pharmacokinetic (PK) parameters were calculated using non-compartmental analysis.

Results: Twenty subjects (17 F/3 M), mean age of 47.9 yrs (SD 9.7) and mean scleroderma disease duration of 11.5 yrs were enrolled. Fifty-five percent of subjects had limited cutaneous scleroderma. Seventeen subjects reached a dose of 2 mg BID and twelve subjects completed the study at the target dose of 4 mg BID. Headache, gastrointestinal complaints (nausea, diarrhea, vomiting), body aches, and flushing were the most commonly reported adverse events. Manipulation of the study drug titration was a successful strategy for managing adverse events. Summary of pharmacokinetic parameters are shown as mean (CV%).

Parameter	2 mg (N=17)	4 mg (N=12)
AUC_{0-12hr} (hr*pg/mL)	7038 (45%)	12668 (43%)
Cmax (pg/mL)	1176 (44%)	2107 (46%)
Tmax (hr); median	4	4
$T_{1/2}$ (hr)	3.6	3.7

Conclusions: TDE SR is absorbed and provided sustained concentrations over the 12 hr dosing interval. Total plasma exposure and peak concentration appeared roughly proportional to dose at these two doses. There were no unexpected adverse effects following escalation up to a dose of 4 mg in SSc patients with occlusive vasculopathy. Selection of individual tolerable dosing regimens may be required in SSc patients, a finding also reported in previous clinical trials of prostacyclins in patients with PAH or Raynaud's phenomenon.

Disclosure: E. Schiopu: United Therapeutics, 2, 8; **L. K. Hummers:** United Therapeutics, 2; **A. A. Shah:** United Therapeutics, 2; **S. Walker:** United Therapeutics, 1, 3; **K. Phillips:** United Therapeutics, 2, 8; **J. R. Seibold:** United Therapeutics, 5, 8; **F. M. Wigley:** United Therapeutics, 2; **K. Rollins:** United Therapeutics, 1, 3.

1223

Outcomes in a Newly Diagnosed Population of Connective Tissue Disease-Associated Pulmonary Arterial Hypertension Patients from the REVEAL Registry. Lorinda Chung[4], Lori Parsons[1], Paul M. Hassoun[2], Michael McGoon[3], David Badesch[6], Dave P. Miller[1], Mark R. Nicolls[5] and Roham T. Zamanian[5]. [1]ICON Clinical Research, [2]Johns Hopkins University, [3]Mayo Clinic, [4]Stanford Univ Medical Center, Palo Alto, CA, [5]Stanford University, [6]University of Colorado

Purpose: We previously examined a large cohort of prevalent and newly diagnosed cases of connective tissue disease-associated pulmonary arterial hypertension (CTD-APAH) patients from the REVEAL Registry. We found that patients with systemic sclerosis (SSc)- and mixed connective tissue disease (MCTD)-APAH had similar 1-year mortality rates, which were significantly higher than in patients with systemic lupus erythematosus (SLE)- and rheumatoid arthritis (RA)-APAH. The objective of this study was to examine outcomes in a newly diagnosed population of CTD-APAH patients followed for 3 years.

Methods: The Registry to Evaluate Early and Long Term PAH Management (REVEAL) is a prospective registry of >3,500 patients with WHO Group I pulmonary hypertension from 55 US centers. For this analysis, we included patients with CTD-APAH diagnosed by right heart catheterization (mean pulmonary artery pressure > 25mmHg and pulmonary capillary wedge pressure (PCWP) ≤ 15mmHg) within 90 days of enrollment into the registry. Patients with significant interstitial lung disease (chest imaging with severe fibrosis OR moderate fibrosis AND total lung capacity < 60% predicted) were excluded. SSc-APAH was used as the reference group. Comparisons of baseline characteristics were evaluated with Student's t-test and chi-square analyses. Kaplan-Meier curves were estimated for survival and freedom from hospitalization from the time of enrollment. Differences in outcomes between the groups were assessed by the log-rank test.

Results: Patients with SSc (N=166, 30 diffuse, 88 limited, 48 unclassified) were older than patients with MCTD (N=22) and SLE (N=30), with a mean age of 61±11 vs. 50±18 and 47±17 years (p<.001), but similar in age to patients with RA (N=17, age 59±18). The majority of patients were female and Caucasian in all groups, except there was a higher proportion of non-Caucasians in the SLE group. The SSc group did not differ from the other CTD groups with regards to functional class, hemodynamics, pulmonary function tests, echocardiographic findings, or brain natriuretic peptide (BNP) levels, except that SLE patients had a lower PCWP (8.4±3.4 vs. 9.1±3.5 mmHg, p=.04), higher FEV-1 (79±25 vs. 68±19 %predicted, p=.04), and lower BNP (255±369 vs. 676±999 pg/mL, p=.03) than patients with SSc. 6 minute walk distance was lowest in the SSc group (298±114 vs. 364±138 in MCTD (p<.001), 372±106 in SLE (p<.001), and 336±129 m in RA (p=.07)). PAH-specific therapies did not differ between the groups. Survival was poorest in the SSc and RA groups, with 1- and 3-year survival estimates of 78% and 54% in the SSc group, and 88% and 61% in the RA group (p=.4 vs. SSc), compared with 84% and 84% in the MCTD group (p=.1 vs. SSc), and 92% and 87% in the SLE group (p=.01 vs. SSc). Similarly, the SSc and

RA patients were less likely to remain free from hospitalization at 3-years (39% in SSc; 35% in RA (p=.98); 60% in MCTD (p=.38); 66% in SLE (p=.03)).

Conclusions: The poorer outcome of patients with SSc reinforces the need for compliance with recommendations for routine screening for PAH in these patients in order to permit early detection and treatment. Patients with RA also have poor outcomes after the initial diagnosis of PAH.

Disclosure: L. Chung: Actelion Pharmaceuticals US, 8, Gilead Sciences, Inc., 2, United Therapeutics, 2; **L. Parsons:** Actelion Pharmaceuticals US, 5; **P. M. Hassoun:** Actelion Pharmaceuticals US, 2, Novartis Pharmaceuticals Corporation, 6; **M. McGoon:** Actelion Pharmaceuticals US, 5, Gilead Sciences, Inc., 2, 5, LungRx, 2, 5, Medtronic, 2, 5, Medtronics, 2, 5; **D. Badesch:** Actelion/CoTherix, 2, 5, Biogen Idec, 5, Eli Lilly & Co/ICOS, 2, 5, Encysive Pharmaceuticals, 2, 5, Gilead/Myogen, 2, 5, GlaxoSmithKline, 5, Lung Rx, 2, 5, mondoBIOTech, 2, 5, NIH/NHLBI, 2, 5, Pfizer Inc, 2, 5, United Therapeutics; **D. P. Miller:** ICON Clinical Research, 3; **M. R. Nicolls:** None; **R. T. Zamanian:** Actelion Pharmaceuticals US, 2, Gilead Sciences, Inc., 5, United Therapeutics, 5.

1224

Patients with Systemic Sclerosis and Anti-Centromere Antibodies Are Affected with Accelerated Atherosclerosis. Annica Nordin[2], Lena Björnådal[3], Kerstin Jensen-Urstad[1] and Elisabet Svenungsson[4]. [1]Dept. of Clinical Physiology, Södersjukhuset, Karolinska Institutet, Sweden, [2]Dept. of Medicine, Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [3]Dept. of Medicine, Rheumatology Unit, Karolinska Institutet, Sweden, Sweden, [4]Dept. of Medicine, Rheumatology Unit, Karolinska Institutet, Sweden

Purpose: If patients with Systemic Sclerosis (SSc) are affected with accelerated atherosclerosis is an unresolved question as previous studies report divergent results. We know that patients with Anti-centromere antibodies often have a limited disease and have a higher risk for vasculopathy such as pulmonary arterial hypertension (PAH), but we dont know if this subgroup of patients also have more atherosclerosis. We investigated surrogate measures of atherosclerosis in a cohort of well-characterized SSc patients and in populationbased matched controls.

Methods: 110 consecutive patients who fulfilled the American College of Rheumatology criteria for SSc and 105 controls matched for age, gender and region of living participated. All underwent a thorough medical examination. Traditional risk factors for cardiovascular disease (CVD), biomarkers of systemic inflammation and autoantibody patterns were investigated. As surrogate measures of atherosclerosis ankle-brachial index (ABI) and carotid ultrasound was performed.

Results: Mean age was 61.8 ± 12.4 years versus 61.4 ± 12.3 years among patients and controls respectively. There was no difference between patients and controls concerning carotid plaque occurence, intima media thickness (IMT) or ABI on a group level but Sedimentation Rate (p=0,007) and Triglycerides (p=0,03) were higher and BMI (p=0,03) lower in patients than controls. In the patient group, 35 (32%) were Anti-centromere Antibody positive (AcA+) and 75 (68%) were Anti-centromere antibody negative (ACA-). Of the 75 ACA- patients 23 (31%) had antibodies to Scl70, 22 (29%) to SSA and/or SSB, 22 (29%) had antinucleolar antibodies (ANA) of unknown specificities and 8 (11%) were ANA negative. Plaque occurred in 65.7% of the AcA+ patients and in 38.7% of the AcA- patients (p= 0.008). ABI was 1.09 ± 0.15 in the AcA+ patients and 1.13 ± 0.09 in the AcA- patients (p=0.05). IMT did not differ between the patient groups. After adjusting for age, Aca+, blood pressure and ever smoked still remained associated with plaque occurrence and Aca+, ever smoked and waist hip ratio remained associated with a low ABI. Waist hip ratio was lower in AcA + patients 0.80±0.07 vs. 0.85 ± 0.10 (p=0.008). Lipid levels, blood-pressure, blood glucose, ever smoked, Body Mass Index or markers of systemic inflammation did not differ between AcA+ and AcA- patients.

We included the variables, which remained associated after age adjustment in multivariable-adjusted logistic regression models. Independent predictors of plaque were age (p=0.0001),systolic blood pressure(p=0.02), ever smoked(p=0.02) and AcA+ (p=0.02)and for ABI age (p=0.02), ever smoked (p=0.008) and waist-hip ratio (p= 0.01)

Conclusion: Atherosclerosis was more prevalent in SSc patients with Anti-centromere antibodies than in SSc patients without these antibodies. AcA+ patients already has a higher risk for vasculopathy such as PAH and this subgroup of SSc patients also seems to have more atherosclerosis and may thus be at higher risk for CVD.

Disclosure: A. Nordin: None; **L. Björnådal:** None; **K. Jensen-Urstad:** None; **E. Svenungsson:** None.

1225

Physician Opinion of Variables That Differentiate Disease Activity and Damage in Systemic Sclerosis. Geneviève Gyger, Ernest Lo, Marie Hudson. Canadian Scleroderma Research Group and Murray Baron, McGill, Canada

Background: An important barrier to the study of systemic sclerosis (SSc) is difficulty in measuring disease activity and damage. We undertook this study to 1) identify the variables that physicians think indicate activity and damage, and 2) identify the variables that, according to physicians, best differentiate activity from damage in SSc.

Methods: We surveyed 18 rheumatologists with a specific interest in SSc. The participants were given a list of 148 variables that represent the spectrum of SSc manifestations. The participants rated the importance of each variable separately for activity and for damage, using a scale of 0 (not relevant) to 20 (absolutely important). The scores of each participant were used to rank the variables from 1 (highest importance) to 148 and the median rank for each variable across all raters was determined. We then compared the median damage rank versus median activity rank for each variable using a Mann-Whitney U test. We considered variables that **differentiated** between activity and damage to be those with the largest statistically significant difference between median ranks (P-values <0.05, after adjustment for multiple testing) AND were in the top 15% of the ranks for either activity or damage but not both.

Results: The variables with the highest median **ranks** for disease activity were: recent renal crisis, digital necrosis/gangrene, extent of change in DLCO in past year, presence of active myositis, and substantial increase in pulmonary systolic pressure in last year. The variables with the highest median **ranks** for damage were: uses home oxygen, needs total parenteral nutrition, worse New York Heart Association class, pulmonary arterial hypertension (PAH), and digital necrosis/gangrene. After excluding the variables that did not differentiate between activity and damage, the most important variables indicative of disease activity included extent decline in DLCO in the last year, active myositis, recent microangiopathy, active volar digital ulcers, and higher swollen joint count and the variables indicative of disease damage included uses home O_2, needs TPN, has PAH, pulmonary fibrosis on Xray or CT scan, and pacemaker (see Table).

Table. Variables that differentiate between activity and damage according to physician opinion with $p < 0.05$, are in top 15% of ranks AND are not in top 15% for both activity and damage

	Symptom	Median Damage Rank	Median Activity Rank	p-value: Damage vs. Activity Ranks
Variables more important for activity than damage	extent of change in past year of DLCO % predicted	52	21	0.03
	presence of active myositis	116.5	21.25	<0.001
	recent microangiopathy by your own assessment	85.5	24.75	0.02
	active volar digital ulcers	65	27.25	0.02
	higher joint count swollen joints	109	28.25	<0.001
	friction rubs anywhere	95.25	29	0.003
	CRP	115	31	<0.001
	pleurisy	90.5	32.75	0.02
	change in skin thickening last month	108.5	34.5	<0.001
	ESR	116.75	35.75	<0.001
Variables more important for damage than activity	uses home O2	16.25	76.25	<0.001
	needs TPN	17.5	64.5	<0.001
	has pulmonary arterial hypertension (PAH)	19.75	69.5	0.04
	degree of fibrosis on x-ray or CT scan	24	99.75	<0.001
	pacemaker	25.75	100.25	0.007
	malabsorption	30.5	67.5	0.003
	recently needed esophageal dilatation	32	54.75	0.02
	ECG conduction abnormalities or arthymias	32	94.5	0.02
	decreased LVEF	34.5	90.75	0.03

Conclusion: While experts felt that many variables were highly relevant to both disease activity and damage in SSc, a subset of variables that differentiates between the two states was identified. The results of this study will help to inform ongoing efforts aimed at developing measures of disease activity and damage in SSc.

Disclosure: G. Gyger: None; **E. Lo:** None; **M. Hudson:** None; **Canadian Scleroderma Research Group:** None; **M. Baron:** None.

1226

Plasma Endogenous Met- and Leu-Enkephalin Levels Are Decreased and Associated with Clinical and Laboratory Parameters in Early Systemic Sclerosis. Terry A. McNearney[4], Kathleen A. Sluka[2], Chul W. Ahn[5], John D. Reveille[6], Michael Fischbach[1] and Maureen D. Mayes[3]. [1]Univ Texas Hlth Sci Ctr at San Antonio, San Antonio, TX, [2]University of Iowa Medical Center, Iowa City, IA, [3]University of Texas -Houston Health Sciences Center, Houston, TX, [4]University of Texas Medical Branch, Galveston, TX, [5]University of Texas Southwestern Medical Center, Dallas, TX, [6]University of Texas-Houston Health Sciences Center, Houston, TX

Objective: Met-and leu-enkephalins are endogenous opioid neuropeptides with potent analgesic, vasoactive, immunomodulatory and anti-apoptotic properties. Endogenous enkephalin levels demonstrate modest effects on vascular patency under normal physiologic conditions in the brain, but have appreciable influence under periods of traumatic or anoxic stress. We hypothesized that clinical or immunological variables of early systemic sclerosis (SSc) might be correlated to plasma enkephalin levels.

Methods: Plasma samples were collected at study entry of the Genetics versus Environment in Scleroderma Outcomes Study (GENISOS) cohort (early SSc, N=136). Plasma met-enkephalin and leu-enkephalin levels (ug/ml) were measured by high performance liquid chromatography (HPLC) and correlated to clinical and laboratory parameters in the GENISOS database. Statistical analyses were performed by nonparametric Wilcoxon rank sum tests and Pearson correlation coefficients.

Results: 1. SSc patient vs matched normal controls study: SSc patients had significantly lower plasma met-enkephalin levels (0.16±0.10 vs 0.28±0.14 mg/ml, p=0.05) and lower plasma leu-enkephalin levels (1.04±0.90 vs 2.45±0.10 mg/ml, respectively, p<0.03); 2. Significantly lower plasma met-enkephalin levels were associated with anti-topoisomerase-I seropositivity (6±8.3 vs 14.9±22.8 ug/ml, p=0.02). 3. Plasma leu-enkephalin levels were significantly higher in SSc patients with digital pulp loss (95.6±130 vs 64.9±101 ug/ml, p=0.03). Lower mean plasma met-enkephalin levels and inversely higher leu-enkephalin levels were noted in SSc patients with Raynaud's phenomena (p=NS). Plasma endogenous enkephalin levels were independent of seasonal temperatures, when analyzed by month or season (p=NS).

Conclusion: Lower plasma levels of endogenous enkephalins in small SSc vs matched control groups may reflect depressed synthesis or increased degradation related to ongoing neurogenic, vasogenic or fibrogenic processes. The associations of plasma enkephalin levels to immunologic or clinical pathologies in early SSc may underscore their vasogenic or fibrogenic significance and potential as therapeutic targets.

Disclosure: T. A. McNearney: None; **K. A. Sluka:** None; **C. W. Ahn:** None; **J. D. Reveille:** None; **M. Fischbach:** None; **M. D. Mayes:** None.

1227

Predictors of Interstitial Lung Disease in Early Systemic Sclerosis: A Prospective Longitudinal Study. Shervin Assassi[2], Roozbeh Sharif[2], Robert E. Lasky[3], Terry A. McNearney[1], Rosa Estrada Y Martin[3], Hilda T. Draeger[4], Deepthi K. Nair[3], Marvin J. Fritzler[6], John D. Reveille[5], Frank C. Arnett[8] and Maureen D. Mayes[7]. [1]Eli Lilly and Co, Indianapolis, IN, [2]Univ of Texas Health Science Houston, TX, [3]Univ of Texas Health Science Houston, [4]Univ of Texas Health Science San Antonio, TX, [5]Univ Texas Health Sci Ctr, Houston, TX, [6]University of Calgary, AB, Canada, [7]University of Texas-Houston, TX, [8]UT Medical School, Houston, TX

Background: Pulmonary involvement is the primary systemic sclerosis (SSc) - related cause of death. Forced vital capacity (FVC, expressed as a percentage of predicted value) has been validated as an outcome measure of interstitial lung disease (ILD) in SSc. Large prospective observational studies examining progression of ILD and the predictive significance of clinical and demographic variables have not been reported. The purpose of this study was to examine the association of baseline demographic and clinical characteristics with sequentially obtained measurements of FVC and to identify predictors of decline rate in FVC over time.

Methods: At the time of analysis, 266 patients were enrolled in Genetics versus Environment in Scleroderma Outcome Study (GENISOS), a prospective, observational cohort of patients with early SSc. In addition to pulmonary function tests (PFT), clinical and laboratory data were obtained from each patient. PFTs were performed at the baseline visit and annually thereafter. The predicted PFT values were calculated according to consistent reference values. The association of baseline parameters with sequentially obtained FVC was investigated in a generalized linear mixed model. Using a similar model, the predictors of decline rate in FVC were examined by the interaction term between the baseline variable and follow up time.

Results: The cohort consisted of 125 white, 54 African American, and 77 Hispanic patients with average disease duration of 2.5 years at enrollment. The mean follow up time was 3.8 years, ranging up to 11.4 years; 59% of patients had diffuse cutaneous involvement. Only 22 patients (8.3%) had received cyclophosphamide before enrollment or during the follow up period. Upon review by a pulmonologist, 926 FVC measurements belonging to 244 patients fulfilled the American Thoracic Society criteria and were included in the analysis.

A number of baseline variables including African American ethnicity (p=0.002), diffuse disease type (p=0.012), baseline PFT values (p<0.001), modified Rodnan Skin Score (p=0.001), fibrosis on chest radiograph (p<0.001), subjective dyspnea (p<0.001), anti-topoisomerase antibodies (p<0.001), lung and skin subscores of Severity Index (p<0.001 and p=0.037, respectively) were associated with sequentially obtained FVC levels. Similar results were seen after adjustment for smoking status.

As expected, the follow up time in the study was associated with a decline in FVC (p<0.001). However, none of the baseline variables predicted the rate of decline in FVC over time. Specifically, ethnicity, disease type, baseline PFT values, Skin Score, chest radiographs, subjective dyspnea, autoantibody status, Medsger Severity Index subscores and smoking status did not predict the rate of decline in FVC. Moreover, an accelerated rate of decline in FVC was associated with poor survival (p=0.001).

Conclusion: Baseline clinical variables, associated with differential FVC levels did not predict the rate of decline in FVC. The association of faster decline in FVC with poor survival emphasizes the need for identification of predictive biomarkers by collection of genetic information and serial blood samples in cohort studies.

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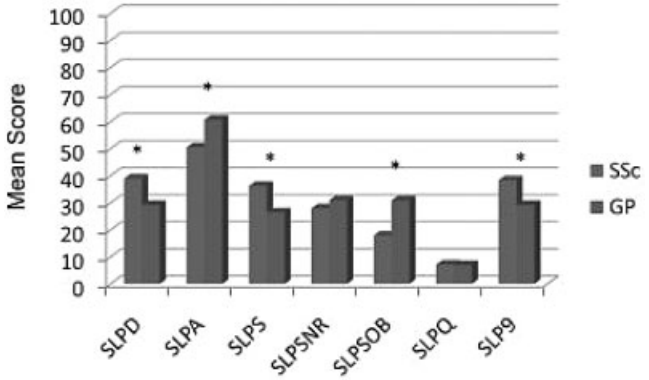
1228

Prevalence and Correlates of Sleep Disturbance in Systemic Sclerosis — Results from the UCLA Scleroderma Quality of Life Study. Tracy M. Frech[1], Ron D. Hays[2], Paul Maranian[3], Philip J. Clements[6], Daniel E. Furst[5] and Dinesh Khanna[4]. [1]Department of Internal Medicine, University of Utah, Salt Lake City, UT, [2]Division of General Internal Medicine, David Geffen School of Medicine, Los Angeles, CA, [3]Division of Rheumatology, David Geffen School of Medicine, Los Angeles, CA, [4]University of California Los Angeles, Los Angeles, CA, [5]University of California Los Angeles Medical School, Los Angeles, CA, [6]University of California Los Angeles School of Medicine, Los Angeles, CA

Objective: Chronic arthritides are associated with sleep disturbances. This study examines the prevalence of sleep disorder and explores its correlates in patients with systemic sclerosis (SSc).

Methods: Participants are 180 SSc patients in the UCLA Scleroderma Quality of Life Study. At baseline, patients completed the Medical Outcomes Study Sleep measure (MOS-sleep scale). In addition, patients completed other patient-reported outcome (PRO) measures (SF-36, HAQ-DI, Functional assessment of Chronic Illness therapy-Fatigue (FACIT-Fatigue), Center for Epidemiologic Studies Depression scale (CESD), and University of California Los Angeles Scleroderma Clinical Trials Consortium Systemic Sclerosis Gastrointestinal Questionnaire (UCLA SCTC GIT 2.0). Descriptive statistics were assessed for 6 scales of MOS-Sleep and sleep problem index (SLP-9). We computed Spearman rank-order correlations between the MOS-sleep scale domains and the HAQ-DI, FACIT-Fatigue, CESD, SSc-GIT 2.0, and SF-36 scales. In addition, we regressed SLP-9 scores on sociodemographic variables, disease severity, and PRO measures outlined above.

Results: Patients SSc patients reported a mean (SD) of 7.1 (1.73) hours slept a night (range 0–11 hours). Patients reported worse scores on 4 of 6 scales (except for snoring and sleep quantity) compared to US General population. SLP9 had "moderate" correlations with the CESD and FACIT-Fatigue (rho's of 0.56 and 0.50) and "low" correlations with the HAQ-DI and UCLA SCTC 2.0 total score (rho's of 0.32 for both). In the multivariate regression model with sociodemographic variables, duration of SSc, patient assessment of disease severity, skin score, and PROs (HAQ-DI, FACIT-Fatigue, UCLA SCTC GIT 2.0 total score, and CESD), the CESD and GIT total scores had significant association with SLP9 index.



Legend: sleep disturbance (SLPD), sleep adequacy (SLPA), daytime somnolence (SLPS), snoring (SLPSNR), awakening short of breath or with headache (SLPSOB), quantity of sleep (SLPQ), sleep problems index (SLP9), scleroderma cohort (SSc), general population (GP), $p<0.05$ (*).

Conclusion: This the first study to evaluate sleep disturbances in SSc. Future studies should assess if successful interventions for GI involvement and depression may have a beneficial impact on sleep quality.

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1229

Prevalence of Associated Autoimmune Diseases in a Spanish Population with Systemic Sclerosis. Esther Francisca Vicente[2], María Jesús García-Arias[2], Rosario García-Vicuña[2], Alicia Humbría[2], Juan Pedro López-Bote[2] and Santos Castañeda[1]. [1]Rheumatology Department, Hospital Universitario de La Princesa, IIS Princesa, Madrid, Spain, [2]Rheumatology Department, Hospital Universitario de La Princesa, IIS Princesa

Background: Systemic sclerosis (SSc) is a connective tissue disease that can occur in isolation or associated with other inflammatory diseases of autoimmune aetiology, modifying their phenotypic expression and/or prognosis. It has been suggested that subtypes of SSc may have an uneven trend towards those associations.

Aims: 1. To determine the prevalence of associated systemic autoimmune diseases in a Spanish population with SSc treated at our centre. 2. To evaluate the existence of differential patterns of association according to the subtype of SSc.

Methods: We performed a cross-sectional study that included a hospital in-patient and out-patient sample of all SSc patients who were assessed at our centre during 2009. Demographic, clinical and laboratory (antinuclear [ANA], anticentromere [ACA] and antitopoisomerase1 [Scl-70] antibodies) variables were collected. The definition of the associated autoimmune diseases (AAID) followed the international classification criteria. Statistical analysis: continuous variables are expressed as mean±SD and categorical variables as number of cases (%). The association between the presence of AAID and the manifestations and subtypes of SSc was analysed with the Student's t test for the continuous variables and the χ^2 test for the categorical ones. Statistical significance was set at $p<0.05$ (Stata v.10).

Results: Sixty one SSc patients were included (93.4% female), 45 (73.8%) with limited cutaneous subset (lcSSc) and 16 (26.2%) with diffuse cutaneous subtype (dcSSc). Mean age was 59.9±18.4 yrs and duration of disease was 9.7±9.5 yrs. The distribution of auto-antibodies was as follows: 91.5% were ANA positive (90.9% of lcSSc and 93.3% of dcSSc), 63.8% had ACA (only lcSSc) and 29.5% had Scl-70 (6.9% of lcSSc and 73.3% of dcSSc). At least one AAID was present in 29 (47.5%) patients: Sjögren's syndrome [SS] (36.1%), primary biliary cirrhosis [PBC] (9.8%), systemic lupus erythematosus [SLE] (3.3%), autoimmune hepatitis [AH] (3.3%), thyroiditis [AT] (3.3%), rheumatoid arthritis [RA] (1.6%) and polimyositis (1.6%). Seven (11.5%) patients combined 2 AAID, being SS and PBC the most frequent association (6.5%). Other combinations were SS and RA (1.6%), SS and SLE (1.6%) and AH and AT (1.6%). The prevalence of SS and AT was similar in both SSc subtypes: 37.8% and 2.2% for lcSSc and 31.2% and 6.2% for dcSSc, respectively. However, the rest of AAID were found only in lcSSc patients, although differences did not reach statistical significance, probably due to the small population size. Neither clinical nor laboratory manifestations of the disease showed significant association with the existence of AAID.

Conclusions: Nearly half of our SSc patients had AAID, being Sjögren's syndrome and primary biliary cirrhosis the most frequent associations. The prevalence of Sjögren's syndrome and autoimmune thyroiditis was similar in both subtypes of SSc. However, our results suggest that lcSSc could exhibit a higher tendency to be associated with other autoimmune diseases.

Disclosure: E. F. Vicente: None; **M. J. García-Arias:** None; **R. García-Vicuña:** None; **A. Humbría:** None; **J. P. López-Bote:** None; **S. Castañeda:** None.

1230

Serum Chemokine and Cytokine Levels as Indicators of Disease Activity in Patients with Systemic Sclerosis. Minoru Hasegawa, Manabu Fujimoto, Kazuhiko Takehara and Shinichi Sato, Kanazawa University

Background: There are no definitive serum markers to estimate the disease activity in the skin or the internal organs in systemic sclerosis (SSc). In most patients, severe organ involvement occurs within the first 3 years of disease onset and skin sclerosis seldom progresses after 5 or 6 years. Therefore, clarifying the disease activity is particularly important for SSc patients with a short disease duration.

Objective: In the present study, we sought to determine if serum chemokines and cytokines were associated with disease activity in SSc patients with a short disease duration.

Methods: Concentrations of 4 chemokines (interferon γ-inducible protein-10 (IP-10, CXCL10), monokine induced by interferon γ (MIG/CXCL9), monocyte chemoattractant protein-1 (MCP-1/CCL2), interelukin 8 (IL-8/CXCL8)) and 6 cytokines (IL-2, IL-4, IL-6, IL-10, tumor necrosis factor (TNF) −α, interferon (IFN) −γ) were measured using cytometric beads array kits in serum samples from 31 patients with active SSc and 20 normal controls. Clinical and laboratory data and serum chemokine and cytokine levels were assessed for each patient at their first visit and each subsequent year for 3 years.

Results: At their first visit, serum levels of IP-10, MIG and MCP-1 were significantly elevated in SSc patients compared with normal controls. In SSc patients, these levels declined, especially during the first year, probably due to the initiation of immunosuppressive treatment. Serum MCP-1 levels at the third year showed significant associations with variations of skin thickness scores during the 3 years. That is, patients with consistently high levels of MCP-1 tended to show intractable skin sclerosis. Unfortunately, serum makers that could estimate variations of skin sclerosis during the 3 years were not found at an earlier point in time (~2 years). When interstitial pneumonia progression was evaluated by variations of %VC, the variations of %VC during the 3 years were inversely associated with serum levels of IP-10 at the second and third years and MIG at the first to third years. That is, patients with increasing IP-10 or MIG levels showed a tendency for subsequent exacerbations of interstitial pneumonia.

Conclusions: These results suggest that MCP-1 is a serological indicator of the activity of skin sclerosis. Serum levels of type 1 helper T chemoattractants such as IP-10 and MIG may reflect interstitial pneumonia disease activity in SSc patients. However, a longer-term prospective study in a larger population will be needed to confirm their clinical utility as predictors of outcomes.

Disclosure: M. Hasegawa: None; **M. Fujimoto:** None; **K. Takehara:** None; **S. Sato:** None.

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Severe Pulmonary Fibrosis Is Uncommon in Scleroderma Patients with RNA Polymerase 3 Antibody. Virginia D. Steen[1], Robyn T. Domsic[2] and Thomas Medsger[2]. [1]Georgetown University, Washington, DC, [2]University of Pittsburgh

Introduction: Patients with systemic sclerosis with diffuse scleroderma commonly have severe pulmonary interstitial fibrosis. However, although patients with RNA polymerase III (POL 3) have very severe diffuse cutaneous skin disease and a high frequency of renal crisis they seem to have less severe lung fibrosis. This study looks at the natural history of lung disease in patients with SSc and a positive POL 3.

Methods: We identified all patients with scleroderma and a positive POL 3 who had pulmonary function tests (PFTs) and compared the demographics, lung function and outcomes to SSc patients with diffuse cutaneous scleroderma without Pol 3 (DNoPol3) We compared the first and last PFTs in those with more than one set of PFTs. Survival and causes of death were determined.

Results: There were 372 patients with a POL 3 and 657 DNoPol3 pts who had PFTs. POL 3 patients were older at onset of disease and had a higher skin score, although they had a lower sedimentation rate and a lower symptom score for lung. Twenty-five percent had an episode of renal crisis (compared to 15% in the DNoPol3 pts, $p<0.001$). The disease duration at last follow up for both groups was more than 12 years. The first recorded forced vital capacity (FVC) in the POL 3 and DNoPol3 was 82% and 69% ($p<0.001$) and the smallest recorded values were 78% and 65% respectively ($p<0.001$). Only 11.3% of the POL 3 patients ever developed a FVC less than 60% predicted, a measure of severe fibrosis, compared to 24.8% in DNoPol3 pts ($p<0.001$). There were 102 POL 3 and 191 DNoPol3 pts who had more than onset of PFTs recorded. Table 1 shows the baseline and last FVC and diffusing capacity (DLCO) for these patients. Comparisons between 1st and last studies and between groups were all highly significant ($p<0.0001$). Only 29% of the POL 3 pts ever had some fibrosis on radiographic imaging compared to 51% in the DNoPol3 ($p<0.0001$). Only 6% of POL 3 pts were ever treated with cyclophosphamide for their lung disease compared to 18% of the DNoPol3 ($p<0.001$)

The 5 and 10 year survivals were 86% and 76% for the POL 3 and 83% and 69% for the DNoPol3 pts, ($p<0.0001$). Only 2% of the POL3 pts have died from pulmonary fibrosis compared to 13% of the DNoPol3 pts, ($p<0.001$). Fewer POL 3 pts died from scleroderma related causes (43% compared to 56% ($p<0.001$) and pulmonary fibrosis was the scleroderma related death in 15% of these patients compared to 25% ($p<0.05$) in the DNoPol3.

Conclusions: POL 3 antibodies are available commercially and are helpful progrostically. While POL 3 patients have severe cutaneous disease and a high frequency of renal crisis, they infrequently get severe lung disease. Premature treatment for pulmonary fibrosis in these patients who rarely get severe fibrosis should be used cautiously.

Antibody	1st FVC	Last FVC	Delta Time	1st DLCO	Last DLCO
POL 3	87%	83%	3.3	76%	79%
TOPO	73%	70%	3.5	61%	58%

Disclosure: V. D. Steen: None; **R. T. Domsic:** None; **T. Medsger:** None.

1232

Survival in Pulmonary Hypertension Associated with Scleroderma-Spectrum Disease: A Single Center Experience. Dinesh Khanna, Rajeev Saggar, Daniel Furst, Paul Maranian, Philip Clements and Rajan Saggar. UCLA

Introduction: SSc-PAH is leading case of mortality in SSc. The impact of SSc-ILD associated PH is not well characterized, however, portends a very poor prognosis. The objective of this study is to investigate the survival and characteristics among SSc-spectrum associated PH.

Methods: SSc patients with PH (defined as mPAP> 25 mmHg and FVC≥ 60%) or ILD associated PH (defined as mPAP> 25 mmHg and FVC< 60%) confirmed by right heart catheterization (performed at a tertiary center) were included in the study. Kaplan-Meier and Cox proportional hazard models were used to compare the survival between SSc-PAH and SSc-ILD associated PH and to identify predictors of survival.

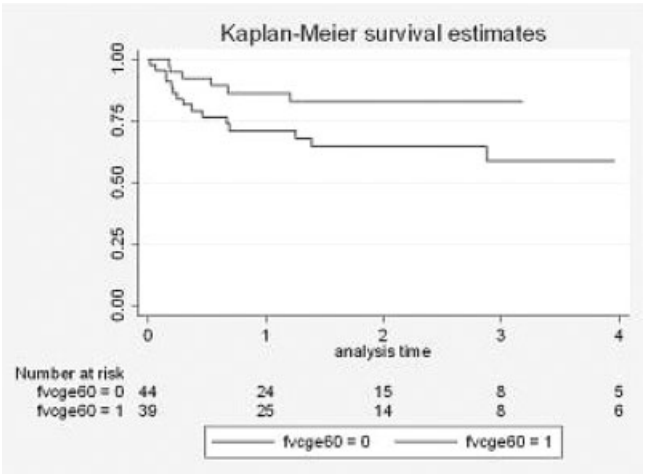
Results: Ninety-three SSc patients (48 with isolated PH and 45 with ILD-PH) were identified. 1-, 2- and 3-year survival for the entire cohort was 80%, 76%, and 73%. Survival was similar for those with isolated SSc-PH and those with ILD associated SSc-PH (1-, 2-, 3-year survival rates 86%, 83%, 82% versus 71%, 65%, 59%), $p>0.05$.

In univariate analysis, gender, FVC%, DLco%, resting oxygen, cardiac output (CO) and pulmonary vascular resistance (PVR) were associated with increase mortality. Using multivariate cox-proportional hazard model, only PVR (HR 1.11) and CO (HR 0.39) were independent predictors of mortality in the overall cohort. Also, younger age had a greater risk of death (HR 0.95) in the CO model.

Baseline lung function and type of therapy did not predict mortality in our model.

Conclusions: Survival in SSc-spectrum associated PH remains poor, however, improved compared to historical cohorts. The prognosis of patients with SSc-ILD associated PH is similar compared to isolated SSc-PAH. This suggests PAH therapies, including parenteral prostanoids, are safe and efficacious in those individuals with significant ILD. Earlier diagnosis and potentially aggressive treatment may improve outcome as worse hemodynamic parameters (PVR) predict increased mortality.

Baseline Characteristics	
Age (years)	54.9 (12.7)
SSc-Type n (%)	92
Limited	50 (54.3)
Diffuse	23 (25)
Overlap	18 (19.5)
FVC, % predicted	59.3 (20.5)
Dlco % predicted	41.2 (19.1)
FVC/DLco	1.7 (0.69)
Heart Rate	81.3 (13.6)
Rest O2 sat (%)	92.8 (5.7)
Hemodynamics (mmHg)	
Right Atrial Pressure	9.6 (5.7)
Mean Pulmonary Pressure	40.3 (13.7)
Pulmonary Wedge Pressure	12.8 (6.5)
Cardiac Output (L/min)	4.8 (1.4)
Cardiac Index (L/min/m2)	2.7 (0.70)
PVR dyn*sec*cm-5	494.8 (209.3)
PAH Therapy n (%)	
ERA	55 (59.7)
PDE-5	34 (36.9)
Treprostinil (IV/SQ)	26 (28.2)



Disclosure: D. Khanna: Actelion Pharmaceuticals US, 2, 8, Gilead Sciences, Inc., 2, 8, NIAMS-NIH, 2; **R. Saggar:** None; **D. Furst:** Actelion Pharmaceuticals US, 2, 8, Gilead Sciences, Inc., 2, 8; **P. Maranian:** None; **P. Clements:** Gilead Sciences, Inc., 2; **R. Saggar:** None.

1233

Systemic Sclerosis Is an Independent Predictive Factor to Coronary Atherosclerosis. Mo Yin Mok, Chak Sing Lau, Sonny Chiu, Annette Tso, Ka Fung Mak, Woon Sing Wong, Pek Lan Khong and Karen S. L. Lam. The University of Hong Kong, Queen Mary Hospital, Hong Kong

Background: Endothelial dysfunction and inflammation are pathogenetic mechanisms shared by scleroderma (SSc) and atherosclerosis.

Objective: To examine coronary atherosclerosis by coronary calcium score and its relation to conventional cardiovascular and disease specific risk factors in SSc patients.

Methodology: Coronary calcium was measured by computed tomography and cardiovascular risk factors were examined in SSc patients compared with age-, sex- and glycaemic status- matched controls. Activity score, antiphospholipid antibodies, high-sensitivity C-reactive protein (hsCRP) and ESR were measured in SSc patients.

Results: 53 SSc (50 female and 3 male) patients and 106 controls were recruited. These patients were 53.1±12.8 years in age with median disease duration of 9 years. SSc patients were found to have significantly lower mean arterial pressure ($p<0.001$), cholesterol ($p=0.001$), LDL ($p=0.001$), HDL ($p=0.01$) levels, waist circumference and body mass index ($p<0.001$) and were more likely receiving vasodilators ($p<0.001$). There were more SSc patients who had absent, minimal to mild, moderate and severe coronary calcification compared to controls ($p=0.01$ linear by linear association). Multiple logistic regression analysis revealed 5.1-fold increased risk of coronary calcification in SSc [95% confidence interval (CI) 1.7–15.3] ($p=0.004$) and 31-fold for coronary calcium score >100 [95%CI 4.2–229.5,

p=0.001] after correction to conventional cardiovascular risk factors. SSc patients who had coronary calcification were older (<0.001), had higher mean arterial pressure (p<0.001), longer disease duration (p=0.006) compared to those with normal coronary arteries. Only age and disease duration were identified by logistic regression analysis as predictive factors for coronary calcification in SSc patients.

Conclusion: SSc was an independent predictive factor for coronary atherosclerosis.

Disclosure: M. Y. Mok: None; **C. S. Lau:** None; **S. Chiu:** None; **A. Tso:** None; **K F. Mak:** None; **W. S. Wong:** None; **P. L. Khong:** None; **K. S. L. Lam:** None.

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The Psychological Impact of Systemic Sclerosis-Related Telangiectases. Holly Ennis[3], Helen L. Richards[1], Claire Cassidy[3] and Ariane L. Herrick[2]. [1]Mercy University Hospital, Cork, Co. Cork, Ireland, [2]Rheumatic Diseases Centre, Trust Salford, United Kingdom, [3]University of Manchester, Manchester, United Kingdom

Background: Systemic sclerosis (SSc)-related telangiectases commonly occur on the face and hands and, although often disfiguring, little is known about their psychological impact. Our objectives were to (a) determine the extent of body image dissatisfaction (BID) in patients with SSc-related telangiectases (b) identify disease-related correlates with telangiectases (c) examine the subjective experiences of patients with telangiectases through qualitative analysis.

Methods: 227 patients aged over 18 years with SSc were invited to participate in a questionnaire survey. Clinical and demographic data was obtained for all participants from a clinical database. Each participant completed the Adjusted Satisfaction with Appearance Scale (ASWAP), the Hospital Anxiety and Depression Scale (HADS) and an open-ended telangiectases questionnaire. Thematic analysis was utilised to describe the qualitative data.

Summary of Results: 141 patients (62%) with SSc responded to the survey (83% female, 70% limited cutaneous SSc, median age 62 years). Telangiectases was reported by 113 (80%). All ASWAP scores (Table 1) were higher in those reporting telangiectases, and this was significant for the 'dissatisfaction with appearance' subscore (p=0.02). Anxiety and depression scores were similar in those with and without telangiectases. Those reporting telangiectases were more likely to be anticentromere positive (40% versus 18%, p=0.02) and to have a history of severe digital ischaemia (38% versus 18%, p=0.04) than those not. Qualitative analysis revealed four themes: changes in behaviour as a result of telangiectases (e.g. social avoidance), public and private self-image (e.g. feeling self-conscious), negative emotional impact of telangiectases (e.g. feelings of sadness or anger) and gaining new perspectives on life (e.g. focusing on positives such as the ability to walk).

Conclusions: BID, as measured by the ASWAP, was higher in patients with telangiectases, especially within the 'dissatisfaction with appearance' subscale. Telangiectases were associated with anticentromere positivity and digital ischaemia, lending further support for telangiectases as a potential marker for vascular involvement. Qualitative analysis provided new insights into the thoughts and feelings of patients with telangiectases, highlighting concerns and also methods of coping with telangiectases. Our findings highlight the impact of telangiectases and the need to address and manage related concerns.

	All participants n=141	Telangiectases n=113	No Telangiectases n=28	p value (Mann-Whitney U)
ASWAP Social impact, median (IQR)*	14 (8–22)	14 (8–22)	12 (8–20)	p=0.67
ASWAAP Dissatisfaction with appearance, median (IQR)*	20 (14–26)	21 (15–27)	15 (12–23)	p=0.02
ASWAAP Total score median (IQR)*	30 (25–36)	37 (27–47)	26 (20–41)	p=0.09
HADS Anxiety, median (IQR)**	7 (4–10)	7 (4–10)	8 (5–12)	p=0.46
HADS Depression, median (IQR)**	6 (3–9)	6 (3–9)	6 (3–8)	p=0.52

* 125 subjects.
** 240 subjects.

Disclosure: H. Ennis: None; **H. L. Richards:** None; **C. Cassidy:** None; **A. L. Herrick:** None.

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The Use of Calcium-Channel Blockers May Prevent the Development of Scleroderma Renal Crisis. Gaia Montanelli, Lorenzo Beretta, Alessandro Santaniello and Raffaella Scorza. Referral Center for Systemic Autoimmune Diseases

Background: Scleroderma renal crisis (SRC) is one of the most severe complications of systemic sclerosis (SSc), with high mortality and morbidity rates. Past studies were conducted to determine which factors may precipitate or protect from the development of SRC. The use of corticosteroids, the diffuse cutaneous subset (dcSSc), the presence of friction tendon rubs, the presence of certain autoantibodies and an aggravating skin score were shown to be risk-factors for SRC. Apart from corticosteroids, which were associated with the onset of SRC, the role of other therapies, including vasodilators or Iloprost, in the progression of or in the protection from SRC is not clear.

Methods: A retrospective study was conducted in all the patients referred to our outpatient clinic between 1990 and 2010, with a disease duration < 5 years at referral. The development of SRC, defined as either hypertensive renal crisis or normotensive renal crisis, up to 5 years (20 trimesters) from referral was sought. Medical records were reviewed to determine whether the patients had been treated with calcium-channel blockers (CCB), Iloprost or steroids. The dose of steroids (expressed as the medium dose Prednisione/day/trimester) was also reviewed.

Univariate Cox regression analysis with or without time-dependent covariates was used to assess the individual risk for SRC for baseline demographic and clinical characteristics and for therapies. Meaningful variables were inserted in a multivariate Cox regression model.

Results: Two-hundred-ninety-one patients (females=89.7%; dcSSc=25.8%) with a disease duration of 13 months at referral (interquartile range [IQR]: 4 – 29), were considered. Fifteen SRC (5.2%; 12 hypertensive, 3 normotensive) were observed, the median time-to-onset of SRC was 6 months (IQR: 3 – 12 months). Overall, 165 patients were treated with steroids with a median maximum dose of 25 mg/day/trimester (IQR: 14 – 50 mg); 260 subjects (89.3%) received CCB and 100 (34.4%) Iloprost, prior or concurrently to corticosteroids. On univariate analysis, gender, disease subset and the use of steroids were associated with a positive risk of SRC, whilst FVC, disease duration prior to referral and the use of CCB were negatively associated with SRC. On multivariate analysis the use of CCB was negatively associated with SRC (HR=0.118, CI95=0.038–0.362, p<0.0001), whilst steroids (HR=1.014, CI95=1.002–1.026, p<0.035) and dcSSc (HR=6.75, CI95=1.988–22.195, p<0.003) increased the risk for SRC.

Discussion: SRC is a relatively rare event in Italian patients. We confirmed that the use of steroids increases the risk for SRC, albeit this risk is relatively low (1.4% for every milligram of Prednisone used in the trimester prior to SRC). Conversely, the use of CCB is highly protective against the development of SRC. In our centre, the vast majority of patients is prescribed first-second generation dihydropyridine agents (Nifedipine or Nicardipine), that acting on L-type calcium channels may favour afferent renal arterioles vasodilatation, and counteract angiotensin II vasoconstrictive effects thus increasing or stabilising the glomerular filtration rate and glomerular filtration fraction.

Disclosure: G. Montanelli: None; **L. Beretta:** None; **A. Santaniello:** None; **R. Scorza:** None.

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Time of Transition through Different Patterns of Nailfold Microangiopathy in Systemic Sclerosis. Alberto Sulli[1], Carmen Pizzorni[2], Francesca Ravera[2], Elisa Alessandri[2], Giuseppe Zampogna[2], Bruno Seriolo[2] and Maurizio Cutolo[1]. [1]Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy, [2]Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy

Background: Nailfold microangiopathy is an early aspect of systemic sclerosis (SSc), and its features may be detected by nailfold videocapillaroscopy (NVC). The evolution from "early", to "active", and to "late" patterns of microvascular damage was described by several studies.

Objectives: To investigate the time of transition through the different patterns of microangiopathy, in SSc patients with the "early" NVC pattern at baseline.

Methods: Thirty-eight SSc patients (mean age 48±12sd years; mean disease duration from Raynaud's phenomenon onset 10±10 years, from the onset of the first SSc symptom different from RP 1±1 year) with the "early"

pattern of nailfold microangiopathy at baseline were followed-up by NVC for a mean time of 90±18 months, every nine months by the same operator. The proper pattern of NVC microangiopathy ("early", "active", "late") was recorded at each visit, as previously reported(1,2). "Early" NVC pattern: few (<33%) giant capillaries, few capillary haemorrhages, relatively well-preserved capillary distribution, no evident loss of capillaries; "active" NVC pattern: frequent (>66%) giant capillaries, frequent capillary haemorrhages, moderate (<33%) loss of capillaries, mild (<33%) disorganisation of the capillary architecture, absent or mild ramified capillaries; "late" NVC pattern: irregular enlargement of the capillaries, few or absent giant capillaries and haemorrhages, severe (>66%) loss of capillaries with avascular areas, disorganisation of the normal capillary array, and ramified/bushy capillaries.

Results: At the end of the follow-up, 17 patients (43%) were still showing the "early" scleroderma-pattern, while the NVC pattern of microangiopathy was changed in 57% of the patients. The NVC pattern was found "active" in 14 patients (38%), "late" in 5 patients (14%), and normal in 2 patients (5%). The mean time of progression from the "early" to the "active" pattern was of 28±20 months, and from the "early" to the "late" pattern it was of 36±29 months. Interestingly, in the subgroup of patients whose microangiopathy progressed from the "early" to the "late" NVC pattern through the "active" pattern, the mean time of progression from the "early" to the "active" pattern was only 8±1 months, discovering a subset of SSc patients (14%) with fast progression of SSc microangiopathy.

Conclusions: The results of this longitudinal study confirm the transition of the SSc microvascular damage through different NVC patterns of microangiopathy. Fourteen % of SSc patients progressed quickly to "late" from "early" NVC pattern of microangiopathy. Patients showing a fast progression from the "early" to the "active" NVC pattern of microangiopathy should be strictly monitored as at risk of rapid progression to the "late" NVC pattern of microvascular damage, characterized by capillary desertification and disorganization.

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1237

Ultrasonographic Assessment of Hand Joint and Tendon Involvement in 30 Patients with Systemic Sclerosis. Emmanuel Chatelus, Hélène Chifflot, Viriginie Clavert, Christelle Sordet, Jacques-Eric Gottenberg and Jean Sibilia. Hospital of Hautepierre, Strasbourg, France

Objective: To evaluate joint and tendon involvement in the hands of patients with systemic sclerosis (SSc) using ultrasonography (US) and their correlation with clinical and X-ray examinations.

Methods: 30 patients with SSc according to ACR criteria (21 diffuse SSc and 9 limited SSc, median (25^{th}-75^{th}) age 55 (44–63) years, median (25^{th}-75^{th}) disease duration 5 (3–11) years, all negative for anti-CCP), were consecutively included in this study and underwent clinical, X-ray and US examinations. Synovial proliferation, joint effusion, bone erosion, tenosynovitis and the Power Doppler signal were evaluated using a Toshiba EUB-5500 with a 14 MHz linear-array transducer.

Results: US detected synovial proliferation in 11 patients (37%), and joint effusion in 10 (33%). US detected synovitis in 47% of patients, higher than that found by clinical examination (27%; p=0.01), which was not associated with the radiological presence of erosion and joint space narrowing. Synovial proliferation and joint effusion were more frequent in diffuse SSc (43% for both) than in limited SSc (22%, 11%, respectively). Lastly, tenosynovitis (24%), bone erosion and Power Doppler (19%) were observed only in diffuse SSc.

Conclusion: US provides relevant information on the hands of patients with SSc that complements that obtained by clinical and X-ray examination. Also, diffuse SSc is a subgroup at greater risk of tendon and joint involvement. US evaluation may therefore be particularly helpful in detecting synovitis and bone erosion early in patients with diffuse SSc, and designing therapy.

Disclosure: E. Chatelus: None; **H. Chifflot:** None; **V. Clavert:** None; **C. Sordet:** None; **J.-E. Gottenberg:** None; **J. Sibilia:** None.

1238

Vaccination Against Influenza in Patients with Scleroderma. Irena Litinsky[3], Alexandra Balbir[2], Devy Zisman[4], Michal Mandelboim[1], Ella Mendelson[1], Marina Anouk[3], Ilana Kaufman[3], Daphna Paran[3] and Ori Elkayam[3]. [1]Central Virology Laboratory, Sheba Medical Center, [2]Department of Rheumatology, Rambam Health Care Campus Background, [3]Department of Rheumatology, Tel Aviv Medical Center, [4]Rheumatology Service, Carmel Medical Center

Purpose: To assess the efficacy and clinical safety of the influenza virus vaccine in patients with systemic sclerosis (SSc) in comparison with healthy controls.

Methods: The study population comprised 2 groups of patients. Group 1 included 26 SSc patients:12 (46.1%) with diffuse type,14 (53.9) with limited scleroderma, 22 (84.6%) women, 4(15.4%) men, mean age 51.7±12.9,disease duration 8.29±6.28 years, median 6.45years). Group 2 comprised 15 healthy controls: 13 women (81%),2 men (19%), mean age 44.5 ± 15.3.In group 1, 7 (26.9%) patients were on immunosuppressive therapy (2 prednisone, 2 cellcept, 2 methotrexate, 1 cuprimine) at the time of vaccination. All the participants were vaccinated with a trivalent influenza subunit vaccine including H1N1 A/Brisbane/59/2007(TGA 2008/81B) (H1N1, H3N2 A/Uruguay/716/2007 (A/Brisbane/10/2007-like, NIBSC 8/124) (H3N2) and B B/Brisbane/60/2008 (TGA 2009/82/B) (B).Disease activity was assessed by Rodnan score, number of ulcers, number of tender and swollen joints, changes of clinical signs (dyspnea, cough, dyspepsia and dysphagia), patient (PDAI) and physician (PHDAI) disease activity evaluation by VAS, ESR and CRP, on day of vaccination and 6 weeks after. The humoral response was tested by Hemagglutination inhibition (HI) antibodies against H1N1 and H3N2 by standard WHO procedure. Response was defined as ≥4-fold rise in antibodies 6 weeks after vaccination, or seroconversion in patients with non-protective baseline level of antibodies (<1/40). Geometric mean titers (GMT) were calculated to assess the immunity of the whole group

Results: At baseline, 62% of patients with scleroderma patients and 40 % of controls had protective levels against H1N1 while 15% of SSc patients versus 46% of controls had protective anti H3N2 antibodies. Six weeks after vaccination, in patients with SSc, the percentage of responders for H1N1 antigen achieved 78%. Surprisingly, the proportion of responders was significantly higher (p=0.0128) in SSc patients than in controls (33%). The proportion of responders against H2N3 was similar in the 2 groups (42% in group 1 vs 33% in group 2).SSc suffering from interstitial lung disease (ILD) demonstrated a significant lower response (p=0.02 for H1N1 AND P=0.03 for H3N1).(Table 1).

Table 1. Proportion of subjects with humoral response to H1N1 and H3N1

	SSc without ILD	SSc with ILD	P
H1N1	88.2	44.4	0.02
H3N1	58.8	11.1	0.03

Parameters of disease activity remained unchanged except for an increase in patient disease activity index (p=0.01)

Conclusions: Influenza virus vaccine generated a satisfactory humoral response in scleroderma patients. The presence of ILD seems to lower the humoral response. Influenza vaccine was found to be safe in this cohort of patients. Yearly, Influenza vaccination is recommended to patients with scleroderma

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1239

Wound Fluid of Skin Ulcers in Systemic Sclerosis: Cellular and Cytokines' Profile Helps To Define Healers Versus Non Healers Characteristics. Stefano Alivernini[1], Barbara Tolusso[2], Mariarita Gigante[2], Annunziata Capacci[2], Francesca Faustini[2], Silvia Laura Bosello[2], Maria De Santis[2] and Gianfranco Ferraccioli[1]. [1]Rheumatology Division, Catholic University of the Sacred Heart, Rome, Italy, [2]Rheumatology Division, Catholic University of the Sacred Heart, Rome, Italy

Background: Skin ulcers, being a common vascular complication in Systemic Sclerosis (SSc), have a relevant impact in the patients' daily life, causing pain, infection and loss of function. Studies on chronic diabetic (DM) skin ulcers showed that the wound fluid (WF) analysis could help to understand the nature of the lesions.

Objective: To evaluate cellular and soluble factors' profile of WF of SSc skin ulcers.

Patients and Methods: SSc patients with skin ulcers attending the Wound Care Outpatient Clinic of Rheumatology division of the Catholic University (Rome) were enrolled in the study. MMP-9, VEGF and IL-6 levels were detected through ELISA and MCP-1, IL-1β, IL-8 and TNFα levels through Flow CytoMix™ technology in plasma and WF, whereas the WF percentages of CD16, CD14, CD3 and CD19 were evaluated through Flow-cytometry at baseline. Each patient underwent skin lesion's evaluation, microbiological analysis and treatment with Suprasorb X® ± PHMB® or Suprasorb A® ± Ag® twice a week. WF collection was done through transparent dressing (Opsite, Smith & Nephew, UK).

Results: 11 SSc patients with skin ulcers (18% in fingertips) were enrolled in the study. A higher healing rate after 3 months of follow-up with the standard protocol was found in SSc compared to DM patients with chronic ulcers treated with the same protocol (8 patients (73%) vs 1/5(20%); $p<0.001$). Compared to healthy controls, SSc patients had higher plasma levels of IL-6 (2.4 ± 1.5 pg/ml vs 6.9±1.8 pg/ml, $p=0.01$), VEGF (17.2±15.4 pg/ml vs 43.11±36.03 pg/ml $p=0.01$), MCP-1 (255.5±59.2 pg/ml vs 528.35±270.78 pg/ml $p=0.001$) and IL-8 (1.66±3.62 pg/ml vs 3.55±3.59 pg/ml $p=0.02$). SSc patients with fingertip ulcers had lower levels of VEGF in WF compared to patients with major lesions (5157.3±3767.3 pg/ml/1g albumin vs 216632.0 ± 515864.0 pg/ml/1g albumin; $p=0.05$).

Direct correlations in WF were found between IL6 and MMP-9 ($r=0.64$, $p=0.04$), MMP-9 and IL-8 ($r=0.82$, $p=0.004$) and between percentages of CD3 and CD19 ($r=0.76$, $p=0.03$). Moreover there were direct correlations between the extension and border scores of ulcers and MCP1 ($r=0.62$; $p=0.05$ for extension and $r=0.63$;$p=0.03$ for border score) and TNFα ($r=0.65$;$p=0.03$ for extension and $r=0.65$;$p=0.02$ for border score) in WF of SSc patients.

SSc patients who healed after 3 months of follow-up had lower WF levels of MCP-1 (5012.9 ± 3600.1 pg/ml/1g albumin vs 505173.1± 576739.8 pg/ml/1g albumin, $p=0.03$), TNFα (248.1±372.8 pg/ml/1g albumin vs 36789.1±79499.5 pg/ml/1g albumin, $p=0.02$) and VEGF (2114.0±3825.7 pg/ml/1g albumin vs 111381.1± 212446.0 pg/ml/1g albumin, $p=0.03$) compared to non healers. All the inflammatory soluble factors (IL-6, IL-1β, TNFα and IL-8) were higher in WF compared to plasma in SSc patients ($p<0.05$).

Conclusions: A standard treatment seems to enhance healing rate in SSc skin ulcers. The plasma-WF polarization of factors such as IL-6, IL-1β, TNFα and IL-8 suggests that ulcers in SSc could be considered an acute phenomenon in a chronic inflammatory background. A stronger control of local inflammation should be looked for in the most inflamed lesions.

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ACR Poster Session B
T Cell Biology and Targets in Autoimmune Disease
Tuesday, November 9, 2010, 9:00 AM–6:00 PM

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A Novel Role for the Jak-Stat Pathway in Rheumatoid Arthritis: Inhibition of TNF-Induced T Cell Attracting Chemokine Synthesis in Fibroblast-Like Synoviocytes (FLS) by Tasocitinib. Sanna Rosengren[2], Gary S. Firestein[2] and David L. Boyle[1]. [1]UCSD Schl of Medicine, La Jolla, CA, [2]UCSD School of Medicine, La Jolla, CA

Purpose: The pan-Janus kinase (Jak) inhibitor, tasocitinib (CP690,550) is currently in Phase III clinical trials for rheumatoid arthritis. Whereas the Jak-Stat signaling in lymphoid and myeloid lineage cells is well understood, less is known about its involvement in FLS signaling in the context of synovitis. Therefore, we measured the effect of tasocitinib on expression and secretion of inflammatory mediators by cytokine stimulated FLS.

Methods: Passage 3–8 RA FLS isolated from tissue obtained at the time of arthroplasty were serum-starved 48 h prior to stimulation. mRNA levels were determined by qPCR, and protein levels in supernatants determined by ELISA or multiplex bead assay. Phosphorylation of Stat proteins was determined by Western blot analysis.

Results: Stimulating FLS with IL-6, but not TNF, induced phosphorylation of Stat1 and Stat3, downstream indicators of Jak activation. Stat activation was inhibited by tasocitinib with IC50 values of approximately 21 and 72 nM, respectively. IL-6 also induced expression of MCP1 mRNA and protein secretion but not other markers of FLS activation such as MMP3. MCP-1 expression was also completely prevented by tasocitinib (200 nM-1 μM). Unexpectedly, tasocitinib also inhibited TNF-induced gene expression and production of several other pro-inflammatory proteins. Time-course studies showed induction of IP-10, RANTES, and MCP1 mRNA expression and protein secretion after 7h but no inhibition by tasocitinib. However, tasocitinib significantly decreased IP-10, RANTES, and MCP-1 mRNA expression after 16 hours of TNF stimulation (96%, 67%, and 55% inhibition, respectively; $p<0.001$ for all). TNF-induced secretion of RANTES and MCP-1 protein at 18h was inhibited by 53% and 38%, respectively ($p<0.005$ for both). A smaller effect was observed on TNF-induced IL-6 and MMP1 expression, whereas other TNF-induced genes like IL-8 and MMP3 were unaffected by tasocitinib. mRNA stability studies showed that the effect of the Jak inhibitor was independent of mRNA half life. However, blocking de novo protein synthesis with cycloheximide abolished the inhibitory effect of tasocitinib on TNF induced IP-10 and RANTES mRNA expression.

Conclusions: TNF induces FLS expression of several chemokines involved in T cell recruitment in a manner that indirectly depends on Jak-Stat activation. TNF-induced FLS expression of these chemokines requires de novo protein synthesis and could involve disrupting late autocrine cytokine networks mediated by Jak-Stat signaling. These findings illuminate a potential novel mechanism of tasocitinib in rheumatoid arthritis: not only does the compound directly inhibit cytokine signaling in T cells, but it also diminishes the production of chemokines by synovial fibroblasts and could limit recruitment of T cells and other infiltrating leukocytes to the synovium.

Disclosure: S. Rosengren: None; **G. S. Firestein:** Pfizer Inc, 5; **D. L. Boyle:** Pfizer Inc, 2.

1241

A Th17 Immune Response Can Be Amplified by Human Th9 Cells. Andreas Ramming[1], Hendrik Schulze-Koops[2] and Alla Skapenko[2]. [1]Division of Rheumatology, University of Munich, Munich, Bavaria, Germany, [2]Division of Rheumatology, University of Munich, Munich, Germany

Interleukin 9 (IL-9) is a pluripotent cytokine produced primarily by T cells in response to transforming growth factor (TGF)-β. Little is known about the role of IL-9 and of the IL-9-producing T cell subset. Herein, we investigated IL-9 production by different mature T helper (Th) cell subsets, and analyzed the effect of IL-9 on T cell differentiation.

CD4+ CD45RA+ naive and CD45RO+ memory, and CD4+CD25+ T cells were isolated from peripheral blood of healthy individuals, stimulated under different conditions, and analyzed for their cytokine profile by intracellular flow cytometry and Luminex.

TGF-β was identified as the master cytokine for the induction of human IL-9-producing T cells. CD45RA+ naive T cells required TGF-β together with IL-4 to convert into IL-9-producing cells. In CD45RO+ memory T cells, TGF-β alone was sufficient to induce IL-9 production. Mature T cell subsets, Th1, Th2, Th17 cells, and CD25+Foxp3+ regulatory T cells (Tregs) did not produce IL-9 together with the respective signature cytokine or transcription factor. Th9 cells itself demonstrated a highly specific cytokine secretion profile characterized by the exclusive production of IL-9. When the effect of IL-9 on T cells was investigated, IL-9 did not influence Th1 and Th2 cell differentiation, but significantly enhanced the differentiation of Th17 effector cells towards IL-17 single producers.

IL-9-producing Th9 cells represent a distinct T cell subset characterized by a highly specific cytokine secretion profile different from other effector cell subsets. Their signature cytokine, IL-9, enhances Th17 differentiation. Therefore, human Th9 cells are likely to exert a pro-inflammatory function.

Disclosure: A. Ramming: None; **H. Schulze-Koops:** None; **A. Skapenko:** None.

1242

Addition of Retinoic Acid and TGF-beta Accelerate the Maturation Naive CD8+ Cells into CD8+CD25+FOXP3+ Regulatory Cells. J. Dixon Gray[1], Stephanie Q. Pan[2] and David A. Horwitz[1]. [1]University of Southern California, Los Angeles, CA, [2]University of Southern California

Purpose: Regulatory T cells (Tregs) maintain immunologic homeostasis and prevent autoimmunity. Defects in the numbers and function of CD4+ Tregs in SLE and other immune-mediated rheumatic diseases are well described. Besides their well described cytotoxic activities, several populations of CD8+ regulatory cells (Treg) have been described that occur

naturally or can be induced ex-vivo and some of these subsets express Foxp3. The conditions required to induce mature functionally competent Foxp3+ Tregs are not well understood. We have reported that human naïve CD4+ cells polyclonally stimulated with IL-2, TGF-β and all-trans retinoic acid (atRA) rapidly become CD25+CD127- Foxp3+ cells with marked suppressive activity both *in vitro* and *in vivo*. Here the objective was to learn whether CD8+ cells could become Treg cells with a similar phenotype and function.

Methods: CD8+ CD28+ CD45RA+ CD127+ CD62L^{hi} CD25- cells from healthy subjects were stimulated with suboptimal numbers of anti-CD3/CD28 coated beads + IL-2 ± TGF-β or atRA for 5 to 7 days. Since all anti-CD3 activated CD8+ cells inhibit T cell proliferation *in vitro*, we investigated their ability to protect into immunodeficient NOD SCID IL-2R common gamma chain−/− (NOG) mice from a human anti-mouse GVHD.

Results: Activation of naïve CD8+ cells with TGF-β doubled Foxp3 expression and the cells became CD103+, but the cells retained a naïve phenotype and remained CD127+. With the addition of atRA to TGF-β, Foxp3 expression was consistently >50%. They remained predominantly CD62L^{hi}, but became CD45RO+ and CD127-, consistent with a regulatory phenotype. The transfer of 20×10^6 human CD25- PBMC to NOG mice results in the rapid demise of these animals. The addition of atRA/TGF-β CD8reg in a ratio of 1: reg to 4 PBMC doubled the survival of the mice. Studies with other epigenetic agents and comparing the effects of CD4 and CD8regs separately and together will be reported.

Conclusions: Although to date, attention has been focused on CD4reg, studies in both mouse and human SLE have documented an important, if not essential, role of CD8regs. The ability to rapidly generate both CD4+ and CD8+ Foxp3+ Tregs using convention cell separation techniques represents a novel, practical strategy to treat patients with SLE and other chronic inflammatory immune-mediated rheumatic diseases.

Disclosure: J. D. Gray: None; **S. Q. Pan:** None; **D. A. Horwitz:** None.

1243

An Assessment of theThromboembolic Potential of CDP7657, a Monovalent Fab' PEG Anti-CD40L Antibody, in Rhesus Macaques. Ian Wakefield[2], Olivier Harari[2], David Hutto[1], Linda Burkly[1], Janine Ferrant[1], Fred Taylor[1], Martyn Robinson[2], Anthony Shock[2], Timothy Bourne[2] and Christopher Peters[2]. [1]Biogen Idec, [2]UCB

Background: CDP7657 is a novel monovalent Fab' PEG anti-CD40L antibody being developed for the treatment of Systemic Lupus Erythematosus (SLE) and currently in a phase I clinical study. Previously, an anti-human CD40L intact IgG_1 mAb, hu5c8 (Antova), has been associated with thromboembolic events in the clinic and subsequent investigations of hu5c8 in Rhesus macaques revealed extensive pulmonary thrombovasculopathy with intimal hyperplasia (IH). CDP7657 and other Fc function-deficient anti-CD40L antibody constructs were evaluated in Rhesus monkeys for their potential to induce thrombosis and vascular lesions as part of a non-clinical safety evaluation program.

Methods: Three studies were conducted in Rhesus monkeys. In the initial study, the hu5c8 mAb was administered *i.v.* weekly at 50mg/kg/week for 8 weeks. A second 8-week study investigated two PEGylated antibody fragments (the monovalent Fab' PEG CDP7657 and a bivalent di-Fab' PEG format using the same variable region) and two intact mAbs (hu5c8, and the Fc function-deficient aglycosyl hu5c8). These agents were administered *i.v.* weekly (50mg/kg) and compared with saline-injected control animals. In the third study, CDP7657 was administered *i.v.* weekly at doses of 20, 50, or 200 mg/kg (8/sex/group) for 12 weeks, while control animals (16/sex) received saline. Reversibility groups were assessed for 4 or 6 months. In all studies, there was extensive histopathology evaluation of the lungs (29 sections/animal).

Results: In the first study, hu5c8 produced widespread severe pulmonary vasculopathy in animals, consisting of intravascular thrombosis and IH. In the second study, hu5c8 also produced pulmonary intravascular thrombosis or IH in the lungs of 5 of 8 animals. Secondary changes were observed including recanalization of arterial thrombi, intra-alveolar hemorrhage, perivascular inflammation and fibrosis and coagulative necrosis of the lung parenchyma. By contrast, CDP7657 and other anti-CD40L antibody constructs lacking a functional Fc region were associated with an incidence of pulmonary changes comparable to that found in control animals. In the third study, CDP7657 showed no evidence of compound-related pulmonary or extra-pulmonary thrombovasculopathy after the treatment or reversibility periods and no other findings of toxicological significance at any dose level.

Conclusions: The pulmonary thrombovasculopathy observed with the hu5c8 mAb in Rhesus macaques is associated with the presence of a functional Fc region, and is not caused by CD40L blockade alone, or on the valency of the blockade, as seen by the absence of these pulmonary effects with the other antibody constructs. These data support the clinical testing of CDP7657 in humans for treatment of SLE and other immune-mediated diseases.

Disclosure: I. Wakefield: UCB, Inc., 3; **O. Harari:** UCB, Inc., 3; **D. Hutto:** Biogen Idec, 3; **L. Burkly:** Biogen Idec, 3; **J. Ferrant:** Biogen Idec, 3; **F. Taylor:** Biogen Idec, 3; **M. Robinson:** UCB, Inc., 3; **A. Shock:** UCB, Inc., 3; **T. Bourne:** UCB, Inc., 3; **C. Peters:** UCB, Inc., 3.

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Blockade of CD40L with a Monovalent Fab' PEG Monoclonal Antibody Inhibits Disease in the Murine Collagen-Induced Arthritis Model. Alexander Vugler[2], Daniel Sutton[2], Diane Marshall[2], Stevan Shaw[2], Linda Burkly[1], Janine Ferrant[1], Ellen Garber[1] and Anthony Shock[2]. [1]Biogen Idec, [2]UCB

Background: Inhibition of CD40L is a potential approach for the treatment of autoimmune diseases. Whole IgG anti-CD40L mAb treatment was associated with thrombotic toxicity in man. A monovalent Fab' PEG antibody format is a promising approach to inhibit CD40L function without causing thrombotic complications. In this study the efficacy of an anti-mouse CD40L Fab' PEG antibody (MR1 Fab' PEG) was assessed in the collagen-induced arthritis model.

Methods: DBA/1 mice were dosed prophylactically with MR1 Fab' PEG (100mg/kg once a week) or PBS by subcutaneous route from 1 day prior to sensitisation. On Day 0, mice were sensitised intradermally with 100mg chick type II collagen (CII) emulsified in complete Freund's adjuvant. On Day 14, mice received a boost injection of 100mg CII in incomplete Freund's adjuvant. Mice were then monitored for signs of arthritis. The study was terminated on Day 48 post-sensitisation. Serum samples were taken to measure anti-CII antibody production and limbs were removed into formalin for histological analysis of joint structure.

Results: Administration of MR1 Fab' PEG resulted in an 81% ($p<0.01$) reduction in the area under the curve of the clinical score and suppressed anti-CII IgG1 and anti-CII IgG2a production by 61% ($p<0.05$) and 82% ($p<0.001$) respectively, as compared to PBS-treated control animals. Histological examination of the joints showed that MR1 Fab' PEG inhibited joint destruction by 86% ($p<0.001$).

Conclusion: These results demonstrate that a monovalent anti-CD40L Fab' PEG approach to blocking CD40L is efficacious in a pre-clinical model of rheumatoid arthritis and suggests that this approach may be beneficial in the treatment of chronic autoimmune diseases.

Disclosure: A. Vugler: UCB, Inc., 3; **D. Sutton:** UCB, Inc., 3; **D. Marshall:** UCB, Inc., 3; **S. Shaw:** UCB, Inc., 3; **L. Burkly:** Biogen Idec, 3; **J. Ferrant:** Biogen Idec, 3; **E. Garber:** Biogen Idec, 3; **A. Shock:** UCB, Inc., 3.

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CDP7657, a Monovalent Fab′ PEG Anti-CD40L Antibody, Inhibits Immune Responses in Both HuSCID Mice and Non-Human Primates. Ian Wakefield[2], Christopher Peters[2], Linda Burkly[1], Ellen Garber[1], Janine Ferrant[1], Fred Taylor[1], Lihe Su[1], Yen-Ming Hsu[1], Martyn Robinson[2], Timothy Bourne[2], Roger Palframan[2], Lisa Berry[2], Olivier Harari[2] and Anthony Shock[2]. [1]Biogen Idec, [2]UCB

Background: CDP7657 is a novel monovalent Fab′ PEG anti-human CD40L antibody being developed for the treatment of Systemic Lupus Erythematosus (SLE) and is currently in a phase I clinical study. CD40L is a key regulator of T-cell dependent activation of accessory cells, particularly B cells and other antigen presenting cells. These studies were designed to evaluate the capacity of CDP7657, and other anti-CD40L antibody contructs, to block the humoral immune response to tetanus toxoid (TT) in both HuSCID mice and Cynomolgus macaques.

Methods: For the HuSCID study, CB17 SCID mice were dosed *s.c.* with CDP7657, hu5c8 (a humanized anti-human CD40L intact IgG_1 mAb) or an aglycosyl (Fc function-deficient) form of hu5c8. Human peripheral blood mononuclear cells (PBMC) and TT were then injected into the mice. The number of antibody forming cells generating human anti-TT IgG was determined on day 14 by ELISpot.

For the Cynomolgus macaque studies, different anti-CD40L mAb constructs were given as a single *i.v.* dose. In addition to CDP7657, hu5c8 and aglycosyl hu5c8, the variable regions of CDP7657 in bivalent di-Fab′ PEG and intact aglycosyl (human IgG_4) mAb formats were also tested. The effect

of these entities on the primary and secondary anti-TT responses was monitored.

Results: In the HuSCID model, CDP7657 demonstrated a dose-dependent inhibition of the anti-TT antibody response with equivalent efficacy to that of aglycosyl hu5c8. Although all three entities were able to completely block the anti-TT immune response, the IgG_1 version of hu5c8 was the most potent in this model system.

In the Cynomolgus macaque, all of the anti-CD40L molecules were capable of inhibiting the primary IgM and IgG anti-TT antibody responses, with a comparable degree of efficacy observed between CDP7657, the diFab′ PEG and the aglycosyl IgG antibody constructs. CDP7657 demonstrated a dose related effect on both primary and secondary (after re-challenge with TT) immune responses and also was able to effectively suppress secondary responses.

Conclusions: CDP7657 dose-dependently inhibited the immune response to TT in both HuSCID mice and Cynomolgus macaques. The inactive Fc formats tested had decreased efficacy in both models relative to hu5c8 which may reflect the potential depleting capacity of this active isotype. Demonstration of the effective inhibition of CD40L-dependent immune responses by CDP7657 supports the therapeutic potential of this molecule for the treatment of human immune-mediated diseases such as SLE.

Disclosure: I. Wakefield: UCB, Inc., 3; **C. Peters:** UCB, Inc., 3; **L. Burkly:** Biogen Idec, 3; **E. Garber:** Biogen Idec, 3; **J. Ferrant:** Biogen Idec, 3; **F. Taylor:** Biogen Idec, 3; **L. Su:** Biogen Idec, 3; **Y.-M. Hsu:** Biogen Idec, 3; **M. Robinson:** UCB, Inc., 3; **T. Bourne:** UCB, Inc., 3; **R. Palframan:** UCB, Inc., 3; **L. Berry:** UCB, Inc., 3; **O. Harari:** UCB, Inc., 3; **A. Shock:** UCB, Inc., 3.

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Characterization of Human Follicular Helper T Cells. Sang Taek Kim[3], Jin-Young Choi[4], Begona Lainez[4], Leah DiPlacido[1], Vivian E. Vlamakis[2] and Joseph E. Craft[4]. [1]Department of Immunobiology, Yale University School of Medicine, New Haven, CT, [2]Division of Rheumatology, University of Washington School of Medicine, Bothell, WA, [3]Section of Rheumatology, Department of Internal Medicine, Yale University School of Medicine, Orange, CT, [4]Section of Rheumatology, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT

Follicular helper T (T_{FH}) cells are specialized $CD4^+$ T cells that are localized in B cell follicles and help B cells produce antigen-specific antibodies via contact and secretion of IL-21 and IL-4. In mouse studies, a spontaneous increase in T_{FH} cells is associated with pathologic germinal center formation and autoantibody secretion, which leads to autoimmune diseases and end-organ damage. In mice, T_{FH} cells are characterized by high expression of CXCR5, PD-1, ICOS, and Bcl-6, and as we have found, low expression of P-selectin glycoprotein ligand-1 (PSGL-1); however, study of T_{FH} cells in human is more limited. Here we characterized T_{FH} cells in human tonsils using flow cytometry and immunofluorescence staining, and compared them using surface markers and cytokine production to traditional Th effector subsets. Samples were obtained from routine tonsilectomy at Yale New Haven Hospital. Both surface and intracellular staining were done with flow cytometry. T cells in human tonsil were sorted into populations of $CD4^+CD45RA^+$ cells (Naive T cells), $CD4^+CD45RA^-PSGL\text{-}1^{hi}PD\text{-}1^{hi}CXCR5^{hi}$ cells, $CD4^+CD45RA^-PSGL\text{-}1^{hi}PD\text{-}1^{lo}CXCR5^{lo}$ cells, $CD4^+CD45RA^-PSGL\text{-}1^{lo}PD\text{-}1^{hi}CXCR5^{hi}$ cells and $CD4^+CD45RA^-PSGL\text{-}1^{lo}PD\text{-}1^{lo}CXCR5^{lo}$ cells. Subsequently sorted populations were stimulated with PMA/Ionomycin for 6 hours. Stimulated cells were used for qPCR/intracellular staining and culture supernatants were used for ELISA. Tissue immunofluorescence staining was done using confocal microscopy to confirm the location of T_{FH} cells. We find that human T_{FH} cells are $ICOS^{hi}IL6\text{-}R^{hi}CD200^{hi}CD27^{hi}CXCR4^{hi}$ and $IL21\text{-}R^{lo}IL7\text{-}R^{lo}PSGL\text{-}1^{lo}CD62L^{lo}CCR7^{lo}$ and they produce both IL-4 and IL-21. Downregulation of PSGL-1 can be used as an additional surface marker for T_{FH} cells as well as an anatomical marker of the B cell follicle by microscopy.

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Chronic Inflammatory Responses in Rheumatoid Arthritis: The Vicious Circle Might Be Related to Interaction of Th17 Cells with FLS or Mesenchymal Stem Cells. Assia Eljaafari[1], Marie-Laure Tartelin[1] and Pierre Miossec[2]. [1]HCL and UCBL, Lyon, France, [2]HCL and UCBL, France

Introduction: TH17 cells have been involved in the initiation and maintenance of several inflammatory and autoimmune diseases, such as Rheumatoid Arthritis (RA). More recently, they gained further interest, due to the demonstration of their involvement in anti-tumor responses.

Hypothesis: Here we postulated that if TH17 cells play a so preponderant role in inflammatory diseases, their development might be facilitated in this context. Therefore, using RA as a model of chronic inflammation, we hypothesized that interaction of T cells with mesenchymal cells, such as synoviocytes (FLS), or mesenchymal stem cells (MSC) could participate in the activation of the TH17 pathway, with the help of the inflammatory environment.

Methods: To investigate this possibility, mononuclear cells (MNC) from healthy blood donors were co-cultured with MSC from healthy controls, or FLS from either RA or osteoarthritic (OA) patients, and were activated with PHA or A/CD3+CD28 mABs, for 1 to 2 days. IL17A, TNFa, and or/IFNg were added or not to these co-cultures. Q-RT-PCR, ELISA,and cytoflurometry technics were used to assess for IL17-A production.

Results: We observed that the interaction of MNC with healthy MSC resulted in an extinction of TH1 and TH2 cell activation, but was sufficient by its own to induce a strong production of TH17 cells, as soon as 24 hours post-activation, as assessed by the increase of IL17A at the mRNA and protein levels and by Th17 staining.The levels of IL17A further increased at 48 hours, and/or in the presence of IL17A, TNFa, and or/IFNg. IL6, IL8, and IL1 mRNA levels increased as well. Interestingly, co-culture with FLS from either OA or RA patients, also resulted in a strong induction of IL17, but not in TH1 inhibition. Finally, TH17 production was partially inhibited in the presence of anti-IL6 mAbs, or CTLA4-Ig fusion molecules, demonstrating thus the roles of IL6 and costimulatory molecules in such a production.

In Conclusion: We show herein, that interaction of MSC,or FLS from RA or OA patients, with MNC results in enhancing the inflammatory response, through production of IL-17, IL6, IL-8 and IL-1 cytokines. Moreover, in the context of an inflammatory environment, i.e: presence of IL-17A, TNFa, and/or IFNg, such an interaction of T cells with MSC results in further amplifying the induction of TH17 cells, leading thus to a vicious circle, that may participate to the chronicity of inflammation.

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1248

Circulating FOXP3+ CTLA-4+ CD25+ Regulatory T Cells in Human Infants Counteract the Maturation and Homing Receptor Switch of CD4+ T Cells at 18 and 36 Months of Age. Hardis Rabe[2], Anna-Carin Lundell[2], Kerstin Andersson[2], Ingegerd Adlerberth[1], Agnes E. Wold[1] and Anna Rudin[3]. [1]Dept of Clinical Bacteriology, [2]Dept of Rheumatology and Inflammation Research, [3]Dept of Rheumatology and Inflammation Research, The Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

Background: FOXP3+ CTLA-4+ CD25+ regulatory T cells are essential to prevent general overactivation of T cells and ensuing autoimmune and inflammatory disease as the lack of these cells leads to a lethal inflammatory syndrome. However, it is not known if the numbers of these cells in the circulation in early infancy of healthy children are associated with lower levels of activation and maturation of the T cells at later ages.

Methods: We followed a cohort of 66 children prospectively from birth to 3 years of age and analyzed T cells in blood samples phenotypically and quantitatively from ages 0 and 4 days, 1, 4 and 18 months and 3 years of age. The analysis of the CD4+ T cells was performed using flow cytometry to investigate the relation of the numbers of regulatory T cells in the circulation to the maturation and homing receptor switch of the CD4+ T cells at older ages. The relationship was analyzed using multivariate analysis by principal component analysis (PCA), orthogonal partial least squares modeling (OPLS) and thereafter univariate analyses as appropriate.

Results: We analyzed the numbers of regulatory T cells using both FOXP3 and CTLA-4 as markers together with CD25. We showed that the T cells expressing FOXP3 and CTLA-4, respectively, were associated in PCA and OPLS at 4, 18 and 36 months of age but not at earlier ages. The numbers of regulatory T cells av 4 and 18 month of age were positively associated with the proportion of immature unactivated CD45RA+ T cells as well as with gut-homing $\alpha4\beta7$+ CD4+ T cells at 18 and 36 months of age. Conversely, the numbers of regulatory T cells were negatively associated with the proportion of mature and previously activated CD45RO+ T cells as well as with CD4+ T cells expressing the extraintestinal homing marker CCR4.

Conclusion: We show for the first time that higher numbers of circulating FOXP3+ CTLA-4+ regulatory T cells in healthy infants are strongly related

to a lower proportion of mature previously activated CD4+ T cells at later ages. We conclude that the number of regulatory T cells in the circulation is important in the function of inhibition of immune activation, probably both to endgenous and exogenous antigens. Therefore, lower numbers of regulatory T cells in the circulation might preceed the onset of inflammatory disease.

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1249

Critical Role of IL-21 in Modulating Th17 Responses and Regulatory T Cells in Behçet Disease. Guillaume Geri[1], Benjamin Terrier[1], Michelle Rosenzwajg[1], Bertrand Wechsler[2], Du Le Boutin[1], Bahram Bodaghi[1], Tu-Ahn Tran[1], Nathalie Costedoat-Chalumeau[2], Lucile Musset[1], David Klatzman[1], Patrice Cacoub[1] and David Saadoun[1]. [1]Pitié-Salpetrière Hospital, Paris, France, [2]Pitie-Salpetriére Hospital, Paris, France

Background: Behçet disease (BD) is a systemic vasculitis of unknown origin. Infectious or environmental factors and Th1 cells producing IFN-γ have been involved in its pathogenesis, but these findings remain controversial.

Objective: To determine the implication of Th1, Th17 and regulatory T cells in the pathogenesis of BD.

Methods: Forty BD patients (20 active untreated [aBD] and 20 treated and inactive [iBD]) fulfilling the international diagnostic criteria and 20 healthy donors (HD) were included. Flow cytometric analysis of peripheral blood mononuclear cells and purified CD4+ T cells was performed for cell surface markers, intracellular production of cytokines and FoxP3 transcription factor. Measurements of cytokine levels in serum and culture supernatants were also performed.

Results: A marked enrichment in IL-17A-producing CD4+ CD45RO+CCR6+ T cells (Th17) was found in peripheral blood of aBD compared with iBD and HD (3.1 vs. 1.0 and 0.6 %, $P<0.0001$ for both), whereas IFN-γ producing CD4+ and CD8+ T cells did not differ between aBD and HD. Th17 expansion was more pronounced in cerebrospinal fluid of aBD with central nervous system involvement. CD4+CD25highCD127-FoxP3+ T cell subset was decreased in aBD compared to HD (1.78 vs. 3.2%, $P=0.02$). We found an increase in serum IL-21 in aBD compared with iBD and HD whereas no significant difference was noted for others cytokines promoting Th17 differentiation. Expansion of IL-21-producing CD4+ T cells was observed in aBD compared with iBD and HD (5.5 vs. 2.8 and 1.8 %, $P=0.002$ and $P<0.0001$, respectively), that correlated positively with Th17 expansion ($r^2=0.43$; $P<0.0001$) and negatively with activated Tregs ($r2=0.45$, $P=0.009$). Stimulation with anti-CD3/CD28 of purified CD4+ T cells, with human recombinant IL-21, significantly increased Th17 cells and decreased FoxP3 expression. The blockade of IL-21 using IL-21R/Fc chimera markedly decreased production of IL-17A and increased FoxP3 expression in sorted CD4+ T cells.

Conclusion: Taken together, these results are the first to demonstrate the implication of IL-21 in the pathogenesis of BD. IL-21 may exert a critical role in modulating Th17 responses and regulatory T cells in BD, and represent a potential target for novel therapy.

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1250

CXCL13 Signals through CXCR5 To Upregulate Nuclear CXCR5 and Bcl-6 and Promote the Development of Follicular T Helper Cells in Autoimmune BXD2 Mice. Yanna Ding[3], Hui-Chen Hsu[1] and John D. Mountz[2]. [1]Department of Medicine, The University of Alabama at Birmingham, [2]Department of Medicine, The University of Alabama at Birmingham; Birmingham VA Medical Center, [3]Department of Pathology, The Univerisity of Alabama at Birmingham

Background: Autoantibody production can be highly associated with B cells activation by Follicular T helper (T_{FH}) cells in germinal centers (GCs). Interaction of cell surface CXCR5 with its ligand, CXCL13, is critical to direct the trafficking of T_{FH} and B cells to GC light zone for their interaction. Bcl-6 is a critical transcription factor for T_{FH} cells while IL-21 is the major functional cytokine produced from T_{FH} cells. The purpose of this study is to determine how CXCL13-CXCR5 signaling is involved in the development of T_{FH} during the development of pathogenic GC response in BXD2 mouse model of autoimmune disease.

Methods: Frozen spleen sections were used for fluorescent confocal imaging analysis. Paraffin-embedded spleen sections were used for immunohistochemistry (IHC) staining. CD4 T cells or total spleen cells of BXD2 and normal B6 mice as well as Jurkat T cells were used for all in vitro experiments. Cells treated with either CXCL13 or neutralizing anti-CXCL13 were subjected to FACS staining with some cells cytospinned for fluorescent imaging analysis. Subcellular expression of CXCR5 in purified CD4 T cells and Jurkat cells was determined by western blot analysis. The expression of *Bcl6* and *Il21* at the mRNA were determined by RT-PCR.

Results: There was a 2.5- and 1.5-fold increased expression of $ICOS^+CXCR5^+$ and IL-21^+ $CD4^+$ T cells, respectively, in the spleens of BXD2 compared with those in B6 spleens. $ICOS^+CXCR5^+$ T_{FH} cells mainly clustered at GCs and were located adjacent to $CD21/CD35^+$ follicular dendritic cells. Surprisingly, CXCR5 exhibited the highest expression in the nucleus of CD4 T cells in the GC light zone. Western blot of cytoplasmic and nuclear fractions further confirmed that there was increased expression of CXCR5 in the nucleus of CD4 T cells from BXD2 mice compared with B6 CD4 T cells. CXCL13 stimulation of purified CD4 T cells from BXD2 mice or the human Jurkat T cell line led to a time-dependent increase of nuclear CXCR5 expression. $CXCR5^+CD4^+$ T cells from BXD2 mice also expressed higher levels of BrdU and lower levels of Fas, compared with those from B6 mice. *In vivo* nuclear expression of CXCR5 co-localized with $Ki67^+$ cells in situ. FACS analysis also showed that CXCL13 treatment promoted development of $CXCR5^+ICOS^+$ CD4 T_{FH} cells and upregulated Bcl-6 expression in this subset in BXD2 spleen cells and in Jurkat T cells. In contrast, anti-CXCL13 treatment decreased T_{FH} cells and downregulated Bcl-6 expression. The RT-PCR result supported the upregulation of *Bcl-6* by CXCL13.

Conclusions: Our study indicates that there was expansion of T_{FH} cells in BXD2 mice. CXCL13 binding to CXCR5 induced nuclear translocation and increased expression of CXCR5 in the nucleus of T_{FH} cells in autoimmune BXD2 mice. CXCL13 also upregulated Bcl-6 and promoted development and increased numbers of T_{FH} cells. Increased nuclear CXCR5 by CXCL13 may play an important role in survival of T_{FH} cells to facilitate autoreactive GC responses in BXD2 mice.

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Decreasing Fli1 Levels in Lupus T Cells Has Effects on Serum Immunoglobulin Levels and T Cell Infiltration in the Kidney. Erin Morris[1], Maria I. Harrell[1], John Svenson[1], Laura Tonks[1], John Zhang[3] and Tamara K. Nowling[2]. [1]MUSC, [2]Ralph Johnson VAMC/MUSC, Charleston, SC, [3]Ralph Johnson VAMC/MUSC

Background: The Ets factor Fli1 is implicated as a key modulator of lupus disease expression. Over-expressing Fli1 in healthy mice, results in the development of an autoimmune kidney disease similar to that observed in lupus. Lowering the global levels of Fli1 in two lupus mouse models significantly improved disease and prolonged survival. Lowering the levels of Fli1 in hematopoietic cells only in MRL/lpr lupus mice resulted in significantly improved kidney disease. The cell type mediating this protective effect is unknown. Here we analyzed the effects of reducing Fli1 levels in MRL/lpr T cells on serum IgG and IgM levels, T cell infiltration in the kidneys and T cell proliferation.

Methods: T cells and B cells were isolated from spleens of lupus prone MRL//lpr Fli1+/+ and MRL/lpr Fli1 +/− mice. The cells were mixed in all possible Fli1+/+ and Fli1+/− T and B cell combinations in a 1:1 ratio and adoptively transferred into Rag-1-deficient mice, which do not produce mature T and B cells. Various markers of autoimmunity were measured in the serum of the recipient mice at 2 and 4 weeks after transfer by ELISA and T cell infiltration in kidneys was examined 4 weeks after transfer by immunofluorescence. Next, we measured the various T cell subsets infiltrating the kidneys of MRL/lpr Fli1+/+ and MRL/lpr Fli1+/− mice by flow cytometry. CFSE staining and Annexin V staining were used to measure proliferation and apoptosis, respectively of Fli1+/+ and Fli1+/− T cells following ex vivo stimulation.

Results: Our adoptive transfer results demonstrated that recipient mice that received Fli1+/− T and +/+ B cells or Fli1+/− T and +/− B cells averaged 50–75% lower levels of IgG and 60–70% lower levels of IgM compared to recipients that received Fli1+/+ T and +/+ B cells. The recipient mice that received Fli1+/− T and +/+ B cells also had approximately 30% fewer T cells (CD3+) present in their kidneys compared to recipients that received Fli1+/+ T and +/+ B cells. Analyses of kidneys from 14–16 week old MRL/lpr Fli1+/+ and MRL/lpr Fli1+/− mice demonstrated that the percent of CD4+ T cells

present was significantly decreased by 25% ($p<0.005$) and the percent of CD8+ T cells present was significantly increased by 57% ($p<0.01$) in the MRL/lpr Fli1+/− compared to MRL/lpr Fli1+/+. A 37% decrease in the number of total T cells and 42% increase in the percent of CD25+ T cells present in the kidney also was observed in the MRL/lpr Fli1+/− mice, but the differences did nto reach statistical significance. Furthermore, T cells isolated from spleen of Fli1+/+ and Fli1+/− mice demonstrated that reducing Fli1 results in a 10–12% increase in T cell proliferation.

Conclusions: The adoptive transfer results demonstrate that reducing Fli1 levels in T cells alone may have a positive therapeutic impact on the progression of lupus nephritis. This positive impact may be mediated by changes in the number and subtypes of T cells infiltrating the kidneys. Mechanistically, the effects of altered Fli1 levels in T cells has yet to be fully explored. Preliminarily, our results suggest that Fli1 may have an effect on proliferation.

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Dendritic Cells and Continued Smoking in Rheumatoid Arthritis. Marina Kazantseva[3], John Highton[1], Lisa K. Stamp[4] and Paul A. Hessian[2]. [1]Univ of Otago Med Sch, Dunedin, New Zealand, [2]University of Otago, Dunedin, New Zealand, [3]University of Otago, Dundein, New Zealand, [4]University of Otago, Christchurch, New Zealand

Purpose: Tobacco smoking is the main environmental risk factor for the development of rheumatoid arthritis (RA). In established RA, smoking is associated with the increased production of rheumatoid factor (RF) and autoantibodies and with increased incidence of extra-articular manifestations that include the development of rheumatoid nodules. However, mechanisms linking smoking with the onset of RA, severity and/or progression of disease and that accommodate the genetic influence of the shared epitope are poorly understood. The aim of this study was to identify the pathogenic mechanism(s) within inflamed RA tissues which are triggered by smoking, with particular emphasis on the cells capable of responding via the aryl hydrocarbon receptor (AHR).

Method: Synovial membrane and subcutaneous nodule tissues were obtained at surgery from patients fulfilling ACR criteria for RA. Retrospective followup established whether patients were smoking at disease onset and/or continued to smoke at the time tissue was obtained, or had ceased smoking prior to tissue collection or had never smoked. All synovial samples were assessed using quantitative real-time PCR assays (Taqman; Applied Biosystems) to establish AHR expression and distinguish AHR activation, through CYP1A1 expression. Cryostat sections of synovial tissue were stained by double immuofluorescence using cell specific antibodies recognising lineage specific markers, in combination with biotinylated AHR- or CYP1A1-specific antibodies to identify cells responding to continued smoking. Genomic DNA was isolated from cryosections or from peripheral blood and genotyping for HLA-DR shared epitopes (SE) allotypes was performed using sequence specific-primer-PCR.

Results: The combination of AHR and CYP1A1 gene expression in synovial membrane distinguishes patients with RA who continue to smoke. CYP1A1 protein was observed in synovia obtained from smokers. Cell-specific markers confirmed both AHR and CYP1A1 were produced by CMRF56+ dendritic cells (DC) and CD3+ T lymphocytes in synovia from smokers. CD20+ B cells, CD14+ monocyte/macrophages CMRF44+ DCs, did not produce either AHR or CYP1A1 protein. No CYP1A1 protein expression was detected in synovial tissues from non-smokers. Synovia obtained from RA patients who smoked and carried a single or double copies of SE genes were largely positive for CYP1A1 gene expression. By comparison CYP1A1 was mainly expressed in nodule tissues from patients who were non-smokers but who carried double copies of SE genes.

Conclusions: Our results show that in rheumatoid synovial tissue, dendritic cells are armed and responsive to the components of cigarette smoke. A subset of T cells is also capable of responding. The response requires continued smoking as CYP1A1 expression, reflecting AHR activation, ceases within months of smoking cessation. The AHR-mediated response to smoking in synovial tissue is heightened in individuals who smoke requiring only a single copy of the HLD-DR shared epitope. This may reflect an increased sensitivity/activation of participating dendritic cells.

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DNA Methylation Affects Gene Expression in CD4+CD28- T Cells through microRNAs. Dipak R. Patel, Anura Hewagama, Sushma Yarlagadda and Bruce C. Richardson, University of Michigan, Ann Arbor, MI

CD4+CD28- T cells are enriched in multiple autoimmune diseases such as rheumatoid arthritis. These cells are capable of enhanced cytotoxicity, and they are more resistant to apoptosis. Extra-articular disease manifestations and disease severity positively correlate with the relative abundance of these cells.

Compared to their CD28+ counterparts, CD28- CD4+ T cells over-express CD70 and other molecules that potentially contribute to their phenotype. Hypomethylation of the DNA in these genes' regulatory elements explains their aberrant expression. Recently, changes in DNA methylation have been shown to affect microRNA (miRNA) expression. MicroRNAs are small non-coding RNA molecules that block the translation of messenger RNAs (mRNAs). The role of miRNAs in regulating gene expression in CD4+CD28- T cells is unknown.

We investigated the role of miRNAs in CD4+CD28- T cell gene expression. CD28+ and CD28- CD4+ T cells were generated by chronic re-stimulation in vitro. Peripheral blood mononuclear cells were stimulated overnight with phytohemagglutinin. CD4+ T cells were then isolated by negative selection, and they were re-stimulated weekly with irradiated antigen presenting cells and IL-2. CD28+ and CD28- CD4+ T cells were separated by flow cytometry after 4–6 weeks of culture. Total RNA, including the miRNA fraction, was then isolated (Qiagen). Expression of miRNAs in each population was compared using a quantitative real-time PCR kit (Systems Biosciences).

In four sets of chronically re-stimulated cell cultures, we found five miRNAs that are over-expressed at least 1.5 fold in CD4+CD28- T cells, compared to their CD4+CD28+ counterparts. Another four miRNAs were over-expressed in all four cultures, though the 1.5 fold threshold was exceeded in only three of the four cultures. Online tools, including TargetScan and miRANDA, were used to predict potential interactions between these miRNAs and mRNAs. Two of the five miRNAs over-expressed in CD4+CD28- T cells did not have any predicted mRNA targets. The remaining three of five miRNAs over-expressed in CD4+CD28- T cells were predicted to interact with mRNAs encoding proteins that are required for DNA methylation and cytokine signaling.

Overall, these experiments identified several miRNAs that are over-expressed in CD4+CD28- T cells. These miRNAs potentially interact with genes encoding proteins required for DNA methylation. If miRNAs targeting DNA methylation are over-expressed, hypomethylation and over-expression of genes causing T cell activity could result. This could explain the increased disease severity seen when CD4+CD28- T cells are abundant in RA. The miRNAs we have identified could then be potential therapeutic targets.

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1254

Dys-Regulation of T-Cell Subsets and Cytokines Is Associated with the Development of Inflammatory Symptoms in ACPA-Positive Asymptomatic Individual. Richard J. Cuthbert[2], Rekha Parmar[2], Jackie Nam[2], Edith Villeneuve[2], Diane Corscadden[2], Karen Henshaw[2], Paul Emery[1] and Frederique Ponchel[2]. [1]Chapel Allerton Hospital, Leeds, United Kingdom, [2]University of Leeds, Leeds, UK

Background: We reported that T-cell subset dys-regulation can predict evolution towards rheumatoid arthritis (RA) from early symptoms, response to treatment in early disease as well as relapse in patients who achieved clinical remission. Naïve cells were the most informative circulating T-cells subset in early disease. Cytokine activated T-cells (IRC) were less informative as systemic inflammation is low in early disease. Asymptomatic ACPA-positive individual are at high risk of developing RA. The aim of the current study is to determine whether T-cell subset and cytokine analysis can predict future development of inflammatory symptoms in this group.

Methods: 35 asymptomatic ACPA+ individuals were enrolled; they were recruited if they had new onset musculoskeletal pain but no synovitis on clinical examination. 6 colour flowcytometry was performed using standard protocols. 36 healthy controls were used to build the age relationship with naïve cell frequency. ELISA were used to measure cytokines and chemokines.

Results: 35 individuals were recruited and followed for 12 months. There was clear difference at baseline between ACPA+ individuals and controls for

naïve (P<0.0001), CD25^{high}Foxp3+ Treg (P=0.020) and CD62L+Treg (P=0.001). IRC were not increased in asymptomatic individuals. During follow-up, 6 individuals were diagnosed with undifferentiated arthritis (UA), 6 with RA, 9 with non-inflammatory osteoarthritis or connective tissue disease and 16 remained with non-specific musculoskeletal symptoms or arthralgia. Analysis based on follow-up showed reduced naïve T-cell (P=0.007) and Treg (P=0.090) in arthralgia and CD62L+Treg frequency were increased (P<0.0001). In the group developing IA, naïve cells were reduced (P<0.0001) but Treg were not different from controls. CD62L+Treg in contrast were significantly reduced (P=0.025). All OA/CTD individuals were close to controls. Furthermore, OA/CTD patients compared to the age-naïve frequency relationship in controls were above normal, the arthralgia group was close to controls and IA patients below. Serum levels of IL-12 and IL-7 cytokines differed in arthralgia individuals compared to controls (P<0.0001) but MIP-1alpha levels were not raised. On follow-up reduced IL-12 (P=0.007) and IL-7 (P=0.019) were observed in the arthralgia group. In the group developing IA, IL-12 (P<0.0001) and IL-7 (P=0.006) were even more reduced and MIP-1alpha raised (P=0.018). In OA/CTD individuals, only IL-12 levels were reduced (P<0.001).

Conclusion: In ACPA+ asymptomatic individuals, the future development of inflammatory symptom appears clearly associated with abnormal immunological parameters at baseline. Furthermore, data suggest that Treg's involvement may be in the true pre-clinical phase and this battle is lost by the time symptoms develop. More work is needed to determine if loss of naïve cells is a cause or a consequence of this dys-regulation on T-cells, however, loss of CD62L+Treg suggests a role for the thymus.

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Expression of $K_{2P}5.1$ Potassium Channels on CD4$^+$ T Lymphocytes Correlates with Disease Activity in Rheumatoid Arthritis Patients. Martin Feuchtenberger[2], Stefan Bittner[3], Nicole Bobak[3], Alexander M. Herrmann[3], Kerstin Goebel[3], Stefan Kleinert[3], Heinz Wiendl[1], Hans-Peter Tony[3] and Sven G. Meuth[3]. [1]University of Muenster, [2]University of Wuerzburg, Wuerzburg, Germany, [3]University of Wuerzburg

Background: CD4+ T cells express $K_{2P}5.1$ (TASK2; KCNK5), a member of the two-pore domain potassium channel family, which has been shown to influence T cell effector functions. Recently, it could be shown that $K_{2P}5.1$ is upregulated upon T cell stimulation. In addition, it has been shown that expression levels of this channel are strongly increased on CD8+ T lymphocytes from the peripheral blood from clinically active relapsing-remitting multiple sclerosis (MS) patients. The aim of this study was to analyze the expression of $K_{2P}5.1$ on T cells in patients with rheumatoid arthritis (RA).

Methods: Expression levels of $K_{2P}5.1$ were measured by RT-PCR in CD4+ and CD8+ T cells in the peripheral blood of 58 patients with RA and correlated with disease activity parameters (C-reactive protein levels, erythrocyte sedimentation rates, DAS28 scores). In a prospective study 20 patients were followed up for 6 months after changing DMARD therapy due to high disease activity. Additionally, synovial fluid was investigated for T lymphocytes expressing $K_{2P}5.1$.

Results: $K_{2P}5.1$ expression in contrast to MS is elevated in active RA only in CD4+ T cells in the periphery. Comparing synovial fluid and PBL $K_{2P}5.1$ expression levels of synovial fluid derived T cells are higher for both RNA level and protein level. In the cross sectional study $K_{2P}5.1$ expression levels in CD4+ T cells show a strong correlation to DAS-28 scores in RA patients (r=0.63). The correlation for serologic markers were r=0.39 for ESR, r=0.28 for CRP. In patients followed prospectively after a change of DMARD therapy for up to 6 months $K_{2P}5.1$ expression levels in CD4+ T cells follow nicely the individual clinical response.

Conclusion: Disease activity in RA patients correlates strongly with $K_{2P}5.1$ expression levels in CD4+ T lymphocytes in the peripheral blood in cross-sectional as well as in prospective, longitudinal observations. Further studies are needed to investigate the exact pathophysiological mechanisms and to evaluate the further use of $K_{2P}5.1$ as a potential biomarker for disease activity in RA.

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Foxp3+ CD4+ Tregs Prevent Arthritis by Promoting Clonal Anergy Induction in Self Ag-Specific CD4+ T Cells. Ryan Martinez[2], Na Zhang[2], Sara Nandiwada[2], Stephanie Thomas[2], Bryce Binstadt[2] and Daniel L. Mueller[1]. [1]University of Minnesota Medical School, Minneapolis, MN, [2]University of Minnesota Medical School

Using a mouse model of self Ag recognition by naive CD4+ T cells, we have investigated the peripheral self tolerance mechanism that prevents the development of autoimmune arthritis in most individuals. As previously reported, an adoptive transfer of glucose 6-phosphate isomerase (GPI)-specific naive KRN TCR-transgenic CD4+ T cells into lymphopenic TCRalpha chain-deficient mice that naturally express GPI/I-A^{g7} complexes led to an intense clonal expansion, the production of anti-GPI IgG1 autoantibody, and the development of severe polyarticular arthritis. Recognition of GPI/I-A^{g7} in normal hosts, however, failed to elicit autoimmune disease, and instead was sufficient to stimulate only an abortive KRN CD4+ T cell clonal expansion and the induction of clonal anergy. Anergic KRN CD4+ T cells demonstrated a reduced proliferative responsiveness to Ag stimulation, the inhibition of IL-2, TNF-alpha, and IFN-gamma synthesis, and high-level expression of CD73 and Folate receptor 4 (FR4). Reconstitution of the T cell-deficient hosts with enriched CD25+ Foxp3+ CD4+ T cells was sufficient to promote the induction of KRN T cell clonal anergy and prevent the development of arthritis. More importantly, use of diphtheria toxin to selectively eliminate Foxp3-expressing cells from T cell-deficient hosts that had been reconstituted with polyclonal CD4+ T cells from Foxp3-GFP-diphtheria toxin receptor transgenic mice, prevented the development of clonal anergy in the transferred naive KRN CD4+ T cells, and led to their induction of autoimmune arthritis. These data suggest that during the initial encounter of naive CD4+ T cells with peripheral self Ag, CD25+ Foxp3+ T regulatory cells ensure that clonal anergy will be induced early during clonal expansion, and autoimmune arthritis can be avoided. Individuals deficient in Foxp3+ T regulatory cell activity or number are prone to autoimmune arthritis as a consequence of exuberant self Ag-specific CD4+ T cell clonal expansion and differentiation, and the provision of pathological helper activity that leads to a breakdown of self tolerance in the B cell compartment.

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Gender and Sex Hormones Influence CD4+ Regulatory T Cells and Their Expression of FoxP3 in Healthy People and in SLE. Ravi K. Dinesh[1], Bevra H. Hahn[2] and Ram P. Singh[1]. [1]David Geffen Schl of Med/UCLA, Los Angeles, CA, [2]University of California Los Angeles School of Medicine, Los Angeles, CA

Purpose: The goal of the present study was to determine the role of gender and the effect of sex hormones on the regulation of Foxp3 gene in healthy individuals and in SLE patients.

Methods: Levels of sex hormones (17 b-estradiol, testosterone), cytokines, and chemokines were measured by ELISA in the serum/plasma of healthy donors and from the culture supernatant of peripheral blood mononuclear cells (PBMC) isolated from SLE patients and healthy controls. PBMC were immunophenotyped by flow cytometry, and mRNA gene expression studies were performed by real time PCR. Protein expression was analyzed by intracellular staining and by Western blot analysis. The *in vitro* effect of sex hormones 17 b-estradiol (60–100, 500pg/ml), and testosterone (100pg/ml) were studied by culturing sorted CD4$^+$CD25^{hi}CD127$_{lo}$ regulatory T cells for 24–72 hours followed by FACS/Western blot analyses.

Results: 1- The numbers of CD4$^+$ CD25^{hi} Foxp3+ and of CD8$^+$ FoxP3+ regulatory T cells are significantly decreased in healthy females compared to healthy males (p<0.01).

2- Both CD4+CD25+^{hi} and CD8+CD25+ subsets of healthy males had 3–4-fold higher Foxp3 mRNA compared to healthy females.

3- Plasma 17b-estradiol levels are significantly increased in female SLE patients compared to healthy females (p<0.01).

4- The addition of 17 b- estradiol (physiologic cycling luteal phase concentrations of 60 pg/ml) for 24 hours to cultured PBMC from healthy women (but not men) increased the total numbers of cells expressing CD4, CD25 and FoxP3. These effects were not seen in cells in women with SLE.

5- Incubation of CD4+ regulatory T cells with 100 pg/ml of 17b-estradiol maintained FoxP3 expression in SLE women, in contrast to the usual increase in CD4+ Treg that occurs in healthy women at this concentration.

6- Testosterone (100 pg/ml) significantly increased FoxP3 expression in CD4+CD25^{hi} cells from women with SLE. In fact, plasma concentrations of testosterone in those women correlated positively with the expression of FoxP3 in their CD4+CD25+ T cells ($p < 0.04$).

Conclusions: Women may be more susceptible than men to SLE and other autoimmune diseases in part because many healthy women have fewer regulatory T cells and less FoxP3 expression in those cells. In addition, women with SLE, compared to healthy women, seem to have less ability to generate CD4+ Treg in response to physiologic concentrations of 17 b-estradiol, whereas the testosterone metabolite increases the generation of Tregs. These data suggest that gender and sex hormones may influence susceptibility to SLE via their effects on regulatory T cells.

Disclosure: R. K. Dinesh: None; **B. H. Hahn:** None; **R. P. Singh:** None.

1258

Identification of a Pathological TCR of Autoantibody-Inducing CD4$^+$ T Cell That Induces Autoantibodies and Lupus-Like Immune Tissue Injury. Kohsuke Yoshida[1], Ken Tsumiyama[2] and Shunichi Shiozawa[3]. [1]Department of Biophysics, Kobe University Graduate School of Health Sciences, Kobe, Hyogo, Japan, [2]Department of Biophysics, Kobe University Graduate School of Health Sciences, Kobe, Japan, [3]Department of Biophysics, Kobe University Graduate School of Health Sciences/Department of Medicine, Kobe University Graduate School of Medicine/The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan

Purpose: The purpose of this study was to identify the T cell receptor (TCR) of autoantibody-inducing CD4$^+$ T (*ai*CD4$^+$ T) cell that induces autoantibodies in naïve recipients with 100% efficiency when transfered. We have previously shown that overstimulation of CD4$^+$ T cell of the mice not prone to autoimmune diseases by repeated immunization with antigen results in *de novo* generation of *ai*CD4$^+$ T cell which had undergone TCR revision and was capable of inducing autoantibodies and lupus-like immune tissue injury (Tsumiyama K, *et al*. PLoS ONE 4(12):e8382, 2009). Here we tried to identify the TCR of *ai*CD4$^+$ T cell that induces autoantibodies, and identified the pathological TCR of *ai*CD4$^+$ T cell.

Methods: BALB/c mice were repeatedly injected i.p. with 25mg staphylococcus enterotoxin B (SEB) or PBS every 5 days and serum IgG-rheumatoid factor (RF) was measured using ELISA. Vβ8$^+$, a known SEB-reactive Vβ chain, and Vβ8$^-$CD4$^+$T cell were isolated from spleen using magnetic beads and cDNAs from these cells were subjected to RT-PCR amplification using Vβ1 to 18 and Vα1 to 20 specific primers. The cells were also transferred into naïve BALB/c mice *via* i.p. (1×10^7 cells/mouse) injection. The recipients received a single i.p. injection of 25mg SEB 24 h after cell transfer and sera was studied 2 weeks afterwards. Statistical analyses were performed using Student's *t* test and the correlation coefficient r was calculated.

Results: SEB-reactive Vβ8$^+$CD4$^+$T cell was significantly decreased in the mice immunized 12x with SEB as compared with PBS (17.4% vs. 21.2%, $P=0.001$), possibly due to clonal deletion because of anergy induction in the SEB-reactive T cell after 2x immunization with SEB. However, in these mice immunized 12x with SEB, the level of RF was positively correlated to the frequency of splenic Vβ8$^+$CD4$^+$T cell ($r=0.83$, $P<0.05$), indicating that once-anergized T cell re-proliferated and simultaneously produced RF. We then transferred either Vβ8$^+$CD4$^+$ T cell or Vβ8$^-$CD4$^+$ T cell from the mice immunized 12x with SEB into naïve mice. We found that Vβ8$^+$CD4$^+$ T cell, but not Vβ8$^-$CD4$^+$ T cell, induced RF ($P<0.001$), indicating that antigen-reactive CD4$^+$ T cell acquires the ability to induce autoantibodies. Further analyses showed that, among series of Va chains in the Vβ8$^+$CD4$^+$ T cell, a positive correlation existed between the selection of Vα13 chain and the level of RF ($r=0.87$, $P<0.05$), strongly suggesting that CD4$^+$ T cell with Vβ8$^+$Vα13$^+$ TCR induces RF.

Conclusion: We have tried to identify the TCR of *ai*CD4$^+$ T cell that induces autoantibodies in naïve recipients with 100% efficiency upon transfer, and identified that Vβ8$^+$Vα13$^+$ TCR is its candidate.

Disclosure: K. Yoshida: None; **K. Tsumiyama:** None; **S. Shiozawa:** None.

1259

IL-23 Suppresses IL-22 Levels and AHR Expression in Human CCR6+ Memory T Cells. Ferry Cornelissen, Jan Piet van Hamburg, Nadine Davelaar, Patrick Asmawidjaja, Anne-Marie Mus and Erik Lubberts. Erasmus MC, University Medical Center

Background: Human CCR6+ T helper (Th) cells were shown to preferentially express the cytokines IL-17A and IL-22 (1). Recently, it became clear that within the CCR6+ Th cell population, cells are present which exclusively expressed IL-22 (2, 3). Although IL-23 and IL-1b are involved in the differentiation of naïve T cells towards effector CCR6+ Th cells (4), their role in the regulation of IL-17A and IL-22 expression by effector CCR6+ Th cells is unknown.

Objective: To investigate the role of IL-23 and IL-1b on the expression of Th17 specific cytokines by human memory CCR6+ Th cells.

Methods: CD4+CD45RO+CCR6+ T cells were FACS sorted from PBMC obtained from healthy individuals. These cells were cultured in the absence or presence of IL-23, IL-1b or the combination of IL-23+IL-1b. After culture, intracellular cytokine stainings for IL-17A, IL-22, and IFN-gamma were analyzed by flow cytometry. Cytokine levels of IL-17A, IL-22, and IFN-gamma were determined in the supernatant by enzyme-linked immunosorbant assay (ELISA). Semi-Quantitative RT-PCR was performed to analyse gene transcription of genes involved in Th differentiation and or function.

Results: IL-23 had no effect on the percentage of IL-17-positive and IFN-gamma-positive cells. However, IL-23 in contrast to IL-1beta significantly decreased the percentage of IL-22-positive CCR6+ memory T cells. This was mainly due to a significant reduction in the proportion of IL-22+IL-17A- and IL-22+IFN-gamma- T cells. In line with this, significantly lower IL-22 levels were found in the supernatant of CCR6+ T cells incubated with IL-23 and significantly lower expression of the transcription factor aryl-hydrocarbon receptor (AhR) in these cells. In contrast to IL-23, IL-1beta increased the percentage of both IL-17A-positive and IFN-gamma-positive CCR6+ T cells. However, the combination of IL-23/IL-1beta significantly and specifically increased the percentage of IL-17A+IL-22- and IL-17A+IFN-gamma- compared to IL-1beta alone, although the suppressive effect on IL-22-positive cells was not increased by this combination compared to IL-23 alone. Significant higher levels of IL-17A but also IFN-gamma were detected after incubation with IL-23/IL-1beta compared to IL-1beta alone. This latter may be due to an increase in IL-17A+IFN-gamma+ double positive CCR6+ memory T cells by IL-23/IL-1beta.

Conclusion: These data revealed that IL-23 specifically suppresses a Th22-like phenotype in CCR6+ memory T cells resulting in lower IL-22 levels and reduced AhR expression. Adding IL-1beta to IL-23 resulted in a specific increase of a Th17/IL-17A-like phenotype in CCR6+ memory T cells resulting in higher levels of IL-17A. However, the total IFN-gamma level was increased by IL-23/IL-1beta as well. These data suggest an important role for IL-23 in combination with IL-1beta in the regulation of human IL-17-positive and IL-22-positive memory T helper cells.

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Disclosure: F. Cornelissen: None; **J. P. van Hamburg:** None; **N. Davelaar:** None; **P. Asmawidjaja:** None; **A.-M. Mus:** None; **E. Lubberts:** None.

1260

IL-23-Mediated RORγt Pathway Is Associated with Thymic Negative Selection of Autoreactive T Cells. Hao Li[2], Hui-Chen Hsu[2], Qi Wu[2], PingAr Yang[2], Jun Li[2] and John D. Mountz[1]. [1]Univ Alabama at Birmingham, AL, [2]Univ Alabama at Birmingham

Background: BXD2 mice develop erosive arthritis and high levels of autoantibodies. Spontaneously increased T_H-17 cells and IL-23 production by follicular dendritic cells have been found in the periphery of BXD2 mice. Since ROR gamma t (RORγt), the transcription factor downstream of IL-23, is expressed by CD4$^+$CD8$^+$ double positive (DP) thymocytes, we determined if IL-23 can regulate thymocyte selection via the RORγt pathway and if dysregulation of this pathway can be found in BXD2 thymus.

Methods: Thymii from B6, D^b/H-Y TCR transgenic (Tg), and BXD2 mice were analyzed. FACS analysis was carried out to determine the expression of IL-23R$^+$ and RORγt in subsets of thymocytes. TUNEL staining was carried out to determine apoptotic thymocytes. Subpopulations of different thymic cells were FACS sorted for qRT-PCR assay to determine the expression of *Il23, Il23r* and *Rorc*. *In vivo* overexpression of IL-23 was achieved by injection of mice with AdIL-23 using AdLacZ as the control (2×10^9 pfu/mouse, tail IV).

Results: D^b/H-Y Tg mice treated with an anti-IL-23 antibody exhibited a defect in thymic negative selection of H-Y specific T cells in male mice and

an increased proliferative response of self reactive spleen T cells to the H-Y antigen. AdIL-23 but not AdLacZ, injection to B6 mice lead to increased apoptosis (12.0±3.7% vs 1.4±0.3%) and a massive reduction of DP thymocytes ($18\pm3 \times10^7$ vs $4\pm1 \times10^7$) at day 5. This AdIL-23-induced thymocyte apoptosis response was partially prevented in RORγt$^{+/-}$ mice. Consistent with this, there was dramatically increased expression of IL-23R (24% vs 1%) and RORγt (15% vs 2%) in DP thymocytes of AdIL-23 vs AdLacZ injected mice at day 6. Autoimmune BXD2 mice exhibited upregulation of IL-23R on DP thymocytes and down-regulation of IL-23 production by thymic CD11C$^+$ dendritic cells compared with those in normal B6 mice. Consistent with this, there was lower IL-23 signaling *in vivo* indicated by a lower expression of RORγt in BXD2 thymocytes compared with B6 thymocytes at both the protein and the transcriptional levels. Administration of AdIL-23 resulted in upregulation of RORγt, leading to a 4-fold increase in apoptosis of DP thymocytes in BXD2 mice (20%) compared with that in B6 mice (5%) at day 3. Interestingly, CD4 single positive thmocytes in BXD2, but not B6 mice, failed to down-regulate IL-23R.

Conclusions: Our results reveal a novel function of IL-23 in that IL-23 can regulate thymocyte negative selection of autoreactive T cells via the RORγt pathway. The IL-23-mediated DP thymocyte apoptosis may be deficient in BXD2 mice, leading to the generation of autoreactive T cells. This is significant since it suggests that although IL-23 has a pro-autoimmune effect in the periphery, it has an opposite action in the thymus to prevent development of self-reactive T cells.

Disclosure: H. Li: None; **H.-C. Hsu:** None; **Q. Wu:** None; **P. Yang:** None; **J. Li:** None; **J. D. Mountz:** None.

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Immune Regulation by Peripheral Suppressor T Cells Induced upon Homotypic T Cell Interaction. Katja Thuemmler[1], Leipe Jan[1], Andreas Ramming[1], Hendrik Schulze-Koops[2] and Alla Skapenko[1]. [1]Division of Rheumatology, LMU Munich, Germany, [2]LMU Munich, Germany

The mechanisms by which regulatory T cells are generated in the periphery are incompletely understood. Interestingly, CD4 T cells up-regulate the expression of surface receptors specific for antigen-presenting cells during activation. The appropriate ligands of these receptors are physiologically expressed on resting CD4 T cells. Here, we tested the hypothesis, that activated T cells may interact with resting T cells and that this interaction results in the differentiation of the later.

CD4 memory T cells (responders) were cultured together with activated stimulator T cells. After five days of co-culture the phenotype and function of the T cells resulting from the responder cells was analyzed both in vitro and in vivo. The mechanisms underlying this homotypic T cell interaction were determined in co-cultures of activators and stimulators in the presence or absence of neutralizing antibodies to surface receptors.

Activated stimulator T cells induced proliferation and production of various cytokines in the responder T cells. Whereas Th1 stimulator T cells promoted the development of IL-10 and/or IFNγ producing cells, T cells cultured with Th2 cells produced IL-4. T cells induced upon homotypic T cell interaction expressed CD25 and reduced levels of CD127, and produced TGFβ. T-T cell communication is both, anchored and tuned through interaction of LFA-1 and its ligands ICAM-1, ICAM-2 and ICAM-3. Blocking of ICAM-1 diminished IFNγ production, whereas ICAM-3 was important for IL-4 secretion. Functionally, homotypic T cell interaction-induced T cells were anergic and inhibited the proliferation of CD25 negative T cells as potently as natural occurring CD25 Tregs in vitro. The inhibitory effect was partly contact dependent and partly dependent on IL-10 secreted after T cell interaction. Moreover, in vitro generated T-T cell induced T cells with a TCR specific for OVA prevented clonotypic expansion of OVA TCR transgenic T cells in BALB/c mice upon antigen challenge in vivo.

Together, the data suggest a negative feedback mechanism of specific immunity involving bystander-activated memory T cells.

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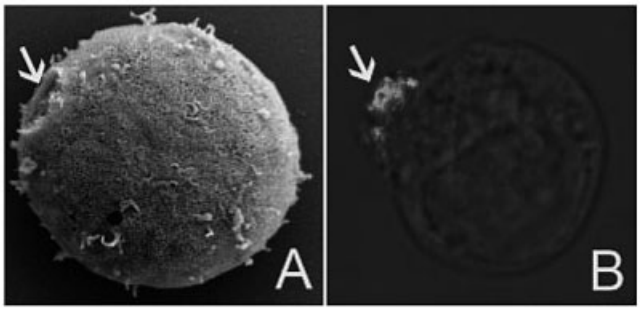
1262

Late Complement Complex in T Cell Function and Cell Death. Anil Chauhan[1], John P. Atkinson[3] and Terry L. Moore[2]. [1]Saint Louis University, [2]St Louis University, St Louis, MO, [3]Washington University School of Medicine, St Louis, MO

Purpose: Recently, complement systems role in T cell modulation has been suggested. Excessive complement activation results in cell death due to the formation of membrnae attack complex (MAC). Lysis of nucleated cells by MAC is explained by the "multi hit hypothesis" that suggests formation of a large number of holes. We tested this hypothesis in human naïve CD4$^+$ T cells by in situ assembly of MAC using purified C5b-6, C7, C8 and C9. Scanning electron microscopy (SEM) and confocal imaging revealed formation of MAC on a single site. Thus, we hypothesize that due to strong affinity of C9 for membrane phopsholipids, sublytic MAC deposit resulted in reorganization of the T cell membrane. This resulted in the formation of a functional 'IS' synapse-like structure by lateral clustering of membrane rafts (MR). Thus, we explored the role of the structure formed by MAC in T cell physiology such as calcium channels, cell activation, proliferation and death.

Methods: MAC was assembled on human CD4$^+$T cells by treating with equimolar ratio of purified late complement proteins along with fifteen molar excess of Alexa 594 labeled C9 protein. These cells were then examined for alteration in membrane structures by confocal and SEM. MR in these cells were localized using cholera toxin B-FITC. Cell proliferation was studied with CFSC labeling and T cell activation by traditional methods. Calcium mobilization was examined using Fura-2 dye.

Results & Conclusions: Unlike present belief of multiple MAC generated holes in erythrocytes, in human T cells, MAC deposited on a single site. The SEM images showed a single hole surrounded by dense structures (A). These structures were also seen in confocal images (B).



The site of MAC was also the site of MR accumulation and formation of synapse-like structures. Signaling protein microclusters accumulated at this site and were phosphorylated. Such structures are also implicated in the function of NK cells. Sublytic doses of MAC trigger a number of events such as DNA synthesis, upregulation of cell cycle associated cyclins, CDK2, growth factors and proto-oncogenes such as NF-κB, c-jun, c-fos, jun-D, and protein kinase C. We have shown that in T cells these structures may participate in activation of the T cell receptor in the presence of immune complexes. However, in lytic doses of MAC, these structures that support cell function result in collapse of cell integrity, thus lysing the cell. Thus, we propose that ICs and MAC participate in the outcome of T cell differentiation by triggering and enhancing T cell activation. Complement activation and altered T signaling are observed in SLE. Here we link immune reactants observed in disease to the cells of adaptive immunity. Better understanding of these processes will allow us to delineate the disease process and design better therapeutic interventions.

Disclosure: A. Chauhan: None; **J. P. Atkinson:** None; **T. L. Moore:** None.

1263

Linking Power Doppler Ultrasound with Th17 Cells in the RA Joint. Nicola J. Gullick[1], Hayley G. Evans[2], Leigh Church[3], David Jayaraj[2], Andrew Filer[3], Bruce W. Kirkham[4] and Leonie S. Taams[2]. [1]CMCBI, King's College London, London, United Kingdom, [2]CMCBI, King's College London, [3]Rheumatology Research Group, University of Birmingham, [4]Rheumatology, Guy's & St Thomas' NHS Foundation Trust

Introduction: Power Doppler ultrasound (PDUS) is increasingly used to assess synovitis in Rheumatoid Arthritis (RA). Prior studies have shown correlations between PDUS scores and vessel counts, but relationships with immunopathology have not been described. This study investigated the presence of Th1, Th17 and TNFα producing CD4+ T cells in peripheral blood (PB), synovial fluid (SF) and synovial tissue (ST) from RA patients and related these data to PDUS scores of either single or multiple joints.

Methods: PB mononuclear cells were isolated from healthy controls or RA patients and stimulated with PMA and ionomycin for 3 hours in the

presence of Golgistop. Paired SF were analysed where available (n=21). ST was obtained at arthroscopic synovial biopsy from six RA patients. Synovial blood flow was evaluated by power Doppler (PD) signal at 10 metacarpophalangeal (MCP) joints, wrists and knee joints. PD signals were graded on a semi-quantitative scale from 0 to 3 (where 0 = no synovial flow; 1 < 25% signal within ST; 2 = 25–50% signal; 3 >50% signal). Intracellular expression of IL17, IFNγ, and TNFα was determined by multicolour flow cytometry. Serum, SF and fibroblast culture levels of vascular endothelial derived growth factor-A (VEGF-A) were assessed by ELISA.

Results: Th17 cells and dual IFNγ/IL-17-expressing cells but not Th1 cells are increased in PB of RA patients vs. healthy controls. These cells are further enriched in both SF and ST relative to PB. The percentage of PB Th17 cells did not correlate with systemic parameters of disease. The percentage of Th17 cells, but not Th1 cells, in SF positively correlated with CRP (r=0.51, p=0.03) and local PDUS-defined synovitis (r=0.62, p=0.003), suggesting a specific role for Th17 cells in active synovitis in RA. Patients with high levels of IL-17+ CD4+ T cells in SF display increased levels of vascular endothelial growth factor-A (VEGF-A) in SF; this was not observed for IFNγ+ T cells. The addition of IL-17 but not IFNγ increased VEGF-A production by RA synovial fibroblasts *in vitro*.

Conclusion: Our data demonstrate a link between the presence of highly inflammatory Th17 cells and RA disease activity assessed by PDUS scores, and offer a novel immunological explanation for the clinical observation that rapid joint damage progression occurs in patients with persistent positive PDUS signal. Furthermore, our findings highlight PDUS as a possible surrogate marker of Th17 cells, which may identify patients who would benefit from early, aggressive therapy, including IL-17 antagonists.

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NKT Cell Is Required for the Break of T Cell Anergy, Inducing Autoantibody, and Generation of Autoantibody-Inducing CD4$^+$ T Cell That Causes Systemic Autoimmunity. Yuko Fujita[1], Ken Tsumiyama[2] and Shunichi Shiozawa[3]. [1]Depertment of Biophysics, Kobe University Graduate School of Health Science, Kobe, Japan, [2]Depertment of Biophysics, Kobe University Graduate School of Health Science, Kobe, Japan, [3]Depertment of Biophysics, Kobe University Graduate School of Health Science/Depertment of Medicine, Kobe University Graduate School of Medicine/The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan

Objective: With regards to how autoantibody-inducing CD4$^+$ T (*ai*CD4$^+$ T) cell is induced, which is the key as the cause of systemic autoimmunity including SLE, we consider the recovery from anergy as the essential step in generating *ai*CD4$^+$ T cell. Here, we studied the contribution of NKT cell to the break of anergy, induction of autoantibodies, and generation of *ai*CD4$^+$ T cell.

Methods: BALB/c mice were repeatedly immunized with staphylococcal enterotoxin B (SEB), staphylococcal enterotoxin A (SEA) and/or α-galactosylceramide (α-GC). SEB stimulates NKT cell and T cells, whereas SEA stimulates only T cells. Mice were also immunized 2x with SEB to induce T cell anergy, and then repeatedly immunized with α-GC. Further, spleen cells of naïve BALB/c mice were stimulated with α-GC *in vitro*, and supernatant from α-GC-activated NKT cells herein termed NKT-sup. This NKT-sup was repeatedly immunized in CD1d KO mice, following immunization 2x with SEB to induce T cell anergy. Spleen cells were stimulated *in vitro* with SEB, and IL-2 and mitotic events were measured. Autoantibodies, phoshorylation of ZAP70, LAT, Akt, the expression of Cbl-b and Ca^{2+} influx in T cell were examined.

Results: The T cells of the mice immunized 2x with SEB were rendered into anergy. However, after further immunization 8x with SEB, this once-anergized T cells were re-activated from anergy to resume IL-2 production and proliferation. This re-activation was accompanied by induction of RF and anti-Sm antibody in 100% of mice, and this property can be transferred by CD4$^+$ T cells into naïve recipients, thereby *ai*CD4$^+$ T cells are generated. Phosphorylation of ZAP70, LAT and Akt and Ca^{2+} influx were inhibited in anergic T cells of the mice immunized 2x with SEB as compared with PBS-immunized control. However, this inhibition was released after immunization 8x with SEB. Further, expression of Cbl-b, an anergy-inducible protein, was increased in the T cell of mice immunized 2x with SEB. The Cbl-b was subsequently down-regulated after further immunization 8x with SEB. As to the contribution of NKT cell to the break of T cell anergy and the generation of *ai*CD4$^+$ T cell, we found that spleen cells of mice immunized 8x with SEA neither induced RF nor secreted IL-2 because SEA did not activate NKT cell. When α-GC, a specific ligand for NKT cell, was co-immunized 8x with SEA, the once-anergized T cell was recovered from anergy and began to secrete IL-2 and RF and resume proliferation. Sole 2x immunization with SEB followed by 8x immunization with α-GC was also sufficient for the break of T cell anergy and induction of RF. Further, the once-anergized T cells of CD1d KO mice lacking NKT cells could be recovered from anergy after 2x immunization with SEB followed by 8x treatment with the NKT-sup, a supernatant of α-GC-activated NKT cells. These results indicate that the NKT cells and its effector molecule can break T cell anergy and induce autoantibodies, finally leading to the induction of *ai*CD4$^+$ T cells.

Conclusion: We show that the activation of NKT cell is indispensable for the re-activation of once-anergized T cell and the induction of autoantibodies, finally leading to the generation of *ai*CD4$^+$ T cell that causes systemic autoimmunity.

Disclosure: Y. Fujita: None; **K. Tsumiyama:** None; **S. Shiozawa:** None.

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Peroxisome Proliferator-Activated Receptor α and γ Agonists Together with TGF-β Convert Human CD4$^+$CD25$^-$ T Cells into Functional Foxp3$^+$ Regulatory T Cells. Hitoshi Hasegawa[1], Jin Lei[2], Takuya Matsumoto[2] and Masaki Yasukawa[2]. [1]Ehime University Graduate School of Medicine, Toon, Ehime, Japan, [2]Ehime University Graduate School of Medicine

Background: Regulatory T cells (Treg) play a crucial role in the prevention of autoimmune diseases. Human peripheral CD4$^+$CD25$^-$ T cells can be induced to express Foxp3 after TCR activation in the presence of TGF-β, but the induced cells (iTreg) lack a regulatory phenotype. Human T cells require multiple stimulations to become a regulatory phenotype. Moreover, induction of functional human Treg cells would have therapeutic implications. Therefore, we screened molecules that would enhance the TGF-β-induced conversion of human CD4$^+$CD25$^-$ T cells into functional Treg cells.

Methods: We obtained three peroxisome proliferator-activated receptor (PPAR)α agonists (bezafibrate, GW7647, and 5,8,11,14-eicosatetraynoic acid) and two PPARγ agonists (ciglitazone and 15-deoxy-prostaglandin J_2) as molecules that increased Foxp3 expression in human iTreg cells from lipid and nuclear receptor ligand libraries. We analyzed the mechanism by which human CD4$^+$CD25$^-$ T cells are converted to functional Treg cells by PPARα and PPARγ agonists together with TGF-β.

Summary of the Results: These PPARα and PPARγ agonist-treated iTreg cells maintained a high level of Foxp3 expression and had suppressive properties. There were no significant differences in the suppressive properties of iTreg cells treated with the three PPARα and two PPARγ agonists, and all of the treated iTreg cells increased the demethylation levels of the Foxp3 promoter and intronic CNS3 regions significantly compared with the control iTreg cells. Furthermore, both PPARα and PPARγ agonists together with TGF-β inhibited more strongly the expression of all three DNA methyltransferases (DNMTs), DNMT1, DNMT3a, and DNMT3b, in activated CD4$^+$ T cells. These results demonstrate that PPARα and PPARγ agonists together with TGF-β elicit Foxp3 DNA demethylation through potent down-regulation of DNMTs and induce potent and stable Foxp3 expression, resulting in the generation of functional iTreg cells. In contrast, there are no differences of cytokine productions such as IL-10 and TGF-β between control and PPAR agonist-treated T cells. PPARγ produced retinoic acid (RA) in human blood monocyte-derived DCs. Addition of PPARγ agonist in the presence of TGF-β may generate antigen-specific Treg cells such as ANCA-associated vasculitis more efficiently upon coculture with antigen-pulsed DC through a RA-dependent mechanism and epigenetic regulation of the Foxp3 gene.

Conclusions: PPAR agonists converted human CD4$^+$CD25$^-$ T cells into functional Foxp3$^+$ regulatory T cells and may be benefical for the treatment of human autoimmune diseases.

Disclosure: H. Hasegawa: None; **J. Lei:** None; **T. Matsumoto:** None; **M. Yasukawa:** None.

1266

Phenotype and Functional Stability of TGF-β-Induced CD4+Foxp3+ Regulatory T Cells in Steady and Inflammatory States. NIng Kong[3], Julie Wang[3], David Brand[4], Hejian Zou[1], Xuezhong Yu[2] and Song Guo Zheng[3]. [1]Fudan University Medical School, [2]H. Lee Moffitt Cancer Center and Research Institute, [3]USC Keck School of Medicine, [4]VA Medical Center, Memphis

Background: Although both natural CD4+Foxp3+ regulatory T cells (nTregs) and TGF-β-induced CD4+Foxp3+ regulatory T cells (iTregs) share many similar phenotypes and biological activities in the prevention of autoimmune diseases, recent studies from several groups observed that Foxp3 expression by iTregs is unstable and adoptive transfer of these cells had poorly therapeutic effect on acute GVHD model in animal although these cells prevented and even treated other autoimmune diseases in animal models. Here we try to determine the phenotype and functional characteristics of iTregs in the steady and inflammatory states.

Methods: iTregs were induced from naive CD4+ cells with IL-2, TGF-β and anti-CD3/CD28 beads or plate-bound anti-CD3 and soluble anti-CD28 antibodies. nTregs were isolated from splenocytes of foxp3-GFP knock in mice and expanded with IL-2 and anti-CD3/CD28 beads. 0.5×106 both Tregs were transferred to SCID mice. The mice were sacrificed in one and two months after adaptively transfer. 5×106 Tregs from DBA1/J mice labeled with CFSE were adaptively transferred to normal or established collagen induced arthritis (CIA) mice and the mice were sacrificed in one, three and six weeks for monitoring donor Treg fates.

Results: In SCID mice, both Tregs had the similar Foxp3 expression (near to 50%) in one and two months after cell transfer. In addition, both Treg subsets maintain the similar levels of Foxp3 expression (about 40%) in one month after transfer to naïve mice. Both nTregs and iTregs donor cells sorted from recipient mice in three weeks after transfer displayed the similar suppressive activities. We observed that suboptimal TCR stimulation was required for the maintenance of Foxp3 expression by iTregs. Of great interest, nTregs but not iTregs in the spleens, particularly in draining lymph nodes mostly lost Foxp3 expression only one week after cell transfer to established arthritis mice. Conversely, iTregs not only maintained Foxp3 expression but also induced more Foxp3+ cells in recipient mice compared to CIA mice received nTregs. We further observed that adoptive transfer of iTregs but not nTregs significantly suppressed the progression of the established arthritis.

Conclusions: iTregs are as stable as nTregs in immune deficient and normal states, and are more stable and functional than nTregs in an inflammatory milieu. We therefore conclude that manipulation of iTregs may have an advantage to treat the autoimmune diseases and inflammatory diseases.

Disclosure: N. Kong: None; **J. Wang:** None; **D. Brand:** None; **H. Zou:** None; **X. Yu:** None; **S. G. Zheng:** None.

1267

Plasmacytoid Dendritic Cells Control Peripheral Treg Conversion to the RNA-Binding Nuclear Self Antigen La/SS-B. A. Darise Farris[1], Christina Lawrence[2] and Zi-jian Pan[2]. [1]Arthritis and Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK

Background: RNA-binding nuclear antigens are a major class of autoantigen targeted in systemic autoimmune diseases. Serologic tolerance to the RNA binding antigen human La/SS-B (hLa) is controlled primarily by $CD4^+$ T cells in transgenic (Tg) mice expressing hLa gene under its natural promoter. The goal of the present study was to uncover peripheral mechanisms of T cell tolerance to this RNA-binding nuclear antigen.

Methods: Genetically marked splenocytes of $TCR\alpha^{-/-}$ 3B5.8 T cell receptor transgenic (TCR Tg) mice, in which essentially all $CD4^+$ T cells are specific for an $I\text{-}E^k$-restricted, immunodominant T cell epitope of hLa (hLa 67–76) but do not recognize the mouse La antigen, were transferred into lymphocyte replete hLa Tg and non-Tg recipients and their phenotype assessed after retrieval from recipients. Impacts of recipient B lymphocytes, plasmacytoid dendritic cells (pDC), and Type I interferon receptor (IFNAR1) on donor T cell phenotype were assessed by administration of depleting or blocking monoclonal antibodies to recipient mice prior to and following transfers.

Results: Donor $CD4^+$ T cells of both $CD25^-Foxp3^+$ and $CD25^+Foxp3^+$ phenotypes were present in hLa Tg recipients on day 7 post-transfer and were absent in recipients that lacked expression of the hLa neo-self antigen. Donor cells retrieved from hLa Tg recipients were hyporoliferative and produced elevated levels of IL-10 following *in vitro* stimulation with irradiated splenocytes and hLa 61–84 peptide compared to donor cells retrieved from control recipients that lacked expression of hLa. Recipient pDC but not B cells directed the appearance of Foxp3-expressing donor T cells in hLa Tg recipients. Both conventional (c) DC and pDC purified from hLa Tg mice presented the hLa epitope constitutively as revealed by their capacity to stimulate IL-2 secretion from a hLa 67–76-specific T cell hybridoma. Treatment of hLa Tg recipients with an IFNAR1-blocking antibody resulted in significantly fewer $Foxp3^+$ donor T cells at day 7 compared to recipients treated with an isotype control antibody.

Conclusions: These studies suggest that peripheral differentiation of antigen-specific $Foxp3^+$ Treg is a mechanism of T cell tolerance to a representative RNA-binding nuclear antigen and that pDC play an important role in this process.

Disclosure: A. D. Farris: None; **C. Lawrence:** None; **Z.-j. Pan:** None.

1268

Protective Human CD4+CD25+FOXP3+ Regulatory T Cells Generated Ex-Vivo with IL-2, Retinoic Acid and TGF-bets Are Resistant to Pro-Inflammitory Cytokines. Xiaohui Zhou[1], Chin Lan[1], Juhua Wang[1], Song-guo Zheng[1] and David A. Horwitz[2]. [1]University of Southern California, [2]University of Southern California, Los Angeles, CA

Purpose: The stability of CD4+CD25+ Foxp3+ regulatory T cells (Tregs) under inflammatory conditions has been questioned. These Tregs may lose Foxp3 and acquire proinflammatory effector functions. Therefore, for Tregs to be used as a potential T cell therapy, they must not only be functionally competent, but also resistant to proinflammatory conversion. We have previously reported that CD4 Tregs induced with IL-2 and TGF-β (iTregs) are resistant to conversion and our objective has been to generate similar Tregs using human naïve CD4+ cells. We have previously reported that human iTregs generated with IL-2, TGF-β and retinoic acid become fully functional Tregs in one week. Here we compare the functional properties of iTregs with expanded endogenous CD4regs after treatment with proinflammatory cytokines

Methods: Naïve human CD4+ cells prepared by negative selection were suboptimally TCR activated for 6 days with anti-CD3/28 coated beads with IL-2, TGF-β1 and all-trans retinoic acid (atRA). Autologous CD4+CD25hi cells (nTregs) were also isolated and expanded with high dose IL-2 and rapamycin. Both iTregs and nTregs were then re-stimulated with with IL-1β and IL-6 and low IL-2 to bring out the inhibitory effects of these proinflammatory cytokines, the Treg subsets were examined for phenotype and function. To assess *in vivo* suppressive activity, sublethally irradiated NOD SCID IL-2R γ $chain^{-/-}$ (NOG) mice were injected IV with human CD25 depleted PBMC and various Treg subsets.

Results: After 6 to 10 days of TCR stimulation with IL-2 and TGF-β and atRA naïve CD4+ cells had become CD25+ CD127lo, CD45RA-/RO+, DR+, Foxp3+ cells that were anergic, produced low amounts of IL-2 and IFN-γ and exhibited strong in vitro suppressive activity. These cells protected NOG mice from a human xeno-GVHD as well as expanded nTregs. After restimulation of iTregs and nTregs with IL-1β and IL-6 nTregs Foxp3 and other Treg markers were down-regulated whereas these markers expressed by atRA/TGF-β induced iTregs were stable. While the protective effects of restimulated iTregs and nTregs was equivalent, the protective effects of nTregs treated with IL-1β and IL-6 decreased and was significantly less than iTregs.

Conclusion: These studies suggest that atRA TGF-β are not only important in the generation of iTregs, but also confer resistance when they are present in an inflammatory milieu.

Disclosure: X. Zhou: None; **C. Lan:** None; **J. Wang:** None; **S.-g. Zheng:** None; **D. A. Horwitz:** None.

1269

RANKL Expression in Human T-Lymphocytes Requires Cooperative Signaling through the T-Cell Receptor and Adhesion Molecule CD2. Bohdan P. Harvey and Zehra Kaymakcalan. Abbott Laboratories, Worcester, MA

Purpose: T-lymphocytes contribute to osteolysis in rheumatic diseases through their production of the osteoclastogenic cytokine RANKL. Mitogenic stimulation of lymphocytes has been shown to induce expression of RANKL;

however, the extracellular events leading to its production have not been identified. We sought to determine whether cell-to-cell interactions through adhesion molecules such as lymphocyte function-associated antigen 2 (CD2) were necessary to promote RANKL secretion from T-cells following T-cell receptor (TCR/CD3) engagement.

Methods: Healthy donor PBMC was isolated by Ficoll gradient. Human CD4+ and CD8+ T cells were purified by negative magnetic bead selection method. PBMC samples from rheumatoid arthritis (RA) patients were obtained from Conversant Healthcare Systems. Cells were cultured in medium supplemented with 2% human serum, IL-2, IL-7, M-CSF and 1alpha,25-dihydroxyvitamin D3 in the presence of various combinations of bead bound anti-CD3, anti-CD2 and anti-CD28 (co-stimulatory receptor) antibodies for 4 days. Total RANKL was determined in culture supernatants by osteoprotegrin (OPG) capture sandwich ELISA, and remainder of supernatants were used in Meso Scale Discovery Multi-spot assay system to evaluate the levels of IFN-γ, TNF-α, IL-10, IL-4, IL-8 and IL-13. T-cell activation was determined by flow cytometry using CD69 and CD25 as markers.

Results: RANKL secretion by healthy donor PBMC was first detected after 72 hr incubation with anti-CD3/CD2/CD28 antibody coated beads with maximal secretion levels being reached following 96 hr. Anti-CD3/CD28 antibody coated beads failed to induce detectable levels of RANKL. When purified T-lymphocyte subsets were evaluated, both CD4+ and CD8+ T-cells produced RANKL only in response to the combined cross-linking of CD3 and CD2 whereas cross-linking of CD3 and CD28 was insufficient to promote RANKL expression even though the T-cells were activated based on the high levels of CD69 and CD25. Those conditions (anti-CD3/CD2) that led to increased RANKL secretion induced significantly lower levels of TNF-α, IL-4, IL-8 and IL-13 as compared to the combinations of anti-CD3/CD28 or anti-CD3/CD2/CD28 antibodies. The combination of anti-CD2 and anti-CD28 antibodies neither induced RANKL secretion nor led to the activation of T-cells. PBMC from RA patients also secreted RANKL in a CD3/CD2-dependent manner and at levels similar to PBMC from healthy donors.

Conclusions: Our results clearly demonstrate that T-lymphocytes (both CD4 and CD8 subsets) can generate RANKL following the co-ligation of the TCR/CD3 and the adhesion molecule CD2 in the absence of the co-stimulatory receptor CD28, suggesting that interactions between T-cells and non-traditional APCs, such as synovial fibroblasts, could lead to the production of osteoclastogenic cytokines without the need for other co-stimulatory signals. Interestingly, the cross-linking of CD3 and CD2 induced RANKL secretion with minimal impact on most of the inflammation-associated cytokines, indicating that RANKL expression is activated by a signaling cascade(s) separate from most other cytokines.

Disclosure: B. P. Harvey: Abbott Laboratories, 3; **Z. Kaymakcalan:** Abbott Laboratories, 3.

1270

Regulation of Human T Cell Activation and Effector Functions by Kv1.3 and KCa3.1 Channels. Gang Chen[1], Vaishali Patel[1], Rothschild Soto[2], Chen Shiow-Ling[2], Sandip Panicker[2], Philip A. Nunn[2] and Julie A. DeMartino[2]. [1]Inflammation Discovery, Hoffmann-La Roche, Inc., Nutley, NJ, [2]Inflammation Discovery, Hoffmann-La Roche, Inc.

Purpose: KCa3.1 and Kv1.3 are major potassium (K+) channels expressed in T cells that have been suggested to play essential roles in the activation and effector functions of central memory T cells (Tcm) and effector memory T cells (Tem), respectively. The goal of this study is to understand the relative contribution of these two K+ channels in human CD4+ T cell effector functions.

Methods: Selective small molecule inhibitors of KCa3.1 [TRAM-34, Icagen 17043 (Ica)], the Kv1.3-selective peptide inhibitor ShK(L5) and a CRAC channel inhibitor RO6712 were used in this study. The responsiveness of primary human T cells to K+ channel blockade was examined in the following manner: 1) Human mixed lymphocyte reaction: responder PBMC were co-cultured with Mitomycin C-treated stimulator PBMC for 4 days. Cell proliferation was measured by 3H-thymidine incorporation; 2) CFSE proliferation: Purified human CD4+ T cells or sorted Tem cells (CD45RA-CCR7-) were labeled with CFSE, pre-treated with the compounds and then stimulated with plate bound anti-CD3/CD28 for 3 days. 3) Cytokine secretion: compound-treated PBMC were stimulated with plate-bound anti-CD3/CD28. Then the levels of IL-2 and IFN-γ were measured in AlphaLISA assays. In a separate experiment, activated CD4+ T cells were re-stimulated with anti-CD2/CD3/CD28 coated beads for 20 hours. 4) For electrophysiological assays, purified human CD4+ T lymphocytes were stimulated for 48 hours using anti-CD3/CD28 coated beads in the presence of IL-2. Cells were then tested for the presence of KCa3.1 and K_V1.3 currents using the whole cell voltage clamp method on either the standard manual rig or an automated electrophysiological platform (QPatch).

Results: First, we found that neither resting Tem nor total CD4+ T cell proliferation could be fully blocked by TRAM-34, Ica or ShK(L5) alone. However, the combination of TRAM-34 or Ica with ShK(L5) could completely suppress resting T cell proliferation and cytokine production in the context of anti-TCR stimulation and MLR. In activated T cells, KCa3.1 blockade was able to suppress IL-2 production significantly. In addition, blockade of both Kv1.3 and KCa3.1 channels exerted similar extent of inhibition on T cell proliferation and cytokine production as CRAC channel blockade. Lastly, electrophysiological analysis showed that activated CD4+ T cells exhibited potassium currents consisting of varying contributions from both channels. Further analysis on the effect of K+ channel blockade on T cell calcium influx will be necessary.

Conclusion: We have demonstrated that in human CD4+ T cells, KCa3.1 and Kv1.3 function in concert in the regulation of the optimal activation and effector functions, possibly through maintaining a sustained CRAC current in these cells. Electrophysiological findings confirmed that human primary CD4+ T cells exhibit varying contributions of potassium flux from both Kv1.3 and KCa3.1 channels. Our data strongly suggest that in human inflammatory diseases driven by pathogenic T cells, targeting both KCa3.1 and Kv1.3 channels simultaneously could potentially provide therapeutic benefit to patients.

Disclosure: G. Chen: Hoffmann-La Roche, Inc., 3; **V. Patel:** Hoffmann-La Roche, Inc., 3; **R. Soto:** Hoffmann-La Roche, Inc., 3; **C. Shiow-Ling:** Hoffmann-La Roche, Inc., 3; **S. Panicker:** Hoffmann-La Roche, Inc., 3; **P. A. Nunn:** Hoffmann-La Roche, Inc., 3; **J. A. DeMartino:** Hoffmann-La Roche, Inc., 3.

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Role for IL-23 in Differentiation of Human Th17 Cells. Hiroshi Kato[1], Laura Cooney[2], Judith Endres[2] and David A. Fox[3]. [1]University of Michigan, Northville, MI, [2]University of Michigan, Ann Arbor, MI, [3]University of Michigan Medical Center, Ann Arbor, MI

Purpose: Th17 cells, which are crucial in host defense, play significant roles in many autoimmune diseases, including RA. In mice, the combination of TGF-beta and IL-6 induces Th17 cells from naive CD4T cells. Whereas TGF-beta was shown to also be essential for human Th17 differentiation, it is unclear what additional pro-inflammatory cytokines are required to induce human Th17 cells. We proposed that IL-23 was dispensable for human Th17 cell differentiation given the expression of IL-23 receptor only after induction of ROR-gammat (master regulator gene of Th17 cells) in mice.

Method: Naive CD4T cells were isolated from peripheral blood mononuclear cells (PBMCs) from healthy adult donors by a naive CD4T cell enrichment kit, and were cultured in RPMI culture media with 10%FCS, 1% Penicillin/Streptomycin, and 2% L-glutamine, with beads coated with anti-CD3/CD28 antibodies, anti-IFN-gamma and IL-4 antibodies (5ug/ml), TGF-beta (0.1, 1 or 10ng/ml), IL-1 (5ng/ml), IL-6 (10ng/ml), and IL-23 (0, 1 or 10ng/ml). Cells were collected on day 5 and incubated for 6h with phorbol ester and ionomycin followed by GolgiPlug. After blocking Fc receptors, cells were fixed, permeabilized in PBS containing 0.5% Saponin, and stained with Phycoerythrin conjugated antibodies against IL-17A, IL-17F, IL-21, or IL-22. IL-17A in culture supernatants was measured by ELISA. On day 3, total cellular RNA was extracted to synthesize cDNA. Expression of ROR-c was assessed by RT-Q-PCR with GAPDH as a reference gene.

Results: Analysis of ELISA data from healthy subjects (n = 5) showed that IL-17A induction was more IL-23 dependent in lower TGF-beta: 0.1ng/ml; 162.8+/−70.2pg/ml (no IL-23), 233.9+/−133.0pg/ml (IL-23: 1ng/ml), 377.4+/−249.6pg/ml (IL-23: 10ng/ml) than in higher TGF-beta: 1ng/ml; 245.0 +/−115.4pg/ml (no IL-23), 338.1+/−168.0pg/ml (IL-23: 1ng/ml), 320.6+/−155.2pg/ml (IL-23: 10ng/ml). ROR-c expression was IL-23 dependent at TGF-beta concentrations of either 0.1ng/ml or 1ng/ml, but was IL-23 independent in 10ng/ml TGF-beta. These data indicate that the role of IL-23 in contributing to human Th17 differentiation varies depending on the concentration of TGF-beta. On flow cytometry, induction of IL-17A+ and IL-22+ cells was relatively independent of the concentration of IL-23. However, induction of IL-17F+ cells was more IL-23 dependent in lower TGF-beta: 0.1ng/ml whereas induction of IL-21+ cells was more IL-23 dependent in higher TGF-beta: 1ng/ml.

Conclusion: Contrary to initial predictions, our data suggest that IL-23 might promote human Th17 differentiation either through distinct mechanisms that are in part independent of TGF-beta or through contribution to low TGF-beta driven pathway. Furthermore, each Th17-derived cytokine may be differentially regulated by IL-23. The level of secretion of Th17 cytokines is not entirely predictable by enumeration of Th17 cells that contain a specific cytokine intracellularly.

Disclosure: H. Kato: None; **L. Cooney:** None; **J. Endres:** None; **D. A. Fox:** None.

1272

Self-Organized Criticality Theory for the Cause of Autoimmunity. Ken Tsumiyama[1], Yumi Miyazaki[1] and Shunichi Shiozawa[2]. [1]Department of Biophysics, Kobe University Graduate School of Health Science, Kobe, Japan, [2]Department of Biophysics, Kobe University Graduate School of Health Science/Department of Medicine, Kobe University Graduate School of Medicine/The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan

Objective: Since 'clonal selection theory of immunity' of F. Macfarlane Burnet and subsequent molecular biological discoveries on V(D)J recombination and the diversity and individuality of immune response, how autoimmunity arises remains unclear. Apart from the term 'autoimmunity' which is now ready-made, in the present study, we tried to see the pathogenesis of autoimmunity from different angle and test the integrity of immune 'system'. The method we have chosen was to stimulate the system maximally by antigen to the levels far beyond its steady-state. In a perfectly reproducible experiments in which the mice not prone to autoimmune diseases were immunized repeatedly with antigen, we have discovered that overstimulation of immune system beyond its self-organized criticality inevitably leads to systemic autoimmunity akin to systemic lupus erythematosus (SLE). We now show that autoimmunity arises not from 'autoimmunity', but as a natural consequence of normal immune response when stimulated maximally beyond system's self-organized criticality.

Methods: BALB/c mice were repeatedly immunized with a conventional antigen such as ovalbumin (OVA), keyhole limpet hemocyanin (KLH) or staphylococcal enterotoxin B (SEB). Autoantibodies including rheumatoid factor (RF), anti-Sm and anti-dsDNA antibody and immune complex (IC) in sera were detected by using ELISA. Tissue injury was assessed by the detection of proteinuria and IC deposition in glomeruli, histopathological study and lupus band test. Splenocytes of mice repeatedly immunized with antigen were adoptively transferred into naïve mice, and the induction of autoantibodies and tissue injury in recipients were examined. Further, we also examined the T cell receptor (TCR) revision in spleen, maturation of $CD8^+$ T cell and antigen cross-presentation in dendritic cell (DC).

Results: Repeated immunization with antigen caused systemic autoimmunity in mice otherwise not prone to spontaneous autoimmune diseases. Overstimulation of $CD4^+$ T cells led to the development of a fully-matured autoantibody-inducing $CD4^+$ T cell type (*ai*$CD4^+$ T cell) which had undergone T cell receptor (TCR) revision and was capable of inducing autoantibodies. The *ai*$CD4^+$ T cell was induced by *de novo* TCR revision but not by cross-reaction to immunizing antigen, and subsequently overstimulated $CD8^+$ T cells, driving them to become MHC class I-restricted, antigen-specific cytotoxic T lymphocytes (CTL). These CTLs could be further matured by antigen cross-presentation, after which they caused autoimmune tissue injury. In fact, autoimmune tissue injury did not appear in $CD8^+$ T cell-deficient mice after repeated immunization with antigen. Further, inhibition of antigen cross-presentation by treating with chloroquine abrogated the generation of CTL and autoimmune tissue injury.

Conclusion: We show that systemic autoimmunity appears to be the inevitable consequence of over-stimulating the host's immune 'system' by repeated immunization with antigen, to the levels that surpass system's self-organized criticality. Thus, we propose here 'self-organized criticality theory' explaining the cause of autoimmunity.

Disclosure: K. Tsumiyama: None; **Y. Miyazaki:** None; **S. Shiozawa:** None.

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SGN-70: Phase 1a Study of a Novel Humanized Antibody Targeting CD70 for the Treatment of Autoimmune Diseases. Jonathan G. Drachman[2], Julie A. McEarchern[2], Che-Leung Law[2], Luis Lopez-Lazaro[1], Gabriele Fabian[1] and Michael Seiberling[1]. [1]Covance Clinical Research Unit AG, Basel, Switzerland, [2]Seattle Genetics, Inc., Bothell, WA

Background: SGN-70 is a humanized IgG1 monoclonal antibody with high affinity for CD70 which can deplete CD70-positive cells via antibody effector mechanisms and can also block interaction of CD70 with its cognate receptor, CD27. CD70, a tumor necrosis factor family member, is expressed on activated T-cells, B-cells, and mature dendritic cells and co-stimulates immune responses. Based on these activities and preclinical studies, SGN-70 could reduce inflammation by targeting CD70+ immune cells while leaving the resting immune system intact.

Methods: A single-dose, dose-escalation, randomized, double-blind, placebo-controlled clinical trial was conducted in healthy volunteers (N=61) to evaluate safety, tolerability, PK, immunogenicity, and pharmacodynamic effects. Blood samples and clinical symptoms were collected for 50 days. Subsequently, a cohort of patients (N=8) with mild-moderate plaque psoriasis were evaluated at a single dose level. Upon randomization, 6 patients received SGN-70 (10 mg/kg) and 2 received placebo. This trial was conducted at a single site in Switzerland.

Results: SGN-70 was well tolerated over a wide dose range (0.0001 – 10 mg/kg) when administered without premedication as a single intravenous injection over 30 minutes (first 3 cohorts) or 60 minutes (higher dose levels). There were no serious adverse events or significant changes in laboratory values, vital signs, or ECGs, and a maximum tolerated dose was not established. Among healthy volunteers, the most frequent adverse events were URI symptoms, headache, and fatigue, which appeared to be balanced between treated and placebo subjects. Both Cmax and AUC appeared to increase linearly with dose level whereas terminal half-life increased at the highest dose levels. This resulted in a mean terminal half-life of 6–7 days for doses up to 1 mg/kg and 10 or 13 days at 3 mg/kg and 10 mg/kg, respectively. Low titer anti-therapeutic antibodies were detected in some subjects, but the effect of repeat dosing could not be assessed. In both the healthy volunteers and the psoriasis patients, a decrease in CD70+ B- and T-cells from peripheral blood could be demonstrated by qPCR or flow cytometry. Although the psoriasis patients had generally mild disease and were not eligible for more than 1 dose, preliminary evidence suggests that at least two of six patients experienced decreased skin thickness and cytokeratin 16 expression as well as modest improvement in PASI scores.

Conclusions: SGN-70 is well tolerated up to 10 mg/kg and has on-target pharmacodynamic activity when administered as a single dose. Based on the novel mechanism of action and ability to impact multiple arms of the activated immune system, this is a promising novel monoclonal antibody for rheumatologic and autoimmune diseases that warrants further evaluation in a multi-dose clinical trial.

Disclosure: J. G. Drachman: Seattle Genetics, Inc., 1, 3; **J. A. McEarchern:** Seattle Genetics, Inc., 1, 3; **C.-L. Law:** Seattle Genetics, Inc., 1, 3; **L. Lopez-Lazaro:** None; **G. Fabian:** None; **M. Seiberling:** None.

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Vitamin D Suppresses the Pathogenic Behavior of Primary Th17 Cells from Patients with Early RA in Synovial Fibroblast Activation. Jan Piet van Hamburg[3], Patrick Asmawidjaja[3], Anne-Marie Mus[3], Mieke Hazes[2], Hans van Leeuwen[1], Edgar Colin[2] and Erik Lubberts[4]. [1]Department of Internal Medicine, Erasmus MC, University Medical Center Rotterdam, [2]Department of Rheumatology, Erasmus MC, University Medical Center Rotterdam, [3]Departments of Rheumatology and Immunology, Erasmus MC, University Medical Center Rotterdam, [4]Erasmus MC, Rotterdam, ZH, The Netherlands

Introduction: Vitamin D is a secosteroid hormone that is produced on the skin under the influence of sunlight or is obtained from the diet. In the liver, the inactive precursor vitamin D3 is converted to the hormonal precursor 25-hydroxyvitamin D3 (25(OH)D3). In the kidneys and extrarenal tissue, 25(OH)D3 is converted into its most active metabolite 1,25(OH)2D3. It has been shown that 1,25(OH)2D3 has immunomodulatory effects in many experimental autoimmune models. Recently, we showed that vitamin D modulated Th17 polarization and IL-22 expression by memory T cells from patients with early rheumatoid arthritis and stimulates IL-4 production by PBMC from early RA patients.

Objective: To identify the effect of vitamin D on the pathogenic behavior of primary Th17 cells on synovial fibroblast (RASF) activation both from patients with early RA.

Methods: From PBMC of patients with early RA, CCR6+ CD45RO+CD4+ Th17 cells were FACS sorted and co-cultured with early RA synovial fibroblasts (RASF) in the absence or presence of Vitamin D. Supernatant of these cultures were analyzed for the production of inflammatory cytokines and matrix metalloproteases (MMPs) with ELISA. Transcrip-

tion of genes involved in the differentiation and function of T cells or genes expressed by activated RASF were analyzed by quantitative RT-PCR analysis. In addition, TNF-alpha and IL-17A blocking experiments were performed in these co-cultures.

Results: Th17-RASF co-culture experiments revealed an increase of IL-6, IL-8, and MMP-1 and MMP-3. Vitamin D significantly suppressed the production of IL-6 and MMP-3 in these co cultures. Interestingly, the specific enhanced autocrine production of IL-17 due to this Th17-RASF interaction was significantly inhibited by vitamin D. In addition, markedly suppressed expression of RORgammat and significantly enhanced expression of GATA3 was noted in the presence of vitamin D. No effect of vitamin D was observed on T-bet and FoxP3 expression. In addition, lower IL-22 and enhanced IL-10 production was found in the presence of vitamin D. The regulatory effects of vitamin D on IL-17 production in the Th17-RASF co culture was comparable to neutralizing IL-17 and on IL-6 production comparable to neutralizing TNF or IL-17.

Conclusion: These data show that vitamin D modulates the pathogenic behavior of primary Th17 cells in their activation of synovial fibroblasts. In addition, vitamin D suppresses the pro-inflammatory IL-17 loop between Th17 and RASF cells. These data suggest that the activation of the vitamin D pathway may have therapeutic potential for the treatment or even prevention of persistent arthritis.

Disclosure: J. P. van Hamburg: None; **P. Asmawidjaja:** None; **A.-M. Mus:** None; **M. Hazes:** None; **H. van Leeuwen:** None; **E. Colin:** None; **E. Lubberts:** None.

ACR Poster Session B
Large-Vessel Vasculitis and Behcet's Disease I
Tuesday, November 9, 2010, 9:00 AM–6:00 PM

1275

18F-Fluorodeoxyglucose Positron Emission Tomography Scanning (FDG-PET/CT) in Evaluation of Disease Activity in Takaysu Arteritis.

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Purpose: To evaluate FDG-PET/CT findings and disease activity in patients with Takayasu arteritis (TA).

Background: The assessment of disease activity may be difficult in TA. Patients can have active and progressing disease in spite of normal levels of ESR and CRP. Unfortunately, specific markers of disease activity are still missing[1]. Edema-weighted MRI does not seem to correlate well with development of new vascular lesions[2] and angiographic methods will only reveal findings compatible with long-standing, irreparable disease.

Since the introduction of FDG-PET/CT, case reports and small studies have reported positive associations between pathological uptake in FDG-PET/CT and disease activity in TA[3]. However, a recent study failed to find such a correlation[4]. Obviously, further studies are needed to clarify the usefulness of FDG-PET/CT in assessing disease activity in patients with TA. In order to evaluate our experience, we retrospectively evaluated the results of FDG-PET/CT in our patients with TA.

Methods: Patients who fulfilled the ACR criteria for TA[5] and had been consecutively investigated with FDG-PET/CT between 2003 and 2009 were included. They were recruited from the Norwegian Registry of connective diseases and systemic vasculitides (n=36) and by a systematic search in our hospital register of diagnoses (n=11). The FDG-PET/CTs were evaluated by nuclear medicine physicians. Semi-quantitative measurements were used to aid the visual evaluation. The scans were performed 60–90 minutes after injection of 370 MBq FDG. Disease activity was assessed by ESR and CRP measured within 15 days of the FDG-PET/CT investigation, by clinical evaluation by a rheumatologist prior to the FDG-PET/CT and by applying the NHI criteria for disease activity[1].

Results: Totally, 45 female and 2 male patients were investigated. Their median age was 31 years (14–69). Disease duration was median 1 year (0–31). Among patients with pathological FDG-PET/CT uptake, the mean level of CRP (28 cases evaluated) were significantly higher compared to patients with normal FDG-PET/CT. Further, based on the clinician's evaluations, 79% of those with increased FDG-PET/CT uptake had active disease compared to 29% among those with negative FDG-PET/CT. However, neither the ESR levels, nor the fulfilments of the NHI criteria for disease activity did not show significant difference between the groups (Table 1).

Table 1. Pathological FDG-PET/CT (PET/CT+) and normal FDG-PET/CT (PET/CT−) by markers of disease activity in Takayasu arteritis

	PET/CT+	PET/CT−	p
n total	15	32	
ESR median (range)	62 (3–100)	26 (3–100)	<0.16^
CRP median (range)	48.5 (1–145)	9 (1–57)	<0.04^
	Active/Inactive	Active /Inactive	
Clinical evaluation*	11 (79%)/3 (21%)	8 (29%)/20 (71%)	0.003^^
Criteria for activity[1] fulfilled	11 (73%)/4 (27%)	15 (47%)/17 (53%)	0.13^^

* Totally, 5 cases could not be evaluated,
^ Man-Whitey-test, ^ ^ Fisher's exact test

Conclusions: We found a significant association between FDG-PET/CT results and disease activity measured by CRP and clinicians evaluation, but not by ESR or the NHI criteria.

Reference List:

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Disclosure: O. Palm: None; **B. Gudbrandsson:** None; **T. Garen:** None; **K. Johnsrud:** None; **J. T. Gran:** None.

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A Double-Blind Placebo Controlled Trial of Infliximab in Patients with Corticosteroid-Dependent Polymyalgia Rheumatica.

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Background: Corticosteroids (CS) constitute the standard treatment of polymyalgia rheumatica (PMR). However, a significant proportion of patients remain CS-dependent. Open label studies have suggested that tumour necrosis factor (TNF) antagonists led to sustained improvement and CS sparing effect in patients with refractory PMR. To confirm these observations, we conducted a randomised, double-blind, placebo controlled trial with infliximab in CS-dependent patients with PMR.

Methods: We randomly assigned patients with CS-dependent PMR (defined as requiring ≥ 5 mg/day after at least 2 years of treatment to maintain remission or ≥ 7.5 mg/day after at least 6 months) to receive Infliximab (5 mg/kg i.v) at 0, 2, 6, 14 and 22 weeks (n = 11) or placebo (n = 11) together with CS that were reduced according to a predefined schedule. The primary outcome was the proportion of responder patients - defined as individuals with both complete clinical and analytical remission without receiving CS for at least three months- at 24 weeks. Secondary outcomes were cumulated CS doses and adverse events

Results: Baseline characteristics were similar in the two groups. The majority of patients were women (81.8% in infliximab versus 63.6% in placebo, $p=0.6$) with a mean age of 68.5±10.4 years in infliximab and 74.7±5.3 years in placebo group ($p=0.3$). PMR duration (median: 30.0 months and 36.0 months in infliximab and placebo groups, respectively; $p=0.8$) and CS dose at baseline (7.4±3.2 mg in infliximab versus 8.1±3.0 mg in placebo group; $p=0.5$) were also similar. At week 24, 17 patients continued in the trial (8 in infliximab and 9 in placebo group), and only 1 patient in the infliximab group and 2 in the placebo group fulfilled the definition of responder (p, NS). During the 24-week period, CS dose was increased according to physician judgment at least once in 36.4% of patients in the infliximab group compared with 72.72% in the placebo group ($p=0.2$). Patients in the infliximab group tended to have lower cumulated dose of prednisone during the first 24 weeks of treatment (533.7±366.8 mg versus 901.1±522.4 mg; $p=0.1$) and received lower CS dose at week 24 (1.1±1.4 mg versus 3.6±2.6 mg; $p=0.06$). There were 26 adverse events (24 mild/moderate) in patients treated with infliximab and 7 (all mild/moderate) in those patients treated with placebo.

Conclusion: The limited number of patients included in this trial does not allow definitive conclusions. The therapeutic role of infliximab in patients with CS-dependent PMR should be evaluated in trials enrolling larger patient cohorts.

The medication of the study (infliximab) was provided by Schering-Plough S.A.

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Adverse Outcomes of Glucocorticoid Therapy among Patients with Giant Cell Arteritis. Laura López Vives, Javier Narvaez, Paula Estrada, Carmen Gómez Vaquero and Joan Miquel Nolla. Department of Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain

Background: Glucocorticoids (GC) are currently the only agents in giant cell arteritis (GCA) with proven efficacy. Two studies have demonstrated that GC therapy carries an important long-term morbidity, with an incidence of GC adverse events ranging from 58% to 86% of the patients[1,2].

Purpose. To evaluate the incidence and risks of adverse events associated with GC therapy in a series of patients with GCA diagnosed in an area of north-eastern Spain over a 23-year period.

Methods: Retrospective follow-up study of an unselected population of 140 patients with GCA diagnosed in 1 center between 1986 and 2008. Medical records of these patients were reviewed, and clinical variables, GC doses, and GC adverse events on each patient were recorded. Multivariate regression analysis were were used to identify variables associated with the development of adverse events.

Results: The series included 94 women and 46 men with a mean age at time of diagnosis of 75 ± 7 years (range, 56 to 92). TAB was positive in 112 (80 %) patients. For the total sample the mean duration of therapy after diagnosis was 41.6 months (range, 12.5 to 180) and the total median dose of prednisone was 10.2 gm.

Adverse events associated with GCs were recorded in 89 (63.6%) patients and 2 or more events occurred in 51 patients (36.4%). The main adverse events and their frequency are presented in the following table:

Major adverse events that occurred in 89 of 140 patients with GCA

Type of adverse event	Patients with the event, number (%)
Diabetes mellitus	22 (15.7%)
Hypertension	41 (29.2%)
Hypelipemia	49 (35%)
Total osteoporotic fractures	27 (19.3%)
Symptomatic vertebral fracture	15 (10.7%)
Hip fracture	7 (5%)
Colies' fracture	3 (2.1%)
Insufficiency fracture of the pelvis	2 (1.4%)
Osteonecrosis	2 (1.4%)
Posterior suboapsular cataract	30 (21.4%)
Glucocorticoid-induced myopathy	3 (2.1%)
Gastrointestinal bleeding	2 (1.4%)
Severe or opportunistic infections	25 (17.9%)

Among those patients experiencing and adverse event, the median duration of therapy was 48.7 months (range, 2 to 180), the total median dose of prednisone was 11.6 gm, and the average daily dose was 9.5 gm. The median time from initiation of therapy to the first adverse event was 8.5 months. In the multivariate analysis, only higher cumulative dose of prednisone (odds ratio = 1.17, 95% confidence interval: 1.05, 1.30) was associated with the development of adverse GC side effects

Conclusion: The incidence of GC adverse events in patients with GCA is high, occurring at least in 63.6% of cases; being this percentage close to that observed in other populations. Adverse events may occur even in low-dose therapy and appear to be dose and duration dependent. Osteoporotic bone fractures and infections were as frequent as cardiovascular adverse events.

References:

1.- *Proven A et al. Arthritis Rheum 2003;49:703–8.*

2.- *Nesher G et al. J Rheumatol 1994;21:1283–6.*

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1278

Alemtuzumab (CAMPATH-1H) as Remission Induction Therapy in Behcet's Disease. Rona M. Smith[1], Yok W. Chow[2] and David R. W. Jayne[1]. [1]Addenbrooke's Hospital, Cambridge, United Kingdom, [2]Hospital Pantai Ayer Keroh Melaka, Malaysia

Introduction: Behcet's Disease is a chronic, relapsing inflammatory disorder, characterised by recurrent oral and genital ulceration, but the more severe, life threatening manifestations are neurological, gastrointestinal or vascular in nature. The precise aetiology and pathogenesis are unclear, but there is increasing evidence that T cells play a key role in the development of disease, and thus T cell depleting agents, such as the anti-CD52 humanised monoclonal antibody, alemtuzumab (CAMPATH-1H) are a potential therapeutic strategy.

Methods: We present a retrospective review of 20 patients treated with alemtuzumab since 1998 in Addenbrooke's Hospital, Cambridge, UK. Two dose schedules were used in this time period; a total dose of 134mg was administered prior to 2003, and 95mg in total in the latter years. Disease activity was measured using the Birmingham Vasculitis Activity Score (BVAS), and sequential evaluation of haematological and biochemical markers were performed.

Results:

Patient Characteristics

15/20 (75%) of patients were female, and the mean age at the time of alemtuzumab therapy was 36.2 years (range 18–59 years). All patients had oral and genital ulceration. 19 (95%) and 18 (90%) of patients had joint and skin involvement respectively. 11 (55%) had eye involvement, 13 (65%) gastrointestinal involvement and 9 (45%) central nervous system disease. Less common features included vascular manifestations (25%), peripheral nervous system involvement (10%) and lung disease (1 patient). Prior to alemtuzumab, the average disease duration was 59.8 months (range 1–203 months), and the mean duration of steroid exposure was 22.7 months (range 1–84 months). 17/20 (85%) of patients had received one or more immunosuppressive agents (including anti-TNF agents, cyclophosphamide, antimetabolites, calcineurin inhibitors and thalidomide) in addition to corticosteroids prior to receiving alemtuzumab The average duration of follow up was 85.47 months (range 20–134 months).

Outcomes

Six months after treatment, 74% of patients were in complete remission. Many of these remissions have been sustained over years, but in those that did relapse, re-treatment with alemtuzumab was effective. There were significant reductions in prednisolone dose and BVAS after treatment (Figure 1).

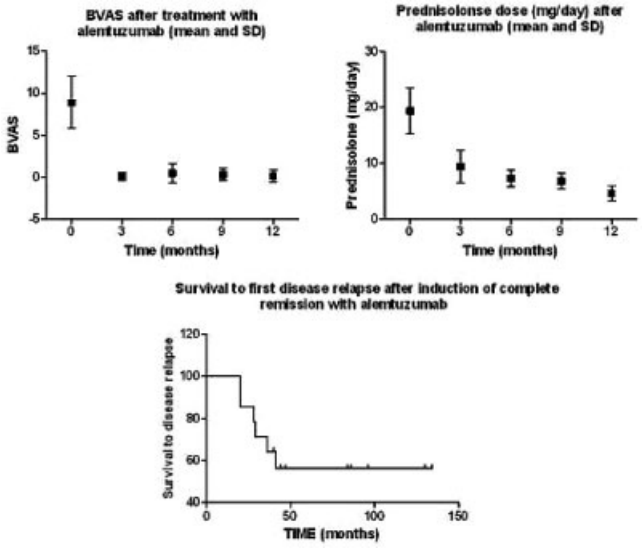

Figure 1. Prednisolone doses, BVAs, and relapse free survival post alemtuzumab.

Adverse events

Alemtuzumab was well tolerated. 25% of patients experienced infusion reactions, but in only one did the reaction necessitate termination of the treatment. There were no infectious complications directly attributable to alemtuzumab, but six patients developed new autoimmune thyroid dysfunction. Autoimmune diseases following alemtuzumab, including thyroid disease and ITP, have also been reported in multiple sclerosis.

Conclusions: Alemtuzumab is a safe and effective therapy for the treatment of Behcet's Disease, particularly in those cases which prove to be refractory or life threatening.

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1279

Ankylosing Spondylitis Associated with Takayasu Arteritis. Süleyman Yildirim, Gülen Hatemi, Sebahattin Yurdakul, Izzet Fresko and Huri Ozdogan. Istanbul University, Cerrahpasa Medical School, Rheumatology

Background: A number of case reports have been published on the association of Takayasu arteritis with ankylosing spondylitis. The aim of this study is to formally evaluate Takayasu patients for ankylosing spondylitis (AS).

Methods: All patients who were followed with a diagnosis of Takayasu arteritis in our clinic were evaluated. Apart from the 114 Takayasu patients who fulfill ACR criteria, 77 rheumatoid arthritis and 29 AS patients were included as controls. Patients were questionned for inflammatory back pain, arthritis and heel pain with a previously validated questionnaire for screening sero negative spondylarthropathies. Patients who gave an affirmative answer to at least one of the questions were further evaluated with physical examination and sacroiliac radiograms. Radiograms were evaluated twice on 2 seperate days by 3 rheumatologists blinded to each others observations and graded according to modified New York criteria. Patients who had bilateral grade 2 or unilateral grade 3 or 4 sacroiliitis on at least 3 of 6 observations were diagnosed as ankylosing spondylitis.

Results: Among the 114 patients with Takayasu arteritis 14 had died. Two of these patients had been diagnosed as AS, and one of them also as Crohn's disease before they died. Among the remaining 100 patients 4 already had a diagnosis of AS, one of them with accompanying Crohn's disease. We were able to reach 75 of the remaining 96 patients. 36 gave an affirmative answer to at least one of the questions. 29 of these 36 patients agreed to come to the clinic for further evaluation. Two of these 29 patients had scaroiliitis. One of them had a diagnosis of Crohn's disease. Among the controls 2/77 RA (3%) patients and 28/29 (97%) AS patients had sacroiliitis. Among the 114 patients with Takayasu arteritis a total of 8 (7%) patients had ankylosing spondylitis. Three of them were known to have Crohn's disease. None of the remaining 5 patients had symptoms related to Crohn's disease. The inter and intra-observer reliability of reading the sacroiliac radiograms was good. (kappa: inter-observer 0.89, 0.89, 0.69 and intra-observer 0.93, 0.69, 0.71)

Conclusion: The frequency of ankylosing spondylitis is increased in Takayasu arteritis. The association seems to include Crohn's disease in at least some of the patients. The HLA B27 status and other features of spondylarthropathy in these patients remains to be studied.

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1280

Association of *VEGF, NOS2, IL6, CCL2* and *IL1RN* Polymorphisms and Haplotypes with Susceptibility to Giant Cell Arteritis. A Simultaneous Study of 130 Potentially Functional SNPs in 14 Candiadte Genes. Anna Enjuanes[4], Yolanda Benavente[8], Jose Hernandez-Rodriguez[6], Carme Queralt[6], Jordi Yagüe[1], Pedro Jares[5], Silvia de Sanjose[7], Elias Campo[3] and Maria C. Cid[2]. [1]Department of Immunology, Barcelona, Spain, [2]Departmentof Systemic Autoimmune Diseases, Hospital Clinic, Barcelona, Spain, [3]Hematopathology Section, Department of Anatomic Pathology, Barcelona, Spain, [4]Hematopathology Section, Department of Anatomic Pathology, Hospital Clinic, Barcelona, Spain, [5]Hematopatholoy Section, Department of Anatomic Pathology, Barcelona, Spain, [6]Systemic Autoimmune Diseases, Barcelona, Spain, [7]Unit of Infection and Cancer, Cancer Epidemiology Research, Catalan Institute of Oncology, Barcelona, Spain, [8]Unit of Infection and Cancer. Cancer Epidemiology Research. Catalan Institute of Oncology

Background: Giant cell arteritis (GCA) is an immune-mediated vasculitis involving large and medium-sized arteries, especially the aorta and its cervico-cranial branches. GCA is probably a polygenic disease and it seems plausible that frequent genetic variants with modest effects may be related to GCA susceptibility. To date, existing studies assessing genetic risk for GCA have only analyzed limited number of candidate genes and restricted number of genetic variants.

Purpose: To investigate the genetic susceptibility to GCA, we performed a case-control study genotyping 130 SNPs in 82 biopsy-proven GCA patients and 166 healthy controls from the Spanish population. The study evaluates SNPs in potentially functional regions (coding and regulatory gene regions) and some tag SNPs in 14 candidate genes related to the inflammatory response (*CCL2*, *CCR7*, *IL10*, *IL12A*, *IL-1A*, *IL-1B*, *IL-1RN*, *IL6*, *IL8*, *INFG*, *LTA*, *NOS2*, *TNF* and *VEGF)*.

Methods: Genomic DNA was isolated from peripheral blood mononuclear cells and genotyping was carried out at the Spanish National Genotyping Centre (CeGen) using an Illumina Bead Array System. Hardy-Weinberg equilibrium (HWE) for each SNP was evaluated in control subjects. To test the hypothesis of association we used multivariate methods based on logistic regression analyses under four inheritance models (codominant, dominant, recessive and log-additive) and adjusted for age and sex.

Results: We found than 9 SNPs located in five genes had a significant statistical association with disease risk ($P < 0.05$) for any of the inheritance models. These SNPs were located in *NOS2* (rs2779251), *VEGF* (rs1885657, rs2010963, rs699946 and rs699947), *IL1RN* (rs17207494), *IL6* (rs7805828 and rs1546766), and *CCL2* (rs1860190) genes. The strongest associations were provided by rs2779251, rs1885657 and rs2010963 ($P = 2.3\ 10^{-5}$, $P = 0.0078$ and $P = 0.0097$, respectively). The association of rs2779251 and GCA risk was statistically significant after strong adjustment for multiple testing ($P\ corr = 0.0024$). The presence of the minor allele of *NOS2* variant rs2779251 had a protective effect for the risk of GCA (OR=0.27, 95% CI:0.14–0.52). Risk alleles for three of the four SNPs located in *VEGF* gene (rs2010963, rs699946 and rs699947), in homozygosis, showed an increase in the GCA risk (OR=4.22, 95% CI:1.38–12.87; OR=9.04, 95% CI:1.58–51.81; and OR=2.38, 95% CI:1.05–5.38; respectively). Minor allele for the other SNP in *VEGF* gene, the rs1885657, had a protective effect for GCA (OR=0.46, 95% CI:0.26–0.84). Moreover, we defined linkage disequilibrium blocks for each candidate gene included in this study and we explored the effect of haplotypes on disease risk. We found four haplotypes that showed significant association with susceptibility to GCA (*IL6,* OR=0.51, 95% CI:0.28–0.94; *VEGF,* OR=2.92, 95% CI:1.03–8.34; *VEGF,* OR=0.42, 95% CI:0.21–0.85; and *IL1B,* OR=2.94, 95% CI:1.29–6.67).

Conclusions: In summary, our results show that common genetic variants in *NOS2, VEGF*, *IL6*, *ILRN1* and *CCL2* genes are associated with risk for GCA, reinforcing a polygenic influence in susceptibility to this vasculitis.

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Behcet's Disease and the Major Histocompatibility Complex: Looking beyond HLA-B51. Michael J. Ombrello[2], Yohei Kirino[2], Fulya Cosan[1], Ahmet Gul[1], Daniel L. Kastner[2] and Elaine F. Remmers[2]. [1]Istanbul Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Istanbul University, Istanbul, Turkey, [2]Laboratory of Clinical Investigation, NIAMS, NIH, Bethesda, MD

Background: Behcet's Disease (BD) is a complex genetic disease of unknown etiology that is characterized by inflammatory lesions of the eyes, skin, and oro-genital mucosa. Family studies reveal a genetic contribution to BD, with estimates of the sibling recurrence-risk ratio from 11–52. Though the class I MHC molecule, HLA-B51 (B51), is reportedly the strongest known genetic risk factor for BD, the gene immediately centromeric to *HLA-B*, *MICA*, has also been implicated in BD. Because of strong linkage disequilibrium (LD) between *HLA-B* and *MICA*, their respective contributions to BD susceptibility have been debated.

Methods: In an effort to clarify the roles of B51, *MICA*, and other MHC locus genes in BD, we performed B51 typing with sequence specific oligonucleotide probes, and examined MHC locus SNP genotypes determined with Illumina Human CNV370 SNP chips in the largest single collection of BD patients ever assembled, 1190 Turkish BD patients and 1257 geographically matched, healthy Turkish subjects. Genotype association testing and regression analysis was performed using SNP Variation Suite 7. Haplotype analysis was performed using Haploview.

Results: We found that B51 was strongly associated with BD (allelic chi square p=5.47E-50, OR=3.49), occurring at allelic frequencies of 0.159 in healthy Turkish individuals and 0.352 in Turkish BD patients. We found 228 statistically significant BD-associated SNPs within the MHC locus (p<2.00E-5). The most strongly associated SNP (rs2848713, p=1.91E-45)

was located centromeric to *MICA*, and was contained within a cluster of 33 BD-associated SNPs within *HLA-B* and *MICA*. Analysis of LD and haplotype structure identified a BD-associated, B51-containing haplotype block (p=1.22E-46, OR 2.81) spanning the entire *HLA-B* and *MICA* genes. An otherwise identical B51-negative version of this haplotype also existed, although it occurred at identical frequencies, 0.04, in cases and controls. B51-containing haplotypes with recombinant events occurring between *HLA-B* and *MICA* continued to convey a risk of BD (OR=1.75, [95CI=1.15–2.58]). Taken together, these data indicate that B51 is essential to the causative nature of this BD-associated extended *HLA-B/MICA* haplotype, whereas *MICA* elements are dispensable. Finally, to identify B51-independent effects of MHC genes on BD susceptibility, we performed conditional analysis of all BD-associated MHC locus SNPs, specifying B51 as a covariate. We identified 23 B51-independent BD-associated SNPs, the strongest of which, rs9260997, was very near to *HLA-A* (p=5.49E-9, OR=1.84). Further analysis accounting for the effects of both B51 and rs9260997 identified additional regions of BD association in *PSORS1C1* (p=1.24E-5, OR=2.01), and *HLA-B* (p=1.18E-5, OR=1.46).

Conclusion: Our study demonstrates B51 to be the largest single contributor to BD susceptibility in Turkish individuals. We identify a common B51-containing BD-associated *HLA-B/MICA* haplotype. B51 was required on the haplotype for the conveyance of significant BD risk, whereas *MICA* variants were dispensable. Finally, we identified additional B51-independent BD associations in the *HLA-A, PSORS1C1*, and *HLA-B* regions.

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Circulating Adipokine, Ghrelin and Acylated Ghrelin Levels in Patients with Takayasu's Arteritis. Hatice Yilmaz[1], Vedat Gerdan[3], Didem Kozaci[4], Servet Akar[3], Gercek Can[3], Aytac Gulcu[2], Volkan Cakir[2], Yigit Goktay[2], Merih Birlik[3], Nurullah Akkoc[3] and Fatos Onen[3]. [1]Internal Medicine, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, [2]Radiology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, [3]Rheumatology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, [4]Science, Technology Research and Aplication Center, Aydin, Turkey

Objective: The follow-up of the disease activity is of great importance as it requires intense treatment in active period of Takayasu's arteritis (TA) of which etiology is unknown. Today, clinic and laboratory activity criteria alone are not quite enough in follow-up. This study aims to investigate serum leptin, adinopectin and plasma ghrelin and acylated ghrelin levels and the relationship of these parameters with the disease activity

Material and Method: 31 TA patients and 32 healthy controls were included in the study. In TA patients, the disease activity was evaluated based on the NIH activation criteria, DEI.TAK scoring, "DEI.TAK-physician's global opinion (PGO)" and radiological investigations (B-mode and Doppler USG and MR angiography). Serum leptin, adinopectin and plasma ghrelin and acylated ghrelin levels were measured by ELISA in all patients and controls. Mann-Whitney U test and Pearson's correlation analysis was used in the comparison of the groups and testing the inter-variety correlations, respectively.

Results: Of the 31 TA patients, 29 were female and 3 were male and the mean age was 44.2± 11.3 years. Distributions of age, sex, waist and hip circumferences and BMI in TA and healthy controls were similar.

Twenty% of TA patients were active based on NIH activation criteria; 19.4% were active, 22.6% were persistent and 58% were inactive based on "DEI.TAK- PGO" and 33% were active based on the radiological findings. There was a positive correlation between NIH activation criteria and DEI-.TAK scoring "DEI.TAK-PGO" and also radiological activity (r=0.566, p=0.001; r=0.603, p=0.001; r=0.409, p=0.031, respectively). Serum ESH, WBC and % neutrophil levels were higher in TA patients than controls (p=0.017, p=0.002 and p<0.001, respectively).

Ghrelin (319.3±202.6 pg/ml) and acylated ghrelin (120,5±94,4 pg/ml) levels in TA patients were significantly lower than controls (623,2±270 pg/ml and 180,9±128,7 pg/ml respectively), (p<0.001 and p=0.031, respectively). They were negatively correlated with serum WBC and % neutrophil levels. Ghrelin levels were significantly lower in active patients than inactive patients according to NIH activation criteria and "DEI.TAK-PGO" (p=0.041 and p=0.016 respectively).

No difference was found between leptin and adinopectin levels in TA patients and healthy controls. However, a significant negative correlation was found between leptin levels and ghrelin and acylated ghrelin levels in TA patients (r=0.344, p=0.006 and r=0.389, p=0.002, respectively). Leptin and adinopectin levels were significantly lower in patients with coronary involvement (p=0.027, p=0.016 respectively). There was a significant positive correlation between mean carotid intima-media thickness (IMT) measurements and adinopectin levels in TA patients (p=0.001 and p=0.004, respectively).

Conclusion: Ghrelin levels were considered to be useful in monitoring the disease activity and adjusting the treatment plan in TA. DEI.TAK scoring, "DEI.TAK- PGO" and radiological activity indicators which are in accordance with NIH activation criteria can also be used for disease follow-up.

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Circulating Endothelial Cells and Endothelial Progenitor Cells in Takayasu Arteritis. Serkan Dogan[2], Dilek Solmaz[4], Ozden Piskin[1], Servet Akar[4], Aytac Gulcu[3], Faize Yuksel[1], Volkan Cakir[3], Gercek Can[4], Yigit Goktay[3], Merih Birlik[4], Nurullah Akkoc[4] and Fatos Onen[4]. [1]Hematology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, [2]Internal Medicine, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, [3]Radiology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, [4]Rheumatology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey

Objective: In Takayasu arteritis (TA) with unknown etiology, it is very important to monitor the disease activity because intensive treatment is needed during active periods. Today's clinical and laboratory activity criteria alone are not very satisfactory for follow-up. This study aims to investigate the numbers of circulating endothelial cells (CEC) and endothelial precursor cells (CEPC) and also the correlation of these parameters with disease activity in patients with TA.

Patients and Methods: 32 patients with TA, 25 with systemic lupus erythematosus (SLE) (patient control group) and 30 healthy subjects were included in this study. Detailed medical history was obtained and full physical examination was done in all patients. The NIH activation criteria, DEI.TAK scoring and ''DEI.TAK-physician's global opinion (PGO)" and also radiological investigations (B-mode and doppler USG and MR angiography) were used to evaluate disease activity in TA patients. The numbers of CEC and CEPC were measured by flow cytometry in patient and control groups.

For comparison of the groups, Krusskall-Wallis analysis or chi square tests were used. When significance were determined between the groups, they were recompared in pairs by way of Mann-Whitney U test. For the purpose of testing the correlations between the variables, Spearman's correlation analysis was applied.

Results: There were 29 female and 3 male patients with TA (mean age: 43.5 years). Mean disease duration was 5.4 years.

According to NIH activation criteria in TA patients, 18.8% of patients were active; according to "DEI.TAK-physician global opinion", 18.8% active, 28.1% persistent and 53.1% inactive and; according to the radiological findings, 31% active. A significant correlation was determined between the NIH activation criteria and DEI.TAK scoring, "DEI.TAK-PGO" and also radiological activity (r=0.529, p=0.002; r=0.540, p=0.002; and r=0.361, p=0.046 respectively).

Serum CRP levels in TA patients (p=0,018) and SLE patients (p=0,009) were significantly higher than in healthy control group. The numbers of CEC were higher in patients with TA (7,02 ± 2,78 n/μl) and patients with SLE (7,24 ± 2,06 n/μl) in comparison to healthy control group (4,90 ± 1,82 n/μl), (p=0,001 and p<0,001, respectively). CEC numbers were correlated positively with serum CRP levels (r=0.228, p=0.34). CEPC numbers were not different between the groups.

Carotid intima-media thickness (IMT) has been found to be significantly higher in TA patients (1,06 ± 0,60 mm) in comparison to SLE patients (0,56 ± 0,11 mm) and healthy controls (0,55 ± 0,11 mm) (p<0.001). The frequency of carotid atherom plaque did not show any statistical difference between the groups

Conclusion: The results of this study suggests that the changes in numbers of CEC might be useful in monitoring the disease activity and planning the treatment in TA patients. The DEI.TAK scoring, "DEI.TAK-PGO" and radiological activity indexes which work parallel to NIH activation criteria may also be used for the purpose of monitoring the disease activity and deciding on the treatment.

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Clinical Characteristics, Treatment and Ethnic/Racial Differences in the Manifestations of 518 Behcet's Syndrome Patients in the United States. Yusuf Yazici, Maria T. Filopoulos, Elizabeth Schimmel, Andy McCraken and Christopher Swearingen. NYU Hospital for Joint Diseases

Background: Behcet's syndrome (BS) is a systemic vasculitis is rare in northern Europe and the US. Previous reports have suggested that there may be ethnic and racial differences in disease presentation and possible clustering of manifestations. We started a dedicated Behcet's clinic in 2004 and now report on the disease characteristics of the first 518 patients.

Methods: All patients seen at the center have completed a MDHAQ, and a questionnaire about past medical history, medication use, Behcet's specific history, ethnic and demographic information. These data are prospectively collected and updated each visit. About 2/3 of patients live within driving distance of New York City while patients from over 45 states have been seen. Patients were analyzed as the whole cohort and then also separated into to 2 groups: Group A= with ethnic background in northern Europe and North America and/or self declared Caucasians without background around the Mediterranean and/or the Far East; Group B= Patients with an ethnic background in the Mediterranean, Middle East, North Africa, and Far East. These groups were compared for disease manifestations, demographic information and medication use.

Results: 518 patients (398 (77%) female, mean (SD) disease duration 4(6.5) years, age 35 (13.6), 324 (60%) fulfilled International Behcet's classification criteria) were analyzed. Disease characteristics of the whole cohort and those fulfilling criteria are given in Table 1. When divided by ethnic background, Group A had statistically more significant GI disease (47% vs. 28%, $p<0.001$) and more females compared to Group B (83% vs. 71%, $p=0.005$) for those meeting criteria. For the whole cohort, less eye disease and vascular involvement than other centers was reported. There was only one blind eye.

	Total cohort (%)	Meeting criteria (%)	Not meeting criteria (%)
N	518	313	205
Oral ulcers	481 (90%)	313 (100%)	151 (74%)
Genital ulcers	376 (73%)	285 (91%)	91 (44%)
Skin	342 (66%)	287 (92%)	55 (27%)
Arthritis	268 (52%)	199 (64%)	69 (34%)
GI	179 (35%)	121 (39%)	58 (29%)
Eye	144 (28%)	127 (41%)	17 (8%)
CNS	81 (16%)	59 (19%)	22 (11%)
DVT	20 (4%)	17 (5%)	3 (1%)
Pathergy	41 (8%)	37 (12%)	4 (2%)
HLA B51	58 (11%)	37 (12%)	21 (10%)

Most commonly used medication at baseline was low dose prednisone (62%), followed by colchicine (46%), TNF inhibitors (21%) azathioprine (19%) and methotrexate (10%).

Conclusions: In this cohort of 518 Behcet's patients, largest cohort to be reported in the US. demographic and clinical differences were noted between patients with different ethnic backgrounds. There were significantly more female patients in the non-ethnic groups. The frequency of GI disease was also significantly more in this group. Eye disease prevalence for the whole cohort was far less than reported from other centers. These finding point to considerable heterogeneity in disease expression in BS at different geographic areas.

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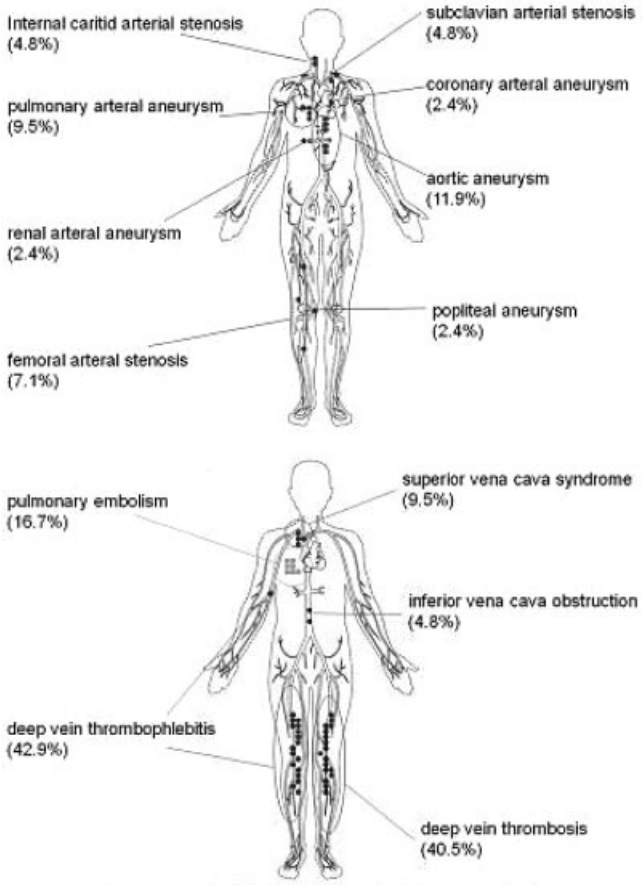
1285

Clinical Features of Behçet's Disease with Vascular Involvement. Hirotoshi Kikuchi[2], Kurumi Asako[1], Maki Takayama[1], Hajime Kono[1], Shunsei Hirohata[4] and Yasuo Ono[3]. [1]Department of Internal Medicine, Teikyo University School of Medicine, [2]Department of Microbiology and Immunology, Teikyo University School of Medicine, Itabashi-ku, Tokyo, Japan, [3]Department of Microbiology and Immunology, Teikyo University School of Medicine, [4]Department of Rheumatology and Infectious Disease, Kitasato University School of Medicine, Kanagawa, Japan

Background: Behçet's disease (BD) is characterized by recurrent oral aphthous stomatitis, ocular involvement, genital ulcer, and skin lesions. Although one of the serious manifestations of BD is vascular involvement (VBD), its pathogenesis remains unclear. The current studies were therefore undertaken to delineate the clinical characteristics of VBD and to explore its pathological features.

Patients and Methods: The clinical records of 277 patients who satisfied the 1990 international criteria for Behçet's disease and were hospitalized in Department of Internal Medicine, Teikyo University School of Medicine, from January 1989 to December 2009 were reviewed.

Results: Forty two patients (25 males and 17 females) had been diagnosed with VBD. The mean age of BD onset was 35.6±11.8 years (mean±SD), and the mean delay for the development of VBD was 5.8 years. The frequency of HLA-B51, HLA-A26, pathergy test and complete type was 34.4%, 13.3%, 42.9% and 38.1%, respectively. The vessels involved were as follows: the most frequent venous lesion was deep vein thrombophlebitis (42.9%), followed by deep vein thrombosis (40.5%), superior vena cava syndrome (9.5%), and inferior vena cava obstruction (4.8%) and frequent arterial lesions were aortic aneurysm (11.9%), pulmonary aneurysm (9.5%), femoral artery stenosis (7.1%), and subclavian arterial stenosis (4.8%).



Seven patients suffered from both venous and arterial lesions.

Seven patients suffered from both venous and arterial lesions. Two patients died because of hemoptysis from pulmonary arterial aneurysms. One of 7 patients who were complicated with pulmonary embolism died.

Conclusion: These results indicate that the frequency of vascular manifestations tended to be higher for venous lesions (81.0%) compared with arterial lesions (28.6%). In particular, the main complication associated with death was pulmonary vessel involvement.

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1286

Clinical Spectrum, Angiographic Findings and Outcome in Takayasu Arteritis, Using the Disease Extent Index for Takayasu Arteritis (DEI.TAK). Sivakumar M. Rajappa. Cerebrovascular and Vasculitis Research Foundation, Chennai, Tamilnadu, India

Background: Takayasu's arteritis (TA) is a chronic, inflammatory large vessel vasculitis affecting the aorta and its major branches, pulmonary and

coronary arteries. Although more common in Asia, the disease has been found worldwide, with different vascular involvement patterns, clinical manifestations and outcome usually affecting young women. The disease involves all the three layers of the vessel walls and results in luminal abnormalities like intima medial thickening, stenosis, occlusion, and aneurysm formation. The Disease Extent Index for Takayasu Arteritis (DEI.Tak), is a validated instrument for assessment of the clinical involvement in Takayasu Arteritis (TA), without need for imaging. The index is also useful to study damage and outcome in TA.

Objective: To analyze data in TA, regarding demographics, race, clinical manifestations, angiographic findings by CT/MR/Digital Subtraction Angiograms, outcome of vascular interventions and mortality over a period of 20 years, using the DEI.Tak.

Methods: This is a prospective cross sectional study 222 TA patients who fulfilled the ACR diagnostic criteria for TA, seen at Chennai, India between January 1988 and March 2010. The clinical findings were entered into a database using the DEI.Tak. All the relevant laboratory parameters like ESR, CRP and imaging modalities like Carotid and Vertebral Duplex Ultrasound and Intima-Media Thickness(IMT), CT/MR/Invasive Angiograms and PET CT scans were performed to classify TA according to Nummano's angiographic classification. The survival of grafts and interventional procedures like Carotid, Subclavian, Renal and Aortic angioplasty and stenting done on TA patients were analyzed. The outcome with treatment and surgery/interventional procedures and mortality over a 22 year period is reported.

Results: A total number of 222 TA patients (151 women and 71 men) were seen with a mean age of 34.62 ± 14.8 years. The systems scored commonly were: Systemic-93(42.66%), Renal-84(38.33%) and Cardiovascular system(CVS)-134(61.46%)[Bruit: 32(14.67%),Pulse Inequality: 42(19.19%),Pulse loss:6429.35%), Claudication:36(16.51%),Aortic incompetence:18(8.25%),Angina:19(8.71%), CCF:21(9.63%).Systems rarely involved were skin, mucous membrane and abdomen. The mean Common Carotid Artery IMT was 0.845 cm. The long term survival of stents with effective immunosuppressive treatment pre and post stenting were 92%, 83% and 72% at the end of 5, 10 years and 15 yeras respectively. The 5 Angiographic distribution of involvement of the aortic arch and its branches were: Type I: 19, IIa: 26, IIb: 37, III: 43,I V: 33 and V: 64. During the follow up of over 20 years, 41 patients expired.

Conclusions: This study involving a large cohort of TA cases, followed up for more than two decades provides a comprehensive assessment of the extent and severity of TA using the DEI.Tak. CVS is the most important system affected and the presence of new pulse loss was a good indicator of active disease. With effective immunosuppressive therapy, there is good long term patency of stents in the Indian subjects with improved morbidity and mortality.

Disclosure: S. M. Rajappa: None.

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Cluster Analysis of Vascular Involvement in Takayasu Arteritis: Extension of the Lesions Is Contiguous in the Aorta and Symmetric in Paired Arterial Beds. Laurent Arnaud[1], Julien Haroche[1], Dan Toledano[2], Patrice Cacoub[1], Nathalie Costedoat-Chalumeau[1], Du Le Thi Huong-Boutin[1], Philippe Cluzel[2] and Zahir Amoura[1]. [1]Department of Internal Medicine, Groupe Hospitalier Pitié-Salpêtriere, UPMC Univ Paris 6, AP-HP, 47–83 bd de l'Hôpital, Paris, France, [2]Department of Radiology, Groupe Hospitalier Pitié-Salpêtrière, UPMC Univ Paris 6, AP-HP, 47–83 bd de l'Hôpital, 75013, Paris, France.

Background: The determinants of vessel targeting are largely unknown in vasculitides. The aim of this study was to identify patterns of vascular involvement in Takayasu's arteritis (TA), using cluster analysis.

Methods: Peripheral vascular Doppler, CT angiography and angio-MRI data of 82 patients with TA (ACR criteria) were studied between Jan. 1995 and May 2006. Cross-involvement between 24 main arteries were assessed using the Phi correlation coefficient. Patterns of vascular involvement were identified using hierarchical cluster analysis.

Results: Data were obtained from 68 women (82.9%) and 14 men (17.1%). The median duration of follow-up was 5.1 years (range: 1 month to 30 years).

For 16 (80%) of 20 paired arteries, the highest correlation of involvement was observed with the contralateral artery ($r=0.31$ to 0.66). Conversely, the involvement of the abdominal aorta best correlated with that of the thoracic descending aorta ($r=0.38$, $p=0.0005$), and this latter best correlated with the aortic arch ($r=0.44$, $p<0.0001$). This suggests contiguous extension in the aorta.

Cluster analysis visually confirmed that all paired arterial beds, but the internal and external carotid arteries, clustered with their contralateral counterpart, and that the aortic arch, the descending thoracic aorta and the abdominal aorta clustered together.

Conclusion: Our study reveals that TA lesions mostly develop in a symmetric manner in paired vascular territories and that disease extension is contiguous in the aorta. This may prove useful for improving the radiological follow-up of patients with TA, and for providing a pattern for further investigations focusing on the mechanisms of vessel-specificity in vasculitides.

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Colchicine Does Not Decrease the Need for Immunosuppressive Use at Long Term in Behçet's Syndrome. Vedat Hamuryudan[3], Gülen Hatemi[3], Sebahattin Yurdakul[3], Cem Mat[1], Koray Tascilar[3], Yilmaz Ozyazgan[2], Emire Seyahi[3], Serdal Ugurlu[3] and Hasan Yazici[3]. [1]Istanbul University, Cerrahpasa Medical School, Dermatology, [2]Istanbul University, Cerrahpasa Medical School, Ophthalmology, [3]Istanbul University, Cerrahpasa Medical School, Rheumatology

Background: A recent survey looking at the long term outcome of patients who had entered a controlled trial of thalidomide showed a trend for less immunosupressive use among those who had previously used colchicine (1). This time we looked at the long term outcome of patients who took part in a 2 year, randomized, placebo controlled trial of colchicine.

Methods: 116 BS patients (60 men, 56 women) with only mucocutaneous and joint involvement were re-evaluated 16.6 ± 1.1 years after the trial ended. The main outcome measure was the need for immunosuppressive use during follow-up.

Results: Outcome information was achieved in 90/116 (78%) patients. Of these, 51 were men and 39 were women (mean age 27.1 ± 5.3, disease duration 8.4 ± 8.1 months at randomization). The group distribution of patients who could not be reached was similar. During follow-up, 18/51 (36%) men and 8/39 (20%) women had received immunosuppressives (Table). There was no difference in immunosuppressive use between patients who had been randomized to colchicine or placebo arms (men: 11/25 colchicine vs 7/26 placebo and women 3/18 colchicine vs 5/21 placebo).

	Men (n=51)		Women (n=39)	
	Colchicine (n=25)	Placebo (n=26)	Colchicine (n=18)	Placebo (n=21)
Eye Involvement	1	–	1	1
DVT	2	2	1	–
Pulmonary artery aneurysm	–	1	–	–
Neurologic involvement	2	1	–	–
Gastrointestinal	1	–	–	1
Arthritis	2	3	1	3
Mucocutaneous involvement	3	–	–	–

Conclusion: Initial use of colchicine does not seem to decrease the need for immunosuppressive use, hence the development of major organ involvement of BS patients at long term.

Reference:
1) Hamuryudan V et al. Rheumatology (Oxford). 2010 Jan;49(1):173–7

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Diagnostic Value of Pathergy Phenomenon in Behcet's Disease. Fereydoun Davatchi, Cheyda Chams-Davatchi, Farhad Shahram, Bahar Sadeghi Abdollahi, Abdolhadi Nadji, Massoomeh Akhlaghi, Tahereh Faezi and Roghieh Larimi. Rheumatology Research Center, Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran

Background: Pathergy phenomenon (PP) is used for the diagnosis of Behcet's Disease (BD). It is an important criterion of many classification/diagnosis criteria. The sensitivity of PP was 83% in Russia, 77% in Morocco, 71% in Iraq, 62% in China and Egypt, 61.5% in Iran, 55% in Germany, 44%

in Japan, and 18% in Saudi Arabia. The sensitivity of PP is changing over the time. It has changed in Iran from 71.8% for the first 1000 patients to 33.9% for patients 5000 to 6000. The aim of this study was to look for the diagnostic value of PP in the present time, and its change over the past 35 years.

Patients and Methods: The Behcet's Disease registry, has the data of 6607 BD and 4292 Control patients from the past 35 years. Patients were divided in 4 groups of 1650 BD and 1073 controls. Sensitivity, Specificity, Positive and Negative Predictive Value (PPV & NPV), Positive and Negative Likelihood Ratio (PLR & NLR), Diagnostic Odds Ratio (DOR), and Youden's Index (YI) were calculated. The first and the 4th quartiles were compared.

Results: Positive PP changed from 64.2% to 35.8% (1st and 4th quartiles) in BD and from 13.4% to 1.6% in control patients (Table 1). Sensitivity, specificity, PPV, NPV, PLR, NLR, DOR, and YI are shown in Table 2.

Table 1. Details of Behcet's Disease and control patients

Patients	First Group	Second Group	Third Group	Fourth Group
BD Patients	1–1650	1651–3300	3301–4950	4951–6607
PP Done	1580	1639	1622	1643
Positive PP	1014	971	820	588
% Positive	64.2	59.2	50.6	35.8
95% CI	61.8–66.5	56.8–61.5	48.2–53.1	33.5–38.1
Control Patients	1–1073	1074–2146	2147–3219	3220–4292
PP Done	1069	1069	980	1061
Positive PP	143	96	10	17
% Positive	13.4	9.0	1.0	1.6
95% CI	11.5–15.6	7.4–10.9	0.5–1.9	1.0–2.6

Table 2. Performance and Diagnostic value of Pathergy Test

Patients and Controls	First Group	Second Group	Third Group	Fourth Group
Sensitivity	64.2	59.2	50.6	35.8
Specificity	86.6	91.0	99.0	98.4
Positive Predictive Value[a]	82.7	86.8	98.1	95.7
Positive Predictive Value[b] 33%	70.2	76.4	96.1	91.7
Positive Predictive Value[c] 0.08%	0.38	0.52	3.89	1.76
Negative Predictive Value[a]	82.7	69.0	66.7	60.5
Negative Predictive Value[b] 33%	83.1	81.9	80.3	75.7
Negative Predictive Value[c] 0.08	99.97	99.96	99.96	99.95
Positive Likelihood Ratio	4.8	6.6	50.6	22.4
Negative Likelihood Ratio	0.41	0.45	0.5	0.65
Diagnostic Odds Ratio	11.6	14.7	101.4	34.3
Youden's Index	0.5	0.5	0.5	0.34

a: Predictive Value of PP without taking in account the prevalence of Behcet's disease
b: Predictive Value calculated for the Behcet's Disease clinic at RRC (prevalence of BD: 33%)
c: Predictive Value calculated for the population of tran (prevalence of BD: 0.08%)

Discussion: The sensitivity of PP decreased while the specificity increased. The difference was statistically significant (Table 2).

PPV shows the probability that the positive test is true positive. PPV is influenced by the prevalence of the disease in the tested population. The prevalence of BD in Iran is 0.08%. In BD clinic, 1/3rd of new patients have BD. PPV improved from 0.38% to 1.76 (population) and from 70.2% to 91.7% in BD Unit (between 1st and 4th quartile). Although the sensitivity of PP has decreased over the time, its value as a diagnostic test, when positive, has improved. NPV shows the probability that a negative test is truly negative. NPV lost a little in the BD Clinic, going from 83.1% to 75.7% (Table 2).

PLR shows the odds of having the disease. PLR improved from 4.8 to 22.4 (1st to 4th quartile), meaning the risk of having BD with positive PP is 22.4 times. The NLR deteriorated from 0.41 to 0.65, meaning the error rate of not having BD increased from 41 to 65%.

The diagnostic odds ratio (DOR) combines the results of PLR and NLR, A value of 1 means no discrimination between patients and controls. Higher values mean better discrimination. DOR improved from 11.6 to 34.3 (from 1st to 4th quartile).

Youden's Index (YI) shows the accuracy of PP. Zero is the worse and one the best. The YI decreased from 0.5 to 0.34, showing a deterioration of precision rate over the time.

Conclusion: PP improved its diagnostic value.

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Disease Activity Assessment in Large Vessel Vasculitis. Luca Magnani[1], Annibale Versari[1], Diana Salvo[1], Massimiliano Casali[1], Giuseppe Germanò[1], Riccardo Meliconi[3], Lia Pulsatelli[2], Debora Formisano[1], Gianluigi Bajocchi[1], Nicolò Pipitone[1], Luigi Boiardi[1] and Carlo Salvarani[1]. [1]Arcispedale S Maria Nuova, Reggio Emilia, Italy, [2]Istituti Ortopedici Rizzoli, Bologna, Italy, [3]University of Bologna, Italy

Purpose: Assessment of disease activity in patients with large vessel vasculitis (LVV) is challenging because clinical, biologic and radiologic data do not always correlate. ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) and serum interleukin-6 (IL-6) may be useful for the assessment of disease activity, however data on their usefulness are not well defined.

The aims of this study were to compare National Institute of Health (NIH) criteria and Indian Takayasu's arteritis activity score (ITAS) with FDG-PET scan results, as well as with erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum IL-6 values for the assessment of disease activity in a group of patients with LVV.

Methods: Fifty-eight patients with LVV (24 with Takayasu's arteritis, 31 with giant cell arteritis according to the ACR criteria, and 3 with chronic periaortitis) underwent a total of 99 PET scans. Images were reviewed by a nuclear medicine physician (AV) who was unaware of the clinical diagnosis and assessed images for pattern and intensity of vascular uptake. LVV activity data, including laboratory tests, were obtained within 14 days of the PET scans.

Results: PET scanning revealed abnormal vascular uptake ($\geq$ 2 on a 0–3 scale in at least 1 of the 7 vascular regions analyzed) in 57.6% of the 99 examinations. According to the NIH criteria, 27 patients had active and 72 inactive disease. Thirty-three patients had ITAS $\geq$ 1 and 66 equal to 0. ESR, CRP and IL-6 levels were stratified into 4 groups according to distribution quartiles. 12.5% of patients (9/72) with inactive disease according to NIH criteria had ITAS $\geq$ 1, while 11.1% of patients (3/27) with active disease according to NIH criteria had ITAS = 0. The agreement between ITAS and NIH criteria was 87.9% (87/99) (kappa value: 0.71). Abnormal FDG vascular uptake was present in 52.8% of patients (38/72) with inactive disease according to NIH criteria, while 30.8% of patients (8/26) with active disease according to NIH criteria had normal FDG vascular uptake. The total agreement between FDG vascular uptake and NIH criteria was 53.1%. Abnormal FDG vascular uptake was present in 53.0% of patients (35/66) with ITAS = 0, while 33.3% of patients (11/33) with ITAS $\geq$ 1 had normal FDG vascular uptake. The agreement between FDG vascular uptake and ITAS criteria was 53.5%. ESR and CRP levels were significantly associated with disease activity according to the NIH criteria and ITAS ($p = 0.0001$). In contrast, there was no association between IL-6 serum levels and disease activity according to NIH criteria and ITAS.

Conclusion: The agreement between NIH criteria and ITAS for disease activity assessment in LVV is excellent. ESR and CRP values are associated with disease activity as assessed by the NIH criteria and ITAS, while FDG vascular uptake and IL-6 serum values are not.

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Disease Assessment in Takayasu's Arteritis: Data from a Literature Search and a Survey of Expert Opinion. Haner Direskeneli[3], Sibel Z. Aydin[3], Peter A. Merkel[2] and Turkish Takayasu Study Group[1]. [1]Istanbul, Turkey, [2]Boston University School of Medicine, West Newton, MA, [3]Marmara University, School of Medicine, Istanbul, Turkey

Purpose: To study approaches to disease assessment in Takayasu's arteritis (TAK) by summarizing published clinical studies and surveying current expert opinion in Turkey.

Methods: A literature search was conducted in "PubMed" with keywords "Takayasu's arteritis", "assessment", "activity", "remission", and "relapse" for studies published in English between 1994–2010 (case reports and reviews excluded). Informed by the literature review, Turkish rheumatologists (n=34, 20 specialists/academicians and 14 rheumatology fellows) and two foreign experts completed a questionnaire on disease assessment in TAK.

Results: Of the 4004 articles with the key-word "Takayasu's arteritis", items associated with disease assessment and activity were present in 62 studies. Among these, 45% (n=28) focused on clinical issues (case series, treatment, outcome), 32% (n=20) on biomarkers/pathogenesis, and 22% (n=14) on vascular imaging. An NIH study *(Kerr et al, 1994*) was most commonly cited for a definition of active disease (48%, n=30). Acute-phase response (ESR/CRP) was part of an "active" disease definition in 84% (n=52), constitutional features in 73% (n=45), clinical features of vascular ischemia in 53% (n=33), and angiographic involvement in 58% (n=36). A composite index of activity was used in three studies (BVAS=2, ITAS=1) and a patient-derived outcome tool (SF-36) in two studies.

After a presentation of the results of the literature search, experts were asked to define a "gold-standard" of disease activity in TAK. New vessel/organ involvement determined clinically or by imaging was chosen by 84%, physician global assessment by 13%; no expert named patient global assessment. The most commonly chosen items for a disease-assessment tool were new bruits or arterial imaging changes (both 100%), new extremity claudication (97%), acute-phase reactants (97%), arterial tenderness (94%), fever (88%), and constitutional symptoms (84%). Although experts felt that a dichotomous assessment (active vs. inactive) was not suitable (63%), they also agreed that damage vs. activity (83%) and grumbling vs. highly active disease (80%) cannot be reliably differentiated in TAK. Some organ manifestations present in BVAS and DEI.Tak (a recently-developed TAK-specific tool) were found suitable for TAK (cardiovascular-100%, CNS-93%, renal-87%, abdominal-83%, ocular-83%, musculoskeletal-72%) whereas others were felt to have a limited value (respiratory-50%, cutaneous-47%, ENT-24%, genitourinary-19%). The majority of experts (62%) agreed that an outcome measure could be developed for large-vessel vasculitis for use in research of giant-cell arteritis and TAK that incorporated manifestations of both diseases.

Conclusion: Outcome measures used in research for TAK vary considerably in content and do not consistently include clinical manifestations that experts give a high value to regarding disease assessment, including vascular imaging and biomarkers. These data are helpful in guiding the process of creating an internationally-accepted core set of outcome measures in large vessel vasculitis.

Disclosure: H. Direskeneli: None; **S. Z. Aydin:** None; **P. A. Merkel:** None; **Turkish Takayasu Study Group:** None.

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Effect of Glucocorticoids on Gelatinase (MMP-2 and MMP-9) Expression in Giant-Cell Arteritis (GCA) Using an *Ex-Vivo* Temporal Artery Culture Model. Marc Corbera-Bellalta, Ana García-Martínez, Ester Planas-Rigol, Ester Lozano, Marta Segarra, Georgina Espígol-Frigolé, José Hernández-Rodríguez, Itziar Tavera and Maria C. Cid. Department of Systemic Autoimmune Diseases. Hospital Clínic. University of Barcelona, IDIBAPS, Barcelona, Spain

Background: GCA is the most frequent systemic vasculitis in the elderly. Increased gelatinase expression and proteolytic activity have been demonstrated in GCA lesions. Gelatinases may play an important role in the progression of inflammatory lesions given their proinflammatory functions and elastinolytic activity and may also participate in vascular remodelling in response to injury. Glucocorticoids (GC) are the cornerstone of GCA treatment but it is not know how GC treatment influences gelatinase expression.

Purposes: To explore the effects of GC on gelatinase expression in GCA lesions using an *ex-vivo* arterial culture system.

Methods: Fresh temporal artery sections obtained from 19 GCA patients and 10 controls were embedded in the reconstituted basement membrane Matrigel™ and cultured for 5 days as described (Arthritis Rheum 2008 (suppl) 58:9; S929–S929). Cultured sections were treated with medium alone or with medium supplemented with 0.5mg/ml of dexamethasone. MMP-2 and MMP-9 mRNA was measured in recovered sections by quantitative real-time PCR (Applied Biosystems). Both gelatinases were also measured in the supernatant fluid by immunoassay (R&D Systems).

Results: MMP-9 mRNA was significantly more abundant in cultured sections from patients compared to controls (1283±1353 vs 304±222 relative units, p=0,039). Contrarily, no differences were observed in MMP-2 mRNA between normal and GCA cultured sections (2097±918 vs 3450±2800 relative units, p=0,758). MMP-9 and MMP-2 protein concentrations were higher in the supernatant from GCA sections compared to controls (48,9±30,3 vs 7,83±7,02 ng/ml, p=0,006 for MMP-9) although differences were not significant for MMP-2 (39,1±31,5 vs 15,3±16,6 ng/ml, p=0,192). Dexamethasone treatment for 5 days highly reduced MMP-9 expression both at the mRNA (861,2±1054 vs 88±110 p=0,018) and at the protein level (48,9±30,4 vs 8,6±5,4 ng/ml, p=0,003) whereas no effect was apparent on MMP-2 expression.

Conclusion: The pattern of gelatinase expression in cultured temporal artery sections parallels what has been observed in fresh biopsies (Ann Rheum Dis. 2007 Nov; 66(11):1429–35). In the present model, dexamethasone treatment dramatically reduced MMP9 expression with a much lesser effect on MMP-2 expression. These findings reinforce a pro-inflammatory role for MMP9 during active disease and suggest a role for MMP2 in vascular remodelling before and after treatment. Supported by SAF 05/06250 and MTV3 06/0710.

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1293

Efficacy of Cerebrospinal Fluid Testing and Magnetic Resonance Imaging for Diagnosis of Neuro-Behcet's Disease: A Multicenter Retrospective Analysis. Shunsei Hirohata[3], Hirotoshi Kikuchi[5], Tetsuji Sawada[6], Hiroko Nagafuchi[4], Masataka Kuwana[2], Mitsuhiro Takeno[1] and Yoshiaki Ishigatsubo[7]. [1]Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, [2]Keio University School of Med, Tokyo, Japan, [3]Kitasato Univ School of Med, Kanagawa, Japan, [4]St Marianna University School of Med, [5]Teikyo Univ School of Med, [6]Tokyo Medical University, Shinjuku Tokyo, Japan, [7]Yokohama City Grad Sch of Med, Yokohama, Japan

Objective: Central nervous system (CNS) involvement in Behcet's disease (BD) is one of its most serious complications (neuro-Behcet's disease [NBD]). Since there are factors causing neurological manifestations other than BD (non-NBD), the diagnosis of NBD is often difficult. The present study was therefore designed to delineate the clinical characteristics of NBD and to determine the reliable diagnostic parameters. Special attention was paid to cerebrospinal fluid (CSF) cell counts and interleukin-6 (IL-6) as well as magnetic resonance imaging (MRI) findings.

Methods: A multicenter retrospective survey was performed on BD patients who fulfilled the diagnostic criteria of the international study group and presented neurological manifestations between 1987 and 2008. The diagnosis of either NBD or non-NBD was confirmed by retrospective review of the clinical records. NBD was further classified into acute NBD and chronic progressive NBD according to the clinical courses.

Results: A total of 144 BD patients were studied, including 76 with acute NBD, 35 with chronic progressive NBD, and 33 with non-NBD. Smoking and HLA-B51 were correlated with chronic progressive NBD (p=0.0024 and p=0.0106, respectively). CSF cell counts were most prominently elevated in acute NBD, but were within normal limits in approximately 15% of chronic progressive NBD. ROC curve analysis revealed that the sensitivity and specificity of CSF cell counts for diagnosis of acute NBD were 97.3 % and 96.7%, respectively, at the cut-off value of 6.5/mm^3. Whereas CSF IL-6 was elevated in both acute NBD and chronic progressive NB, it was decreased only in acute NBD after treatment. Moreover, the sensitivity and specificity of CSF IL-6 for differential diagnosis of chronic progressive NBD from

recovery phase of acute NBD were 86.7 % and 94.7%, respectively, at the cut-off value of 16.55 pg/ml. High intensity lesions on MRI T2-weightened images were found in 60.5% of acute NBD, 54.2% of chronic progressive NBD, and 42.4% of non-NBD, whereas brainstem atrophy was observed in 7.5% of acute NBD, 71.4% of chronic progressive NBD, and 9.0% of non-NBD.

Conclusion: The results indicate that CSF cell count is a useful marker for diagnosis of acute NBD, whereas determination of persistent elevation of CSF IL-6 along with brainstem atrophy on MRI is pivotal for diagnosis of chronic progressive NBD. The data have also disclosed that T2 high intensity lesions on MRI are neither sensitive nor specific for diagnosis of NBD.

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1294

Endothelin-1 (ET-1) Induces Collagen Type I and Type III Production by Temporal Artery-Derived Myointimal Cells. A Mechanism Potentially Leading to Intimal Hyperplasia in Giant-Cell Arteritis (GCA). Ester Planas-Rigol, Marc Corbera-Bellalta, Ester Lozano, Montserrat Butjosa, Sergio Prieto-González, José Hernández-Rodríguez, Marta Segarra and Maria C. Cid. Department of Systemic Autoimmune Diseases. Hospital Clínic. University of Barcelona, IDIBAPS, Barcelona, Spain

Background: GCA is a granulomatous vasculitis involving large and medium-sized arteries. The inflammatory process leads to intimal hyperplasia and vascular occlusion with the ensuing ischemia of supplied tissues. Intimal hyperplasia results from proliferation and matrix production by myointimal cells. Recent studies demonstrate up-regulation of the ET system in GCA lesions and increased ET-1 concentrations in plasma from patients with cranial ischemic complications (Ann Rheum Dis. 2010 Feb; 69(2):434–42). ET-1 is one of the most potent vasoconstrictor agents and may create a microenvironment prone to the development of vasospasm, contributing to ischemic events.

Purpose: To investigate whether ET-1 may additionally contribute to vascular occlusion by inducing pro-fibrotic responses in cultured human temporal artery-derived myointimal cells (HTAMC) potentially participating in the development of intimal hyperplasia.

Methods: HTAMC were obtained from cultured temporal artery sections from patients with GCA as described (Ann Rheum Dis. 2008 Nov; 67(11): 1581–8). Transforming growth factor b (TGFb), collagen type I (COL1) and type III (COL3) expression was assessed by quantitative real-time PCR (Taqman^{R} Gene Expression Assay) from Applied Biosystems.

Results: ET-1 up-regulated TGFb and COL1 expression by HTAMC in a dose-dependent manner. A delayed increase in COL3 expression was also observed which was partially mediated by TGFb. Study of underlying mechanisms is in progress.

Conclusions: ET-1 may contribute to intimal hyperplasia directly by inducing collagen type I and indirectly by inducing the synthesis of the fibrogenic cytokine TGFb by human temporal artery-derived myointimal cells. These preliminary results suggest that ET receptor antagonists may prevent vascular occlusion in GCA.

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1295

Expansion of Peripheral Blood Plasma Blasts Reflects Disturbances of B Cell Homeostasis in Patients with Takayasu Arteritis and Success of B Cell Depletion Therapy. Bimba F. Hoyer[3], Imtiaz M. Mumtaz[3], Udo Schneider[2], Rolf Keitzer[1], Gerd-Rüdiger Burmester[2], Andreas Radbruch[5] and Falk Hiepe[4]. [1]Dep. Pediatric Rheumatology, Charité Universityhospital Berlin, [2]Dep. Rheumatology and Clin. Immunology, Charité Universityhospital Berlin, [3]Dep. Rheumatology and Clin. Immunology, Charité Universityhospital Berlin and German Rheumatism Reserach Center Berlin, Berlin, Germany, [4]Dep. Rheumatology and Clin. Immunology, Charité Universityhospital Berlin and German Rheumatism Reserach Center Berlin, [5]German Rheumatism Reserach Center Berlin

Purpose: Takayasu arteritis (TA) is a rare form of chronic large vessel vasculitis mainly affecting the aorta and its branches.

The etiology of TA is yet unknown but highly suggestive of T cell-mediated autoimmunity. The presence of autoantibodies against endothelial cells (AECA) however indicates that autoreactive B cells and plasma cells may be involved in the pathogenesis.

Therefore, we comprehensively analysed the peripheral blood B cell subpopulations from TA patients.

Methods: 14 patients suffering from TA (7 active, 7 inactive) were analysed. As controls, 10 patients with active SLE and 9 healthy donors were investigated.

PBMCs were surface stained for expression of CD27, CD19, CD20 and MHCII and analysed by flowcytometry. Plasmablasts were characterized as being $CD19^{+}CD20^{-}CD27^{+++}$ and $MHCII^{++}$. All $CD27^{+++}$ $CD20^{-}CD19^{+}$ cells represent both newly generated plasmablasts and plasma cells. Sera of patients were tested for the presence of Anti-Endothelial-Cell-Antibodies (AECA).

Data was analysed using Flowjo-Software. Statistical analysis was done with SPSS.

Results: Patients with active TA revealed significantly more peripheral blood plasmablasts compared to patients with inactive disease as well as healthy persons. Absolute numbers of plasmablasts in patients with active TA (mean 0,0068/nl, SD 0,0049/nl) were comparable to active SLE patients (mean 0,01908/nl, SD 0.02/nl) whereas inactive patients (mean 0,001629/nl SD 0.0016/nl) show numbers comparable to healthy persons (median 0,001057/nl, SD 0.0005/nl). The same is true for the frequency of plasma cells within the B cells.

In addition a significant correlation between the frequencies of $CD27^{+++}CD20^{-}CD19^{+}$ cells in the B cell population and Crp-level could be observed as well ($r=0{,}731$ $p=0{,}0029$, Pearson-Test).

No correlation could be found with the presence of AECA.

Based on these results we successfully treated three patients refractory to conventional immunosuppressive drugs and TNF blockers with B cell depletion.

Conclusion: For the first time disturbances in the B cell homeostasis in TA that might be crucial in the pathogenesis are described. Therefore B cells and plasma cells should be considered as a target for therapeutic approaches as successful treatment of three patients by B cell depletion underlines.

Analysis of peripheral blood plasmablasts seem to emerge as biomarker, which characterizes disease activity in TA and can be helpful for therapeutic decisions.

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1296

Expression and Function of Toll Like Receptors in Peripheral Blood Mononuclear Cells of Patients with Polymyalgia Rheumatica and Giant Cell Arteritis. Lorena Alvarez-Rodriguez[4], Marcos Lopez-Hoyos[4], Cristina Mata[1], Ana Fontalba[4], Jaime Calvo-Alen[1], Maria Jose Marin[4], Jose Luis Fernandez-Luna[4], Jesus Agüero-Balbin[4], Maitane Aranzamendi-Zaldunbide[4], Ricardo Blanco[4], Ignacio Villa[2], Orlando Pompei[4], Marien Peiro[4], Teresa Ruiz[1] and Victor M. Martinez-Taboada[3], [1]Hospital de Sierrallana, Spain, [2]Hospital de Sierrallana, Spain [3]Hospital Universitario Marques de Valdecilla, Santander, Spain, [4]Hospital Universitario Marques de Valdecilla

Objective: To investigate the expression and function of the TLR family in PBMCs of patients with polymyalgia rheumatica (PMR) and giant cell arteritis (GCA).

Methods: We analyzed 70 patients with PMR, 20 with GCA and 24 healthy controls (HC). TLR expression was assessed by flow cytometry. TLR function was studied by stimulating PBMCs with specific ligands.

Results: A significant increased expression of TLR7 in PBMCs of patients with active disease compared with HC was found. Despite an increased expression of TLR7, circulating monocytes from patients showed a significant lower *in vitro* response to TLR7 agonists. No amino acid substitutions predicted to be functionally damaging were found in TLR7. A normal response to specific TLR7 agonists in patients in complete remission eliminated a genetic defect. The expression profile on PBMCs from HC induced by plasma from PMR and GCA were marked by up-regulation of type I IFN-response transcripts, suggesting that the diminished response to TLR7 agonists in active disease was secondary to receptor saturation with natural ligands. We attempted to identify the presence of a set of respiratory virus in plasma from patients without conclusive results.

Conclusion: These data suggest the activation of TLR7 by a natural(s) ligand(s) in patients with PMR and GCA that is followed by a selective desensitization of the receptor. Despite the failure to identify a responsible virus in plasma from patients, the up-regulation of type I IFN-response genes

after stimulation with patients' plasma suggests a possible viral etiology in these two syndromes.

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Extracellular HMGB1 Is Increased in Patients with Behcet's Disease with Intestinal Involvement. Joong Kyong Ahn[2], You Sun Lee[3], Eun-Jung Park[4], Ji-Won Hwang[4], Ji-Min Oh[4], Jaejoon Lee[4], Chan-Hong Jeon[1], Eun-Mi Koh[4] and Hoon-Suk Cha[4], [1]Bucheon Hospital, Soonchunhyang University College of Medicine, [2]Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, [3]Masan Samsung Hospital, Sungkyunkwan University School of Medicine, [4]Samsung Medical Center, Sungkyunkwan University School of Medicine

Objective: Behcet's disease (BD) is a chronic multisystemic inflammatory disorder of unknown etiology consisting of orogenital ulceration, ocular inflammation, and skin lesions. HMGB1 (High-Mobility Group Box 1 protein) has been demonstrated to play an important role in chronic inflammatory diseases including rheumatoid arthritis, systemic lupus erythematosus, and inflammatory myositis. HMGB1 is a crucial cytokine that mediates the response to infection, injury and inflammation. HMGB1 activates macrophages and monocytes to release proinflammatory cytokines, upregulates endothelial adhesion molecules, and stimulates epithelial cell barrier failure. We performed this study to investigate the association between extracellular HMGB1 expression and disease activity and clinical features of Behcet's disease.

Method: Extracellular HMGB1 expression from the sera of 42 BD patients and age- and sex-matched 22 healthy controls (HC) was measured using ELISA.

Results: According to the activity criteria based on clinical manifestation at the time of study, 42 patients with BD comprised 25 active and 15 inactive patients with mean age of 47 years (range 22–65 years). The HMGB1 concentration was significantly increased in BD patients compared to HC (78.70±20.22 vs. 10.79±1.90 ng/ml, p=0.002). In addition, HMGB1 concentration was significantly elevated in patients with intestinal involvement compared to those without (179.61±67.95 vs. 61.89±19.81, p=0.04). Patients with vascular involvement showed decreased trend of serum HMGB1 expression compared to those without vascular involvement (36.79±12.63 vs. 95.47±27.41 ng/ml, p=0.059). There was no significant association between HMGB1 concentration and clinical manifestation, including genital ulcer, erythema nodosum, ocular involvement or musculoskeletal symptoms. No significant difference in the serum HMGB1 level was found between inactive and active BD patients (58.78±18.46 vs. 92.26±31.63 ng/ml, p=0.367). No significant correlation was found between HMGB1 concentration and leukocyte counts, ESR, or CRP.

Conclusion: This is the first study to evaluate the expression of HMGB1 in Behcet's disease. An important finding in our study is that extracellular HMGB1 concentrations are significantly increased in BD patients compared to HC, and are significantly increased in the sera of BD patients with intestinal involvement compared to those without intestinal involvement. These results suggest that extracellular HMGB1 may play an important role in the pathogenesis of BD.

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Eye Involvement in Behcet's Syndrome Patients in a North American Cohort. Johannes Nowatzky[3], Maria T. Filopoulos[4], Christopher Swearingen[1] and Yusuf Yazici[2]. [1]Biostatistics UAMS Pediatrics, [2]Hospital for Joint Diseases, Hastings on Hudson, NY, [3]NYU Hospital for Joint Diseases, Brooklyn, NY, [4]NYU Hospital for Joint Diseases

Background: Ocular disease has been reported in up to 75 % of patients with Behcet's Syndrome (BS) in endemic regions where permanent visual loss is common. The prevalence of eye disease in North American BS patients is unknown, but felt to be lower than in endemic regions. More prevalent and severe eye disease is expected in North American populations with an ethnic background in those regions.

Methods: A BS center was established in New York City in 2004. Patients at the center completed an MDHAQ, BSAS (Behcet Syndrome Activity Score), questionnaires about past medical history, medication use, Behcet's specific history, ethnic and demographic information. These data were prospectively collected over 5 years and updated on each visit. Patients fulfilling the International Behcet's Classification Criteria were analyzed as one cohort and then in 2 groups: Group A= with ethnic background in northern/central Europe and North America and/or self declared Caucasians without Mediterranean, Middle Eastern and/or Far Eastern background; Group B= Patients with Mediterranean, Middle Eastern, North African, or Far Eastern ethnic background. These groups were compared for their prevalence, type and outcome of ocular disease.

Results: 471 patients were seen for suspected BS. 296 (62.8%) fulfilled the International Behcet's Classification Criteria and were included in the present study. Of those, 121 (40.9%) patients had eye disease, which included 56 (18.9%) with uveitis, 8 (2.7%) with retinitis, 11 (3.7%) with episcleritis, and 42 (14.2%) with other eye disease. There was no statistically significant difference between Groups A (n=163) and B (n=133) regarding the prevalence of eye disease (41.1% vs. 40.6%, p<0.93), types of involvement: uveitis (19.6% vs. 18.0%, p<0.729), retinitis (1.8% vs. 3.8%, p<0.311), episcleritis (3.1% vs. 4.5%, p<0.514), baseline disease activity and use of immunosuppressive medications. None of the patients presented with or developed blindness during the study period.

Conclusions: Eye involvement was less prevalent and seemed to have better outcomes in this North American cohort of BS patients than in cohorts studied in high-incidence/endemic BS regions. Contrary to our expectations, there was no significant difference in prevalence or outcome of Behcet's eye disease between North Americans of non-Mediterranean European ancestry compared to individuals of Mediterranean, Middle- or Far Eastern descent living in the US. These findings could suggest a role of environmental factors in the phenotypic expression of BS in general, and in the pathogenesis of Behcet's eye disease in particular.

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Glucocorticoid Therapy in Giant Cell Arteritis: Duration and Predictors for Long-Lasting Remission. Paula Estrada, Javier Narvaez, Laura Lopez Vives, Carmen Gomez Vaquero and Joan Miquel Nolla. Department of Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain

Purpose: To analyze the clinical course and duration of glucocorticoid (GC) therapy in a series of patients with giant cell arteritis (GCA), identifying those predictors for the achievement of a long-lasting remission.

Methods: Retrospective follow-up study of an unselected population of 140 patients with GCA diagnosed in 1 center between 1986 and 2008. The end-point of patient follow-up was the date of the last clinic visit or the date of death. Long-lasting remission was recorded as the date of permanent discontinuation of treatment without recurrence of symptoms for at least 1 year.

Possible correlations between the duration of therapy and demographic, clinical, laboratory and treatment variables were explored. Multivariate regression analysis were used to identify variables associated with the achievement of long-lasting remission.

Results: The series included 94 women and 46 men with a mean age at time of diagnosis of 75 ± 7 years (range, 56 to 92). TAB was positive in 112 (80 %) patients. The median follow-up duration after diagnosis was 36.6 months (range, 12.5 to 180).

All patients were treated with GCs and responded rapidly (mean initial dosage of prednisone: 50.1 ± 13.7 mg/day). The dosage was later reduced according to the treating physicians' judgment. The median duration required to achieve a maintenance dose of less than 10 mg prednisone/day was 8.5 months. Relapses or recurrences occurred in 82 (52.6%) patients, with a mean of 2.7 ± 1.7 relapses per patient.

In 60 (42.8%) patients, GCs were discontinued and permanent remission achieved after a median of 26.7 months of treatment, with a range of 13 to 90 months. The median cumulative dose of prednisone taken by these patients was 8.51 gm. Only in 33.3% (20/60) of these patients GCs could be withdrawn within the first 2 years of treatment. This percentage increased to 73% (33/60) at 3 years, 81.6% (49/69) at 4 years, and 88.3% (53/60) at 5 years, with only 11.6% (7/60) of the patients requiring therapy for more than 5 years.

At the time of last follow-up, 80 (57.2%) of the 140 patients were still taking GCs with a median treatment duration of 36 months; in 50% of these patients the duration of treatment was longer than 3 years.

A significant correlation was found between the duration of therapy and ***(1)*** diagnostic delay (r=0.240; p=0.004), ***(2)*** age at disease onset (r = −0.237; p = 0.004), ***(3)*** the value of pre-treatment erythrocyte sedimentation rate (r=0.154; p=0.047), and ***(4)*** total dose of prednisone (r=0.824; p=<0.0001). In the multivariate analysis, the only variables associated with the achievement of long-lasting remission were the age at disease onset

(OR=0.93, 95% CI: 0.87, 1.00) and the cumulative dose of prednisone (OR=0.85, 95% CI: 0.77, 0.95)

Conclusion: Results of the currtent study show that it is rare to stop steroid therapy before at least 2 years of treatment (only achieved in 14% of the patients). In the majority of cases the disease follows a protracted course requiring long-term treatment with GCs, with a subset of patients who need low dose prednisone indefinitely. Some baseline parameters can help to identify those patients at high risk for prolonged steroid use.

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Infliximab Therapy Is Beneficial for Intestinal Behcet's Disease in Japan. Reikou Watanabe, Mitsuhiro Takeno and Yoshiaki Ishigatsubo. Department of Internal Medicine and Clinical Immunology, Yokohama City Graduate School of Medicine

Objects: Intestinal involvement is one of the most serious manifestations in patients with Behcet's disease. The therapy is not established. Although there are a few English written reports concerning clinical efficacy of infliximab (IFX) for intestinal Behcet's disease, the therapy is not uncommon in Japan. We conducted a nationwide survey of clinical efficacy and safety issues in IFX therapy for patients with intestinal Behcet's disease in Japan.

Methods: We retrospectively collected clinical data of 121 patients who had received infliximab therapy more than once for intestinal Behcet's disease from 38 institutes in Japan by using questionnaires. Of them, 89 patients (male 45, female 42, 43.3 + 14.3 y.o) who met the Japanese criteria revised in 1987 were included in the study.

Results: The major clinical features in the patients were abdominal pain (88%), diarrhea (55%), and gastrointestinal bleeding (51%). The lesions were mainly distributed in ileum (84%), cecum (45%), and ascending colon (34%). Before starting the IFX, the patients had received corticosteroids (83%), mesalazine (69%), colchicine (55%), and any immuosuppressants such as cyclosporine, azathioprine, and methotrexate (70%). Surgical operation was conducted in 31 patients (35%). IFX (3 to 5 mg/kg) was give one to 48 times. Nineteen patients received IFX more than 20 times over three years. Subjective improvement was noted in 81% of patients. Endoscopic improvement and/or steroid sparing effect were confirmed in 52%. Favorable responses were found in patients having ocular lesions and arthritis, latter of which was proven as an independant factor by multivariate logistic regression analysis. On the other hand, patients having concurrent esophageal lesions showed a poor response to the therapy. Eleven adverse events including 8 infections were noted. The therapy was discontinued in 24 patients (27%) because of remission (5 patients), adverse events (10 patients) and exacerbation or insufficient efficacy (9 patients).

Conclusions: IFX therapy showed favorable clinical outcomes even in Behcet's disease patients who had refractory intestinal lesions to conventional therapies.

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Influence of CD40 rs1883832 Polymorphism in the Susceptibility to and Clinical Manifestations of Biopsy-Proven Giant Cell Arteritis. Luis Rodríguez-Rodríguez[8], Santos Castañeda[4], Tomás R. Vazquez-Rodriguez[7], Inmaculada C. Morado[3], Beatriz Marí-Alfonso[1], Carmen Gómez-Vaquero[5], Jose A. Miranda-Filloy[7], Javier Narvaez[5], Norberto Ortego-Centeno[2], Ricardo Blanco[6], Benjamín Fernández-Gutiérrez[3], Javier Martín[9] and Miguel A. Gonzalez-Gay[6]. [1]Department of Internal Medicine, Corporació Sanitaria Parc Taulí, Instituto Universitario Parc Taulí, UAB, Sabadell, Barcelona, Spain, [2]Department of Internal Medicine, Hospital Clínico San Cecílio, Granada, Spain, [3]Department of Rheumatology, Hospital Clinico San Carlos, Madrid, Spain, [4]Department of Rheumatology, Hospital de la Princesa, Madrid, Spain, [5]Department of Rheumatology, Hospital Universitario de Bellvitge-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain, [6]Department of Rheumatology, Hospital Universitario Marqués de Valdecilla, IFIMAB, Santander, Spain, [7]Department of Rheumatology, Hospital Xeral-Calde, Lugo, Spain, [8]Instituto de Parasitología y Biomedicina López-Neyra, C.S.I.C., Granada, and Department of Rheumatology, Hospital Clinico San Carlos, Madrid, Spain, [9]Instituto de Parasitología y Biomedicina López-Neyra, C.S.I.C., Granada, Spain

Objective: The purpose of this study was to assess the potential association between CD40 rs1883832 polymorphism and biopsy-proven GCA. We also studied whether this polymorphism might influence the phenotypic expression of this vasculitis, in particular the development of visual ischemic manifestations.

Methods: 305 Spanish patients with biopsy-proven GCA and 788 matched controls were assessed. DNA from patients and controls was obtained from peripheral blood. Samples were genotyped for the CD40 rs1883832 C/T polymorphism using a predesigned TaqMan allele discrimination assay and by polymerase chain reaction amplification.

Results: Biopsy-proven GCA patients showed a trend towards a higher frequency of the minor allele homozygote of rs1883832 (TT) compared to healthy controls (12.1% vs. 8.3%, respectively; p= 0.05, odds ratio-OR: 1.54 [95% confidence interval-CI: 0.98–2.40]). Also, a marginally significant increased frequency of the minor allele T was observed in GCA patients with visual ischemic manifestations (36.9%) compared to those without visual ischemic manifestations (27.7%); OR: 1.53 [95% CI: 0.99–2.34], p=0.04). In this regard, biopsy-proven GCA patients carrying the minor allele T (either TT or TC) experienced visual ischemic manifestations more commonly than those carrying the CC genotype (58.5% versus 44.2%, OR 1.78 [95% CI: 0.99–3.22], p=0.04).

Conclusions: Our results suggest a potential implication of the CD40 rs1883832 C/T polymorphism in the susceptibility to visual ischemic manifestations in individuals with biopsy-proven GCA.

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Large-Vessel Involvement in Newly-Diagnosed Giant Cell Arteritis: A Case-Control Study Using Color-Doppler Sonography. Alessandra Ghinoi[1], Luigi Boiardi[1], Nicolò Pipitone[1], Giovanna Restuccia[1], Alberto Nicolini[1], Mauro Silingardi[1], Giuseppe Germanò[1], Gianluigi Bajocchi[1], Ilaria Chiarolanza[1], Luca Magnani[2], Pierluigi Macchioni[1], Andrea Caruso[1] and Carlo Salvarani[1]. [1]Arcispedale S Maria Nuova, Reggio Emilia, Italy, [2]Arcispedale S Maria Nuova, Reggia Emilia, Italy

Purpose: The prevalence of large-vessel vasculitis (LVV) in newly diagnosed giant cell arteritis (GCA) is still poorly documented. Two studies have estimated such prevalence at 30**%** and 83% using Color-doppler sonograhy (CDS) (1) and ^{18F}-FDG PET (fluoroxedoxyglucose positron emission tomography) (2), respectively. CDS allows to visualize the temporal, axillary, and subclavian arteries, as well as the aortic arch, abdominal aorta and supra-aortic vessels. The presence of a hypoechoic halo around the arterial walls is considered quite specific for GCA.

The aim of this study was to investigate the prevalence of LVV in newly diagnosed GCA using CDS and to compare the clinical findings of GCA patients with and without LVV.

Methods: Sixty-two consecutive patients with a diagnosis of new-onset GCA according to the American College of Rheumatology criteria who had a CDS performed were analyzed. The identified patients with LVV were randomly matched to an equal number of GCA patients without LVV.

Results: In 19 out of 62 patients (30.6%), CDS showed the characteristic halo sign in at least one vessel examined. Comparing patients with and without LVV, no significant difference was found for any of the following parameters: gender (male:female 0.0/100% versus 21.1%/78.9%), positivity of the temporal artery biopsy (82.4% versus 88.2%), presence of a transmural infiltrate (78.6% versus 86.7%) or periadventitial infiltrate (21.4% versus 13.3%), temporal arteries' abnormalities on inspection (85.7% versus 92.3%), cranial (77.8% versus 94.1%) and constitutional (66.7% versus 35.3%) manifestations. Similarly, the ESR was similar in both groups (91±30 versus 72±25 mm/1st hour).

Conclusion: LVV evidenced by CDS occurred in 30.6% pts with newly diagnosed GCA. This prevalence is very similar to that found in a previous study with a similar design. Constitutional manifestations were more frequent and cranial manifestations were less frequent in our GCA patients with LVV, although the difference did not reach significance. Early diagnosis of LVV in GCA can help tailor treatment accordingly and may prevent vascular complications.

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1303

New Disease Activity Indices in the Management of Behcet's Disease: A Comparative Study of Patients from Turkey and the USA. Gonca Mumcu, Yusuf Yazici, Nevsun Inanc, Tulin Ergun, Maria Filopoulos and Haner Direskeneli. Faculty of Health Sciences, Department of Health Informatics and Technologies, Marmara School of Medicine

Purpose: The aim of this study was to evaluate and compare oral ulcer activity by Composite index (CI) and general disease activity by Behcet Syndrome Activity Score (BSAS) in patients from Turkey (TR) and the USA with Behcet's disease (BD).

Methods: In this cross-sectional study, age- matched 30 Caucasian active female patients from TR (mean age: 41.10 ±11.04 years) and 30 Caucasian active female patients from USA (mean age: 41.40± 11.56 years) with BD were included. Patients from TR were examined in Marmara University Hospital, Department of Rheumatology whereas patients from USA were examined in NYU, Hospital for Joint Disease in the same time span. Composite index (CI) was previously validated (1) for oral ulcer activity. It evaluates both pain scored by visual analogue scale (VAS) and functional status. Behcet Syndrome Activity Score (BSAS) (2) is a general disease activity index and evaluates clinical activities according to organ involvement in BD. CI and BSAS were filled by both patients from Turkey (TR) and USA. Scores could be between 0 and 10 in CI and 0 –100 in BSAS, (0=inactive disease). Oral health related quality of life was evaluated by oral health impact profile-14 (OHIP-14) in both groups. Better oral health-related quality of life was indicated with lower scores in OHIP-14 (range 0–56).

Results: No significant difference was found in OHIP-14 scores between patients from TR (21.4±13.7) and USA (21.9±12.7) ($p=0.886$). Although the number of oral ulcers was higher in patients from TR than patients from USA (4.3±2.5 and 3.3±2.8, respectively), this was not statistically significant ($p=0.161$). Yet, CI index score and pain score evaluated by VAS as its subscale score, were higher in patients from TR (7.8±1.6, 52.7±22.1) compared to the US patients (4.2±1.5, 35.9±27.8) ($p<0.001$ and $p=0.013$, respectively). CI score was correlated with BSAS score in patients from TR ($r=0.36$ $p=0.04$) and USA ($r=0.44$ $p=0.02$).

BSAS score was higher in patients from USA (44.5±18.5) compared to patients from TR (23.4±15.4)($p<0.0001$). In accordance with these results, majority of patients from USA (76.7 %) were treated with immunosuppressive medications compared to patients from TR (6.7 %) ($p<0.0001$).

Conclusions: CI and BSAS, two patient derived disease activity measures, showed moderate correlation with the manifestations of BD and moderate correlation with one another in these two different patient populations They may be suitable tools for use both in routine clinical care and clinical studies in BD patients.

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Disclosure: G. Mumcu: None; **Y. Yazici:** None; **N. Inanc:** None; **T. Ergun:** None; **M. Filopoulos:** None; **H. Direskeneli:** None.

1304

Normal Sedimentation Rate and C-Reactive Protein at Diagnosis in Biopsy-Proven Giant Cell Arteritis. Tanaz A. Kermani, Cynthia S. Crowson, Steven R. Ytterberg, Gene G. Hunder and Kenneth J. Warrington, Mayo Clinic, Rochester, MN

Purpose: 1) To determine the frequency of normal erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) at diagnosis in biopsy-proven giant cell arteritis (GCA) and 2) to evaluate clinical factors associated with discordant or normal ESR/CRP.

Methods: In this retrospective cross-sectional study, medical records of all patients with biopsy-proven GCA evaluated between January 1, 2000 and December 31, 2008 were reviewed. Only subjects with ESR and CRP available at the time of diagnosis were included. Clinical information was abstracted. Subjects with both ESR and CRP normal and those with discordant ESR/CRP were identified. We used our laboratory cut-off values for elevated ESR (>22 mm/hour for men and >29 mm/hour for women) and CRP (>8 mg/L). Fisher's exact test was used to compare categorical variables between patients with discordant results to those with concordant ESR/CRP, and GCA patients with normal ESR/CRP to those with elevated ESR/CRP. Rank sum tests were used to compare continuous variables between the above two groups.

Results: Two-hundred and forty patients were diagnosed with biopsy-proven GCA at a single institution during the study period. Of these, 160 subjects (78%) had ESR and CRP available prior to GCA diagnosis. The final study population included 119 women (74.4%) and 41 men (25.6%); mean age at diagnosis 74.3 years (±7.59). Nine patients (5.6%) had discordant ESR and CRP of whom 7 had elevated CRP but normal ESR. Mean age at diagnosis of GCA, mean duration of symptoms, clinical symptoms and laboratory findings at GCA diagnosis were similar in patients with discordant ESR/CRP compared to patients with concordant results ($p>0.05$).

Both ESR and CRP were normal in 18 patients (11.3%), 11 of whom were on prednisone and were excluded from the analysis. However, 7 patients (4%) had normal ESR and CRP at diagnosis in the absence of prednisone use. Table 1 compares the clinical manifestations and laboratory findings of these 7 patients to those with elevated ESR or CRP. A greater proportion of patients with normal ESR and CRP had polymyalgia rheumatica (PMR) symptoms compared to patients with elevated ESR or CRP ($p=0.02$). Furthermore, fewer patients with normal ESR and CRP had anemia ($p<0.001$) and there was a trend toward less thrombocytosis ($p=0.09$) compared to subjects with elevated ESR or CRP.

Table 1. Clinical manifestations of GCA patients with normal ESR and CRP to those with elevated ESR and/or CRP

Clinical Variable	ESR, CRP elevated, No (%) N=126	ESR and CRP normal, No (%) N=7	p-value
Female gender	92 (73)	6 (85.7)	0.68
Mean age at diagnosis, years	74.3 (±7.88)	70 (±5.87)	0.12
Median duration symptoms, days	53	113	0.32
Mean duration from laboratory testing to biopsy, days	6.1 (±8.34)	8.7 (±9.07)	0.52
New headache	79 (62.7)	4 (57.1)	1.00
Jaw claudication	61 (48.4)	2 (28.6)	0.45
Scalp tenderness	43 (34.1)	2 (28.6)	1.00
Permanent vision loss	11 (8.7)	1 (14.3)	0.49
Fever	31 (24.6)	0 (0)	0.20
Anorexia	16 (12.7)	0 (0)	0.60
Weight loss	42 (33.3)	1 (14.3)	0.43
Polymyalgis rheumatica	33 (26.2)	5 (71.4)	0.02
NSAID use	61 (49.6)	2 (28.6)	0.44
Anemia	89 (70.6%)	0 (0)	<0.001
Thrombocytosis	43 (36.4)	0 (0)	0.09

Conclusions: CRP is considered a more sensitive marker in GCA. This is the largest, single center study to date evaluating the prevalence of normal CRP in biopsy-proven GCA. While ESR and CRP were concordantly elevated in most patients, discordant results were noted in 5.6%. More significantly, 4% of patients in this study had both normal ESR and CRP at diagnosis. They were more likely to present with PMR symptoms. Absence of a systemic inflammatory response does not exclude GCA and biopsy should be pursued in patients with high clinical suspicion of GCA, especially if PMR symptoms are present.

Disclosure: T. A. Kermani: None; **C. S. Crowson:** None; **S. R. Ytterberg:** None; **G. G. Hunder:** None; **K. J. Warrington:** None.

1305

Pediatric Behçet's Disease, PED-BD: An International Cohort Study of 110 Patients. One-Year Follow-Up Data. Isabelle Koné-Paut[11], Martha Darce Bello[11], Farahd Shahram[15], Marco Gattorno[7], Rolando Cimaz[10], Seza Özen[2], Michael Hofer[14], Ilknur Tugal-Tuktun[5], Samir Assaad-Khalil[3], Jasmin Kümmerle-Deschner[16], Saida Benamour[4], Soulaymane Al Mayouf[8], Christine Pajot[13], Jordi Anton[9], Albert Faye[12], Susan Nielsen[6], Alexia Letierce[1] and Tu-Anh Tran[11], [1]Bicêtre University Hospital, Clinical Research Unit, Le Kremlin-Bicêtre, France, [2]Hacettepe University, Department of Pediatrics, Ankara, Turkey, [3]Hospital Alexandria Hospital, Alexandria, Egypt, [4]IBN Rochid University Hospital, Casablanca, Morocco, [5]Istanbul University-Ophtalmology, Istambul, Turkey, [6]Pediatric Clinic, Blegdamsvej, Copenhagen, Denmark, [7]Pediatric Rheumatology G. Gaslini Scientific Institut, Genoa, Italy, [8]Pediatric Rheumatology King Fayçal Hospital, Riyadh, Saudi Arabia, [9]Pediatric Rheumatology Unit, Sant Joan de Déu University Hospital, Esplugues de Llobregat, Spain, [10]Pediatric Rheumatology, A. Meyer Institut Florence, Florence, Italy, [11]Pediatric Rheumatology, Bicêtre University Hospital, Le Kremlin-Bicêtre, France, [12]Pediatric Rheumatology, Robert Debré University Hospital, Paris, France, [13]Pediatric Rheumatology, Toulouse University Hospital, Toulouse, France, [14]Pediatric Rheumatology, Vaudois University Hospital, Lausanne, Switzerland, [15]Rheumatology Research Center, Shariati Hospital, Tehran, Islamic Republic of Iran, [16]Rhumatology, Childrens Hospital, University of Tuebingen, Tübingen, Germany

Aim of the Study: To set up an algorithm for definition of pediatric Behçet's disease (PED-BD) based on international cohort of children suspected with BD

Patients and Methods: An international expert committee has defined the inclusion criteria as follows: Recurrent oral aphthosis (ROA) associated with at least one of following: genital ulceration (GU), erythema nodosum, folliculitis, pustulous/acneiform lesions, positive pathergy test, uveitis, venous/arterial thrombosis, family history of BD. Onset of disease is before the 16th birthday, disease duration is ≤ 3 years, minimum future follow up duration is 4 years and to obtain informed consent. Clinical data are updated every year. Accordingly, the included patients are classified by the expert committee into 3 groups: definite PED-BD, probable PED-BD and no PED-BD. Statistical analysis are performed at the end to compare the 3 groups of patients. Centers specializing in PED-BD have been called to collaborate and document their patients into a single database, (available online).

Results: In January 2010, 110 patients (56M/54F) from 16 centres of 11 countries have been included. Mean age at first symptom: 8.1 y (median 8.2,). Mean age at BD suspicion: 11.8 y, (median 14.4y). At inclusion 38 % of them had only 1 symptom associated with ROA, 31% had 2 and 31% had at least 3. 106 first evaluations have been done. Chronology of symptoms at presentation: 59 patients with 1 symptom (ROA: 45, and fever:5 being the most frequent)), 26 with 2 symptoms (OA + GU: 6), 14 with 3 and 3 with 4.

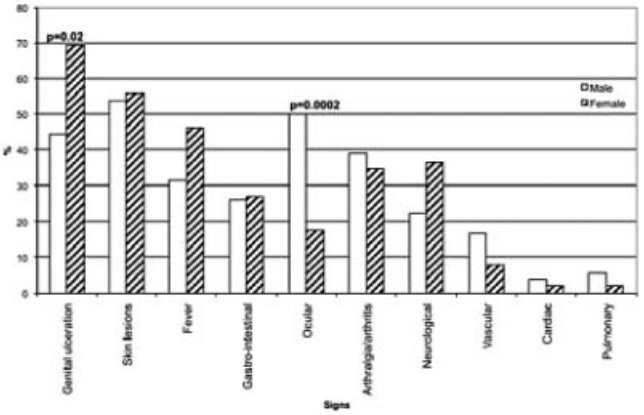

Figure 1. Clinical signs (percentages) at first visit, according to their gender, in 106 PED-BD patients.

93% were receiving treatment: colchicine 59%, steroids 58%, and azathioprine 14%. Fifty-seven patients underwent the first year evaluation and 36 had no new symptom, 12 had one, and 9 had 2. The expert committee has examined 48 files and classified 30 as definite and 18 as probable. Among our patients classified as definite, 26 (87%) fulfilled the ISG criteria. 17/18 classified as probable did not meet the international criteria ($p < 0.001$)].

Table. List of symptoms in addition to oral aphthosis in patients classified as definite and probable by the committee of experts.

	Confirmed n=30	Probable n=18
Genital ulceration*	21	7
Skin lesions**	22	3
Uveitis	16	6
Arthralgia/arthritis	11	7
Gastro-intestinal	12	6
Neurological***	12	3
Vascular	7	1
Urological	1	0
Fever	13	6
Pulmonary	3	0
Cardiac	3	0
Family history	3	4

Significant values: *p=0.03; **p=0.0001; ***p=0.09

Conclusion: The expert committee has classified the majority of patients in the BD group although they presented with few symptoms independently from BD classification criteria.

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1306

Plasma Fibrinogen Is More Specific Than Either ESR or CRP for Confirmation of Response to Treatment in Patients with Active Polymyalgia Rheumatica. Eoghan M. McCarthy[2], Paul A. MacMullan[4], Shibeb Al-Mudhaffer[4], Anne Madigan[4], Suzanne Donnelly[4], Conor J. McCarthy[3], Eamonn S. Molloy[5] and Geraldine M. McCarthy[1]. [1]Mater Misericordiae Univ. Hosp, Dublin, Ireland, [2]Mater Misericordiae University Hospital, Dublin, Ireland, [3]Mater Misericordiae University Hospital, Dublin, Ireland, [4]Mater Misericordiae University Hospital, [5]St Vincent's University Hospital, Dublin, Ireland

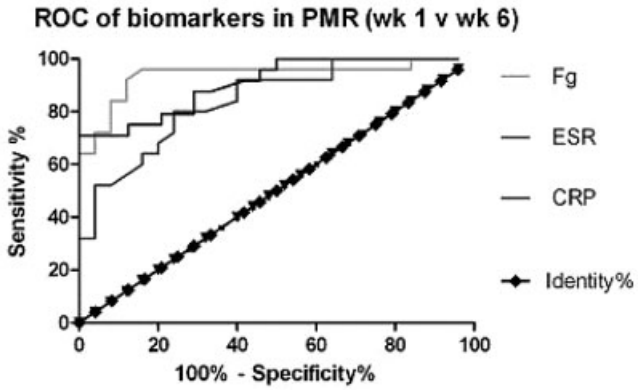
Purpose: To evaluate fibrinogen as a marker of disease activity in polymyalgia rheumatica (PMR).

Background: Measurement of disease activity in PMR is challenging due to the subjective nature of symptoms and absence of consistent physical signs in an elderly population. ESR and CRP are used in clinical practice to guide therapeutic decisions. Both are non specific markers of inflammation. Disease activity in PMR has been shown to correlate with interleukin 6(IL6) levels. IL6 also regulates fibrinogen production. We sought to prospectively evaluate plasma fibrinogen as a biomarker of active inflammation in patients with PMR.

Methods: 60 patients with PMR (as per Jones Hazleman criteria) were divided into Active disease (group 1, n=25) or Inactive disease(group 2,n=35), based on symptoms, physician assessment and standard biomarkers ESR and CRP. Plasma fibrinogen was also assayed. Both groups underwent clinical and laboratory assessment at baseline and 6 weeks. The following disease activity data was collected: Duration of morning stiffness(mins), Visual Analogue Scale(VAS) for pain(Vaspain) and VAS for patient assessment of disease activity(VasDA). Demographic data and categorical variables were assessed using Fischers Exact Test. Between group disease activity data were assessed using Wilcoxon Signed Rank Test. Receiver operator curves (ROC), predictive values, and likelihood ratios were calculated for all biomarkers measured.

Results: Demographic data was similar in all groups. Median steroid dose was 15mg (range 10 –60mg) in the active group and 5mg (range 0–15mg) in the inactive group. There were significant differences in steroid dose between the two groups($p<.001$).Mean scores for Vas pain (7.44 versus 2.8), Vas disease activity (7.38 vs 2.77) and duration of morning stiffness(72mins vs 9mins) improved significantly in the Active group between week 1 and week 6 ($p<0.001$).Mean fibrinogen reduced from 5.2g/L to 3.5g/L (normal<4g/L) between weeks 1 and 6. ESR and CRP reduced from 59.6 mm/hr to 24.3 mm/hr (normal <20mm/hr) and 45.9mg/L to 12.66mg/L(normal<5mg/L). There was no significant difference between the mean disease scores at week 6 in the Active group and the Inactive group at either week 1 or 6

ROC curve analysis revealed fibrinogen to be more specific than either ESR or CRP for the detection of response to treatment in patients with active PMR (Fig 1).



Values above the upper limit of normal for fibrinogen, CRP and ESR were associated with likelihood ratios for active disease of 20.53, 2.9 and 2.8 respectively ($p<0.001$).

Conclusion: Plasma fibrinogen was more specific for the confirmation of both active PMR and response to treatment than either ESR or CRP. While validation by other studies is required, this data suggests that measurement of fibrinogen as an adjunct to ESR and CRP in patients with suspected active PMR may enhance accuracy of diagnosis and guide therapeutic decisions.

Disclosure: E. M. McCarthy: None; **P. A. MacMullan:** None; **S. Al-Mudhaffer:** None; **A. Madigan:** None; **S. Donnelly:** None; **C. J. McCarthy:** None; **E. S. Molloy:** None; **G. M. McCarthy:** None.

1307

Prevalence of Behçet's Disease in Southern Sweden. Aladdin Mohammad[1], Thomas Mandl[3], Gunnar K. Sturfelt[2] and Mårten Segelmark[2], [1]Helsingborg Hospital, Helsingborg, Sweden, [2]Skåne University Hospital, Lund, Sweden, [3]Skåne University Hospital, Malmö, Sweden

Background: Behçet's Disease (BD) is a chronic inflammatory disease of unknown etiology characterized by recurrent oral and genital ulcerations and a variety of systemic manifestations, most of which are believed to be due to vasculitis. BD has a distinct geographic distribution with highest prevalence in the countries of East Asia, the Middle East and the Mediterranean (the old Silk Route).The epidemiology of BD in Sweden is largely unknown. Studies from other European countries have shown significantly higher prevalences among immigrants in comparison to populations with European ancestry.

Objectives: To estimate the prevalence of Behçet's Disease (BD) in a well defined multiethnic population in southern Sweden.

Method: The study area is two health care districts in the southern part of Skåne, the southernmost county in Sweden. The study population (adult $\geq$ 15 years) at the date of prevalence estimate was 582347 inhabitants (51 % females). The majority of the population was Scandinavian but about 23 % were of non-Scandinavian ancestry. Patients with BD living within the study area were identified by search in clinical registries at the departments of Rheumatology, Nephrology and Ophthalmology at the 3 hospitals within the study area. The search period was between 1997 and the end of 2009. All case records were reviewed to ascertain the diagnosis. Only patients fulfilling the criteria for diagnosis of BD according to the International Study Group for Behçet's Disease were included. The date of point prevalence was January, 1st, 2010.

Results: A total of 21 patients (five women) fulfilling the diagnosis criteria for BD were included in the study. The main clinical and demographic features of all patients are summarized in Table 1. Eighty one percent of patients (17 of 21) were of non-Scandinavian ancestry, mostly from the Middle East, Iraq and Turkey. The prevalence of BD was 36.1/million adults, and was significantly higher among subjects of non-Scandinavian ancestry in comparison to subjects of Scandinavian ancestry (125.8 *vs.* 8.9/million adults, $p<0.001$). For the entire study population, the gender-specific prevalence rate of BD was significantly higher among men than women; 55.9/million *vs.* 16.9/million ($p=0.013$).

Table 1. Clinical and demographic characteristics of patients with Behçet's Disease In southern Sweden

	All patients (n=21)	Men (n=16)	Women (n=5)	P[1]
Prevalence/million adult (95% CI)				
All patients, n=21 (5 women)	36.1 (20.6–51.5)	55.9 (28.5–83.3)	16.9 (2.1–31.7)	0.013
Scandinavian, n=4 (3 women)	8.9 (0.2–17.7)	4.6 (0–13.5)	13.2 (0–28.1)	0.336
Non-Scandinavian, n=17 (2 women)	125.8 (66.0–185.5)	223.9 (110.6–337.1)	29.3 (0–70.0)	0.001
Diagnosis delay[2], months, median (range)	42 (4–96)	48 (10–96)	36 (4–72)	0.618
Age at diagnosis, yrs, median (range)	30 (15–42)	31 (15–42)	24 (19–38)	0.380
Age at point prevalence, yrs, median (range)	41 (27–66)	42 (27–66)	40 (31–54)	0.809
Clinical features[3], N (%)				
Oral ulceration	21 (100)	16 (100)	5 (100)	
Genital ulceration	17 (81)	13 (81)	4 (80)	0.819
Skin lesions	17 (81)	12 (75)	5 (100)	0.072
Eye lesions	13 (62)	10 (63)	3 (60)	0.920
Arthritis/arthralgia	5 (24)	4 (25)	1 (20)	0.819
Venous thrombosis	4 (19)	4 (25)	0 (0)	0.214

[1] men vs. women, [2]time from first symptom to diagnosis, [3]occurring anytime throughout the disease course

Conclusions: The prevalence of BD in our area was significantly higher among subjects of non-Scandinavian ancestry in comparison to subjects of Scandinavian ancestry. These findings are consistent with previous epidemiologic reports from other European countries.

Disclosure: A. Mohammad: None; **T. Mandl:** None; **G. K. Sturfelt:** None; **M. Segelmark:** None.

1308

Safe, Rapid-Onset, and Sustained Biological Activity of IL-1β Regulating Antibody XOMA 052 in Resistant Uveitis of Behçet's Disease: Results of a Pilot Trial. Ahmet Gül[2], Bahar Artim-Esen[2], Alan M. Solinger[4], Linda Giustino[4], Charles Dinarello[3] and Ilknur M. Tugal-Tutkun[1], [1]Istanbul, Turkey, [2]Istanbul University, Istanbul, Turkey, [3]University of Colorado, Aurora, CO, [4]XOMA (US) LLC, Berkeley, CA

Introduction: Behçet's disease (BD) is a vasculitic multi-system inflammatory disorder of unknown etiology. Increased expression of proinflammatory cytokines, including IL-1β has been considered to play a critical role in the pathogenesis of BD. Uveitis is a major manifestation of BD, and recurrent attacks can cause permanent vision loss in patients resistant to immunosuppressive drugs. XOMA 052 is a recombinant humanized monoclonal antibody. It binds and regulates IL-1β activity, and its administration may produce rapid and sustained reductions in symptoms in IL-1β-mediated systemic inflammatory diseases.

Aim: To evaluate the safety and PK of XOMA 052 in BD uveitis. Additional assessments were planned as exploratory measures of biologic and clinical activity, particularly of uveitis.

Methods: This pilot open-label study enrolled BD patients who developed a posterior/panuveitis or retinal vasculitis attack despite cyclosporine and/or azathioprine treatment. XOMA 052 was administered as a single 0.3 mg/kg intravenous infusion. Subjects suspended their immunosuppressive treatments and maintained prednisolone at $\leq$10 mg/day (6 patients) or 20mg/day (one patient) without any increase.

Results: Seven patients enrolled in and completed the study period of 98 days. No adverse events related to XOMA 052 were observed. Preliminary PK analysis of the first 6 patients showed a clearance of 2.6 mL/day/kg, a beta half-life 26.7 days and a volume of distribution for the central compartment of 54 mL/kg. Intraocular inflammation started to resolve in all patients on Day 1, and complete resolution of retinal findings and vitreous haze was achieved in 4 to 21 days. Five patients were in remission on Day 28, and one was still in remission at Day 98 with a single infusion. One of the patients received increased doses of prednisolone for new retinitis attack in the contralateral eye on Day 25, and other received intravitreal methyl pred-

nisolone for cystoid macular edema (CME) on Day 22 as rescue. After a protocol amendment, five patients received a second infusion for new retinal infiltrates between Day 49 and Day 95, and one patient for CME in the contralateral eye on Day 29. All patients responded to the repeat infusions. Five patients, who had recurrent oral ulcers and folliculitis before the trial, experienced recurrences of those manifestations despite resolution of intraocular inflammation.

Conclusions: Findings of this pilot trial suggest that IL-1β plays a major role in BD uveitis. Administration of XOMA 052 appears safe, and regulation of IL-1β using XOMA 052 shows a rapid-onset effect for the treatment of intraocular inflammatory attack. This favorable effect of XOMA 052 was observed despite discontinuation of immunosuppressives as of infusion day and without any increase in corticosteroids. Results of this pilot trial warrant additional studies. Responses of non-ocular disease manifestations to XOMA 052 need also be studied further.

Disclosure: A. Gül: Xoma (US) LLC, 2, 5; **B. Artim-Esen:** None; **A. M. Solinger:** Xoma (US) LLC, 3; **L. Giustino:** Xoma (US) LLC, 3; **C. Dinarello:** Xoma (US) LLC, 5; **I. M. Tugal-Tutkun:** Xoma (US) LLC, 5.

1309

Serum Hepcidin Is Elevated in Patients with Giant Cell Arteritis and Is Inversely Associated with Serum Iron Levels. Curry L. Koening[2], Jose Hernandez-Rodriguez[1], Marc Corbera-Bellalta[1], Maria C. Cid[1], Bradley Katz[3] and Ivana De Domenico[3]. [1]University of Barcelona, [2]University of Utah, Salt Lake City, UT, [3]University of Utah

Background: Giant cell arteritis (GCA) is a systemic inflammatory blood vessel disease characterized by an elevated sedimentation rate and anemia of chronic disease (ACD). ACD is primarily mediated through hepcidin, a peptide hormone that causes iron retention in macrophages when expressed at high levels. Iron retention in macrophages leads to serum hypoferremia and decreased red blood cell production. Hepcidin is expressed primarily by hepatocytes and mononuclear cells and is upregulated by proinflammatory cytokines such as interleukin 6 (IL-6) and IL-1. Both IL-1 and IL-6 play a role in the pathogenesis of GCA. We hypothesized patients with GCA would have higher serum hepcidin levels than that of controls and that these values would be inversely proportional to serum iron levels.

Methods: The serum of 20 patients with biopsy-proven, untreated GCA was analyzed for hepcidin using a competitive assay. Serum levels of iron and IL-6 were also analyzed. Results were compared to 41 healthy control patients with similar age and gender. Continuous variables were compared using the Student's t test. Categorical variables were compared using Chi square test. Pearson's correlation test was used to test the association between two variables. P values <0.05 were considered significant.

Results: The average age of patients with GCA and controls did not differ (79.1; SD 6.6 vs 81.4; SD 5.0; P=0.19). Females were more predominant in the control group (80%) than in patients with GCA (60%). Differences in gender were not statistically significant between the two groups (P=0.09). The mean serum hemoglobin value for patients with GCA was 11.1 (SD 1.3) g/dl. Serum hepcidin levels in patients with GCA were 361.2 (SD 124.1) ng/ml compared to 82.9 (SD 6.3) ng/ml in controls (P<0.05). Patients with GCA were significantly more hypoferremic than controls. Serum iron levels in patients with GCA were 80.1 ug/dl (SD 22.9) compared to 213.8 ug/dl (SD 215.7) in controls (P=<0.05). Serum hepcidin levels were directly proportional to serum IL-6 values (CC 0.75; P<0.05) and inversely proportional to serum iron values (CC −0.32; P<0.05). For patients with GCA, no significant correlation was seen between the serum hemoglobin and hepcidin values (CC 0.43; P=0.06).

Conclusions: Patients with active GCA have higher levels of serum hepcidin than controls. These values were inversely correlated with serum iron but directly proportional to serum IL-6 values. Serum hepcidin values did not correlate with hemoglobin values since circulating red blood cells are not affected by hepcidin. Furthermore, the effect of hepcidin on red blood cell production may not be immediate. For patients with GCA, increased expression of hepcidin is associated with lower serum iron values, which may reduce red blood cell production. Hepcidin appears to be involved in the development of ACD in patients with GCA.

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1310

Severe and Opportunistic Infections during Giant Cell Arteritis Course: A Case-Control Study. Javier Narvaez[1], Laura López Vives[1], Paula Estrada[2], Nuria del Castillo[1], Montserrat Robustillo[1] and Joan Miquel Nolla[1]. [1]Department of Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain, [2]Department of Rheumatology, Barcelona, Spain

Purpose: To assess the incidence of severe and opportunistic infections in GCA patients as compared to age- and sex-matched, population based randomly selected controls.

Methods: Case-control study including 140 cases with GCA diagnosed in 1 center from 1986 to 2008. Patients were diagnosed with GCA if they had a positive temporal artery biopsy (TAB) or, in cases with negative biopsy or no biopsy, if they fulfilled the 1990 ACR criteria for the classification of GCA and had a prompt and persistent response to glucocorticoid (GC) treatment. The end-point of patient follow-up was the date of the last clinic visit or the date of death. For each GCA patient, 2 subjects without GCA of the same sex and similar age an time of follow-up were randomly selected from the population of patients attended in our outpatient clinic due to osteoporosis, osteoarthritis or gout. Severe infection was recorded as any bacterial infection leading to hospitalization.

Results: The series included 94 women and 46 men with a mean age at time of diagnosis of 75 ± 7 years (range, 56 to 92). TAB was positive in 112 (80 %) patients. The median duration of follow-up after diagnosis was 36.6 months (range, 12.5 to 180).

All patients were treated with GCs and responded rapidly (mean initial dosage of prednisone: 50.1 ± 13.7 mg/day). The dosage was later reduced according to the treating physicians' judgment.

During follow-up, severe and/or opportunistic infections were recorded in 17.9% (25/140) of GCA patients compared to 3.5% (10/280) in the control group (odds ratio (OR) = 5.87, 95% confidence interval (CI): 2.73, 12.61).

Among GCA patients, opportunistic infections occurred in 5.7% (8/140) of the patients (including 1 case of tuberculosis, 6 cases of herpes zoster and 2 cases of candidiasis) compared to 1.4% (4/280) in the control group (OR = 4.18, 95% CI: 1.23, 14.14). Several bacterial infections occurred in 13.6% (19/140) of the cases compared to 2.14% (6/280) in the non-GCA subjects (OR = 7.17; 95% CI: 1.79, 18.4).

Interestingly, the incidence of tuberculosis (TB) in our GCA patients, in whom prophylaxis with isoniazid was not regularly administered, was 181/100,000 patient-years (1 case in 550 patient-years of follow-up). During the same period (1990–2008) the pooled annual incidence of TB infection in the general population of Spain ranged from 23 to 30 cases/100,000 individuals. This data reflects that the incidence of TB in GCA patients receiving GC is at least 6 times higher than in the general population.

Only one of the GCA patients died due to pulmonary TB complicated with upper gastrointestinal bleeding. The overall mortality was similar in cases and controls (p>0.05).

Logistic regression models identified the cumulative dose of prednisone (OR=6.19, 95% CI: 1.61, 23.71; p=0.007) and the presence of large-artery complication (aortic involvement and/or large-artery stenosis) (OR=11.35, 95% CI: 2.24, 57.33; p=0.003) as significant predictors of severe/opportunistic infections.

Conclusion: The incidence of severe and opportunistic infections is increased in GCA. This increased risk is mostly influenced by GC therapy. We found a 6-fold increased risk of TB infection in patients diagnosed with GCA.

Disclosure: J. Narvaez: None; **L. López Vives:** None; **P. Estrada:** None; **N. del Castillo:** None; **M. Robustillo:** None; **J. M. Nolla:** None.

1311

Significance of "Healed Arteritis" (HA) on Temporal Artery Biopsy. Rahul Sehgal, Elise Belilos, Matthew Geller, Lorna Ogden, Steven E. Carsons and George K. Turi, Winthrop University Hospital, Mineola, NY

Purpose: Although temporal artery biopsy (TAB) is the gold standard for the diagnosis of Giant Cell Arteritis (GCA), the presence of skip lesions, and atypical biopsy features limit its utility. In particular, the pathologic diagnosis of HA is controversial. Many changes described for HA may be seen in aging and atherosclerosis alone. We attempted to determine the significance of HA by comparing pathologic features, clinical and laboratory manifestations, and corticosteroid (CS) requirements of HA patients to those displaying classical GCA on TAB.

Methods: We performed a retrospective cohort study, comparing the clinical presentation, laboratory data and CS requirements of 8 cases having a

pathology report indicating HA to 12 cases of classical GCA. To validate the pathologic impression of HA for our cases, a literature review was performed to identify the pathologic features most commonly reported in HA. These were found to include intimal thickening, medial fibrosis, scarring and calcification and internal elastic lamina (IEL) fragmentation. If present, inflammatory cells must be focal or scant. All slides (~25 sections/patient) were reviewed by 3 pathologists to 1) quantitate the features of HA and GCA and 2) to ensure that any cases with inflammatory infiltrates graded more than scant or focal (0–1 on a scale of 0–4) were excluded from the HA group. Clinically, all 20 patients were treated for GCA. CS exposure prior to TAB was also recorded.

Results: Other than the presence of significant medial and/or adventitial inflammation in GCA, there were no significant differences in the pathologic features previously identified to be associated with HA when slides from HA and GCA were compared. Although there was slightly more medial fibrosis, scarring and calcification in the HA group, this was not significant. The proportion of headache, jaw claudication, visual symptoms, fever, weight loss and scalp tenderness did not significantly differ between groups. No difference was noted in ESR. A trend towards higher alkaline phosphatase levels in GCA vs. HA (36% vs. 0%; p=0.11) was seen. Only the presence of PMR was significantly associated with HA (86% vs. 8.3%; p=0.002). Although the mean CS dose at Day 1 was significantly higher for GCA (150mg GCA vs. 45 mg HA; p=0.045), no significant differences in subsequent CS dosing at days 30, 60 or 90 was seen. Importantly, cumulative pre-biopsy CS exposure was nearly identical (357 GCA vs. 366 mg HA; p=0.857).

Conclusion: The presence of only scant or focal inflammation on TAB and a significant association with PMR symptoms were the only pathologic or clinical features that distinguished HA from GCA. CS courses were similar as well. Pre-biopsy CS exposure is not responsible for this phenotype, thus, use of the term "healed arteritis" should be reexamined. "Mild arteritis" may be appropriate for biopsies demonstrating scant or focal inflammation. Intimal thickening, medial fibrosis, scarring and calcification in the absence of any inflammation appear indistinguishable from changes due to aging and atherosclerosis.

Disclosure: R. Sehgal: None; **E. Belilos:** None; **M. Geller:** None; **L. Ogden:** None; **S. E. Carsons:** None; **G. K. Turi:** None.

1312

Some Manifestations Disappear Earlier Than Others in Behcet's Syndrome (BS). Sevgi F. Sacli[2], Emire Seyahi[4], Yilmaz Ozyazgan[3], Cem Mat[1] and Hasan Yazici[4]. [1]Cerrahpasa Medical Faculty, Dermatology Department, Turkey, [2]Cerrahpasa Medical Faculty, Internal Medicine Department, Turkey, [3]Cerrahpasa Medical Faculty, Ophthalmology Department, Turkey, [4]Cerrahpasa Medical Faculty, Rheumatology Department, Turkey

In a 20 year outcome study, we had observed that the frequency of all mucocutaneous lesions and arthritis decreased in frequency with the passage of time (1). In this study we investigated whether some manifestations disappeared before others.

Patients and Methods: We studied consecutive BS patients who were seen in the rheumatology outpatient clinic at Cerrahpasa Medical Faculty in Istanbul between February 2009 and April 2010. Only BS patients whose disease duration and follow-up were 10 years or longer were included in the study. With the help of a questionnaire, patients were asked whether skin mucosa lesions, arthritis and uveitis attacks occurred for the preceding one year. If not, they were asked about the date when the manifestation occurred for the last time. Information given by the patients was confirmed with the patient charts whenever it was possible. Also a pathergy test was done to those who volunteered.

Results: We studied 115 (60 M, 55 F) patients. The mean age of the patients was 48 ± 8 and the mean disease duration 20 ± 6 years. 63 patients had eye, 20 vascular and 6 neurological disease. Vascular and neurological attacks were not evaluated due to rarity. The frequency of those with any BS manifestation during the preceding one year including pathergy positivity was decreased significantly at the final visit compared to that found at the beginning.

Table. Frequency of BS manifestations

Frequency n (%)	Initial visit	Final visit	P
Oral ulcers	115 (100)	84 (73)	<0.001
Genital ulcers	105 (115)	13 (11)	<0.001
Papulopustular lesions	104 (90)	61 (53)	<0.001
Erythema nodosum	72 (63)	23 (20)	<0.001
Arthritis	39 (34)	8 (7)	<0.001
Pathergy positivity	85/109 (78)	6/39 (15)	<0.001

As seen in the Kaplan-Meier curve, eye attacks were the first to cease followed by arthritis, genital ulcers and skin lesions.

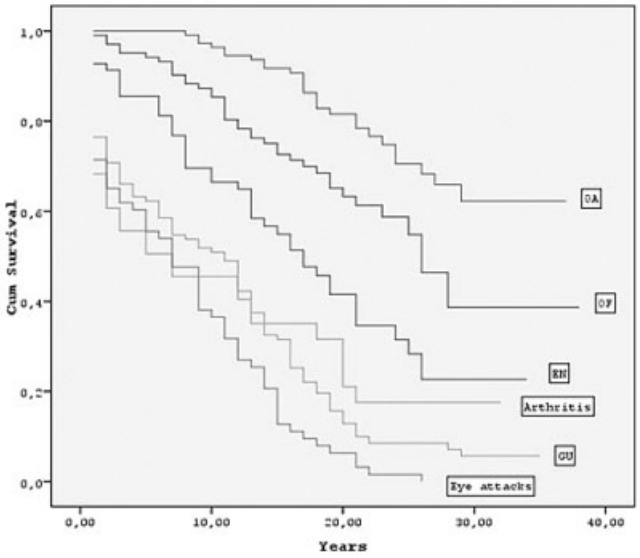

Figure. Kaplan Meier survival plot for duration of BS manifestations.

This was most prominent among females. Oral ulcer was the most frequent lesion after 30 years of disease course.

Conclusions: In BS some disease manifestations disappear earlier than others. These findings may have important pathogenetic and clinical implications. Since our survey was cross-sectional to retrospective caution is required in interpretation.

Reference:

1) Kural-Seyahi E, Fresko I, Seyahi N, et al. The long-term mortality and morbidity of Behcet syndrome: a 2-decade outcome survey of 387 patients followed at a dedicated center. Medicine (Baltimore). 2003; 82:60–76.

Disclosure: S. F. Sacli: None; **E. Seyahi:** None; **Y. Ozyazgan:** None; **C. Mat:** None; **H. Yazici:** None.

1313

Takayasu's Arteritis Is Associated with HLA-B*52, but Not with B*51, in Turkey. Turkish Takayasu Study Group. Turkey

Aim: HLA-B*51 and B*52 are two close HLA alleles with minor amino acid differences. However, they are associated with two different vasculitides (B*51 with Behcet's disease and B*52 with Takayasu's arteritis-TAK) with major clinical and immunological differences. This study aimed to screen a large cohort of TAK patients from Turkey for the presence of HLA-B*51 and B*52 alleles as susceptibility factors.

Material and Methods: TAK patients (n=305) followed by 15 centers were included in the study. The mean age of the patients was 37,8 years and 86% (n=264) were female. DNA samples of the patients and healthy controls (n=210) were isolated by salting-out technique. HLA-B*51 and B*52 were investigated by using polymerase chain reaction (PCR) with sequence specific primers (SSP). The presence of the alleles were compared by chi-square method.

Results: B*52 has shown a significant association with TAK (67/305 (22,3%) vs. 14/210 (6,6%), p<0.0001, OR: 4,07, CI: 2,19-7,36). However, the distribution of B*51 did not differ between TAK and control groups (24.6% (75/305) vs. 24.8% (52/210), OR: 0.99). Trends towards an association of B*52 presence with limited aortic involvement (Type I: OR: 0.4, p=0.05), medically refractory disease (OR: 1.8, p=0.14) and late-onset (OR: 0.25, p=0.009) were observed. No significant association of B*52 was present with surgical procedures.

Conclusion: In this study, the previously reported association of TAK with B*52 in Japanese and other populations was confirmed in patients from Turkey, whereas no association with B*51 was observed. This association might have implications about the functional relevance of B*52 in TAK pathogenesis, which has to be further explored.

Disclosure: Turkish Takayasu Study Group: None.

1314

Treatment with Angiotensin Converting Enzyme Inhibitors (ACEI) or Angiotensin II Receptor Antagonists (ARA) Is Associated with Higher Frequency of Ischemic Complications but Better Response to Therapy in Patients with Giant-Cell Arteritis (GCA). Marco A. Alba[3], Ana Garcia-Martinez[1], Georgina Espigol-Frigole[3], Itziar Tavera[2], Montserrat Butjosa[3], Sergio Prieto-Gonzalez[5], Jose Hernandez-Rodriguez[4] and Maria C. Cid[2]. [1]Emergency Department, Hospital Clinic, Barcelona, Spain, [2]Systemic Autoimmune Diseases, Hospital Clinic, Barcelona, Spain, [3]Systemic Autoimmune Diseases. Hospital Clinic, Barcelona, Spain, [4]Systemic Autoimmune Diseases. Hospital Clininc, Barcelona, Spain, [5]Systemic Autoimmune Diseases.Hospital Clinic, Barcelona, Spain

Background: GCA is a chronic inflammatory disease involving large and medium-sized arteries. Involvement of cranial arteries is particularly symptomatic. About 15–20% of patients develop cranial ischemic events derived from occlusion of involved vessels. Previous studies have shown that angiotensin receptor 1 is expressed in vascular lesions from patients with GCA (Ophthalmology 2009; 116: 990–6). Angiotensin II is an important mediator of angiogenesis and vascular remodelling.

Purpose: To investigate whether ACEI or ARB therapy is related to vascular complications or response to glucocorticoid therapy in patients with GCA.

Methods: Between 1995 and 2005, 160 patients were diagnosed with biopsy proven GCA at our institution. Among them patients with the following criteria were selected: prospective treatment and follow-up by the authors according to uniform criteria, prospective recording of GCA-related complications, relapses and glucocorticosteroid doses, and a follow-up duration of at least 3 years. Eighty-four patients fulfilled the selection criteria and were eligible for this study. Although retrospective in design, the study was performed on a prospectively followed cohort. Fisher exact test and Kaplan-Meyer survival analysis/log-rank test were used for statistical comparison.

Results: Eighteen patients (21%) were receiving ACEI (12 patients) or ARB (6 patients) at the time of diagnosis. GCA-related complications (amaurosis fugax, diplopia, anterior ischemic optic neuritis, transient ischemic attack or stroke) occurred in 18 (21%) of patients at disease presentation. Ischemic complications occurred in 5 (27.8%) of patients receiving ACEI or ARB compared to 5 (7.6%) of those not receiving these therapies ($p = 0.033$). The proportion of patients who relapsed at least once was lower among those receiving ACEI or ARB (54% vs 75%, $p = 0.06$). Patients with multiple relapses were significantly less frequent among the ACEI/ARB treated group ($p = 0.03$). Patients receiving ACEI/ARB tended to achieve a maintenance prednisone dose < 10 mg/day earlier than patients not receiving these therapies (71 vs 82 weeks, $p = 0.07$).

Conclusions: Previous ACEI/ARB use is associated with higher frequency of ischemic complications at the time of GCA diagnosis but is associated with better response to glucocorticoid treatment. These preliminary data suggest that ACEI/ARB effects on angiogenesis or vascular remodelling nay be relevant to patients with GCA.

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1315

Use of Peri-Operative Glucocorticoids and Post-Operative Complications in Patients with Takayasu's Arteritis Undergoing Vascular Surgical Procedures. Bijal A. Jayakar[1], Gary S. Hoffman[3] and Carol A. Langford[2]. [1]Cleveland Clinic, Cleveland, OH, [2]Cleveland Clinic Foundation, Cleveland, OH, [3]Cleveland Clinic Foundation, Pepper Pike, OH

Purpose: The risks and benefits of peri-operative glucocorticoids (POGC) in patients with Takayasu's arteritis (TAK) undergoing vascular surgery have been unclear. We studied the relationship between POGC and disease activity in TAK patients who received vascular surgery to determine if these factors influenced the risk of infection, vascular events, and other complications.

Methods: Retrospective chart review of TAK patients undergoing vascular surgery at the Cleveland Clinic from 1979–2008. Standardized definitions were used for the diagnosis of TAK, disease activity, and POGC. POGC was defined as prednisone use within 1 month prior to or after surgery and analyzed as 0mg, $<$ 20mg, and $\geq$20mg. Variables including POGC, other immunosuppression, disease activity, age at diagnosis, age at surgery, disease duration at surgery and sex were examined by univariate and multivariate analysis using SAS 9.2.

Results: In this study we identified 40 TAK patients who underwent 56 vascular surgical procedures. Mean age at diagnosis was 33.5 years and at surgery was 40 years. Mean duration of disease at surgery was 6.2 years (0–28.3). Mean time between surgery and last follow-up was 2.1 years (0–8.7). Active disease was present in 24/56 procedures (43%). Histology was obtained in 42/56 (75%) procedures with 8/42 (19%) being histologically active. Discordance between clinical and histological activity was seen in 17/42 (40%). Erythrocyte sedimentation rate (ESR) was increased in 18/44 (41%) measurements including 12/20 (60%) with active disease and 6/24 (25%) with inactive disease. POGC doses were prednisone=0 in 21/56 (37%), <20mg in 10/56 (18%), ≥20mg in 25/56 (45%). 28/56 (56%) were on other immunosuppressives. 42 complications occurred in 30 patients, consisting of 11 infections, 12 vascular events, and 19 other complications. Relapses occurred in 25/56 (45%) with 6 (11%) being within 3 months of surgery. There were 5 deaths, 2 from strokes in the immediate post-operative period. POGC were not associated with a higher frequency of infections ($p = 0.84$). For inactive TAK, total complications were no lower in those who did not receive POGC ($p=0.11$). This lack of association remained present for each subgroup: infection ($p=0.90$), vascular ($p=0.22$), and other complications ($p=0.37$). In active TAK, there was no difference in the occurrence of total complications between those on and not on POGC ($p=0.67$). Although this lack of association was present for other complications ($p=0.74$), subset analyses were not possible for infection or vascular complications because of absence of an event.

Conclusions: The absence of an increased risk of infection in this study support that POGC can be used in TAK patients felt to have active disease at the time of vascular surgery. These results did not support that POGC should be routinely used in all patients with TAK undergoing surgical procedures as the risk of complications was no different in patients who received this. Performance of surgery is not associated with a high rate of immediate relapse, although relapses are common over time in TAK. ESR and clinical definitions remain imperfect measures of disease activity and underscore the need for better biomarkers in TAK.

Disclosure: B. A. Jayakar: None; **G. S. Hoffman:** None; **C. A. Langford:** None.

ACR Poster Session B
ACR/ARHP Poster Session B - ARHP: Osteoporosis
Tuesday, November 9, 2010, 9:00 AM–6:00 PM

1316

Application of the Generalizability Theory for Determining Inter-Rater and Inter-Trial Reliability of Spine Curvature Measures in Postmenopausal Women with Osteoporosis of the Spine Using the Flexicurve Ruler and the Digital Inclinometer. Norma J. MacIntyre[1], Lisa Bennett[2], Alison Bonnyman[2] and Paul W. Stratford[2]. [1]McMaster University, Hamilton, ON, Canada, [2]McMaster University

Purpose: Spine curvatures are often measured in physical therapy practice using a flexicurve ruler to calculate kyphotic index (KI) and lordotic index (LI) or a digital inclinometer to quantify the angle at the cervicothoracic (CT), thoracolumbar (TL) and lumbosacral (LS) junctions. Generalizability theory (G-Theory) provides tools that characterize the sources of variation, or facets, in a measurement procedure and permit identification of a protocol that provides optimal reliability. The purpose of this study was to use the tools of G-Theory to investigate the inter-rater and inter-trial reliability of these spine curvature measures and to establish an optimal measurement protocol.

Methods: Nine postmenopausal women over the age of 60 years with established osteoporosis of the spine were recruited for this cross-sectional observational study. Two raters completed triplicate measures of spine curvatures using both the flexicurve ruler and the digital inclinometer according to a standardized protocol. G-Theory was applied through a Generalizability Study to estimate G-coefficients (analogous to the reliability coefficient in the Classical Test Theory). The facets included were participants (P), raters (R) and trials (T). Three-way ANOVAs were used to generate variance components for the following terms: P, R, T, PxR, PxT, RxT and error. G-coefficients were calculated as the proportion of the overall variance that can be attributed to the facets and interactions and the proportions of variance attributed to rater and trial. Follow-up Decision Studies were performed to identify a measurement protocol that minimized error and optimized reliability. G-coefficients ≥ 0.8 were considered desirable and 0.70 to 0.79 were considered acceptable.

Results: Inter-rater reliability is excellent for KI, LI, TL and LS (G-

coefficient = 0.97, 0.91, 0.85 and 0.80, respectively) and acceptable for CT (G-coefficient = 0.74) using our protocol for measuring spine curvatures. Three raters are required to achieve excellent inter-rater reliability for CT (0.81). A single trial would result in excellent reliability for all measures (G-coefficient ≥ 0.94 for all except LI where G-coefficient = 0.84). Triplicate trials improve inter-trial reliability (G-coefficient ≥ 0.98 for all except LI where G-coefficient = 0.94). Little gains are achieved by increasing trials beyond three; eight trials are needed to raise the inter-trial reliability of LI measures to 0.98.

Conclusions: This study demonstrates the application of G-Theory to identify a protocol for measuring spine curvatures in osteoporotic women which optimizes reliability by testing the gains achieved by increasing the number of raters or the number of trials. If more than one rater is involved in assessing spine curvatures, triplicate measures acquired using the flexicurve ruler will be most reliable. For a given rater, inter-trial reliability is optimized by measuring in triplicate whether using the flexicurve ruler or the digital inclinometer.

Disclosure: N. J. MacIntyre: None; **L. Bennett:** None; **A. Bonnyman:** None; **P. W. Stratford:** None.

1317

Baseline Serum Interleukin-6 (IL-6), Tumor Necrosis Factor-α (TNF-α) and C-Reactive Protein (CRP) Do Not Predict Subsequent Hip Bone Loss in Men or Women: The Framingham Osteoporosis Study. Robert R. McLean[3], Xiaochun Zhang[4], Joao D. T. Fontes[2], James B. Meigs[7], L. Adrienne Cupples[1], Douglas P. Kiel[5] and Marian T. Hannan[6]. [1]Boston University School of Public Health, [2]Framingham Heart Study and Boston University, [3]Hebrew Senior Life, Boston, MA, [4]Hebrew SeniorLife, [5]Hebrew SeniorLife and Harvard Medical School, [6]Hebrew SL & Harvard Med Sch, Boston, MA, [7]Massachusetts General Hospital

In vitro studies suggest that several pro-inflammatory cytokines increase bone resorption and that their activity is amplified following estrogen withdrawal. Yet there is little epidemiologic evidence that circulating concentrations of inflammatory markers predict bone loss in men and women, or that estrogen status may influence this relation. We therefore examined the associations of serum concentrations of the cytokines IL-6 and TNF-α, and CRP, a marker of systemic inflammation, with bone loss among men and women in the Framingham Offspring Study. We hypothesized that increased baseline concentrations of inflammatory markers would be associated with greater bone loss, and that this association would be strongest among postmenopausal women not using hormone replacement therapy (HRT). Baseline fasting blood samples were obtained (1998–2001) from 501 men, 106 premenopausal women, 206 postmenopausal using HRT at baseline, and 334 postmenopausal not using HRT. Serum IL-6 (pg/mL) and TNF-α (pg/mL) were measured using ELISAs and CRP (mg/L) using a high-sensitivity assay. Total femur bone mineral density (BMD; g/cm^2) was measured at baseline with a Lunar DPX-L (1996–2001) and at follow-up using a Lunar Prodigy (2002-05), accounting for equipment change. Bone loss was calculated as percent BMD change per year. Within each of the 4 groups defined by sex, menopause status and HRT use, participants were categorized into tertiles of inflammatory markers. We used analysis of covariance to compare mean bone loss in each of the upper 2 tertiles to the lowest tertile and test for a linear trend across tertiles, adjusting for baseline age (y), BMI (kg/m^2), height (in), physical activity, and current smoking (y/n). Mean age at baseline was 61 y (range 29–85 y), and mean follow-up time was 4.6 y (range 1.5–7.9 y).

Least squares-adjusted mean annual % change (SE) in total femur BMD for tertiles of inflammatory biomarkers in Framingham Offspring men and women.

	T1 (Low)	T2	T3 (High)	P trend
Men				
IL-6	−0.01 (0.08)	0.12 (0.07)	−0.03 (0.08)	0.90
TNF-α	0.08 (0.09)	−0.04 (0.09)	−0.05 (0.09)	0.34
CRP	0.04 (0.08)	−0.03 (0.07)	0.07 (0.08)	0.79
Premenopausal women				
IL-6	−0.46 (0.16)	−0.15 (0.16)	−0.02 (0.18)	0.07
TNF-α	−0.08 (0.18)	−0.29 (0.18)	0.05 (0.18)	0.62
CRP	−0.44 (0.17)	−0.13 (0.16)	−0.07 (0.19)	0.16
Postmenopausal women				
HRT users				
IL-6	0.17 (0.12)	0.22 (0.12)	−0.13 (0.13)	0.12
TNF-α	0.31 (0.13)	−0.05 (0.14)	0.11 (0.14)	0.29
CRP	0.09 (0.13)	−0.02 (0.12)	0.19 (0.13)	0.60
HRT non-users				
IL-6	−0.23 (0.12)	−0.20 (0.11)	−0.29 (0.11)	0.72
TNF-α	−0.19 (0.13)	−0.23 (0.12)	−0.47 (0.12)	0.12
CRP	−0.37 (0.12)	−0.23 (0.11)	−0.13 (0.12)	0.18

There were no statistically significant associations between inflammatory markers and total hip bone loss in any of the sex/menopause/HRT groups (Table). Our findings suggest that circulating biomarkers of inflammation are not associated with hip bone loss in men or groups of women categorized by menopause status and HRT use. Future investigations of inflammation and BMD should address limitations of our study by including longitudinal measures of inflammatory markers, more precise measures of estrogen status (e.g. sex hormones), and larger samples that could detect the small bone loss effects suggested by our results.

Disclosure: R. R. McLean: None; **X. Zhang:** None; **J. D. T. Fontes:** None; **J. B. Meigs:** None; **L. A. Cupples:** None; **D. P. Kiel:** None; **M. T. Hannan:** None.

1318

Development of a Motivational Interviewing Protocol for Clinical Application in Osteoporosis. Maura D. Iversen[3], Laura Rekedal[1] and Daniel Hal Solomon[2]. [1]Boston, MA, [2]Brigham and Womens Hospital, Boston, MA, [3]Northeastern University, Boston, MA

Background: While many effective therapies exist for osteoporosis (OP), most people do not adhere to such treatments long-term. Few proven interventions exist to improve OP medication adherence. Motivational interviewing (MI) is a counseling technique that may improve adherence. We report on methods used to develop MI skills among 5 health educators to promote patient adherence to OP medications.

Methods: Five health educators (HE) participated in an initial 2 day educational session led by a rheumatologist, a behavioral scientist and a certified MI trainer which detailed information on MI techniques and OP. Reinforcement of MI was provided via semi-monthly calls with the study team over one year. Two additional telephonic MI training sessions were provided at the trial midpoint based on two 20–30-minute audio taped client conversations. A second certified MI trainer listened to tapes, coded the MI performance using the Motivational Interviewing Treatment Integrity code (MITI) and then provided feedback using examples from the tapes. The MITI contains 5 domains: evocation, autonomy, collaboration, direction and empathy and MI global spirit. Scores range from 0 (low) to 5 (high). Conversations with clients were also coded based on the ratio of total reflections to questions used. This information was then used to individually tailor feedback about the use of MI techniques for each health educator.

Results: All HEs were female. Mean age was 42 years and range of experience was 7 to 15 years. One health educator was a registered nurse, one a dietician, and one a social worker. At baseline, only one of the five health educators had any experience using MI; two were familiar with MI concepts but had not received training and one was not familiar with MI. Scores across the five MITI domains suggested the HE performance was strongest in the areas of providing direction (all received scores of 3.5 or better) and empathy (average range 2.5–4.5).

Table: MITI Performance Scores for Each Health Educator For MITI Domains During Two Separate Audiotaped Conversations

Global Domains		001	002	003	004	002	005
Evocation	*Tape 1*	3	2	3	3	4	3
	Tape 2	2	3	3	2	4	2
	Average	2.5	2.5	3	2.5	4	2.5
Collaboration	*Tape 1*	2.5	2	3	3	3	3
	Tape 2	2	3	3	2	3	2
	Average	2.25	2.5	4	2.5	3	2.5
Autonomy/Support	*Tape 1*	3	3	3	4	3	3
	Tape 2	3	3	4	4	3	2
	Average	3	3	3.5	4	3	2.5
Direction	*Tape 1*	5	3	5	4	5	5
	Tape 2	5	4	5	4	5	5
	Average	5	3.5	5	4	5	5
Empathy	*Tape 1*	3	2	5	4	4	4
	Tape 2	4	3.5	4	3	4	3
	Average	3.5	2.75	4.5	3.5	4	3.5
Global Spirit Score	*Tape 1*	2.8	2.3	3.0	3.3	3.3	3.0
	Tape 2	2.5	3.0	3.3	2.6	3.3	2.0
		2.65	2.65	3.15	2.95	3.3	2.5

The areas which needed improvement were the domains of evocation, collaboration and autonomy/support. With respect to total reflection to

question ratios, on average the ratio across HEs was 1.3 suggesting the need for the HEs to allow more time for client reflection during conversations.

Discussion: Among a group of health educators who did not use MI skills in their routine counseling activities, a multi-faceted training program in MI over the course of one year led to improvements in the health educators ability to apply MI skills to patient counseling. The strategies which required the most focus were evocation, collaboration and autonomy/support. Both group and individually tailored education sessions were used to promote the use of MI in patient counseling and resulted in competent performance of MI techniques over the course of the clinical trial.

Disclosure: M. D. Iversen: None; **L. Rekedal:** None; **D. H. Solomon:** Abbott Immunology Pharmaceuticals, 2, Amgen Inc., 2, Bristol-Myers Squibb, 9.

1319

Type of Activity Pacing Instruction Affects Physical Activity Variability in Adults with Symptomatic Knee or Hip Osteoarthritis. Susan L. Murphy[2], Dylan M. Smith[1] and Angela K. Lyden. [1]StonyBrook University, [2]University of Michigan, Ann Arbor, MI

Objective: In a recent trial, we examined the effect of two different activity pacing interventions, general versus tailored, on symptom management for people with knee or hip osteoarthritis and found that fatigue was improved after the tailored compared to the general intervention. The current study was done to examine the secondary effect of activity pacing instruction on objective physical activity patterns (using ambulatory monitoring).

Methods: Thirty two adults with knee or hip osteoarthritis, who were randomly stratified by age and gender, received either tailored or general activity pacing instruction. Both interventions involved two sessions with an occupational therapist. All participants wore an accelerometer for five days that measured physical activity and allowed for repeated symptom assessment at baseline (which was used for tailored activity pacing instruction) and at the 10 week follow-up period. Activity patterns were assessed by examining: physical activity variability, measured using the standard deviation of 5-day average activity counts per minute, and average activity level, the 5-day average activity counts per minute.

Results: Physical activity variability decreased in the tailored group and increased in the general group. Participants in the tailored and general groups did not have significant changes in their average physical activity from baseline to 10 week follow-up.

Conclusion: The type of activity pacing instruction affected the objective physical activity of adults with symptomatic knee or hip OA. Tailored activity pacing was more effective at reducing high and low activity bouts corresponding to the message of keeping a steady pace to reduce symptoms.

Disclosure: S. L. Murphy: None; **D. M. Smith:** None; **A. K. Lyden:** None.

ACR Poster Session B

ACR/ARHP Poster Session B: ARHP: Behavioral Science

Tuesday, November 9, 2010, 9:00 AM–6:00 PM

1320

A Prospective, Longitudinal Cohort Study Evaluating Psychosocial Risk and Protective Factors for Post Lyme Disease Syndrome. Afton L. Hassett[6], Terry Shlimbaum[2], Diane C. Radvanski[4], David J. Herman[1], Ronald Nahass[1], Steven Buyske[3] and Leonard H. Sigal[5]. [1]ID CARE, [2]Phillips-Barber Family Health Center, [3]Rutgers University, [4]UMDNJ-Robert Wood Johnson Medical School, Union City, NJ, [5]UMDNJ-Robert Wood Johnson Medical School, [6]University of Michigan Medical School, Ann Arbor, MI

Background: Rarely do patients manifest objective evidence of ongoing infection with *B. burgdorferi* after antibiotic treatment and yet it has been estimated that at least one third of treated Lyme disease patients report chronic pain, fatigue, and cognitive problems. The condition referred to as Post Lyme Disease Syndrome, may be more appropriately thought of as fibromyalgia triggered by an infectious disease. There is evidence that illness factors at baseline, such as symptom severity and functional status are associated with symptom persistence and functional status after treatment; however, little is known about psychosocial risk and protective factors.

Methods: In a multicenter longitudinal study, 99 patients newly diagnosed with Lyme disease underwent comprehensive psychometric and medical/laboratory assessments at baseline. All patients received antibiotic treatment and at one year after diagnosis completed the Fibromyalgia Impact Questionnaire revised for Lyme disease (FIQ-LD) to evaluate the presence of chronic symptoms and functional status. Psychosocial factors assessed at baseline included: functional status (FIQ-LD), symptoms checklist, depression (PRIME-MD PHQ), catastrophizing (Coping Strategies Questionnaire-Catastrophizing subscale), negative affect and positive affect (Positive and Negative Affect Scale). At one year, patients with persistent symptoms ascribed to Lyme disease were compared to patients with resolved symptoms.

Results: Of the 74 patients who completed the 1-year assessment, 24 (32.4%) reported chronic symptoms – predominantly pain (VAS mean PLDS: 3.38±2.63 vs. Recovered: 0.43±0.85) and fatigue (VAS mean PLDS: 5.98±1.83 vs. Recovered: 1.56±1.96). Compared with patients who reported no chronic symptoms at one year, only functional status (45.00±18.23 vs. 31.90±21.19, $p<0.01$) and positive affect (31.57±6.63 vs. 35.92±4.96, $p<.003$) at baseline differed between groups. After correcting for multiple comparisons, positive affect alone remained significant. Logistic regression showed that group membership (PLDS vs. recovered from Lyme disease) was predicted by positive affect ($p=0.003$, Somers' Dxy rank correlation of 0.40) and baseline functional status ($p=0.01$, Somers' Dxy rank correlation of 0.35). No other variables were predictive of group status at one year. At baseline, positive affect and functional status were not correlated ($r=0.06$).

Conclusion: Almost one third of Lyme disease patients will manifest chronic symptoms post antibiotic treatment. Consistent with others, we found worse functional status at baseline to be predictive of PLDS. Further, we found that a resilience factor, positive affect, was the most valuable factor for predicting outcome in this population. Patients with higher levels of positive affect were more likely to fully recover from Lyme disease after treatment. Typically, psychological batteries only measure negative factors, but these data are consistent with emerging data in other fields that suggest that positive factors at baseline may better predict outcomes than negative factors.

Disclosure: A. L. Hassett: None; **T. Shlimbaum:** None; **D. C. Radvanski:** None; **D. J. Herman:** None; **R. Nahass:** None; **S. Buyske:** None; **L. H. Sigal:** None.

1321

Changing Shoes: Metaphorical Descriptions of Rheumatoid Arthritis and Identity. Catherine L. Backman[1], Anne Townsend[2] and Linda C. Li[1]. [1]University of British Columbia, Vancouver, BC, Canada, [2]W. Maurice Young Centre for Applied Ethics, University of British Columbia

Background: People lead storied lives and narrative inquiry makes sense of human experience through analyzing stories told. Personal accounts of episodes and events include narrative/rhetorical devices, like metaphors, which help us understand how individuals interpret and apply meaning to their experiences. These interpretations are central to their sense of self and may influence how people engage in future activities and collaborate with health care providers. This study explored how descriptions of emotional and physical adjustments to living with rheumatoid arthritis (RA) serve as metaphors for the impact of RA on identity.

Method: A secondary analysis of two qualitative studies was undertaken using a narrative approach. Study one explored the impact of RA on the role of mother in 12 women; study two explored the help-seeking process in 37 women diagnosed with RA in the year prior to recruitment. During the original data analysis for both studies, narrative devices were observed in descriptions of daily life experiences that had been disrupted by RA, and this prompted the present analysis. All 49 transcripts were reviewed and metaphorical descriptions of how RA experiences shaped sense of self or identity were extracted. Representative metaphors were then written by research team members, supported by verbatim passages from transcripts, and revised until consensus was achieved by the team as a whole.

Results: A number of metaphors illustrate the process of adapting to RA, characterized by adjustments to daily routines from the most basic of self care to participation in valued life roles. A powerful example is "changing shoes" or "no more shoes." This metaphor arises from descriptions of actual events where women could no longer wear the shoes that reflected their style, preference, or life roles. Underlying the seemingly superficial loss of favored shoes was a loss of self – a professional self, a country-club self, a stylish self. "Changing shoes" then becomes a metaphor for a shift in identity from a healthy person to one living with chronic illness and the new work that entails. The things women did to accommodate arthritis, either on their own or on the advice of a health professional, are shown through narrative analysis to represent emotional and physical adaptation to everyday activities that are meaningful to each individual. Metaphors were also observed to exemplify

key concepts specific to identity in current occupational therapy and rehabilitation theories that are intended to inform practice and clinical reasoning.

Conclusion: Metaphor was used to interpret stories of women living with RA. In the example presented here, changing shoes represents not only a physical adjustment to accommodate pain and apply joint protection principles, but also part of an internal process of reshaping identity. Appreciating how small changes carry greater meaning with regard to one's identity may foster more effective patient-provider communication and client-centered practice.

Disclosure: C. L. Backman: None; **A. Townsend:** None; **L. C. Li:** None.

1322

Emotional Response to Serial Doppler Echocardiography Examinations as a Screening Method To Detect Developing Congenital Heart Block in SSA/Ro Positive Pregnancy. Joanna Tingström[2], Mia Barimani[1], Sven-Erik Sonesson[1], Marie Wahren-Herlenius[2] and Elisabet M. B. Welin Henriksson[3]. [1]Karolinska Institutet, Stockholm, Sweden, [2]Karolinska Institutet CMM, Stockholm, Sweden, [3]Karolinska Institutet Rheum, Stockholm, Sweden

Objective: Congenital heart block may develop in the fetus during pregnancy in SSA/Ro52 autoantibody positive women. The aim of this study was to investigate how women with SSA/Ro52 autoantibodies experience their pregnancy focusing on the period between gestational weeks 18–24 when serial Ultrasound/Doppler examinations were performed to detect early signs of congenital heart block. The implementation of a new screening method has the benefit of detecting heart block early and allowing treatment at the stage when it is most effective, but may also cause negative side effects such as increased stress for the women.

Methods: Data were collected through individual semi-structured interviews with Swedish SSA/Ro52 positive women post pregnancy (n=14). None of the women gave birth to a child with congenital heart block. The interviews were audio taped, transcribed verbatim and analyzed by qualitative content analysis.

Results: Three categories emerged from the responses; information, emotional response and support. The information received prior to and during early pregnancy was focused on the need for attending a specialized antenatal clinic, and information on the risk for congenital heart block was scarce or missing. During gestational week 18–24 when the ultrasound/Doppler examinations were performed all women described increased stress in some way. However, nobody wanted to renounce the examinations and the interaction with the caregivers made the women feel more safe and secure. Several women described that they did not emotionally acknowledge the pregnancy and could not fully take in that they were pregnant until after gestational week 24. None had been offered psychological support.

Conclusions: There is a need for structured information and organized programs for surveillance of SSA/Ro52 positive pregnancy. Despite the increased stress the women described in connection with the ultrasound examinations, all women felt that the advantages outweighed the disadvantages of the procedure. Further, offering psychological support to the women and their families to give them tools to handle the stress and to facilitate the early attachment to the child should be considered.

Disclosure: J. Tingström: None; **M. Barimani:** None; **S.-E. Sonesson:** None; **M. Wahren-Herlenius:** None; **E. M. B. Welin Henriksson:** None.

1323

Psychological Factors but Not Clinical Markers of Disease Activity Predict Adherence among Rheumatoid Arthritis (RA) Patients Receiving DMARDs and Adalimumab (ADA): Results from the British Society for Rheumatology Biologics Register (BSRBR). C. Morgan[1], J. McBeth[2], L. Cordingley[2], K. D. Watson[2], BSRBR Control Centre Consortium, K. L. Hyrich[2], D. P. M. Symmons[2], I. N. Bruce[2] and on Behalf of the BSR Biologics Register. [1]The University of Manchester, Manchester, United Kingdom, [2]The University of Manchester

Background: Drug adherence rates amongst RA patients are reported to be between 30–78%. Psychological factors such as illness perceptions and coping mechanisms are important predictors of adherence. The aim of this study was to establish the relative contributions of demographic, physical and psychological factors to adherence.

Methods: The analysis included 610 patients recruited between 01/05/07–30/04/09 to the BSRBR, a UK national observational cohort study monitoring the long term safety of biologic agents in RA patients receiving anti-TNF therapy. Two patient groups were identified for this analysis: (i) those taking ADA as a monotherapy or in combination with a DMARD and (ii) those taking a DMARD-only based regime as mono or combination therapy. At baseline, demographic data, DAS28, physical function (HAQ), quality of life (SF36) and psychological data including illness perception, coping strategies and belief about medication use were collected. Adherence was assessed indirectly using the validated 19-item patient self-complete Compliance Questionnaire Rheumatology (CQR) at baseline. The CQR yields a total score between 0–100, with higher scores indicating higher levels of adherence. Linear regression (adjusted for age, gender and disease duration) was used to investigate the relationships between baseline factors and CQR scores.

Results: A total of 358 ADA and 252 DMARD patients were available for analysis of which 75% were female. Compared to the DMARD group, ADA patients had a younger age at disease onset (median 44 v 51 years, $p<0.001$), longer disease duration (median 9 v 5 years, $p<0.001$) and higher disease activity (mean DAS28, SD: 6.5, 0.9 v 5.4, 0.9, $p<0.001$). 287 (80.2%) of the ADA group were also taking a DMARD, and in the DMARD-only group, 101 (40.1%) were taking ≥ 2 DMARDs at time of study. The median CQR score for the DMARD and ADA patients were 71.9 (IQR 64.9–78.9) and 75.4 (IQR 64.9–82.5), respectively. The DAS28 and HAQ did not predict CQR score in either group. In both treatment groups a lower CQR score was predicted by poor physical health (physical component summary (PCS) SF36). Perceiving RA to be a chronic illness, that medication was a necessity, and adopting positive coping mechanisms were all associated with higher CQR scores while increasing concern over medication use was associated with lower scores in both groups. Perceived control over treatment also predicted higher CQR scores in the ADA group alone.

Regression results* for significant associations with total CQR score

	DMARD group (n=252)		ADA group (n=358)	
Factor	β co-efficient	95% CI	β co-efficient	95% CI
Poor physical function (PCS, SF36)	−0.2	−0.3, −0.08	−0.1	−0.2, −0.006
Perception of illness being chronic	0.7	0.3, 1.2	0.6	0.3, 0.96
Necessity of medication	1.8	1.5, 2.2	1.6	1.2, 1.9
Positive coping mechanisms	1.5	0.8, 2.3	1.1	0.3, 1.9
Medication concerns	−0.3	−0.7, 0.06	−0.5	−0.8, −0.3
Perceived control over treatment	−0.1	−0.7, 0.4	0.8	0.4, 1.2

* adjusted for age, gender and disease duration

Conclusion: Wider recognition of the role of beliefs about medication adherence would have substantial clinical benefits in RA. In the biologics era, it may also have important health economic benefits. This study has identified modifiable psychological factors that are putative targets for strategies to improve adherence.

Disclosure: C. Morgan: None; **J. McBeth:** None; **L. Cordingley:** None; **K. D. Watson:** None; **BSRBR Control Centre Consortium:** None; **K. L. Hyrich:** None; **D. P. M. Symmons:** None; **I. N. Bruce:** None; **on Behalf of the BSR Biologics Register:** None.

1324

Spousal Social Support and Well-Being among Persons with Rheumatoid Arthritis: Is Support in the Eye of the Beholder? Allen J. Lehman[1], Anita DeLongis[3], Daniel D. Pratt[3], John B. Collins[3] and John M. Esdaile[2]. [1]Arthritis Research Centre of Canada; Simon Fraser University, Vancouver, BC, Canada, [2]Arthritis Research Centre of Canada; University of British Columbia, Vancouver, BC, Canada, [3]University of British Columbia, Canada

Background: Much evidence suggests that social support is beneficial to persons with RA, both in terms of disease course and quality of life. It is essential that research identify the pathways through which support is beneficial. Several recent studies of people undergoing relatively chronic, but ultimately time-limited stress, suggest that spousal support is most health protective when it is "invisible" (the beneficiary of support is unaware that it has been provided). The stress associated with living with RA, however, is not time-limited. Whether extant findings on invisible support can be extended to couples in which one spouse has RA is unclear. Our study objective was to determine if invisible support for the person with RA is associated with significantly better well-being for the recipient than when both spouses agree that support was provided.

Methods: English speaking adults with RA ≥ 6 months and their spouses (N=222 couples) independently completed standardized questionnaires that assessed the perceptions of each regarding social support received by the person with RA and support provided by the spouse, as well as relationship satisfaction, positive affect, and depression. A dummy-coded 2×2 table summarized spousal congruence or divergence on perceptions of support for the person with RA (present, absent). Couple congruence on support present for the person with RA served as the reference category. Separate hierarchical regression models tested the effects of spousal support congruence or divergence on persons with RA's relationship satisfaction, positive affect, and depression, after adjusting for gender, RA severity, and spouse depression.

Results: Questionnaire response rate for couples was 82%. Of the persons with RA, 73% were female, the mean RA duration was 12 yrs, with mean relationship duration 31 yrs. Spousal congruence or divergence on perceptions of support for the person with RA include congruence on support present (65%) or absent (16%), and "invisible support" (13%). Even after statistically adjusting for the effects of RA, gender, and spouse depression on well-being among persons with RA, couple congruence or divergence on perceptions of support explained additional variability in relationship satisfaction ($R^2 = 0.492$, $p<0.001$), positive affect ($R^2 = 0.099$, $p<0.001$), and depression ($R^2 = 0.084$, $p<0.001$). Invisible support from the spouse showed a significant negative association with well-being in the person with RA, including poorer relationship satisfaction ($\beta=-0.503$, $p < 0.001$), less positive affect ($\beta=-0.269$, $p < 0.001$), and higher depression levels ($\beta=0.168$, $p < 0.01$).

Conclusion: Perceptions of social support from the spouse were significantly associated with positive well-being among persons with RA, regardless of whether the spouse reported having provided support. Contrary to findings of previous studies in non-RA samples, invisible support was associated with poorer well-being. Our findings suggest that what is most important is the recipient's perception of support received from the spouse. Such findings will be useful in designing evidence-based family and couple clinical interventions for those with RA and their families.

Disclosure: A. J. Lehman: None; **A. DeLongis:** None; **D. D. Pratt:** None; **J. B. Collins:** None; **J. M. Esdaile:** None.

1325

Sustained Reduction in Fatigue Impact in Rheumatoid Arthritis: RCT of Cognitive Behavioural Therapy. Sarah E. Hewlett[5], Nicholas Ambler[2], Bev Knops[2], Alena Cliss[1], Celia Almeida[6], Denise Pope[3], Alison Hammond[4], Annette Swinkels[6], Karen Kitchen[3] and Jon Pollock[6]. [1]Frenchay Hospital, Bristol UK, [2]Frenchay Hospital, Bristol, UK, [3]University Hospitals Bristol, UK, [4]University of Salford, Matlock Derbyshire, United Kingdom, [5]University of the West of England, Bristol, United Kingdom, [6]University of the West of England, Bristol UK

Aim: Up to 90% of RA patients experience distressing, unmanageable fatigue that impacts profoundly on life. In other long-term conditions, fatigue self-management programmes of cognitive behavioural techniques (CBT) show benefit. This randomized controlled trial tested CBT for RA fatigue.

Methods: CBT was delivered by a clinical psychologist and specialist occupational therapist in 6 × 2hr weekly group sessions (1hr booster at wk 14), addressing thoughts, feelings and behaviours, underpinned by goal-setting. Included were activity pacing, self-monitoring diaries for energy management, achieving balance (prioritizing), stress, communication, assertiveness, sleep, and managing setbacks. The information-only control arm comprised a 1hr group session based on the Arthritis Research UK fatigue leaflet. Entry criteria were fatigue VAS ≥6/10 and no change in major medication in previous 16 wks (steroids 6 wks). Assessments: VAS 0–10 for fatigue impact, severity and coping, Multi-dimensional Assessment of Fatigue (MAF 0–50), quality of life (RAQoL 0–30), sleep (good/poor), anxiety and depression (HADS 0–21), helplessness (AHI 5–35).

Results: Of 168 patients randomized, 41 withdrew before entry, 51 did not complete all datasets, 76 completed to wk 18 (no significant baseline differences for age, gender, disease duration). At baseline, the 76 patients (38 CBT, 38 Control) comprised 55F, 21M, mean age 60.4 yrs (95% CI 57.8–62.9), disease duration 11 yrs (10–15). All data were tested for normality and outcomes transformed where necessary. Analysis was adjusted for group and for baseline scores. At baseline, CBT and Control patients only differed by better RAQoL in CBT arm: 13.7 (11.8–15.6) vs 17.3 (14.8–19.9).

At the end of the programme (6 wks) the CBT group had significantly better scores than the Control group for every fatigue and every well-being outcome, which were maintained at 18 wks, except for RAQoL (see Table). More CBT than Control patients reported better sleep quality (6 wks 22/38 vs 19/38, p=0.024; 18 wks 30/38 vs 20/38, p=0.012).

	Week 6		Week 18	
	CBT n=38 mean (95% CI)	Control n=38 mean (95% CI)	CBT n=38 mean (95% CI)	Control n=38 mean (95% CI)
Fatigue:				
Impact	4.2 (3.4–5.1)	6.0 (5.1–6.9)	4.2 (3.3–5.1)	6.0 (5.1–6.9)
Severity	4.7 (3.8–5.5)	6.3 (5.5–7.1)	4.8 (4.0–5.6)	6.2 (5.2–7.1)
Coping (high good)	7.3 (6.6–8.0)	5.3 (4.4–6.1)	7.2 (6.6–7.9)	5.8 (4.9–6.6)
MAF	24.7 (21.3–28.0)	30.7 (27.2–34.4)	24.0 (20.2–27.7)	28.8 (24.9–32.7)
Well-being:				
RAQoL	10.8 (8.7–12.8)	16.8 (14.1–19.5)	10.9 (8.8–13.1)	14.8 (11.5–18.2)*
Anxiety	5.7 (4.3–7.1)	8.6 (6.8–10.4)	5.2 (3.6–6.7)	7.8 (6.2–9.4)
Depression	4.7 (3.7–5.8)	7.5 (6.0–9.0)	4.75 (3.5–6.0)	7.2 (6.2–9.3)
Helplessness	13.4 (11.9–14.9)	18.7 (17.0–20.3)	13.6 (12.3–15.0)	18.0 (16.3–19.8)

High scores are worse, except for Coping
All p=0.001 to 0.045
* p=0.480

Interim assessment at 10 wks showed the CBT group was still significantly better than the Control group in all except 3 outcomes that just failed to reach statistical significance (Anxiety p=0.057, Fatigue Coping p=0.066, Fatigue Severity p=0.064). The planned booster session was delivered at 14 wks. At 18 wks these outcomes were all significantly different again (Table).

Conclusion: CBT for fatigue self-management in RA significantly improves fatigue and well-being, maintained at 3 months. The loss of significance in three variables before the booster session and subsequent improvement afterwards may indicate the value of 'top-up' sessions in clinical practice. As clinical psychology provision is often limited, the efficacy and cost of a lower-intensity CBT approach provided by the clinical team (with training and support) should be explored.

Disclosure: S. E. Hewlett: None; **N. Ambler:** None; **B. Knops:** None; **A. Cliss:** None; **C. Almeida:** None; **D. Pope:** None; **A. Hammond:** None; **A. Swinkels:** None; **K. Kitchen:** None; **J. Pollock:** None.

1326

The Effect of Social Support from Physicians and Partners on the Health-Related Quality of Life of Vasculitis Patients in Relapse and Remission. Delesha M. Carpenter[2], Jessica A. Kadis[2], Robert F. DeVellis[2], Susan L. Hogan[3] and Joanne M. Jordan[1]. [1]Chapel Hill, NC, [2]UNC, Chapel Hill, NC, [3]UNC

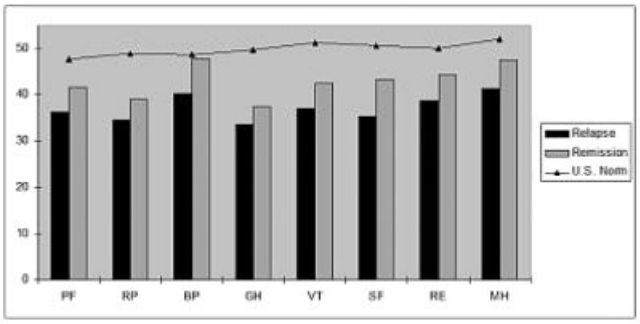
Background: Although social support has been shown to positively impact the physical and mental health of chronic disease patients, few studies have explored whether the benefits of support vary by level of disease activity.

Objective: Our goal was to determine whether the disease status (relapse vs. remission) of vasculitis patients moderated the effect of physicians' and partners' social support on patients' health-related quality of life (HRQOL).

Methods: Vasculitis patients (n=228) completed two online surveys. The baseline survey assessed demographic information, self-reported disease status (relapse vs. remission), and social support from physicians and partners. The 3-month follow-up survey measured 8 dimensions of HRQOL (SF-36): physical functioning (PF), physical role limitations (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), emotional role limitations (RE), and mental health (MH). Higher scores indicate better HRQOL. We compared the HRQOL of patients in relapse and remission. We also determined whether disease status moderated the effect of physician support and partner support on patient HRQOL; Wilks' Λ indicated whether the physician support-by-disease-status and partner support-by-disease-status interaction terms were significant.

Results: Relapsing patients reported significantly worse health when compared with non-relapsing patients for 7 of 8 HRQOL dimensions: physical functioning, bodily pain, general health, vitality, social functioning, emotional role limitations, and mental health (Figure 1). Disease status did not moderate the effect of physician (Wilks' Λ=0.49, p=.86) or partner social support (Wilks' Λ=1.49, p=.16) on HRQOL. However, social support from

both physicians and partners was associated with better HRQOL. Specifically, physician support predicted better HRQOL for 6 of 8 dimensions (all except for except bodily pain and vitality). Partner support predicted fewer physical and emotional role limitations and better social functioning.



Conclusion: Vasculitis patients experience compromised HRQOL when compared with U.S. population norms, but the magnitude of the compromise is greater for patients experiencing a relapse. Social support from physicians and partners is beneficial for patient HRQOL regardless of where the patient is in the relapse/remission cycle.

Disclosure: D. M. Carpenter: None; **J. A. Kadis:** None; **R. F. DeVellis:** None; **S. L. Hogan:** None; **J. M. Jordan:** None.

ACR Poster Session B
ACR/ARHP Poster Session B: ARHP: Foot
Tuesday, November 9, 2010, 9:00 AM–6:00 PM

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Foot Pain in Relation to the Foot Biomechanical Measures of Plantar Peak Pressures and Pressure Time Intergral. Virginia A. Casey[3], Andrew M. Galica[3], Alyssa B. Dufour[1], Robert R. McLean[1] and Marian T. Hannan[2]. [1]Hebrew Senior Life, Boston, MA, [2]Hebrew SL & Harvard Med Sch, Boston, MA, [3]IFAR Hebrew SeniorLife, Boston, MA

Introduction: Foot pain is a major cause of mobility limitation, however, the mechanisms that lead to foot pain are not completely understood. Small laboratory studies have shown that uneven distribution of the forces applies to the foot during normal walking result in areas of high pressure, which are associated with foot pain. Yet, these relations between plantar peak pressures and pressure-time integrals have not yet been investigated in a large, population-based sample. Thus, we examined the associations between generalized foot pain and peak pressure (PP) and pressure time integral (PTI) in men and women of the population-based Framingham Foot Study. We hypothesized that individuals reporting foot pain would exhibit higher peak pressure in specified foot areas compared to those reporting no foot pain.

Methods: Foot pressure data were obtained from 200 men and 262 women enrolled in the Framingham Foot Study. Between 2002 and 2005, plantar pressure values were collected using a Tekscan Matscan pedobarographic system (resolution of 1.4 sensels/cm^2) while participants walked at a comfortable pace barefoot across the mat. Novel software was used to calculate PP and PTI from 12 segments of the right foot (toes, submetatarsal heads 1–5, medial arch and heel, lateral arch and heel). Self-reported foot pain was determined by the response to the question: "On most days, do you have pain, aching or stiffness in either foot?" Two-tailed Student's T-tests assessed differences in PP and PTI between those with and without foot pain, separately for men and women.

Results: Study participants were 66% female with mean age of 65 years, and mean BMI of 28. In women who reported foot pain, there was significantly greater PP at the 2nd and 3rd metatarsal heads ($p<0.0001$) compared to those who did not report foot pain. In men, significant differences in PP were only seen at the 5th metatarsal head ($p<0.001$). There were no significant findings for foot pain and PTI measures in either men or women.

	Peak Pressure, N/cm^2			Pressure Time Integral, (N/cm^2βsec		
Foot Region	No Foot Pain	Foot Pain	P Value*	No Foot Pain	Foot Pain	P Value*
Female	n=187	n=75		n=184	n=75	
Submetatarsal head 1	17.8 ± 6.1	16.9 ± 5.8	0.32	8.3 ± 3.9	8.4 ± 4.1	0.77
Submetatarsal head 2	22.6 ± 4.7	21.0 ± 5.1	0.01	10.8 ± 3.3	10.6 ± 5.0	0.73
Submetatarsal head 3	22.1 ± 4.7	20.4 ± 5.0	0.01	10.5 ± 3.2	10.4 ± 4.6	0.81
Submetatarsal head 4	17.3 ± 5.4	16.5 ± 4.8	0.28	7.8 ± 2.9	7.6 ± 2.6	0.65
Submetatarsal head 5	14.2 ± 6.1	13.9 ± 5.8	0.69	5.9 ± 3.2	6.0 ± 3.3	0.80
Male	n=164	n=36		n=164	n=36	
Submetatarsal head 1	18.9 ± 6.3	19.5 ± 6.1	0.61	9.1 ± 5.1	9.5 ± 4.7	0.61
Submetatarsal head 2	22.9 ± 4.1	23.4 ± 4.5	0.53	11.0 ± 4.4	11.6 ± 3.9	0.45
Submetatarsal head 3	22.8 ± 4.1	23.5 ± 4.5	0.34	11.0 ± 4.8	11.5 ± 3.5	0.46
Submetatarsal head 4	18.9 ± 4.7	20.3 ± 5.2	0.13	8.6 ± 3.6	9.2 ± 2.6	0.21
Submetatarsal head 5	15.4 ± 6.2	17.8 ± 5.0	0.03	6.9 ± 4.8	7.7 ± 2.9	0.18

* Two-Tailed Students T-Test

Discussion: In a large population-based sample, general foot pain was associated with higher PP under several of the metatarsal heads, albeit differently in men and women. Significant findings were not observed for the pressure-time integral measures. It may be that the accumulation of pressure loading over time does not cross a pain threshold as easily as peak pressure. We are unaware of differences in gait between men and women, or other reasons for different PP and reports of foot pain. Future work should investigate specific foot pain location in relation to areas of plantar pressure loading to elaborate on potential mechanisms.

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1328

Hallux Valgus and Foot Bimechanics: Relation between Structure and Function. Andrew M. Galica[5], Alyssa B. Dufour[1], Marian T. Hannan[2], Virginia A. Casey[5], Jocelyn C. Frey[4], Mark W. Lenhoff[4] and Howard J. Hillstrom[3]. [1]Hebrew Senior Life, Boston, MA, [2]Hebrew SL & Harvard Med Sch, Boston, MA, [3]Hospital Special Surgery, New York, NY, [4]Hospital Special Surgery, New York, NY, [5]Institute for Aging Research

Background: While there are many clinical and case reported studies of hallux valgus (HV), the etiology and biomechanics of the pathology remain poorly understood. Although previous studies have noted differences in peak pressures in various regions of the foot between individuals with and without HV, results are inconsistent and have not been confirmed in larger studies. The purpose of this research is to describe peak plantar pressures and pressure-time integrals in an epidemiological population-based study and to investigate whether these measures differ between those with and without HV as defined by standardized foot examinations. We hypothesize that it is possible to distinguish individuals with and without HV based on differences in peak pressure and pressure-time integral measures.

Methods: Data were obtained from a subset of participants enrolled in the Framingham Heart Study (N = 464; 57% female; mean age, 65 years; mean BMI, 28). Between 2002 and 2005, plantar pressure values were collected using a Tekscan Matscan system (model 3150, resolution of 1.4 sensels/cm^2) while participants walked at a comfortable pace barefoot across the mat. Data was imported into Novel software and masked into 12 segments (toes, submetatarsal heads 1–5, medial arch and heel, lateral arch and heel). Peak pressure and pressure time integral values were then calculated. Two-tailed Students T-tests assessed differences between those with and without HV.

Results:

Foot Region	Peak Pressure, N/cm²			Pressure Time Integral, (N/cm²)×sec		
	No Hallux Valgus	Hallux Valgus	P Value	No Hallux Valgus	Hallux Valgus	P Value
FEMALE	n=172	n=87		n=171	n=87	
Hallux	18.5 ± 6.1	18.4 ± 6.1	0.84	7.9 ± 3.9	8.0 ± 4.6	0.90
Submetatarsal head 1	17.7 ± 5.8	17.1 ± 5.8	0.46	8.4 ± 3.7	8.0 ± 4.2	0.50
Submetatarsal head 2	22.2 ± 4.8	21.9 ± 5.1	0.67	10.7 ± 3.1	10.9 ± 5.1	0.72
MALE	n=155	n=45		n=155	n=45	
Hallux	19.3 ± 7.0	18.0 ± 7.3	0.27	7.7 ± 4.5	8.2 ± 5.8	0.61
Submetatarsal head 1	18.9 ± 5.9	19.3 ± 7.6	0.8	8.7 ± 3.7	10.5 ± 7.9	0.15
Submetatarsal head 2	23.0 ± 3.9	22.8 ± 5.2	0.82	10.9 ± 3.1	11.9 ± 7.0	0.38

Preliminary analysis revealed significant sex differences in plantar pressures. Therefore, subsequent analyses were stratified by gender. Since the right foot is considered more dominant, only these results are reported. Tables 1 and 2 present a subset of the 12 analyzed foot areas. Female subjects with HV exhibited greater peak pressure values under the lateral arch than those without HV ($p = 0.046$). No significant differences were found in pressure-time integrals for females with and without HV, regardless of foot area. Male subjects with HV exhibited greater peak pressure ($p=0.007$) and pressure-time integral ($p=0.015$) values than those without HV under groupings of the 3rd, 4th, and 5th toes.

Conclusions: Significant gender differences in peak pressures and pressure time integrals were noted. The data did not support our hypothesis as analyses did not distinguish between those with and without HV based on pressure-related measures. It is possible that the accuracy and resolution of Tekscan, in comparison to other foot mat systems, may have affected our results. It is also possible, since both groups contained concomitant pathologies, the plantar loading effects for HV washed out. Future work may investigate whether consideration of additional foot disorders or deformities may better use the plantar pressure measures to distinguish foot pathologies.

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Hallux Valgus and Pes Cavus Are Highly Heritable in Older Men and Women: The Framingham Foot Study. Marian T. Hannan[4], Yi-Hsiang Hsu[3], L. Adrienne Cupples[2] and Joanne M. Jordan[1]. [1]Chapel Hill, NC, [2]BUSPH, Boston, MA, [3]Hebrew SeniorLife, HSPH and Harvard Medical School, Boston, MA, [4]Hebrew SL & Harvard Med Sch, Boston, MA

Foot disorders are common among adults, affecting 20–60% of adults and often linked to mobility limitations. Although genetics are commonly suspected in foot disorders, only one family aggregation study has been done, reporting that 90% of 350 participants with hallux valgus had a family history, and inheritance may be an autosomal dominant transmission. To our knowledge, no other studies have examined the association between foot disorders and genetics in humans. We have the unique opportunity to link data that we have collected on specific foot disorders to a wealth of genetic data in the community-based Framingham Study. Our aim was to evaluate the possible heritability of two common foot disorders, using the pedigree structure in the Framingham Study.

The Framingham Foot Study (n=2179) was designed to examine common foot disorders and functional limitations. A trained examiner used a validated foot exam to assess 20 foot disorders in 2179 participants between 2002–2005. Of participants, 959 men and 1220 women had been genotyped. We estimated overall, sex-specific and age (< 60, 60+y) heritability of hallux valgus and pes cavus (our most common and least common foot disorders) in the Framingham participants. Hallux valgus (present/absent) was defined as the angular deviation of the hallux with respect to the first metatarsal toward the lesser toes at >=15°. Pes cavus was defined using a digital recording of foot pressure while walking (MatScan pedobarographic device, Tekscan, Inc. Boston MA), that allowed calculation of the ratio of arch width (medial to lateral, to nearest 0.01 cm) to heel width. Pes cavus was defined as either foot as having a weight-bearing arch width=0, regardless of heel width. We estimated heritability of hallux valgus and pes cavus by the threshold model of a standard quantitative genetic variance-components model implemented in the Sequential Oligogenic Linkage Analysis Routines (SOLAR) package.

Mean age was 66y (range 39–99y); 57% were female. The prevalence of hallux valgus (HV) was 31% (675 hallux valgus cases with available pedigree structure). The overall HV heritability was 0.39 for women and 0.38 for men. For persons aged < 60y, the HV heritability was 0.89. The prevalence of pes cavus (PC) was only 7% (154 cases with available pedigree structure have pes cavus). The PC heritability was 0.68 for women and 0.20 for men. For individuals < 60y of age, the PC heritability was 0.99 for women and 0.63 for men. Thus, hallux valgus and pes cavus are highly heritable, especially for younger adults.

This study breaks new ground in an area that has received very little attention, yet is critically important to public health. Our study documented for the first time, the high heritability (strongly suspected by many) of two specific foot disorders phenotypes. Foot disorders are common and it is important to identify persons at high risk, as effective interventions exist and may also be targeted to individuals to lessen the impact of foot disorders or prevent development. Genome-wide association analyses are planned to identify potential genetic determinants for these common foot disorders.

Disclosure: M. T. Hannan: None; **Y.-H. Hsu:** None; **L. A. Cupples:** None; **J. M. Jordan:** None.

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Racial Differences in Foot Disorders: The Johnston County Osteoarthritis Project. Yvonne M. Golightly[2], Marian T. Hannan[1], Alyssa B. Dufour[1] and Joanne M. Jordan[2]. [1]Institute for Aging Research, Hebrew Senior Life, [2]University of North Carolina at Chapel Hill

Background: Clinical impressions are that African Americans have pes planus (flat feet) and hallux valgus (bunions) more frequently than Caucasians, but few population-based studies exist. This cross-sectional analysis describes racial/ethnic differences in the prevalence of physical disorders of the foot in a large, bi-racial cohort of individuals 45 years of age or older.

Methods: Of the1,540 Johnston County Osteoarthritis Project participants clinically evaluated in 2006–2010, four with lower extremity amputation were excluded, leaving 1,536 available for analyses (mean age 69 years, mean body mass index [BMI] 31.5 kg/m2, 68.4% female, 30.3% African American). Presence of specific foot conditions (coded as present or absent) were evaluated using the Foot Assessment Clinical Tool, a validated clinical examination with specific criteria to assess 10 foot disorders (Table). The most common foot disorders were identified (prevalence of ≥ 10%), and logistic regression was used to compare each foot problem by race, controlling for age, BMI, and gender, as these factors may affect foot disorders. Effect modification between race (African American versus Caucasian) and age, BMI (categorized as >30 or ≤30 kg/m2), or gender were examined ($p<0.10$ for interaction was considered statistically significant).

Results: In 1536 participants, the 5 most common foot conditions were hallux valgus (62.8%), hammer toes (35.6%), overlapping toes (31.8%), pes planus (22.5%), and corns (20.5%). In adjusted models, African Americans were almost 3 times as likely as Caucasians to have pes planus and corns (Table). Non-obese (BMI ≤30 kg/m2) African Americans were almost twice as likely as non-obese Caucasians to have hallux valgus (aHR=1.90, 95% CI= 1.29–2.78) and over twice as likely to have hammer toes (aHR=2.30, 95% CI=1.62–3.27). These conditions did not differ significantly by race among the obese (BMI >30 kg/m2). There were no other interactions by age or gender. African Americans were 70–80% less likely than Caucasians to have Tailor's bunion and pes cavus (Table).

Table. Prevalence of Foot Disorders by Race.

Foot Disorder	African American N=466 (%)	Caucasian N=1,070 (%)	Adjusted* Odds Ratio (95% Confidence Interval)
Hallux Valgus	40.3	28.4	Non-obese: 1.90 (1.29–2.78)
	27.9	32.0	Obese: 1.28 (0.94–1.74)
Hammer Toes	22.1	16.6	Non-obese: 2.30 (1.62–3.27)
	19.1	16.6	Obese: 1.10 (0.80–1.50)
Claw Toes	3.7	2.8	1.56 (0.85–2.89)
Overlapping Toes	33.5	31.1	1.16 (0.91–1.47)
Corns	32.0	15.5	2.89 (2.20–3.79)
Tailors Bunion	1.5	6.7	0.21 (0.10–0.47)
Morton's Neuroma	8.8	7.9	1.11 (0.74–1.65)
Plantar Fasciitis	5.6	4.6	1.10 (0.67–1.82)
Pes Cavus	1.5	5.6	0.28 (0.12–0.61)
Pes Planus	37.6	16.0	2.89 (2.24–3.73)

* Adjusted for age, body mass index, and gender.

Conclusions: Foot disorders are common among adults 45 years of age or older, and these conditions tend to be more prevalent among African Americans than Caucasians. The racial differences in the prevalence of hallux valgus and hammer toes are most evident among those who are not obese, suggesting that obesity equalizes the odds of having these conditions, regardless of race.

Disclosure: Y. M. Golightly: None; **M. T. Hannan:** None; **A. B. Dufour:** None; **J. M. Jordan:** None.

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Risk Factors for Hallux Valgus (HV) in a Population-Based Study of Older Adults: The Framingham Foot Study. Alyssa B. Dufour[4], Virginia A. Casey[5], Andrew M. Galica[5], David R. Gagnon[1], Howard J. Hillstrom[3] and Marian T. Hannan[2]. [1]Boston University School of Public Health, Boston, MA, [2]Hebrew SL & Harvard Med Sch, Boston, MA, [3]Hospital Special Surgery, New York, NY, [4]Institute for Aging Research, Hebrew SeniorLife & Boston University School of Public Health, Boston, MA, [5]Institute for Aging Research, Hebrew SeniorLife, Boston, MA

HV is common in older adults, but its risk factors and relation with foot pain are understudied. The few studies of risk factors have reported conflicting results and had small samples, with limited age ranges. Our purpose was to determine if HV is associated with foot pain and potential risk factors in large numbers of community-dwelling older men and women.

This cross-sectional study included 3415 ambulatory adults from the population-based Framingham Study. We used a validated foot exam done by trained examiners with criteria to assess H valgus, foot pain, pes planus, and current and past high heel use. HV was present if the angle of the hallux toward the lesser toes was observed to be >15°. Pes planus was defined using a weight-bearing ratio of arch width to rear-foot width on a computerized pressure mat (y/n if ratio>.75 on either foot). Foot pain (y/n) was queried: "on most days, do you have pain, aching or stiffness in either foot?" High heel use in women was determined by the subject choosing high heels/pumps from a list of 13 shoe types as the shoe most typically worn currently and in their past. Past high heel use was categorized into 3 groups: main shoe between ages 20–64y; main shoe at some ages between 20–64y; not worn between 20–64y. Age, sex, and body mass index (BMI, grouped <25, 25–30, >30 kg/m^2) were also collected. Sex-specific multivariate logistic regression models were performed to examine the effect of the above risk factors on HV.

1498 men & 1917 women had mean age of 67 ± 10.6 y (range 40–100 y). 20% of men and 41% of women had HV. Current high heel use was not associated with HV in women and thus excluded. Table shows risk factors for HV by sex. Foot pain and older age increased the odds of having HV in both women and men (all p<0.03), even after adjusting for other factors. In women only, having pes planus increased the odds of HV by 70% (p=0.01); BMI>30 was protective, decreasing the odds by 35% (p=.0007); and wearing high heels as main shoe during ages 20–64y increased the odds of HV by 22% (p=0.01), after adjusting for the other factors. To extend the BMI findings, we examined a biomechanical measure (1st met-head peak pressure) in a subset (n=573) and found no interaction with BMI (p<0.56). Adding peak pressure to the model did not change the effects of BMI (ORs~0.99).

Risk Factors for Hallux Valgus (adjusted for all other risk factors)

	Male		Female	
	Prevalence (%)	OR (95% CI)	Prevalence (%)	OR (95% CI)
Age (10 year increment)		1.15 (1.01, 1.31)		1.20 (1.09, 1.31)
BMI <25 (referent)	18.2	1.00	33.5	1.00
BMI 25–30	45.0	0.95 (0.67, 1.36)	35.1	0.96 (0.76, 1.21)
BMI >30	36.9	0.72 (0.49, 1.06)	31.4	0.65 (0.51, 0.83)
Foot pain (yes/no)	18.8	1.81 (1.33, 2.47)	28.5	1.36 (1.10, 1.69)
Pos Planus (yes/no)	8.8	1.45 (0.84, 2.25)	6.4	1.68 (1.13, 2.60)
Past high heel use (never, referent)	–	–	43.2	1.0
Past high heel use (some)	–	–	38.9	1.45 (1.09, 1.93)
Past high heel use (always)	–	–	18.0	1.22 (0.99, 1.51)

We saw strong relations between HV and foot pain and increased age in both men and women. While current high heel use was not linked to HV, several other factors were associated with this structural foot disorder in women. Results for BMI>30 are in agreement with ≥1 previous study showing a protective effect. Perhaps this is due to differing weight distributions and thus different foot biomechanics in obese women versus those with BMI<25. Future studies should include additional risk factors such as occupational weight bearing load, pregnancies and toe box structure of shoewear.

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ACR Poster Session B

ACR/ARHP Poster Session B: ARHP: Patient Education/Support

Tuesday, November 9, 2010, 9:00 AM–6:00 PM

1332

A Model of Quality Patient-Health Care Provider Communication. Elizabeth Salt[1] and Graham Rowles[2]. [1]University of Kentucky, Lexington, KY, [2]University of Kentucky

Background: Quality treatment of rheumatoid arthritis (RA) includes effective communication between patients and health care providers (Lempp, Scott, & Kingsley, 2006). Effective patient-health care provider communication may have a positive effect on health outcomes, medication adherence, and a trusting patient-health care provider relationship, and a negative effect on the number of complaints to medical regulatory authorities (Berrios-Rivera et al., 2006; Tamblyn et al., 2007; Viller et al., 1999; Wolfe, 1995). The purpose of this study is to develop a model of the patient's perception of quality patient-health care provider communication.

Methods: Following Medical Institutional Review Board approval, a sample of 15 English-speaking patients with RA were recruited from a university rheumatology clinic to participate in two focus groups sessions (n = 6) and individual interviews (n = 9). Verified transcripts from the audio-recorded interviews were analyzed using constant comparative analysis (Straus & Corbin, 1990). The resulting codes were collapsed into themes which were organized into a model of the patient's perception of quality patient-health care provider communication.

Findings: The model of the patient's perception of quality patient-health care provider communication involves dynamic interactions between the patient and health care provider. Participants described entering the encounter with past experiences and outside influences. They explained their symptoms and concerns and asked their health care provider questions. Participants felt that their health care provider should both listen to them and believe the information reported. Participants reported that the health care provider, who can come to the encounter with assumptions, should disseminate information, ask questions, and make recommendations. The participants in this study felt that providers should be personable, empathetic, respectful, un-hurried and caring during this interaction. They also felt that health care providers should be honest, straightforward, positive, and decisive when providing accurate information using face-to-face conversation or visual aids.

Conclusion: A model of the patient's perception of quality patient-health care provider communication has been developed. This model, if substantiated, can further our understanding of patient-health care provider communication and provide direction for future research.

Disclosure: E. Salt: None; **G. Rowles:** None.

1333

Comparison of Physician- and Nurse Prescriber-Led Dose Adjustment of DMARD Therapy in RA. Grainne Murphy, Mary Daly, John Ryan, Fergus Shanahan, Sinead Harney and Molloy Michael. Cork University Hospital

The advent of nurse prescribing has greatly enhanced the role of the specialist nurse in the care of the rheumatology patient. Patient education and monitoring of patients receiving disease-modifying (DMARD) therapies has been a pivotal part of the rheumatology nurse specialists (RNS) scope of practice. The importance of frequent review and DMARD dose adjustment in early RA has been repeatedly highlighted. Improved clinical responses in those seen on a monthly basis in comparison to those seen every 3 months were observed in patients treated with methotrexate (MTX). The ability of the advanced nurse practitioner (ANP) to review patients in this timely manner may be more feasible than that of physician directed clinics.

Objective: To assess the effectiveness of the ANP in the appropriate escalation of MTX and dose reduction of prednisone and to assess the patient response to such interventions.

Methods: We included all patients who attended the ANP-led clinic in a

12 month period who underwent a dose adjustment in either MTX or prednisone. Treatment records were retrospectively reviewed and the frequency and magnitude of dose escalation (MTX) or reduction (prednisone) were assessed. Patients were asked to complete a retrospective questionnaire to assess the effectiveness of the consultation. Consecutive patients attending a physician led clinic were used as a control group. The ANP prescriptions were audited for appropriateness and safety.

Results: We identified 33 consultations for adjustment of MTX and 74 consultations for prednisone. Of 1282 attendances at the ANP clinic 107 included a consultation in which a medication dose adjustment occurred. The mean increase in MTX was 2.63mg/month (+/− 0.25mg) for the ANPs clinic in comparison with 0.87mg/month (+/− 0.09) for the physician - led clinic, p=0.000. In relation to prednisone, the ANP achieved a 2.57mg/month dose reduction. All patients attending the ANPs clinic felt adequately informed about their treatment and, by recall, were educated in relation to the nature, administration and side-effects of their medication. Patients demonstrated high levels of confidence in the ANP; 83.3% would be as likely to adhere to the ANP decision as the physician led approach and only 11.1% felt that they would have more confidence in a physician-prescribed adjustment. Interestingly, 61.1% felt they would have received less information in the physician led clinic. No episode of inappropriate or unsafe treatment alteration was identified.

Conclusion: We demonstrated that ANPs can effectively and safely escalated DMARDs with the added benefit of steroid dose reduction. This is in contrast with the sub-optimal dose escalation previously demonstrated in physician-led clinics. This study supports the expanded role of ANPs in delivering optimal care or RA patients.

Disclosure: G. Murphy: None; **M. Daly:** None; **J. Ryan:** None; **F. Shanahan:** None; **S. Harney:** None; **M. Michael:** None.

1334

Developing an Interactive Health Communication Application within Rheumatology: What Do Patients Want? Rosalie van der Vaart[2], Constance H. C. Drossaert[2], Erik Taal[1] and Mart A. F. J. van de Laar[2]. [1]Arthritis Centre Twente, Institute for Behavioural Research, University of Twente & Medisch Spectrum Twente, Enschede, The Netherlands, [2]Arthritis Centre Twente, Institute for Behavioural Research, University of Twente & Medisch Spectrum Twente

Background: The potential of Interactive Health Communication Applications (IHCA's) to improve health care has been acknowledged and the development of online health applications is quickly evolving, for various chronic conditions. For rheumatic patients, however, no IHCA's exist yet and research on online applications within rheumatism is scarce. In this project we aim to develop a hospital based rheumatology IHCA. To ensure acceptation and future use of it, a needs assessment among patients was conducted.

Objectives: To examine patients' current disease related internet use and their intentions to use various online support tools on a rheumatology IHCA. Furthermore, we examined which variables are associated with the intention to use these support tools.

Methods: We conducted a survey among a random sample of patients of a large teaching hospital's rheumatology clinic (N=484). Inclusion criteria were: having visited a rheumatologist in the past 6 months and an age below 70 years. Questions included demographics and health related variables as well as patients' current disease related internet use and their intention to use seven different support tools: (1) disease and treatment information, (2) care and support information, (3) peer communication, (4) patient-provider communication, (5) symptom monitoring, (6) self-management support and (7) an online personal health record.

Results: The response rate was 47% (N=227). Current disease related internet use was mainly limited to searching information. Nevertheless, many patients reported they intended to use six of seven possible support tools when offered in a hospital rheumatology IHCA (49% - 68%). An exception was peer communication; only 11% of patients intended to use this tool. Of all support tools the personal health record was mostly preferred, followed by information provision. Although we found some small significant correlations between this reported intention and participants characteristics, these were all small (below 0.21) and showed no clear predictors.

Conclusion: Our results reveal a discrepancy between the low current health related internet use and the high interest to use online support tools offered by the hospital. Patients are especially positive about the option of an online personal health record. Demographics and health related variables showed no clear relation to intention to use.

Disclosure: R. van der Vaart: None; **C. H. C. Drossaert:** None; **E. Taal:** None; **M. A. F. J. van de Laar:** None.

1335

Does an RA Peer Support Program Impact Disease Outcomes? Melanie Zibit[3], Jing Cui[4], Christine K. Iannaccone[2], Nancy A. Shadick[1], Michael E. Weinblatt[1], Meghan Courtney[3], Margo Hanlan[3], Husen Tsao[3] and Anne Fossel[3]. [1]Brigham & Womens Hospital, Boston, MA, [2]Brigham and Woemens Hospital, Boston, MA, [3]Brigham and Women's Hospital, Boston, MA, [4]Brigham and Womens Hospital, Boston, MA

Purpose: A diagnosis of RA can lead to loss of function, increased pain, depression, and complex medical care. Peer support, used effectively in other illnesses, may provide support that can lead to improvement in RA disease outcomes. This pilot study evaluates whether a peer support program for RA patients can improve fatigue, pain, functional status, self-efficacy, emotional health, and medication adherence.

Methods: RA patients at a hospital arthritis clinic seeking peer support enrolled in a peer support program. Patients wishing to provide support to others (mentors) were trained by a social worker to learn how to help other patients with concerns, coping strategies and medical decision-making. Mentors and mentees were partnered based on age, disease duration, comorbidities, lifestyle, physical activity, and employment status. Mentors contacted mentees by phone once a week for 6 weeks, with some email or a face-to-face meetings. To evaluate the efficacy of the program, mentees seeking support were compared with controls from an RA registry at baseline and at 6 month follow up. Both groups filled out questionnaires concerning fatigue and pain (VAS), flares, self-efficacy(Arthritis Self-Efficacy), emotional health and functional status (SF12 Health Status Survey), and medical adherence (ASK20). Univariate analyses were done to compare both groups at baseline and a linear regression model was used to compare differences after 6 months.

Results: 10 mentees and 6 controls, to date, have completed baseline and 6 month questionnaires. There were no differences in disease duration (p=0.98) and gender (P=0.89), but age distribution differed (p=0.02) between mentees and controls. Analysis at 6 months, using linear regression analyses, showed that mentees had a significant improvement in self-efficacy compared to the controls (p=0.05) (see Table 1). Subjects completing the program to date showed a trend toward less fatigue (p=0.11) and improvements in medical adherence (p=0.12).

Conclusions: This pilot study suggests that RA patients who have active disease and receive peer support show improvement in self-efficacy. Peer support programs may be effective in enhancing patients' coping skills. Further analyses are needed to demonstrate the impact of the program on patient self-reported outcomes of fatigue and medical adherence.

Table 1. Linear Regression Analysis Mentees (N=10) compared to Controls (N=6)

Age		
20–45	3 (30%)	0
46–55	2 (20%)	5 (83.3%)
>55	5 (50%)	1 (16.7%)
Disease duration		
mean (±SD)	15.6 (12.28)	15.7 (12.36)
median	14.5 (1–37)	17 (0–36)
Gender (female)	9 (90%)	6 (100%)

	Mentees		**Controls**		
	Pre Mean (± SD)	**Post Mean (± SD)**	**Pre Mean (± SD)**	**Post Mean (± SD)**	**p**
Self-efficacy	**53.52 (± 21.56)**	**64.26 (± 16.75)**	**81.11 (± 14.32)**	**74.44 (± 9.87)**	**0.05**
Fatigue (0–100)	55.5 (± 34.36)	56 (± 29.04)	29.17 (± 26.35)	51.67 (± 28.75)	0.11
Medical Adherence ASK20 (20–100)	42.9 (± 13.37)	39.1 (± 8.58)	35.7 (± 13.54)	39.7 (± 10.46)	0.12
Pain (0–100)	61.5 (± 25.5)	60.5 (± 24.77)	30 (± 33.62)	45.0 (± 25.50)	0.22
SF-12 (MCS)	44.19 (± 12.22)	45.39 (± 14.65)	54.44 (± 4.26)	52.30 (± 9.36)	0.91
SF-12 (PCS)	31.08 (± 12.00)	34.83 (± 16.36)	48.00 (± 13.20)	40.38 (± 14.85)	0.35

Disclosure: M. Zibit: Amgen Inc., 2; **J. Cui:** Biogen Idec, 2, Crescendo Bioscience, 2; **C. K. Iannaccone:** Biogen Idec, 2, Crescendo Bioscience, 2; **N. A. Shadick:** Amgen Inc., 2, Biogen Idec, 2, Crescendo Bioscience, 2; **M. E. Weinblatt:** Biogen Idec, 5, Crescendo Bioscience, 5; **M. Courtney:** Biogen Idec, 2, Crescendo Bioscience, 2; **M. Hanlan:** Amgen Inc., 2; **H. Tsao:** Biogen Idec, 2, Crescendo Bioscience, 2; **A. Fossel:** Biogen Idec, 2, Crescendo Bioscience, 2.

1336

Educational Needs Assessment among Patients with Rheumatic Diseases in Kenya. Ines Colmegna[1], Susan J. Bartlett[1], Sharon Kodhek[2], Omondi G. Oyoo[3] and International League of Associations for Rheumatology East Africa Initiative. [1]McGill University, Montreal, QC, Canada, [2]Nairobi SLE Support Group, Nairobi, Kenya, [3]University of Nairobi, Nairobi, Kenya

Background: In Africa, access to comprehensive musculoskeletal (MSK) health care is very limited. Patient education and self-management have been shown to reduce inequities and improve functional status, pain, psychological wellbeing, employment, and even disease activity. Educational interventions need to be tailored and contextualized to meet individuals' specific needs.

Objective: To assess educational needs among patients with rheumatic conditions in Africa as a first step in developing interventions to reduce the gap in health service provision.

Methods: English-speaking patients who attended community lectures sponsored by ILAR in Nairobi on rheumatic diseases completed a questionnaire about demographics, diagnosis, pain and disability. Topics also queried included overall interest in learning about arthritis, specific needs, preferred learning modalities as well as internet access.

Results: The sample consisted of 61 patients, mostly female (87%) with a mean ± SD age of 41.4 ± 13.5 yrs and education of 14.6 ± 3.7 yrs. Most reported working full (76%) or part time (10%) and lived with family or others with only 14% living alone. Diagnoses reported included SLE (37%), RA (30%), other (19%), "RA+SLE" (9%) and gout (5%). Nearly half (48%) reported having pain every day. The highest MHAQ scores were associated with RA (0.7 ± 0.7), "RA + SLE" (0.6 ± 0.6), and SLE (0.4 ± 0.5).

Across conditions, disease knowledge was suboptimal; only 33% reported having "enough" to a "great deal" of knowledge and almost all (95%) wanted to learn more about their condition. Most reported it to be "very" to "extremely important" to learn more about pain (100%), medications (98%), fatigue (98%), exercise (96%), expectations about disease (96%), use of heat and cold (94%), and coping with emotions (90%). One fourth expressed interest in learning about diet and reproductive issues. Preferred learning modalities included groups (43%) and videos (26%) at hospitals (54%) or online (15%). Most (77%) reported having Internet access. Half (50%) reported current or previous participation in support groups. Support group participation was not associated with demographics, disease characteristics or specific interests or educational needs.

Conclusions: There is a clear need for rheumatic disease education among patients in Kenya. Participation in support groups does not appear to lessen interest or select for specific educational needs, a finding that is consistent with other studies showing that "experienced" patients are still eager to learn about their illness and treatment. Leaders in Rheumatology from developed countries have unique opportunities to empower patients in developing parts of the world using internet-based technologies.

Disclosure: I. Colmegna: None; **S. J. Bartlett:** None; **S. Kodhek:** None; **O. G. Oyoo:** None; **International League of Associations for Rheumatology East Africa Initiative:** None.

1337

Phone Administration Compared to Self-Administration on Paper of the Main Instruments Used To Evaluate Ankylosing Spondylitis Patients. Rafael Ariza-Ariza, Blanca Hernández-Cruz, Victoria Navarro-Compán and Federico Navarro-Sarabia, Hospital Virgen Macarena, Sevilla, Spain

Background: BASDAI, BASFI, and other instruments used to evaluate Ankylosing Spondylitis (AS) patients are usually self-administered on paper. However, it limits their use in daily clinical practice because paper forms are resource demanding regarding the time spending for filling them. A phone administration previously to the medical visit it would facilitate the use of these tools.

Objective: to assess the performance of the instruments used to evaluate AS patients when administered by phone in comparison with the traditional self-administration on paper.

Methods: Design: a test-retest study. Patients with AS (modified NY criteria) consecutively selected in a tertiary care center were included. Patient global assessment on numerical rating scale (NRS), patient global pain assessment on a NRS, patient night pain assessment on a NRS, BASDAI, BASFI, and ASQoL were administered by phone. 48 later the same instruments were self-administered on paper at the hospital. Descriptive statistics were done. Agreement between the two tests was assessed by the intraclass correlation coefficient. Spearman correlation coefficient was also calculated.

Results: 51 patients, 76% males, with age 47.7±13 years were included. The time between phone administration and self-administration on paper was 1.5±1.0 days. Mean±SD values of the instruments obtained by phone administration and self-administration on paper, intraclass correlation coefficients (ICC) and Spearman correlation coefficients (rho) were as follows: patient global assessment on a NRS: 3.8±2.8, and 3.8±2.4, ICC: 0.80*, and rho: 0.80*; patient global pain assessment on a NRS: 3.9±2.9, and 3.7±3.0, ICC: 0.89*, and rho 0.82*; patient night pain assessment on a NRS: 3.6±3.0, and 3.4±3.0, ICC: 0.90*, and rho: 0.87*; BASDAI: 3.9±2.6, and 3.5±2.5, ICC: 0.91*, and rho: 0.92*; BASFI: 3.6±2.7, and 3.5±2.7, ICC: 0.91*, and rho: 0.92*; and ASQoL: 6.2±5.3, and 6.1±4.9, ICC: 0.93*, and rho: 0.87*, respectively. *p<0.001.

Conclusions: the phone administration of these instruments is comparable to their self-administration on paper. It can facilitate their use in daily clinical practice.

Disclosure: R. Ariza-Ariza: None; **B. Hernández-Cruz:** None; **V. Navarro-Compán:** None; **F. Navarro-Sarabia:** None.

1338

Rheumatology Health Professionals' Care: Current and Future Tasks and Education. Emalie J. Hurkmans[3], Rinie Geenen[1], John Verhoef[4] and Thea P. M. Vliet Vlieland[2]. [1]Clinical and Health Psychology, Utrecht University & University Medical Center, Utrecht, The Netherlands, [2]Department of Rheumatology and Orthopaedics, Leiden University Medical Center, Leiden, The Netherlands, [3]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands, [4]Faculty of Health, University of Applied Sciences, Leiden, The Netherlands

Background: In the Netherlands, as in many other countries, advanced arthritis training for HPs (clinical nurse specialists, physical therapists, occupational therapists, social workers and psychologists) is organized separately for each discipline. A study of their actual and preferred tasks and education may lead to recommendations for improvement of education and, eventually, care provided by HPs.

Objectives: To examine which tasks currently are performed and preferred by Dutch HPs involved in the care of patients with rheumatic diseases, and to what extent the required knowledge and skills are and should be covered in advanced arthritis training.

Methods: For this cross-sectional study a questionnaire was developed, based on a comparable project of the UK Arthritis Research Campaign and interviews with experts from the various disciplines involved. The first part pertained to the current en preferred performance of 19 diagnostic and 27 therapeutic tasks (yes/no). The second part included 13 "knowledge" and 22 "skills" items. It was asked whether the items were not, globally or in detail covered in their advanced arthritis training. Part 1 was administered to all members of the Dutch Allied Health Professionals in Rheumatology (NHPR) (n = 416) whereas part 2 was sent to all NHPR members, rheumatologists (n=263), and 200 patients with rheumatic diseases.

Results: The response rates were 44% for the HPs, 38% for the rheumatologists and 80% of the patients, respectively. On average clinical nurse specialists and physical therapists each perform 23 of the 46 included tasks, occupational therapists 21, social workers 17 and psychologists 12. Of the 46 included tasks, 35 were performed by >50% of two or more groups of HPs. The least provided tasks were medical tasks, such as ordering and judging X-rays and prescribing medication. The majority (>50%) of 4/5 groups of HPs indicated a wish to apply (more) measurement instruments and to provide (more) education. The majority of all knowledge and skills items (27/35) was not sufficiently covered in the advanced training according to >50% of 2 or more HP groups. According to >50% of the HPs and rheumatologists medical tasks should not or only globally be covered in the advanced arthritis training for HPs. In contrast, >50% of the patients thought that all tasks (including medical tasks) should be covered in the advanced arthritis training.

Conclusion: There is considerable overlap in the tasks performed by Dutch HPs in rheumatology. HPs did not express a need to expand their daily tasks with medical tasks. A large number of knowledge and skills items were found not sufficiently covered in the current advanced arthritis training. These findings suggest that there is room for the improvement of the current advanced arthritis training for Dutch HPs. Given the overlap in current tasks and preferences with respect to education, the development of common educational modules appears to be a good option.

*And the Project Steering Group: Prof. dr. JWJ Bijlsma, drs. H Bloo, drs. JE Voorneveld-Nieuwenhuis, L Wassenberg, drs. G Geven, dr. M Veehof, drs. C Veldhuizen.

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1339

Accuracy of the Early Detection of Juvenile Idiopathic Arthritis Questionnaire—A Multicenter Study. Claudio A. Len[7], Luciana T. P. Paulo[7], Maria Teresa R. A. Terreri[7], Silvana B. Sacchetti[3], Virginia P. L. Ferriani[5], Clovis A. A. Silva[4], Cássia M. P. Barbosa[1], Simone Lotufo[2] and Roberto Marini[6]. [1]Hospital Darcy Vargas, São Paulo, Brazil, [2]Hospital Menino Jesus, São Paulo, Brazil, [3]Santa Casa de São Paulo, São Paulo, Brazil, [4]Universidade de São Paulo, São Paulo, Brazil, [5]Universidade de São Paulo, Ribeirão Preto, São Paulo, Brazil, [6]Universidade Estadual de Campinas, São Paulo, Brazil, [7]Universidade Federal de São Paulo, São Paulo, Brazil

Background: Many factors are associated to the delay in the diagnosis of juvenile idiopathic arthritis (JIA), some of them related to the disease and other to the difficulty in referring patients to specialists. The Early Detection of Arthritis Questionnaire (EDA-12) was designed to be used as an auxiliary tool for screening of suspect cases in general practice. However, its reliability was tested only in a small number of subjects.

Objective: To assess the reliability of EDA-12 in the detection of suspect cases referred to outpatient pediatric rheumatology reference clinics in 3 large urban areas.

Methods: EDA-12 (score range 0–12) was applied to parents of children (0 –18 y) who sought spontaneously or were referred for evaluation in 7 outpatient pediatric rheumatology clinics. Diagnostic suspicion was recorded in the first consultation (initial diagnosis), and definitive diagnosis was recorded after, at least, 6-month period of follow-up.

Results: Six hundred and sixty patients (57% girls) were included, with age (mean) of 9 years-old. JIA initial diagnosis was performed in 12% of the consultations, being also observed in the definitive diagnosis (12% of the consultations), with a high agreement between the first suspicion and the diagnostic confirmation (kappa coefficient = 87.2%). A ROC curve was used in the assessment of a score able to distinguish JIA children from non-JIA children, being obtained a value of 5 (five) in the first consultation, with sensibility of 93% and specificity of 76%.

Conclusion: The EDA-12 has demonstrated reliability for discrimination of suspect cases of JIA and reinforces its relevance as an auxiliary tool in the first medical consultation.

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1340

Engaging Youth in a Web Based Transition Intervention: Usability and Feasibility of Rheumtogrow.org. Peter Scal, Ann Garwick and Keith Horvath. University of Minnesota

Purpose: This pilot study tests the usability and feasibility of a theoretically grounded, internet based intervention for youth with Juvenile Arthritis (JA)

Method: We developed Rheumtogrow.org for youth with JA based on Self-Determination Theory (SDT) through a user centered and participatory process. This intervention seeks to increase the likelihood that youth will engage in behaviors that reduce the impact that arthritis has on their lives across multiple domains including the transition from child to adult focused care. We enrolled 32 youth (age 14–18) and provided them with access to the site for six weeks. We collected self-reported assessment measures pre and post intervention via an internet based questionnaire and measured actual intervention site use.

Results: Of the 32 enrolled youth, 1 (3.1%) did not complete pre-test and 2 (6.3%) completed the pretest but did not login to the intervention site during the trial. Pre and post test questionnaires were completed by 29 (90.6%). Most users agreed or strongly agreed that the intervention site was be easy to understand (82.7%) and easy to use (72.4%) that it was contained creditable information (96.5%), was sensitive to teen issues (89.7%) and relevant to their life (71.4%). Most would use the site again (88.9%) and recommend it to a friend (88.9%). Open ended responses indicated that users most liked the ability to learn from the experiences of other teens and that they site would be more appealing if there were an opportunity to connect with other teens through a message board, chat or instant messaging. Site use varied considerably between users in the total time (range 2 minutes to 6 hours 33 minutes, median 42 minutes) and the number and content of the pages viewed. Youth report of a stronger belief that a website is a good way to learn more about arthritis and that others think it should be used were significant predictors (linear regression, $p \leq .05$) of site use (greater number of page views). Fewer page views were predicted by the belief that a website would be a way to connect and share with other teens with arthritis suggesting that the discrepancy between youth expectations and intervention approach is problematic.

Conclusions: We found youth eager to participate in this pilot of an internet based program for JA. Participants found the intervention site to be relevant and engaging, especially the opportunity to learn from the experiences of other teens. Users had a strongly stated preference for improving the youth-to-youth interactivity on the site which is consistent with their current patterns of use and expectations of technology. Interest in learning more about JA and the influence of others was associated with greater site use while expectations that the site would have real-time youth-to-youth interaction (when it did not) was associated with lower use. Youth engagement in a web-based intervention for JA is influenced by individual and social characteristics and the nature of the technology. Rheumtogrow.org offers a promising foundation on which to refine and test intervention for youth with JA.

Disclosure: P. Scal: None; **A. Garwick:** None; **K. Horvath:** None.

1341

FEAR (False ELISA Associated Rheumatic) Syndrome in Children. Donald P. Goldsmith[1], Carolann Martucci[3] and Svetlana Lvovich[2]. [1]St Christopher Hosp Children/Drexel University College of Medicine, Philadelphia, PA, [2]St Christopher's Hosp Children/Drexel University College of Medicine, Philadelphia, PA, [3]St Christopher's Hospital for Children, Philadelphia, PA

Introduction: Non specific arthralgias associated with a positive ANA remain a common referral source to the pediatric rheumatologist. Multiple studies have documented the unlikely progression to a recognizable inflammatory disorder and allow the pediatric rheumatologist to effectively alleviate parent and patient anxiety. There is now increased use of ANA reflex panels which use solid phase ELISA assays rather than indirect immunofluorescence. If positive, even without a reported quantitative titer, these panels automatically cascade (with increased cost) to additional antibody tests. Children are now being referred for isolated positive ELISA tests such as anti centromere, anti SS-A/B, anti SCL-70, anti Sm/RNP, and anti dsDNA antibodies.

Purpose: To characterize and bring to attention increasing numbers of children with a positive ANA screen without a quantitative titer and one or more positive additional specific antibody tests.

Methods: A retrospective outpatient chart review from 06/01/2008 to 01/01/2010)

Results: Of 415 new patient assessments seen over this 18 month period we identified 20 (5%) children with a positive ANA screen and one or more additional positive antibody tests. All children had non specific complaints, primarily arthralgias, myalgias, and/or transient cutaneous eruption. These tests had been obtained prior to consultative assessment. There were 19 F, 1M; 16 White, 3 African-American, and 1 Hispanic. Mean age 11.4 y (range 6–17). Within this group of children there were 6 positive tests for anti SS-A, 4 anti SS-B, 4 anti SCL-70, 3 anti centromere, 3 anti RNP, 2 anti Smith, and 2 anti dsDNA. Four children had more than 1 antibody present. The average duration of symptoms prior to laboratory assessment was 18 months (range 4–48). Prior to assessment 15(75%) of the parents had seriously web researched those disorders associated with each of these antibodies. None of these children have thus far developed a characteristic pediatric rheumatic disorder.

Conclusions: Although these children require careful follow-up observation, in view of the extended duration and non specific nature of symptoms prior to the recognition of each positive antibody as well as the lack of corroborative physical findings we predict it's unlikely that significant morbidity will develop. As 5% of our recent new patient assessments/year, this represents a significant number of children. Parent/patient fear and anxiety is considerable and in our opinion lead to subtle variants of the vulnerable child syndrome. To minimize the creation of FEAR syndrome we need to better inform our referring physician base about the most suitable, if any, ANA tests to order. Commercial laboratories should fully disclose the nature of each panel and not solely offer cascading tests on pre-printed forms.

Disclosure: D. P. Goldsmith: None; **C. Martucci:** None; **S. Lvovich:** None.

1342

Physiotherapy Management of Children with Hypermobility: A Review of an Out-Patient Self Management Exercise Programme. Susan M. Maillard[1], David Adkins[2], Elaine Haggart[2] and Swati Bhagat[2]. [1]Great Ormond Street Hospital, London, Maidenhead, United Kingdom, [2]Great Ormond Street Hospital, London, United Kingdom

Background: The recognition of hypermobility in the paediatric population has increased and common complaints associated with this are pain and fatigue. Great Ormond Street Hospital, UK has implemented a self management exercise programme, which is specific and progressive to key muscle groups. It utilises open chain exercises with high repetitions (30) and low weights (0.5–2.5kg), in order to manage these patients from an outpatient-based clinic.

Objectives: To establish whether this specific muscle training programme can be effectively used in the paediatric hypermobile population, to increase muscle strength, decrease pain and improve overall function.

Method: A retrospective case note review of children who had attended the hypermobility out-patient service between Nov 2009 and March 2010 was completed (comparing initial assessment and follow up). Assessments of muscle strength, school attendance, Childhood Health Assessment Questionnaire (CHAQ), parental visual analogue scale (VAS) of general well being and pain VAS were collected on the children. All children were provided with an exercise programme at the initial assessment, based on 4–5 key exercises, focusing on increasing repetitions and weights. An excel database was used to compile findings.

Results: Data from 20 children (10 males:10 females) who had already been diagnosed with hypermobility (Beighton score of >4/9), was collected. The mean age was 11 years (range 5–16 years). The primary complaints within the cohort were of pain and fatigue longer than 6 months in duration. School attendance for all but one patient was 100%.

On initial assessment the mean muscle strength score was 3.5/5 (oxford manual muscle score) in hip abductors, hip extensors and inner range quadriceps (range 2.5–5) and 7.25/10 repetitions for plantar flexors (range 2–10). At 8–12 week follow up, all children were completing 30 repetitions and using an average weight of 1.5kg (range 0.5–2.5kg). There was an average increase in muscle strength of hip abductors (60%), hip extensors (70%), inner range quadriceps (55%) and plantar flexors (40%).

The average score of the CHAQ on assessment was 1.15/3, pain VAS was 4.6/10cm and parental VAS of general well being 3.9/10cm (10=most unwell).There was a 60% decrease in the score of CHAQ between visits. Pain and parental VAS diminished by 55% and 45% respectively and all parents reported an improvement in fatigue.

Conclusion: The use of a specific progressive resisted muscle strengthening programme using open chain exercise, with high reps and low weights has been shown to increase muscle strength, improve overall function and decrease pain in children with hypermobility. This can therefore considered to be an effective method of managing hypermobile children within an outpatient clinic.

Disclosure: S. M. Maillard: None; **D. Adkins:** None; **E. Haggart:** None; **S. Bhagat:** None.

1343

Stress in Adolescents with Idiopathic Musculoskeletal Pain. Juliana Molina[2], Flavia H. Santos[1], Maria Sylvia Vitalle[2], Maria Odete E. Hilário[2], Maria Teresa R. A. Terreri[2], Simone G. L. Silva[2] and Claudio A. Len[2]. [1]Universidade Estadual de São Paulo, Assis, São Paulo, Brazil, [2]Universidade Federal de São Paulo, São Paulo, Brazil

Background: Musculoskeletal pain syndromes are raising complaints at pediatrics practice, affecting mainly children and adolescents from 5 to 14 years. Adjacently to the pain, reports of emotional and cognitive difficulties are also common.

Objective: To investigate the presence of stress in the attended population in a Pediatric Rheumatology outpatient clinic.

Method: Nineteen adolescents from 14 to 16 years with idiopathic musculoskeletal pain (IMP) were assessed regarding to stress symptoms through Lipp's Inventory of Stress Symptom for Adults, and compared to a control group of 20 matched healthy adolescents.

Results: IMP adolescents had significantly higher stress scores comparing to the control group. Thus, 79% of IMP adolescents had complaints related to stress, while the same scores were observed in only 35% of the control group. The differences between groups (t-test) were notable in the intermediate stage of stress, known as resistance phase (p=0.009), followed by exhaustion phase (p=0.023), final stage of stress where the organism becomes vulnerable to diseases. Also, regarding to complaints, the differences were pointed out either for physical (p=0.013) or emotional (p=0.030) aspect.

Conclusion: Adolescents with chronic pain have physical, social, emotional, and behavioral aspects in their lives affected by a chronic process of pain. In our sample we have demonstrated that the complaints presented by adolescents and their parents also show a stress response in a worsening process.

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1344

To Explore the Use of the PedsQL Subjective Questionnaire To Assess Levels of Fatigue in Children with Juvenile Dermatomyositis. Susan M. Maillard[1], Amy Todd[2], Kiran Nistala[3], Clarissa Pilkington[2] and Abdul Hassan[2]. [1]Great Ormond Street Hospital, London, Maidenhead, United Kingdom, [2]Great Ormond Street Hospital, London, [3]Institute of Child Health, London

Background: Fatigue is one of the regularly reported clinical features of Juvenile Dermatomyositis (JDM), however there is no standardised method of assessing the degree of fatigue. The PedsQL Fatigue score (FS) is a self reported questionnaire and a Visual Analogue Scale (FVAS) which has been developed to measure fatigue in children with paediatric inflammatory diseases. Great Ormond Street Hospital has a specialist service for children with JDM and the FS and FVAS were used to assess whether they were an effective measure of disease related fatigue.

Objectives: To establish if the PedsQL FS measures fatigue in children with JDM compared to clinical outcome measures of active JDM including muscle strength and function.

Methods: All children attending the JDM clinic were routinely assessed using the Childhood Myositis Assessment Score (CMAS), manual muscle testing score (MMT8), parental VAS score of general wellbeing (PaVAS), physicians VAS of disease activity (PVAS), 6 minute walk test (6MWT) and Childhood Health Assessment Questionnaire (CHAQ). The PedsQL questionnaire was given out separately to both parents and children and includes a fatigue VAS (FVAS), a pain VAS as well as specific questions about cognitive fatigue, physical activity and sleep. The data was analysed using SPSS v16.0.

Results: The patient cohort comprised of 52 children (39 F: 13 M). The mean age was 11.92 years (range 3–19). The mean disease duration was 9.42 years (range 0.2–13yrs)

The PedsQL FS (both parent and child) showed statistical significance with pain VAS, Pa VAS and CHAQ however did not show significance with the objective markers- MMT8 and CMAS. The child and parent FVAS shows statistically significant results with the pain VAS, MMT8 and the CHAQ. Additionally, the child FVAS statistically shows a correlation with the CMAS. Neither the PedsQL FS or FVAS showed any statistical correlation with the 6MWT or the PVAS.

Spearman's Correlation		Pain VAS	CMAS	MMT8	PaVAS	PVAS	6MWT	CHAQ
Parent FS	Correlation	−.632**	.222	.286	−.427**	−.029	.129	−.406**
	Sig (2-tailed)	.000	.162	.060	.006	.868	.490	.008
Child FS	Correlation	−.648**	.087	.144	−.445**	.029	.137	−.411**
	Sig (2-tailed)	.000	.577	.363	.005	.876	.478	.009
Parent FVAS	Correlation	.550**	−.303	−.313*	.280	.110	−.280	.417**
	Sig (2-tailed)	.000	.057	.041	.085	.537	.134	.007
Child FVAS	Correlation	.535**	−.304*	−.415**	.311	.004	−.324	.545**
	Sig (2-tailed)	.000	.044	.006	.054	.984	.086	.000

Conclusions: It appears that the PedsQL FS does not fully objectively measure fatigue but combined with the FVAS may be a reasonable tool for assessing fatigue in JDM. However it is also recognised that psychological and psychosocial factors also play a role in patient self reported fatigue and further research is required into this area.

Disclosure: S. M. Maillard: None; **A. Todd:** None; **K. Nistala:** None; **C. Pilkington:** None; **A. Hassan:** None.

1345

Utilizing Social Media To Reach Young Arthritis Patients. Jane S. Brandenstein[1], Emily Cope[3], Allison J. Kerr[2], Ashley M. Boynes[2], Carol D. Popp[2] and Lori Knapp[2]. [1]Freedom, PA, [2]W Pa Arthritis Foundation, Pittsburgh, PA, [3]WPa Arthritis Foundation, Pittsburgh, PA

Background: Many people in their teens through thirties affected by Arthritis can feel like they are the only one with this disease. Young people often have difficulty finding age appropriate resources and peers with similar chronic diagnoses. School, work schedules and family commitments make traditional arthritis exercise classes and self management programs challenging to access for this population. This isolation and lack of information can be very stressful and harmful to arthritis patients mental well being.

Objective: To create an online community and informative online resources for young people with arthritis.

Summary: Social media was used to connect to the target audience of young people affected with arthritis. To do this the organization created and regularly maintains accounts on Twitter, facebook, and YouTube. Since the online community's creation it has gained 1,634 followers on Twitter, 164 fans on facebook and uploaded 12 videos to YouTube.

The organization also created *Rheum for Wellness*, a blog, which serves as an outlet for all arthritis-related topics. The blog has featured posts on cooking, rare forms of arthritis, personal stories of hope, physical activity and much more. Another hugely popular feature of the blog is a series entitled *The Journey to Wellness.* In this series a young woman blogs about her personal battle with several inflammatory diseases and her quest to remain positive and reach out to others with similar issues. *Rheum for Wellness* has sparked online conversations and connected readers from all over the world. This blog has had 99 posts, 493 comments, and 73,775 views. There has been overwhelming feedback in support of the blog. Readers constantly comment that it makes them feel understood and not alone and that they have a voice. Mariah posted, "I want to say Thank You for writing this! I also 'live' with autoimmune disease, as well as other things. It is such a great feeling to know that someone out there knows how I truly feel everyday." Elizabeth said, "Thank You! Someone needed to express what we are all feeling, and you did it so eloquently."

Arthritis Radio, a podcast, was established showcase the many voices of arthritis. The podcast features interviews with health professionals, community leaders, physical therapists and many others. The goal of the show is to make knowledgeable experts accessible to all of those affected with arthritis. *Arthritis Radio* has had 16 episodes, 9,558 channel visits and 732 subscribes. Listeners have described this podcast as "a wonderful learning tool you have provided people who have arthritis" and state that the interviews on cutting edge research give them hope for the future.

Conclusion: Social media can be successfully utilized to provide information, resources and support to young arthritis patients. This target population benefits from supplementing traditional forms of communication with online communities and social networks.

Disclosure: J. S. Brandenstein: None; **E. Cope:** None; **A. J. Kerr:** None; **A. M. Boynes:** None; **C. D. Popp:** None; **L. Knapp:** None.

ARHP Concurrent Abstract Sessions
Physical and Psychosocial Challenges in Scleroderma
Tuesday, November 9, 2010, 9:15 AM–10:15 AM

1346

Frequency and Impact of Symptoms Experienced by Patients with Systemic Sclerosis: Results from a Canadian National Survey. Marielle Bassel[1], Marie Hudson[3], Suzanne S. Taillefer[4], Orit Schieir[1], Murray Baron[1] and Brett D. Thombs[2]. [1]Jewish General Hospital, Montreal, QC, Canada, [2]McGill University, Montreal, QC, Canada, [3]McGill University and Jewish General Hospital, [4]SMBD Jewish General Hospital, Montreal, QC, Canada

Background: Patients with systemic sclerosis (SSc) report a number of problems that have been linked to disability and reduced quality of life. Due to the rarity and heterogeneity of SSc, not enough is known about the range of problems faced by individuals living with SSc. Several studies have assessed problems faced by patients with SSc, however, knowledge about the relative importance of these different problems is limited by the small number of studies that have been conducted, the relatively narrow scope of potential problems assessed in existing studies, and the small sample sizes in these studies. The objective of the present study was to identify, in a large SSc sample, symptoms of SSc that patients rated as frequent and that highly impacted their ability to carry out daily activities.

Methods: Patients with SSc were recruited to complete the anonymous Canadian Scleroderma Patient Survey of Health Concerns and Research Priorities through patient advocacy group websites, Canadian magazines, scleroderma-related newsletters, and support groups across Canada. The survey included questions regarding the frequency and impact of 69 SSc symptoms, which were generated from a panel of Canadian Scleroderma Research Group and Scleroderma Society of Canada members using existing questionnaires, symptom checklists and research articles. Descriptive analyses were performed dichotomizing symptom frequencies into *never* or *rarely* versus *sometimes*, *most of the time* or *always* and symptom impact on daily activities into *no or minimal impact* versus *moderate* to *severe* impact. In addition, for each item, among patients with symptom frequency of at least *sometimes*, the percentage of patients with at least *moderate* impact on daily activities was calculated.

Results: Our study included 464 Canadian persons with SSc. The 5 highest-rated symptoms in terms of frequency were fatigue (89%), Raynaud's phenomenon (86%), hand stiffness (81%), joint pain (81%) and difficulty sleeping (76%). The same 5 symptoms were the highest-rated in terms of having a moderate to severe impact on daily activities, in the order of fatigue (72%), Raynaud's phenomenon (67%), joint pain (64%), hand stiffness (59%), and difficulty sleeping (59%). In addition to these symptoms, items related to decreased hand function (difficulty making a fist; difficulty holding objects; difficulty opening hand; difficulty faucet) were frequently endorsed by more than 400 patients and of these patients, at least 67% endorsed a moderate to severe impact on daily activities.

Conclusion: The results of this study confirmed the importance of core symptoms of SSc with respect to quality of life, such as fatigue. Limitations in hand function, another area identified by patients as being significant, is common and contributes to overall disability levels. However, little literature exists testing the effectiveness of rehabilitation techniques to improve hand function among patients with SSc. Other areas with very little research that appear to play important roles in daily functioning include sleeping problems and male sexual functioning. A patient- researcher consensus is suggested in order to focus future SSc research.

Disclosure: M. Bassel: None; **M. Hudson:** None; **S. S. Taillefer:** None; **O. Schieir:** None; **M. Baron:** None; **B. D. Thombs:** None.

1347

Sociodemographic and Disease Correlates of Body Image in Systemic Sclerosis (SSc). Lisa R. Jewett[2], Marie Hudson[3], Murray Baron[1], Brett D. Thombs[2] and Canadian Scleroderma Research Group (CSRG), [1]Jewish General Hospital, Montreal, QC, Canada, [2]McGill University, Montreal, QC, Canada, [3]McGill University and Jewish General Hospital

Background/Objective: Systemic sclerosis (SSc) is a chronic disease that results in significant disfigurement to socially relevant body parts, including the face and hands. There is very little research, however, on body image concerns in SSc. The objective of this study was to identify socioedemographic and disease-related correlates of dissatisfaction with appearance and social discomfort among patients with SSc. Furthermore, the study aimed to identify disfigured areas of the body most closely related to body image dissatisfaction and social discomfort.

Methods: The sample of SSc patients came from the 15-center Canadian Scleroderma Research Group Registry. Sociodemographic information was based on self-report, and patients' medical histories and disease characteristics were obtained via clinical histories and examinations by study physicians. The Brief-SWAP was used to assess social discomfort and dissatisfaction with appearance. Structural equation models were conducted with MPlus to determine the relationship of the dissatisfaction with appearance and social discomfort factors of the Brief-SWAP with age, sex, marital status, total body skin involvement, disease duration, and telangiectasias. A secondary model assessed relationships between each factor and skin involvement scores from specific body areas, including face, hands/fingers, arms, chest/abdomen, thighs, and lower legs.

Results: A total of 788 SSc patients (94 men and 694 women) were included. Subjective dissatisfaction with appearance was significantly associated with greater skin involvement (standardized regression coefficient $=.26$, $p<.01$) and longer disease duration (.08, $p=.04$). Social discomfort was significantly associated with greater skin involvement (0.24, $p<.01$), presence of telangiectasias (0.06, $p<0.01$), longer disease duration (.09, $p=.03$), younger age (-0.17, $p<.01$), and being unmarried ($-.08$, $p=.04$). Model fit was good, ($\chi 2(14)=38$, CFI=0.99, TLI=0.99, RMSEA=0.05). Secondary

analysis found that skin involvement of the face, hands/fingers, and chest/abdomen were significantly related to both social discomfort and subjective dissatisfaction with appearance. Model fit was again good, ($\chi 2(18)=42$, CFI=0.99, TLI=0.99, RMSEA=0.04).

Conclusion: This study found that appraisal of appearance (dissatisfaction with appearance) was related to SSc disease factors, most prominently skin involvement. Social discomfort, in addition to being associated with disease characteristics, was also linked to younger age and being unmarried, which is highly relevant for social interactions, particularly in the context of establishing intimate relationships. The prominent association of disfigurement to the face and hands/fingers with body image concerns is not surprising. Chest/abdomen disfigurement, which is much less common, may be a proxy for overall severity of disfigurement. In sum, the results of this study underline the need to attend to both disease and social contexts in understanding the impact of disfigurement on body image distress among patients with SSc.

Disclosure: L. R. Jewett: None; **M. Hudson:** None; **M. Baron:** None; **B. D. Thombs:** None; **Canadian Scleroderma Research Group (CSRG):** None.

1348

Development and Validation of the Brief-Satisfaction with Appearance Scale (Brief-SWAP) for Measuring Body Image in Systemic Sclerosis (SSc). Lisa R. Jewett[4], Marie Hudson[5], Jennifer A. Haythornthwaite[3], Leslie Heinberg[1], Fredrick M. Wigley[3], Murray Baron[2], Brett D. Thombs[4] and Canadian Scleroderma Research Group (CSRG), [1]Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, [2]Jewish General Hospital, Montreal, QC, Canada, [3]Johns Hopkins University School of Medicine, [4]McGill University, Montreal, QC, Canada, [5]McGill University and Jewish General Hospital

Background: Systemic sclerosis (SSc) often results in disfiguring physical changes that commonly occur in visible and socially relevant areas of the body, including the face, mouth, and hands. The few studies that have investigated body image in SSc have found that patients with more severe SSc reported higher levels of body image dissatisfaction and low appearance self-esteem. These studies, however, used general measures of body image distress developed for use in eating disorders and not validated among patients with acquired disfigurement from disease or injury. Recently, a measure of body image originally developed for patients with burn injury, the Satisfaction with Appearance Scale (SWAP), was validated for use in SSc. The 14-item SWAP, however, which measures social discomfort and dissatisfaction with specific body parts, includes numerous items that are highly redundant and some that are less relevant for patients with SSc. The objective of this study was to develop and cross-validate a brief 6-item version of the SWAP in order to increase SSc-relevancy, reduce item redundancy, and improve feasibility of body image assessment in SSc.

Methods: Female SSc patients in a developmental sample (Johns Hopkins Scleroderma Center) and a validation sample (Canadian Scleroderma Research Group Registry) completed the 14-item SWAP. Items for the 6-item Brief-SWAP were selected based on theoretical considerations and psychometric data from the developmental sample. In both samples, internal consistency reliability, convergent validity (depressive symptoms, physical and mental health function, pain), and the hypothesized two-factor structure (Perceived Social Impact and Subjective Dissatisfaction) were compared between the Brief-SWAP and SWAP. Confirmatory factor analysis models were conducted with MPlus.

Results: 217 women from the developmental sample and 654 women from the validation sample completed the SWAP. Cronbach's alpha for the Brief-SWAP was 0.82 in both samples compared to 0.90 and 0.91 for the full SWAP. Correlations between the Brief-SWAP and SWAP were 0.94 and 0.95 in the developmental and validation samples. All correlations of the Brief-SWAP and SWAP with measures of convergent validity were substantively equal with no statistically significant differences in either sample. Based on confirmatory factor analysis, model fit for the Brief-SWAP was good in the developmental ($\chi 2(4)=9.0$, CFI=0.99, TLI=0.99, RMSEA=0.07) and validation samples ($\chi 2(4)=19.5$, CFI=0.99, TLI=0.99, RMSEA=0.08) and better than for the SWAP in both samples.

Conclusion: The Brief-SWAP is a reliable and valid measure of body image dissatisfaction and social discomfort related to disfigurement in SSc. Compared to the full 14-item SWAP, the 6-item Brief-SWAP reduced item redundancy, increased relevance to the experience of SSc patients, and demonstrated good psychometric properties including reliability and validity, thus providing a less burdensome and more feasibly administered scale. The results from the current study constitute a significant step towards the improvement of measurement of important body image constructs for individuals with SSc.

Disclosure: L. R. Jewett: None; **M. Hudson:** None; **J. A. Haythornthwaite:** None; **L. Heinberg:** None; **F. M. Wigley:** None; **M. Baron:** None; **B. D. Thombs:** None; **Canadian Scleroderma Research Group (CSRG):** None.

1349

Work as a Daily Challenge: Working with Scleroderma. Cindy F. Mendelson[2], Janet L. Poole[3] and Saralynn H. Allaire[1]. [1]Boston Univ School of Medicine, Boston, MA, [2]Univ of New Mexico, Albuquerque, NM, [3]University of New Mexico, Albuquerque, NM

Background: Systemic sclerosis (SSc) may severely limit one's ability to participate in paid employment, which may threaten an individual's economic, social, physical, or mental well being. This study identified challenges in the work environment and adaptations made by persons with SSc.

Study Sample: 32 persons were recruited from the Scleroderma Foundation website. The participants mean age was 47.3 years, mean disease duration was 9.6 years and mean education level was 17.1 years. The majority of participants were in professional or managerial jobs and had been at their current jobs for mean of 9.8 years. 56.2% had diffuse scleroderma, 59.4%were married, and 71.9%worked 35 hours or more a week.

Methods: Each participant engaged in a single structured interview. Questions were posed about challenges getting to/from work, the work environment, managing the physical/mental demands of the job, working with others, performing essential job functions, balancing work/home activities, changes to work hours or job type, and adaptations made to keep working. Interviews were audio taped and transcribed. Interviews were coded using the interview guide questions as an initial framework. Content analysis were used to determine the key content of the code and a summary statement generated for each code. Working from the summary statements the data was aggregated into four themes and a single overarching theme.

Results: Employees with SSc experience *work as a daily challenge*. This overarching theme described the work experience for most participants, who, on a daily basis, dealt with the details of work, such as getting to work in the cold knowing that their Raynauds will be triggered or shuffling paper with limited hand mobility. Four subthemes describe their experiences. Their *work environment presented options, opportunities and challenges.* Participants discussed work options such as home offices, part-time or flex time schedules, and problems within the work environment such as the temperature or inaccessible buildings. Successful employees were skillful at *managing the present while looking forward*. Most planned to either stay at their current job or occupation. However, they also were mindful of future opportunities and potential problems and planned by watching for opportunities to move into less physically demanding positions. Participants remained hopeful about the future and the possibility to work until retirement. *Managing the tasks of work* described how participants performed their daily jobs. For most participants this was the least problematic part of their work, as they found ways to modify the job, use adaptations, found help, or left positions that were a poor fit. Employees had a network that included *family, friends, colleagues and their employer,* who contributed to their success by lessening the load at home, providing a supportive emotional network, helping with tasks at work, and providing accommodations at work.

Conclusions: It is in the best interest of all of us that those who can work continue to work. We found that our participants wanted to continue to work, and were anxious to find win-win scenarios that allowed them to work and that benefited their employer.

Disclosure: C. F. Mendelson: American College of Rheumatology Research & Education Foundation, 2; **J. L. Poole:** American College of Rheumatology Research & Education Foundation, 2; **S. H. Allaire:** None.

ACR Plenary Sessions

ACR Plenary Session II: Discovery 2010

Tuesday, November 9, 2010, 11:00 AM–12:30 PM

1350

Suppression of Collagen-Induced Arthritis in Mice by Anti-CD19 Antibody That Co-Engages BCR and Inhibitory Receptor FcγRIIb: Efficacy Does Not Require B Cell Depletion. Saso Cemerski[1], Seung Y. Chu[2], Erik Pong[2], Holly M. Horton[2], John R. Desjarlais[2] and David E. Szymkowski[1]. [1]Xencor, Inc., Monrovia, CA, [2]Xencor, Inc.

Background: The B cell is a clinically validated target in autoimmune disease, yet current therapeutic approaches that involve B cell depletion (such as anti-CD20 antibodies rituximab and ocrelizumab) are associated with increased infection risks, including viral reactivation leading to PML. On the other hand, approaches that target individual B cell survival factors including BLyS and APRIL (such as belimumab and atacicept) are reportedly safer but less efficacious, possibly due to redundant activities of other survival factors. We have therefore developed a new therapeutic antibody that globally suppresses B cell functions without promoting B cell depletion. This biologic exploits the natural ability of immune complex to suppress humoral immunity by coengaging B cell receptor with the inhibitory receptor FcγRIIb.

Methods: XmAb5871, an anti-human CD19 antibody with >400-fold increased FcγRIIb affinity relative to native IgG1 Fc, was produced as described (Chu et al. Mol. Immunol. 2008; 45:3926). For use in mouse models, we generated surrogate antibodies against mouse CD19 and CD20 including XENP8206 (with identical Fc domain to XmAb5871), XENP8243 (a surrogate for rituximab), and their Fc and isotype controls. For humanized SCID mice, 3×10^7 human PBMCs were engrafted prior to immunization and treatment with therapeutic antibodies. For collagen-induced arthritis models, C57BL/6 mice transgenic for human FcγRIIb were obtained from J. Ravetch (Rockefeller). CIA was induced in transgenic mice and littermate controls using chicken collagen as described in Inglis et al. (Arth. Res. Therap. 2007; 9:R113). Suppression of B cell activation was assayed by calcium flux, as described in Chu et al. (2008).

Results: Antibodies coengaging CD19 and FcγRIIb suppressed humoral immunity to foreign antigens in both human PBMC-engrafted SCID mice and huFcγRIIb-transgenic mice. XENP8206, but not control anti-CD19 antibodies with native IgG1 or Fcγ receptor knockout Fc domains, suppressed BCR-mediated activation of splenic B cells from transgenic mice. XENP8206 also suppressed joint inflammation in CIA induced in huFcγRIIb-transgenic C57BL/6 mice, an arthritis model known to possess a strong T cell-mediated disease phenotype. Notably, therapeutic efficacy of XENP8206 occurred without depletion of peripheral B cells in mice, in contrast to XENP8243 (mouse surrogate for rituximab), which potently depleted such B cells.

Conclusions: We show that a recombinant antibody engineered for enhanced binding to FcγRIIb via its Fc domain is a potent suppressor of B cell activation that inhibits humoral immune responses and arthritis in humanized mouse models. In contrast to other B cell-targeted therapeutic approaches, this antibody suppresses activated B cells without depletion, thus mimicking the natural function of immune complex. Our results demonstrate the critical role of FcγRIIb in regulating human and murine humoral immunity, and suggest that replication of immune complex-mediated immunosuppression by XmAb5871 has potential as a novel therapy for rheumatoid arthritis and other autoimmune diseases.

Disclosure: S. Cemerski: Xencor, Inc., 1, 3; **S. Y. Chu:** Xencor, Inc., 1, 3; **E. Pong:** Xencor, Inc., 1, 3; **H. M. Horton:** Xencor, Inc., 1, 3; **J. R. Desjarlais:** Xencor, Inc., 1, 3; **D. E. Szymkowski:** Xencor, Inc., 1, 3.

1351

Micro RNA 155 Deficiency Protects from the Development of Inflammatory Arthritis. Stephan Blüml[1], Michael Bonelli[2], Birgit Niederreiter[1], Antonia Puchner[1], Georg Mayr[1], Marije Koenders[3], Smolen Josef[1] and Redlich Kurt[1]. [1]Medical University Vienna, Austria, [2]Medical University Vienna, Austria [3]Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

Objective: Micro RNAs are a new class of regulatory elements in various biological processes. Altered expression of certain micro RNAs has been demonstrated in rheumatoid arthritis. However, the pathogenic role of micro RNAs is not known in the development of this disease. The aim of this study was to assess the role of microRNA 155 in the development of murine inflammatory arthritis.

Methods: Collagen-induced arthritis (CIA) as well as K/BxN serum transfer arthritis was in induced in wild-type (wt) and microRNA 155 knock out ($miR155^{-/-}$) mice. Clinical scoring was performed on a weekly basis. Histological analysis of synovial inflammation as well as local bone destruction was performed. Cytokine production was measured in serum as well as from supernatants of cultured lymph node cells after immunization after induction of CIA. The humoral as well as T cell response to collagen as well as T cell polarization was assessed in serum, spleen and lymph node, respectively. The cellular composition of the draining LN in CIA was analyzed by flow cytometry.

Results: We show that mice $miR155^{-/-}$ mice are protected from clinical as well as histological signs of CIA. Analysis of anti-collagen antibodies revealed strongly reduced levels in $miR155^{-/-}$ mice compared to wt. However, relative numbers and expression of costimulatory molecules on B cells were not different between the two groups. Furthermore $miR155^{-/-}$ mice showed reduced antigen-specific proliferation of T cells. In addition, T cells of $miR155^{-/-}$ mice produced significantly diminished levels of the Th17 cytokines IL-17 and IL-22, whereas Th1 and Th2 cytokine IL-4 and IFN-γ were not different. Using K/BxN serum transfer arthritis, which is only dependent of innate effector mechanisms, we show that both wt and $miR155^{-/-}$ mice develop arthritis. However, $miR155^{-/-}$ mice showed significantly reduced local bone destruction due to reduced generation of osteoclasts.

Conclusions: MiR155 deficiency protects from the development of CIA by inhibiting the generation of pathogenic self reactive T as well as B cell responses. Furthermore, miR155 controls the development of local bone destruction by inhibition of osteoclastogenesis. These data identify miR155 as a possible novel target in the therapy of autoimmune arthritis.

Disclosure: S. Blüml: None; **M. Bonelli:** None; **B. Niederreiter:** None; **A. Puchner:** None; **G. Mayr:** None; **M. Koenders:** None; **S. Josef:** None; **R. Kurt:** None.

1352

Down-Regulated MicroRNA-152 Induces Aberrant DNA Methylation in Scleroderma Endothelial Cells by Targeting DNA Methyltransferase 1. Yongqing Wang, Omar R. Kahaly and Bashar Kahaleh. University of Toledo, Toledo, OH

Objectives: The underlying mechanism of epigenetic imprinting in SSc microvascular endothelial cells (MVEC) remains unknown. MicroRNAs (miRNAs), which are noncoding RNAs that regulate gene expression, are involved in diverse biological functions. In this study, we investigated whether miRNAs are aberrantly expressed in SSc-MVEC and if they are involved in the regulation of epigenetic imprinting in SSc.

Methods: The expression levels of the 376 most abundantly expressed miRNAs in the human genome were determined in SSc and control MVEC (derived from 6 SSc and matched control subjects) by RT^2 microRNA PCR array. Control and SSc MVEC were transfected with 1.0ug of miRNA isolated from SSc or control MVEC. After 48 hours, cells were harvested and the expression levels of endothelial nitric oxide synthase (*NOS3)* and DNA methyltransferases1 (*DNMT1)* were measured by real-time PCR. The expression levels of miR-152 were determined by quantitative PCR. Finally, miRNA-152 was forced expressed or inhibited in SSc and control MVEC.

Results: Significant differences in the expression levels of miRNAs were noted in SSc-MVEC. To understand the role of altered miRNAs expression in SSc, control-MVEC were transfected with SSc- derived miRNAs which resulted in significant increase expression of *DNMT1* (2.5± 0.3 folds, mean ±SD) and reduced *NOS3* expression level (25±9%, percent of control). While, the transfection of SSc-MVEC with control miRNAs resulted in decreased expression of *DNMT1* and increased expression of *NOS3.* Since *DNMT1* is one of the predicted direct targets of miR-152, we investigated the expression levels of miR-152 in SSc and control MVEC. Levels were frequently down-regulated in SSc-MVEC and were inversely correlated to *DNMT1* expression levels. Forced expression of miR-152 in SSc-MVEC led to a reduction in *DNMT1* expression at both the mRNA and protein levels in comparison with the negative control, while inhibition of miR-152 expression in control- MVEC enhanced *DNMT1* expression levels in association with reduced *NOS3* expression level.

Conclusions:

· SSc-miRNAs transfection into control-MVEC can induce SSc-MVEC phenotype.

· miR-152 expression is down regulated in SSc-MVEC and inversely correlates with DNMT1 expression level.

· The forced expression of miR-152 corrected SSc-MVEC phenotype and its inhibition induced SSc phenotype in control MVEC.

· miR- 152 may play a causal role in DNA methylation changes in SSc-MVEC.

Disclosure: Y. Wang: None; **O. R. Kahaly:** None; **B. Kahaleh:** None.

1353

SNAPIN: A Novel Endogenous TLR Ligand in Rheumatoid Arthritis. Bo Shi[3], Qiquan Huang[3], Margriet J. Vervoordeldonk[1], Paul P. Tak[2] and Richard M. Pope[4]. [1]Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [2]Academic Medical Center, University of Amsterdam, [3]Northwestern University, Chicago, IL, [4]Northwestern University

Background: Toll-like receptor (TLR) signaling may contribute to the pathogenesis of rheumatoid arthritis (RA) resulting in the persistent activation of macrophages and the expression of inflammatory cytokines, mediated by endogenous TLR ligands produced and released locally within the joint. While a number of potential ligands have been identified, it is unclear which, if any, is clinically important. Therefore, a yeast-two hybrid system was employed to identify TLR2 and TLR4 binding proteins by screening a cDNA library generated from RA joint tissue.

Methods: In yeast-two hybrid system, the extracellular domains of TLR2 or TLR4 were used as bait. The prey was a cDNA library generated from highly inflammatory RA synovial tissues. Positive colonies were selected by growing yeasts on nutritional dropout agar plates. The plasmids from the positive yeast colonies were isolated and the cDNA inserts were sequenced. Co-immunoprecipitation was performed using HA-tagged *in vitro* translated SNAPIN with TLR2-Fc or TLR4-Fc fusion proteins. The agonistic function of SNAPIN was examined using HEK-TLR2 and HEK-TLR4 reporter cells.

Results: The TLR2 bait interacted with 60 protein sequences, which represented 11 unique proteins, while the TLR4 bait identified 54 sequences, which represented 34 unique proteins. 33 of the 60 sequences interacting with TLR2 and 7 of the 56 interacting with TLR2 represented SNAP-associated protein (SNAPIN), a protein important in endosomal fusion. SNAPIN co-immunoprecipitated with TLR4-Fc, but more strongly with the TLR2-Fc fusion protein. In the functional assays, recombinant SNAPIN activated HEK cell lines expressing TLR2 and TLR4. Heat inactivation of SNAPIN for 10min at 96 °C and pre-incubation with 50mg/ml protease K completely abolished TLR activation, while treatment with polymyxin B did not inhibit TLR activation, suggesting that the effects were not due to endotoxin contamination. Furthermore, neutralizing anti-TLR2 antibody inhibited SNAPIN's effect on TLR2 signaling, suggesting the SNAPIN specifically targets TLR2. SNAPIN was expressed in synovial fluid macrophages, determined by immunoblot analysis.

Conclusion: We identified SNAPIN as a novel endogenous TLR2 and TLR4 ligand in the synovial tissue of patients with RA. SNAPIN is known to function as a regulator for membrane docking and fusion for synaptic vesicles as well for late endosomal-lysosomal fusion. Studies are underway to determine the potential role of SNAPIN in the pathogenesis of RA.

Disclosure: B. Shi: None; **Q. Huang:** None; **M. J. Vervoordeldonk:** None; **P. P. Tak:** None; **R. M. Pope:** None.

1354

TLR9 Induced Macrophage Activation Syndrome Is Driven by IFNγ Produced by Lymphocytes and Natural Killer Cells but Is Dampened by Lymphocyte Produced IL-10. Edward M. Behrens[2], Katharine Slade[3], Sheila Rao[3], Portia A. Kreiger[1], Michele Paessler[3], Taku Kambayashi[5] and Gary A. Koretzky[4]. [1]A.I. DuPont Hospital for Children, [2]Childrens Hospital of Phil, Philadelphia, PA, [3]The Children's Hospital of Philadelphia, [4]University of Pennsylvania, Philadelphia, PA, [5]University of Pennsylvania

Purpose: Macrophage Activation Syndrome (MAS) is a clinical entity consisting of massive inflammation, cytopenia, and multi-system organ failure associated with an overproduction of IFNγ. Previous murine models implicate genetic defects in CD8+ T-cell cytotoxicty as the cause of the syndrome. However, this model does not explain the link of MAS with genetically normal patients having rheumatologic disease or Epstein Barr Virus (EBV) infections. To investigate the pathoetiology of MAS in inflamed, genetically normal animals, we utilized a system of chronic inflammation driven by Toll-like receptor (TLR) stimulation.

Methods: Mice treated with every other day i.p. injection of CpG (TLR9 agonist) for 10 days. Cytokines were measured by ELISA, cell surface markers by flow cytometry, and organs were taken for histology. Natural killer (NK) cells were depleted using the PK136 anitbody (100 μg i.p. every day).

Results: CpG treated mice develop pancytopenia, splenomegaly, microthrombosis, hepatitis, hyperferritinemia, and elevated serum IFNγ consistent with MAS. None of these changes occur in PBS injected control mice. Only a small population of CD8+ T-cells are activated by the CpG treatment as measured by CD69 levels. In contrast, Natural Killer (NK) cells show a more robust CD69 upregulation. Consistent with previous MAS models, disease is dependent on IFNγ as IFNγ−/− CpG treated mice are protected from disease. Unlike previous models, CpG treated β2m−/− mice lacking CD8+ T-cells develop disease to the same extent as wild type mice showing that CD8+ T-cells are not required. Furthermore, Rag−/− mice develop CpG induced disease, showing that all B- and T-cells are dispensable. NK cell depleted mice develop disease suggesting NK cells are dispensable. However, Rag/common gamma chain (Rag/cgc −/−) doubly deficient mice missing B-, T- and NK cells have greatly reduced disease. Thus, in the absence of adaptive immunity, NK cells are required for full disease expression. Interestingly, consistent with incomplete protection, Rag/cgc −/− CpG treated mice produce half as much IFNγ as Rag−/− mice suggesting that an IFNγ producing myeloid cell also contributes to disease. IL-10 is also produced by CpG treated mice, but is reduced in IFNγ−/− mice suggesting it is produced in response to IFNγ induced inflammation. IL-10 is also reduced in CpG treated Rag−/− mice, which develop enhanced liver disease, suggesting both that the source of IL-10 is from lymphocytes, and that its production is protective.

Conclusions: Our novel mouse model shows that MAS can result from TLR stimulation. This provides a rationale for the link between MAS and rheumatic diseases such as Still's Disease and lupus, both of which are associated with TLR activation, as well as the association of MAS with EBV, a TLR9 stimulating virus. We show that NK cells are important mediators of disease, a cell population implicated in the etiology of Still's Disease. We show that IFNγ is critical for driving disease, but that IL-10 from a lymphocyte origin is protective. Interestingly, these studies also suggest a role for an IFNγ producing myeloid cell, a population whose relevance has been controversial, in driving this disease process.

Disclosure: E. M. Behrens: None; **K. Slade:** None; **S. Rao:** None; **P. A. Kreiger:** None; **M. Paessler:** None; **T. Kambayashi:** None; **G. A. Koretzky:** None.

1355

Genome-Wide Association Study of Ankylosing Spondylitis Identifies New Loci, a Tag SNP for HLA-B27, and an Interaction between HLA-B27 and Variants in ERAP1. Matthew A. Brown, on Behalf of the Wellcome Trust Case-Control Consortium 2 and Australo-Anglo-American Spondyloarthritis Consortium. The University of Queensland Diamantina Institute, Brisbane, Queensland, Australia

In order to identify genetic variants predisposing to risk of Ankylosing Spondylitis (AS), we performed a gwas of 1782 British and Australian cases fulfilling modified New York Criteria, and 5167 historical controls from the Wellcome Trust Case Control Consortium 2 (WTCCC2). After imputing to Hapmap, the study was combined with existing results from the Australo-Anglo-American AS Consortium (TASC) involving a non-overlapping cohort of Australian, British and North American cases and ethnically matched controls, using inverse variance meta-analysis. Replication was then performed in 2109 cases and 4410 controls from Australia, Britain, and the Canadian SPARCC consortium.

As well as confirming known associations at *HLA, IL23R, ERAP1, KIF21B*, 2p15 and 21q22, we identified and subsequently replicated risk predisposing variants in *RUNX3* (combined $p=3.3 \times 10^{-12}$), *IL12B* ($p=1.8 \times 10^{-8}$), and *LTBR* ($p=4.5 \times 10^{-10}$), and found suggestive association at *PTGER4* ($p=7.8 \times 10^{-8}$), and *TBKBP1-TBX21* ($p=5.9 \times 10^{-8}$), as well as providing further support for previously reported loci with suggestive association with AS, including *ANTXR2* ($p=3.8 \times 10^{-7}$), *CARD9* ($p=1.2 \times 10^{-6}$), and *TRADD* ($p=4.1 \times 10^{-6}$).

We also identified a single SNP, rs4349859 near the gene *MICA*, which tagged HLA-B27 with near perfect sensitivity (98%) and specificity (99%) in 531 cases and 729 controls of Australian and British origin. These findings were confirmed in independent sets of Sardinian and Azorean cases, and show that whilst rs4349859 tagged the non-AS associated *HLA-B*2709* subtype, it did not tag the AS-associated *HLA-B*2707* subtype, indicating that rs4349859 is not AS causative, and further reducing the likelihood that a B27-linked gene is responsible for the association of B27 with AS.

In most common diseases the proposed genetic model involves interaction between loci, but to date no convincing examples of such interaction have been demonstrated. In the current study however, we identified an interaction between HLA-B27 and variants within *ERAP1* in the WTCCC2 ($p=0.008$), TASC ($p=0.004$) and replication datasets ($p=0.004$). Specifically, risk variants in *ERAP1* increased odds of disease in HLA-B27-positive, but not B27-negative, cases (combined interaction $p=1.4 \times 10^{-6}$). In contrast, *IL23R* was associated with disease in both B27+ve and –ve cases. This result indicates that B27+ and B27-ve forms of disease have substantially different but overlapping aetiologies. The findings support mechanisms of association of B27 and ERAP1 with AS that involve peptide presentation, and that ERAP1 contributes to disease risk through its action in trimming peptides prior to loading into nascent HLA class I molecules, rather than by cleaving pro-inflammatory cytokine receptors on the cell membrane.

In summary, we have identified several new loci that affect risk of AS, bringing the total number of confirmed AS genetic susceptibility loci to 14,

report a single SNP variant that tags HLA-B27 which may be used in the future as a cheap alternative to expensive B27 typing, and have discovered one of the first convincingly replicated examples of a genetic interaction affecting risk of a complex disease.

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ACR Concurrent Abstract Sessions
Antiphospholipid Syndrome
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TLR-4 and Annexin A2 Involvement in Endothelial Cell Activation by Anti-Phospholipid Antibodies: Specific Silencing by Small Interfering RNAs. Elena Raschi[2], Valentina Broggini[3], Maria Orietta Borghi[4], Claudia Grossi[2] and Pierluigi Meroni[1]. [1]Instituto G. Pini University, Milano, Italy, [2]IRCCS Istituto Auxologico Italiano, Milan, Italy, [3]University of Milan, Italy, [4]University of Milan; IRCCS Istituto Auxologico Italiano, Milan, Italy

Background: Antiphospholipid Syndrome (APS) is characterized by recurrent fetal losses and arterial/venous thrombosis in the presence of antiphospholipid antibodies (aPL). aPL are directed against anionic phospholipid binding proteins: mainly prothrombin and b2 glycoprotein I (b2GPI). The complex formation between circulating aPL and b2GPI expressed on the cell membranes induces signalling and triggers cell activation. Accordingly, aPL-mediated endothelial cell (EC) perturbation is thought to be a key pathogenic event leading to the prothrombotic diathesis as supported by in vitro and in vivo models. The exact nature of the EC receptors for b2GPI is still matter of research: β2GPI has been shown to bind heparan sulphate, Annexin A2 and apoER2 (on platelets). Furthermore there is also evidence that aPL trigger TLR-4.

Objectives: to address the role of TLR4 and AnnA2 in anti-b2GPI Abs-mediated EC activation pathway.

Methods: we performed: i) in vitro experiments with or without blocking antibodies directed to Annexin A2 and TLR-4 ii) small interfering RNA experiments for silencing TLR-4 and Annexin A2 expression in suitably transfected HUVEC.

Results: aPL binding to HUVEC was partially inhibited by both anti-Annexin A2 and anti-TLR-4 blocking antibodies. Anti-TLR-4 also reduced aPL-induced E-Selectin and ICAM-1 expression. TLR-4 silencing by siRNA significantly inhibited both binding and activation of aPL-exposed HUVEC, while Annexin A2 silencing only affected binding.

Conclusion: Our results suggest that more than one receptor may be involved in aPL-mediated EC activation. As Annexin A2 is unable to transduce signals into the cells owing to the lack of a cytoplasmic tail, TLR-4 could act as coreceptor. Understanding the nature of the receptor/co-receptor and its interaction with β2GPI will lead to identify new strategies for treatment and prevention of pro-thrombotic and pro-inflammatory state in APS.

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Role of Reactive Oxigen Species and ROS-Dependent Downstream Signalling in the Prothrombotic State Elicited by Antiphospholipid Antibodies from Primary Antiphospholipid Syndrome Patients. Chary Lopez-Pedrera[1], Patricia Ruiz-Limon[1], Maria Angeles Aguirre[1], Nuria Barbarroja[1], Antonio Rodriguez-Ariza[1], Carlos Perez-Sanchez[1], Eduardo Collantes-Estevez[1], Jose Manuel Villalba[4], Francisco Velasco[1], Munther A. Khamashta[2] and Maria Jose Cuadrado[3]. [1]Reina Sofia Hospital-IMIBIC, Cordoba, Spain, [2]The Rayne Institute, London, United Kingdom, [3]The Rayne Institute, London, United Kingdom, [4]University of Cordoba, Cordoba, Spain

Background: The role of antiphospholipid antibodies (aPL) in the induction of a procoagulant state is clearly established; yet, the precise intracellular mechanisms are poorly understood. Besides their role in tissue vascular injury, reactive oxygen species (ROS) may act as important signalling molecules, activating redox-sensitive signalling cascades that potentially link the activation of receptors by their agonists to gene expression.

Aim: We investigated the relevance of ROS in the prothrombotic/proinflammatory state elicited by aPL and studied ROS-dependent downstream signalling pathways leading to monocyte activation.

Design and Methods: Monocytes from healthy individuals were treated with affinity purified IgG from 7 APS patients (aPL-IgG), or IgG normal human serum (IgG-NHS) from 7 healthy donors. Then, time and dose-dependent ROS production was analyzed. Inhibitory studies on ROS production were performed by preincubation of the treated monocytes 1h with antioxidants N-acetyl-L-cysteine (NAC), and vitamin C (vit C), as well as with the mitochondrial inhibitor, rotenone. Peroxides, peroxynitrite generation and mitochondrial membrane potential (MMP), were analysed by flow cytometry using specific fluorescent probes. As procoagulant/proinflammatory markers, cell surface TF, VEGF and Flt1 expression were evaluated by flow cytometry and western blot respectively. Nitric oxide (NO) levels and Total Antioxidant Capacity (TAC) were measured in the supernatant of the cell cultures. N-Tyr, iNOS expression, p38MAPK activation and IkappaB degradation were evaluated by Western blot. NFkB activity was quantified by EMSA.

Results: Independent incubation of monocytes with aPL-IgG from 7 patients increased cellular ROS production and mitochondria depolarization, which were prevented by the antioxidants Vit C and NAC. Inhibition by rotenone further indicated an involvement of the mitochondrial transport chain as a source of ROS. The reduction of supernatant TAC after aPL-IgG treatment was abolished by ROS inhibitors. Moreover, aPL-induced iNOS, N-Tyr, and NO expression levels were reduced by treatment with ROS inhibitors. ROS produced by aPL-IgG treatment activated p38 MAPK and its subsequent target, the nuclear factor kappa B (NFκB), and controlled the up-regulation of TF, VEGF, and Flt1 in monocytes.

Conclusions: Our data indicate that the binding of aPL-IgG to the monocyte membrane elicited a redox-sensitive signalling pathway that controls the procoagulant phenotype of that cells in the setting of APS. Thus, oxidative stress by aPL-IgG represents a new pathway potentially contributing to the thrombotic complications of APS. Supported by JA0042/2007, JA0246/2009, P08CVI04234 and PS09/01809.

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Peptide & NMR Spectroscopy Studies of Recombinant Domain I Confirm Conformationally Correct Domain I and Non-Linear Epitope Binding to Anti-Domain I Antiphospholipid Antibodies. Charis Pericleous[2], Toluwape Disu[4], Jennifer Miles[1], Diego Esposito[1], Acely Garza-Garcia[1], Paul C. Driscoll[1], David S. Latchman[4], David A. Isenberg[3], Ian Giles[4], Anisur Rahman[4] and Yiannis Ioannou[4]. [1]National Institute of Medical Research, London, UK, [2]University College London, London, United Kingdom, [3]University College London, London, United Kingdom, [4]University College London, London, UK

Purpose: Recombinant Domain I (DI) is increasingly being utilised in the development of diagnostic assays and being developed as an inhibitor of pathogenicity. The critical epitope R39-R43 as well as the DI/DII interlinker region have been shown to be important in binding antiphospholipid antibodies. We undertook NMR spectroscopy studies as well as linear epitope peptide binding assays to confirm that recombinant DI was indeed conformationally correct and ascertain the potential binding abilities of different linear peptides based on the defined epitopes.

Methods: Sera from 8 patients with APS (8/8 female; mean age 46.7$\pm$16.4; 7/8 Caucasian, 1/8 Asian; 8/8 with previous thrombosis, 4/8 with previous pregnancy morbidity) were tested in a standard direct anti-β2GPI assay and the appropriate dilution corresponding to 50% of maximal binding (MBD) was identified. Linear peptides containing region R39-R43 (PEP1, 9aa, 1kDa), DI-II interlinker (PEP2, 9aa, 1kDa), or both (PEP3, 26aa, 3kDa) were designed and synthesised (Sigma, UK). 7KDa wild type recombinant human (WT) DI was expressed in E.coli cells and folded in vitro in a cysteine/cystine-rich buffer for disulfide bond formation. Sera at a dilution that conferred 50% MBD anti-β2GPI activity were incubated (2h, RT) with increasing doses of WT DI (0, 20, 40, 60, 80 or 100μg/ml) or equimolar doses of PEP1–3, and their anti-β2GPI activity was assessed. Percentage binding was calculated based on the change in OD405nm in the presence of inhibitor. To confirm WT DI was conformationally correct, NMR spectroscopy was employed following standard triple resonance 3D NMR protocols. The Chemical Shift Index (CSI) and TALOS computer programs were used to compare the secondary structure of WT DI alone with that in whole human β2GPI based on the published 3D crystal structure.

Results: The inhibitory ability of WT DI was statistically superior compared to all peptides, throughout the entire range of inhibitor concentrations tested ($p<0.05$ for 20μg/ml WT DI and equimolar PEP1–3; $p<0.001$ in all other cases). By calculating the mean percentage binding ($\pm$standard deviation) of all 8 sera tested, a clear positive correlation between the concentration of WT DI and level of inhibition was identified (from 75.7$\pm$29.9% with 20μg/ml WT DI to

25.0±22.0% with 100μg/ml WT DI), as opposed to PEP1–3 where binding did not fall below 91.3±30.3% (with PEP3 at the highest dose). NMR-derived parameters of WT DI were entirely consistent with the secondary structure of crystallised DI in whole β2GPI. The 3D structure of WT DI superimposed well with the β2GPI crystal structure, indicating that in solution WT DI adopts the anticipated polypeptide fold.

Conclusions: NMR studies demonstrate that bacterially expressed recombinant DI adopts its native conformation supporting the use of this peptide in diagnostic assays and as an inhibitor of pathogenicity. Furthermore, whole DI peptide is necessary to inhibit as patient anti-DI sera failed to recognise linear epitope peptide derivatives.

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A Novel, Simple Fluid Phase Binding Assay for the Detection of Serum Anti-Domain I Antibodies in Patients with the Antiphospholipid Syndrome. Charis Pericleous[2], Acely Garza-Garcia[1], Paul C. Driscoll[1], David S. Latchman[4], David A. Isenberg[3], Ian P. Giles[4], Anisur Rahman[4] and Yiannis Ioannou[4]. [1]National Institute of Medical Research, London, UK, [2]University College London, London, United Kingdom, [3]University College London, London, United Kingdom, [4]University College London, London, UK

Purpose: Domain I (DI) of beta-2-glycoprotein I (β2GPI) has been established as a critical immunodominant region for pathogenic antiphospholipid antibodies (aPL) in patients with the antiphospholipid syndrome (APS). A direct enzyme-linked immunosorbent assay (ELISA) to detect anti-DI antibodies in APS sera could be affected by conformational changes in immobilised DI and has required considerable efforts to optimise by multiple groups including our own. Here we present an alternative concept for detecting anti-DI activity based upon inhibiting anti-β2GPI activity with recombinant DI in the fluid phase.

Methods: Sera from 15 anti-β2GPI positive patients fulfilling APS classification criteria (15/15 female; mean age 47.4±11.9; 14/15 Caucasian, 1/15 Asian; 14/15 with a thrombotic history, 7/15 with previous pregnancy morbidity), and 5 patients with circulating anti-β2GPI aPL (but without APS, aPL+/APS-) were serially diluted (from 1:50) and tested in triplicate using a standard solid phase anti-β2GPI ELISA. The appropriate dilution of serum corresponding to 50% of maximal binding (MBD) was identified for each patient. In each case this gave an OD405nm >0.4. For the new anti-DI assay, each serum sample at the 50% MBD was firstly incubated (2hr, RT) with increasing doses of in-house bacterially-expressed recombinant human DI (0, 20, 40, 60, 80 or 100 μg/ml) and then a standard anti-β2GPI assay was performed. For each patient sample the percentage binding was calculated based on a change in OD405nm in the presence of DI.

Results: Mean percentage binding (± standard deviation, SD) to β2GPI for all 15 APS sera was calculated in the presence of increasing concentrations of DI; the same was performed for the 5 aPL+/APS- samples. The presence of DI significantly reduced binding for APS samples compared to aPL+/APS- samples, in a dose-dependent manner (Table 1).

Table 1. The inhibitory ability of recombinant human DI in the fluid phase

Concentration of DI added (μg/ml)	Mean (SD) binding for APS samples as a percentage of binding in the absence of inhibitor (n=15)	Mean (SD) binding for aPL+/APS- samples as a percentage of binding in the absence of inhibitor (n=5)	P value
20	75.0 (20.3)	96.3 (12.4)	<0.01
40	62.0 (15.6)	99.7 (12.0)	<0.01
60	56.9 (18.1)	94.0 (13.2)	<0.01
80	44.3 (22.9)	89.1 (17.1)	<0.01
100	37.5 (21.7)	85.1 (16.1)	<0.01

Conclusions: Using the well-established direct anti-β2GPI assay, serum inhibition of anti-β2GPI activity by fluid phase recombinant DI is both remarkably simple and selective of pathogenicity in this small sample of patients. The ability to express recombinant human DI in a bacterial system allows for the cost-effective production of large amounts of DI for use in this assay. The findings from this proof-of-concept novel and simple approach to measuring anti-DI activity in an anti-β2GPI positive patient warrant further exploration to further characterise specificity and sensitivity, and hence clinical diagnostic and prognostic utility.

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Apolipoprotein E Receptor (apoER2) Is Involved for Thrombotic Complications in a Murine Model of Antiphospholipid Syndrome. Z. Romay Penabad[1], T. Shilagard[1], G. Vargas[1], R. Aguilar-Valenzuela[1], P. de Groot[2] and S. Pierangeli[1]. [1]Univ of TX Med Branch, Galveston, TX, [2]University Hospital Utrecht, Utretch, The Netherlands

Background: Antiphospholipid antibodies (aPL) recognize $\beta_2$glycoprotein I(β_2GPI)-bound to receptor(s) in target cells (i.e.: endothelial cells [EC], platelets, monocytes) and trigger a pro-coagulant/pro-inflammatory phenotype (i.e.: up-regulation of tissue factor [TF] that lead to thrombosis). The interaction of β_2GPI with target cells may involve more than one protein. Previous publications suggest that β_2GPI-aPL antibody complex binds to apoER2 in cell surface, inducing activation of platelets or EC. Moreover, it has been shown that a soluble binding domain I of apoER2 (sBDI) inhibits the binding of β_2GPI to apoER2.

Objectives:: To determine whether apoER2 mediates pathogenic effects of murine and human aPL antibodies in vivo.

Methods: Wild type (apoER2$^{+/+}$) and apoER2-deficient (apoER2$^{-/-}$) mice were injected twice with IgG purified from one patient with "primary" antiphospholipid syndrome (IgG-APS) or with control IgG (IgG-NHS) or with a murine monoclonal anti-β_2GPI antibodies (named E7) or with control murine monoclonal antibody [1kMPOC-21(Sigma Aldrich)](MuMoAbC). Some wild type mice were also injected i.p. twice with 50 μg of soluble binding DI of apoER2 (sBD1), 30 minutes before each injection with aPL antibodies. Several procedures were done in treated and controls mice to study pathogenicity of aPL antibodies: a) dynamics of thrombus formation, b) TF activity in homogenates of carotid arteries and in peritoneal macrophages, and c) TF expression in macrophages using quantum dot nano crystals and two-photon excitation laser scanning microscopy.

Results: Significantly larger thrombi and increased TF activity in carotid artery homogenates and in peritoneal macrophages was observed in apoER2$^{+/+}$ mice treated with (IgG-APS or E7) when compared to controls. Importantly, apoER2$^{-/-}$mice treated with murine or human aPL antibodies shown partial but significantly abrogation of thrombogenic effects compared with their counterparts injected with control antibodies. In addition, thrombogenic effects of IgG-APS were significantly abrogated in apoER2$^{+/+}$ mice by sBD1, hence confirming the ApoER2 involvement in vivo.

Mice/ treatment	Thrombus size (μm^2)	TF activity carotids (pmol/mg · mL^{-1} protein)	TF activity macrophages (pmol/mg · mL^{-1} protein)	TF expression (AU)
apoER2$^{+/+}$ IgG-APS	*4094 ± 1037	*21.4 ± 8.4	*10.1 ± 1.2	*11.9 ± 2.8
apoER2$^{+/+}$ IgG-NHS	287 ± 110	5.8 ± 0.9	3.2 ± 0.8	3.2 ± 0.4
apoER2$^{-/-}$ IgG-APS	**1675 ± 781	14.6 ± 1.8	**5.9 ± 1.5	4.8 ± 0.9
apoER2$^{-/-}$ IgG-NHS	514 ± 115	5.3 ± 1.7	2.7 ± 0.8	5.9 ± 0.9
apoER2$^{+/+}$ IgG-APS + sBD1	†665 ± 173	†14.7 ± 1.6	†4.4 ± 0.6	†4.3 ± 0.9
apoER2$^{+/+}$ IgG-NHS + sBD1	486 ± 164	4.5 ± 3.3	3.1 ± 2.5	3.2 ± 0.6
apoER2$^{+/+}$/E7	*2599 ± 766	*70.3 ± 15.2	*13.9 ± 2.8	n/a
apoER2$^{+/+}$ MuMoAbC	827 ± 294	13.5 ± 1.8	4.2 ± 1.7	n/a
apoER2$^{-/-}$ E7	**827 ± 294	**24.3 ± 10.5	**9 ± 0.6	n/a
apoER2$^{-/-}$ MuMoAbC	436 ± 125	11.8 ± 2.5	4.3 ± 0.2	n/a

(*) statistically significant different from their negative controls in apoER2$^{+/+}$ mice.
(**) statistically significant different from their negative controls and apoER2$^{+/+}$ mice counterparts.
(†) statistically significant different from apoER2$^{+/+}$ mice treated with IgG- APS

Conclusions: Altogether these data show that apoER2 is a mediator of aPL thrombogenic effects *in vivo*. These data may have important implication in the design of new targeted treatments for APS.

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C6-Deficient Mice Are Protected from the Pathogenic Effects of Antiphospholipid Antibodies. A. L. Carrera-Marin, R. Aguilar-Valenzuela, Z. Romay Penabad, E. Papalardo and S. Pierangeli. Univ of TX Med Branch, Galveston, TX

Background: The pathogenic mechanisms mediated by antiphospholipid (aPL) antibodies are partially understood. Recent studies have demonstrated the complement involvement in the thrombogenic effects of aPL antibodies. Furthermore, inhibitors for the C5 axis can abrogate aPL effects. The complement membrane attack (C5b-9 MAC) complex has been shown to induce tissue factor (TF) expression (procoagulant effect). However whether C5b-9 MAC plays a role in the pathogenesis of thrombosis in Antiphospholipid Syndrome (APS) is unknown.

Objective: To study the effects of human and murine aPL antibodies on thrombosis in C6 deficient ($C6^{-/-}$) mice.

Methods: $C6^{-/-}$ mice and the corresponding wild-type ($C6^{+/+}$) were injected twice with either a] 500 μg/ml IgG isolated from two patients with APS (IgG-APS1 and IgG-APS2) or with normal IgG (IgG-NHS), b) 100 μg/ml murine anti β2GPI monoclonal antibodies (4G4) or with mouse IgG 1κMPOC-21(MuMoAb) (Sigma Aldrich) as control or c) 500 μg/ml IgM isolated from a patient with APS (IgM-APS3). Seventy two h after the first injection the size of induced thrombi in the femoral vein was determined. TF activity was determined in homogenates of carotids and peritoneal macrophages using a chromogenic assay. TF expression in macrophages was also determined using quantum dot nano crystals and two-photon excitation laser scanning microscopy.

Results: Thrombus sizes were significantly larger in $C6^{+/+}$ mice treated with all different IgG-APS and IgM-APS when compared with healthy controls ($p<0.001$). Similarly, MuMoAb 4G4 shown significantly difference in thrombus size compared with control MuMoAb. Importantly, $C6^{-/-}$ mice treated with IgGs -APS or IgM- APS or MuMoAb 4G4 had smaller thrombi compared to their $C6^{+/+}$ counterparts ($p<0.001$) and there were not significant differences among the control groups.

Thrombus size (μm^2)

Treatments	$C6^{+/+}$ mice	$C6^{-/-}$ mice
IgG-NHS	544 ± 99	383 ± 119
IgG-APS 1	*1649 ± 493	732 ± 272
IgG-APS 2	*1914 ± 386	936 ± 514
MuMoAbC	419 ± 122	416 ± 178
MuMoAb 4G4	*1366 ± 332	388 ± 111
IgM-NHS	334 ± 117	393 ± 113
IgM-APS 3	*2268 ± 1004	356 ± 122

(*) statiscally significant different from their controls and $C6^{-/-}$ mice counterparts.

TF activity in carotids and in peritoneal macrophages in $C6^{-/-}$ mice treated with IgG-APS1 were significantly diminished. Similarly result was obtained in macrophages TF expression.

All mice injected with IgG-APS had medium-high titers of aCL.

	TREATMENTS			
	IgG-NHS		IgG-APS 1	
Tissue Factor	$C6^{+/+}$ mice	$C6^{-/-}$ mice	$C6^{+/+}$ mice	$C6^{-/-}$ mice
TF *activity* in carotids (pmoles/mg · ml^{-1} protein)	17.3 ± 0.2	19.2 ± 1	*51.1 ± 5.6	29.9 ± 1.8
TF *activity* in peritoneal macrophages (pmoles/ mg · ml^{-1} protein)	12.6 ± 4.3	4.6 ± 1.2	*28.5 ± 13.3	14.8 ± 9.1
TF *expression* in peritoneal macrophages (AU)	16.0 ± 2.1	3.7 ± 2.7	*40.7 ± 18.2	9.2 ± 8.5

(*) statiscally significant different from their controls and $C6^{-/-}$ mice counterparts.

Conclusions: These data indicate that the C6 component of the complement system mediates aPL-thrombogenic effects. The data underscore the possibility of complement inhibition as a new therapy for clinical manifestations of APS.

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Short-Term Effects of Caffeinated Beverage Intake on Risk of Recurrent Gout Attacks. Tuhina Neogi[1], Clara Chen[3], Christine Chaisson[3], David J. Hunter[4] and Yuqing Zhang[2]. [1]Boston Univ Schl of Med, Boston, MA, [2]Boston Univ School of Medicine, Boston, MA, [3]Boston Univ School of Medicine, [4]University of Sydney, Boston, MA

Purpose: Long-term caffeine intake has been associated with decreased risk for incident gout attacks and lower serum uric acid levels. Acute effects of caffeine, however, can potentially increase uric acid, for example, through a diuretic effect with volume depletion, and impaired glucose tolerance. Further, caffeine, which is a methyl xanthine, can competitively inhibit xanthine oxidase, and therefore may have effects similar to allopurinol in terms of precipitating a flare in the short-term. Given these potential conflicting effects on gout attack risk, we evaluated whether caffeinated beverage intake was associated with risk for recurrent gout attacks.

Methods: We conducted an internet-based case-crossover study to assess a set of putative risk factors thought to trigger recurrent gout attacks. This methodology uses each participant as his/her own control by comparing the frequency of a particular risk factor during periods of gout attacks with that during periods when they are not having an attack, thereby eliminating between-person confounding. Subjects with gout who had an attack within the past year were recruited online and asked to provide access to medical records pertaining to their gout diagnosis. Data were obtained on the amount of caffeine (coffee, tea, other caffeinated beverages) consumed over the 24-hour period before a gout attack and over a 24-hour period during an intercritical period, as well as non-caffeinated beverages (non-caffeinated coffee, tea, sodas, juices). We did not ask about use of sugar in the beverage. We examined the relation of amount of caffeinated beverage intake (0, 1, 2, 3, 4, 5–6, >6 servings per 24-hours) with the risk of recurrent gout attacks using conditional logistic regression adjusting for diuretic use, alcohol consumption, and purine intake, and additionally for all other fluid intake. We repeated the same analyses for non-caffeinated beverage intake.

Results: Of the 633 participants who experienced recurrent gout attacks during the study period, 78% were male, 89% were White, and 58% had a college education. Of the 486 medical records reviewed to date, 82% met the ACR classification criteria for gout. Higher levels of caffeinated beverage intake in the prior 24 hours were associated with increased risk for recurrent gout attacks, even after accounting for other fluid intake, while non-caffeinated beverages were not associated with risk for recurrent gout attacks (Table).

Table. Association of Caffeinated and Non-Caffeinated Beverage Intake, respectively, with Risk for Recurrent Gout Attacks

Caffeinated beverage servings, # (prior 24 hours)	Case/ Control periods	Crude OR	Adjusted* OR (95% CI)	Adjusted** OR (95% CI)
0	214/279	1.0 (ref)	1.0 (ref)	1.0 (ref)
1	154/223	1.08	1.14 (0.79–1.62)	1.13 (0.79–1.62)
2	238/366	1.25	1.23 (0.87–1.73)	1.22 (0.86–1.70)
3	195/256	1.56	1.38 (0.95–1.99)	1.37 (0.94–1.98)
4	174/191	2.09	1.78 (1.19–2.65)	1.76 (1.18–2.64)
5–6	160/194	2.10	1.66 (1.09–2.53)	1.65 (1.08–2.52)
>6	112/80	4.86	3.35 (1.98–5.68)	3.33 (1.96–5.65)
P for trend			p<0.0001	p<0.0001
Non-caffeinated beverage servings, # (prior 24 hours)				
0	443/568	1.0	1.0	1.0
1	215/307	0.90	0.83 (0.64–1.08)	0.84 (0.65–1.09)
2	219/298	0.96	0.78 (0.60–1.02)	0.79 (0.61–1.04)
3	118/169	1.01	0.78 (0.55–1.10)	0.81 (0.57–1.14)
4	87/110	1.10	0.85 (0.58–1.25)	0.88 (0.60–1.30)
5–6	94/56	1.56	1.02 (0.67–1.55)	1.06 (0.70–1.61)
>6	71/51	1.81	0.93 (0.55–1.58)	0.96 (0.56–1.63)
P for trend			p=0.6	p=0.7

* adjusted for diuretic use, purine and alcohol intake
** additionally adjusted for all other fluid intake (including non-caffeinated beverages, dairy, and water for the caffeinated beverage analyses: including caffeinated beverages, dairy, and water for non-caffeinated beverage analyses).

Conclusions: Increases in or episodic caffeinated beverage intake in the short-term appears to increase risk for recurrent gout attacks. In contrast, we did not find such associations with non-caffeinated beverages. Since these beverages may have had varying amount of fructose that we did not measure, further study is warranted to evaluate the effects of caffeine independent of fructose.

Disclosure: T. Neogi: None; **C. Chen:** None; **C. Chaisson:** None; **D. J. Hunter:** None; **Y. Zhang:** None.

1363

Prevalence of Hyperuricemia in the US General Population: The National Health and Nutrition Examination Survey (NHANES) 1999–2008. Yanyan Zhu[1], Bhavik Pandya[2] and Hyon Choi[1]. [1]Boston University of School of Medicine, Boston, MA, [2]Takeda Pharmaceuticals International, Inc, Deerfield, IL

Objective: There is a direct causal relation between serum urate (sUA) levels and the risk of gout. Thus, the population's sUA levels are accurate surrogate indicators for the scope of the disease burden of gout in the population. Our objective was to estimate the trends of sUA levels and prevalence of hyperuricemia based on a recent, nationally representative sample of US men and women (NHANES 1999–2008).

Methods: Using data from 24,693 participants (11,816 men and 12,877 women) aged 20 years and older from NHANES 1999–2008, we estimated overall, gender-specific, and age-specific mean sUA levels and prevalence of hyperuricemia. sUA was measured by oxidization with the specific enzyme uricase to form allantoin and hydrogen peroxide, using participants' blood samples collected during home interview or examination session. We used an NHANES definition of hyperuricemia (sUA level >7.0 mg/dL in men and >5.7 mg/dL in women). We estimated the number of people with hyperuricemia by applying our prevalence estimates to the corresponding US population estimates from the Census Bureau.

Results: The overall prevalence of hyperuricemia among US adults was 20.1%, which corresponded to an estimated 31.9 million individuals with hyperuricemia. The prevalence of hyperuricemia among men was 21.1% (16.1 million) and 19.2% (15.8 million) among women. The overall mean sUA level was 5.41 mg/dL (95% CI, 5.38 to 5.44 mg/dL). The mean sUA level was 6.10 mg/dL (95% CI, 6.06 to 6.14 mg/dL) among men and 4.77 mg/dL (95% CI, 4.73 to 4.80 mg/dL) among women. The prevalence of hyperuricemia increased with age, ranging from the lowest (15.6%, 4.5 million) in individuals aged 20 to 29 years to the highest (36.7%, 2.4 million) in individuals aged 80 years or older. The prevalence of hyperuricemia among individuals aged 65 years or older was 31.3%, which corresponded to an estimated 8.4 million US adults with hyperuricemia (Table).

Table. Prevalence of Hyperuricemia and Mean sUA Levels in NHANES 1999–2008

	Hyperuricemia Estimates (in Millions)	Prevalence, % (95% CI)	Mean sUA Level, mg/dL (95% CI)
Overall	31.9	20.1 (19.2–21.0)	5.41 (5.38–5.44)
Gender			
Male	16.1	21.1 (19.8–22.4)	6.10 (6.06–6.14)
Female	15.8	19.2 (18.0–20.3)	4.77 (4.73–4.80)
Medicare Age Category (Yrs)			
20–64	23.5	17.8 (16.8–18.8)	5.34 (5.31–5.38)
65+	8.4	31.3 (29.7–32.9)	5.73 (5.67–5.78)
Age Category (Yrs)			
20–29	4.5	15.6 (13.9–17.2)	5.26 (5.21–5.31)
30–39	4.7	15.3 (13.4–17.2)	5.24 (5.16–5.31)
40–49	5.9	17.0 (15.3–18.6)	5.33 (5.27–5.39)
50–59	6.0	21.4 (19.4–23.4)	5.48 (5.42–5.54)
60–69	4.7	27.1 (24.7–29.5)	5.63 (5.56–5.69)
70–79	3.7	30.0 (27.8–32.2)	5.70 (5.62–5.77)
80+	2.4	36.7 (32.9–40.5)	5.84 (5.72–5.97)

Conclusions: These findings from the latest nationally representative sample of US adults in NHANES 1999–2008 suggest that the prevalence of hyperuricemia is substantial, particularly among older individuals.

Disclosure: Y. Zhu: None; **B. Pandya:** Takeda Pharmaceuticals International, Inc., 3; **H. Choi:** Takeda Pharmaceuticals International, Inc., 5.

1364

Obesity Is Associated with a Younger Age at Gout Incidence. Mara A. McAdams[4], Janet W. Maynard[2], Judith A. Bolton Hoffman[4], Alan N. Baer[3], Allan C. Gelber[1] and Josef Coresh[4]. [1]Baltimore, MD, [2]Johns Hopkins Univ, Baltimore, MD, [3]Johns Hopkins University, Baltimore, MD, [4]Johns Hopkins, Bloomberg School of Public Health

Background: Obesity is an established risk factor for gout; however, the influence of obesity on the age of gout onset is unclear. We tested the hypothesis that obesity is associated with an earlier age of incident gout diagnosis in a population-based cohort, CLUE II.

Methods: At cohort entry (1989), CLUE II enrolled 26,147 individuals residing in Washington County, Maryland. We included participants who reported on 2003 and 2007 follow-up questionnaires that they had been diagnosed with gout by a healthcare professional and recalled their age at gout diagnosis. We limited this study to incident gout cases that developed gout after 1989. In 1989, participants reported their current weight and height as well as their weight at age 21. Body mass index was calculated (kg/m^2) and obesity defined as BMI $\geq$ to 30 kg/m^2. We compared the mean age at gout incidence by obesity status, both at baseline and at age 21, using t-tests. Multivariate linear regression was used to estimate the independent association of BMI with age at gout incidence.

Results: There were 281 participants with incident gout. 70% were male, and 49% reported alcohol consumption. At baseline, the mean BMI was 25.8 kg/m^2, systolic blood pressure was 126.5 mm Hg and the diastolic blood pressure was 80.7 mm Hg. After adjustment for sex, blood pressure and alcohol intake a one kg/m^2 change in BMI was associated with a 0.15 year decrease in the age at gout incidence (p-value=0.38). For every one kg/m^2 increase in BMI at age 21 years, there was a 1.13-year, adjusted, decrease in the age at gout incidence (p-value<0.001).

Participants who were obese at baseline had a younger age at gout incidence compared to non-obese participants (Table, p-value=0.009). The relationship was statistically significant in men and women but more significant in the group of men with gout. Obese men, at cohort entry, developed gout on average 5.5 years earlier than their non-obese counterparts. Obesity at age 21 was associated with a 12-year earlier age of gout incidence compared to non-obese participants (p-value<0.001) in both men and women.

One limitation of the study is that participants had to be alive to report gout incidence on the 2003 and 2007 questionnaires. However, sensitivity analysis suggest that prevalent gout was not related to reporting on the 2003 and 2007 questionnaires.

Age at gout incidence according to obesity status, at baseline and age 21, in CLUE II cohort

	Total		Women		Men	
	N	Mean age in years (SD)	N	Mean age in years (SD)	N	Mean age in years (SD)
Baseline BMI						
Not obese*	194	59.7 (12.7)	52	63.8 (13.9)	142	58.2 (11.8)
Obese*	87	55.3 (13.6)	30	60.2 (14.4)	57	52.7 (12.6)
Difference (95% CI)		4.4 (1.1, 7.7)*		3.6 (−2.8, 10.1)		5.5 (1.74, 9.3)*
BMI at age 21						
Not obese*	262	59.2 (12.8)	77	63.6 (13.6)	185	57.4 (12.1)
Obese*	18	46.9 (9.4)	5	45.4 (11.9)	13	47.5 (8.7)
Difference (95% CI)		12.3 (6.3, 18.4)**		18.2 (5.8, 30.6)*		9.9 (3.2, 16.7)*

** P-value <0.001
* P-value <0.01

Conclusion: Obese men and women are more likely to develop gout at an earlier age than non-obese counterparts. Those who were obese at age 21 years developed incident gout 12 years earlier than those who were not obese. Physicians should be aware that obesity impacts the age at gout incidence in this population-based cohort.

Disclosure: M. A. McAdams: None; **J. W. Maynard:** None; **J. A. Bolton Hoffman:** None; **A. N. Baer:** None; **A. C. Gelber:** None; **J. Coresh:** None.

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Health Related Quality of Life (HRQOL) in Tophaceous vs. Non-Tophaceous Gout. Puja Khanna[2], Jay Persselin[3], Ron Hays[1], Daniel Furst[1], Harold Paulus[1], Paul Maranian[1] and Dinesh Khanna[1]. [1]UCLA, [2]UCLA and West LA VA, [3]West LA VA

Objective: Gout is a chronic disorder of uric acid metabolism resulting in acute painful episodes of arthritis. Tophaceous gout is associated with greater number of attacks, more erosive disease, inadequate pain control, and results in joint destruction when untreated. We assessed the impact of chronic tophaceous gout on HRQOL in an ongoing, prospective, 1-year observational study.

Methods: 71 patients with tophaceous and non-tophaceous gout were recruited at VA and University Hospitals. Tophi were assessed by a physician and HRQOL was assessed at baseline using SF-36 v2, HAQ-DI and a disease-specific Gout Impact Scale (GIS). Health utilities were elicited using computerized software, U-Maker ® in structured interviews. Direct preference-based measures to evaluate disutility of gout included health rating scale (RS, 0–100), time tradeoff (TTO, 0.0–1.0), and standard gamble (SG, 0.0–1.0). Disutility was assessed by subtracting preference scores for current health states with gout from those for current health without gout. Patients were questioned on how much money they would be willing to pay out of pocket as a one time payment to cure their gout permanently. Patients were also asked to list their comorbidities and rank them from most to least concerning.

Results: Non-tophaceous were similar to tophaceous subjects in age (68 years), number of flares (3 per year), disease duration (12.4 years), Charlson comorbidity index (3.0), and serum urate levels (7.1 mg/dl, $p > 0.05$). Patients with tophi had greater evidence of radiographic damage ($p < 0.05$), worse HAQ-DI score ($P = 0.06$) and rated their gout as more severe ($p = 0.0008$). The 2 groups did not differ in SF-36 and GIS scores. However, tophaceous subjects assigned greater disutility to their gout on RS (12.4 vs. 7.4) and (SG 0.07 vs. 0.009), were willing to pay a significantly higher dollar amount out of pocket for a cure ($p = 0.04$), and had worse functional capacity to perform usual activities of daily living ($p = 0.008$) compared to the non-tophaceous. Gout was ranked as the top most health concern in 25% with tophaceous gout compared to 17% with non-tophaceous gout.

Conclusion: Although the patients with chronic tophaceous and non-tophaceous gout were comparable in demographics, the tophaceous group had worse functional disability, assigned higher disutility to gout, and was willing to pay more for a cure. SF-36 and GIS were not able to discriminate between 2 groups. Our data quantifies the decrement in quality of life of patients with tophaceous gout and their willingness to pay for treatment of a debilitating and disabling disease. Our finindgs have implications for decision and cost-effectiveness analyses.

Demographics & Clinical characteristics	All (N=71)	Nontophaceous (N=45)	Tophaceous (N=26)
Severity of Gout scale 0–10	3.0 (2.9)	2.1 (2.3)	4.7 (3.2)*
Health Status:			
1. SF-36 a) PCS	37.1 (9.6)	37.6 (9.4)	36.2 (10.1)
b) MCS	47.2 (13.5)	48.2 (12.1)	45.4 (15.7)
2. HAQ-DI (0–3)	0.9 (0.7)	0.7 (0.6)	1.1 (0.8)*
3. GAQ: Gout Concern Overall	65.4 (25.8)	62.8 (25.6)	70.0 (25.9)
Gout Medications Side Effects	53.9 (25.1)	55.0 (25.2)	51.9 (25.4)
Unmet Gout Treatment Need	44.5 (19.7)	43.9 (21.0)	45.5 (17.5)
Well Being During Attack	58.0 (27.5)	57.9 (25.3)	58.2 (31.5)
Gout Concern During Attack	55.1 (25.6)	54.9 (22.1)	55.5 (31.3)
Health Utilities:			
1. Rating Scale, (0–100)	9.2 (17.9)	7.4 (19.3)	12.4 (15.0)
2. Time Tradeoff, (0.00–1.00)	0.02 (0.11)	0.02 (0.08)	0.01 (0.16)
3. Standard gamble, (0.00–1.00)	0.03 (0.12)	0.01 (0.05)	0.07 (0.19)*
Willingness to pay in $, median (IQR)	400 (60, 1000)	100 (30, 1000)	500 (200, 3500)*
ACR Functional Class: I&II	57 (81.4)	40 (90.9)	16 (85.4)*
III&IV	13 (18.6)	4 (9.1)	9 (34.6)

* $p<0.05$ for comparison between tophaceous and non-tophaceous Gout

Disclosure: P. Khanna: ACR REF, 2; **J. Persselin:** None; **R. Hays:** None; **D. Furst:** None; **H. Paulus:** None; **P. Maranian:** Savient Pharmaceuticals, 2; **D. Khanna:** Savient Pharmaceuticals, 2.

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Cherry Consumption and Risk of Recurrent Gout Attacks. Yuqing Zhang[3], Clara Chen[1], David J. Hunter[4], Christine E. Chaisson[1], Hyon K. Choi[5] and Tuhina Neogi[2]. [1]Boston Univ Medical Ctr, Boston, MA, [2]Boston Univ Schl of Med, Boston, MA, [3]Boston Univ School of Medicine, Boston, MA, [4]Sydney University, Sydney, Australia, [5]Univ of British Columbia, Vancouver, BC, Canada

Anecdotal evidence implicates that consumption of cherries and cherry products may reduce levels of serum uric acid (SUA) and the risk of gout attacks. A recent study of 10 healthy women reported that SUA levels were reduced by 15% 5 hours after consuming two servings (280 grams) of cherries. Other studies have also reported that cherry fruit/cherry products may provide anti-inflammatory benefits. To date, no large-scale study has examined whether cherry consumption reduces the risk of recurrent gout attacks.

Methods: We conducted an online case-crossover study to assess a set of putative risk factors for recurrent gout attacks. Subjects who had experienced a gout attack within the past year were recruited online and were asked to provide access to medical records for verification of gout diagnosis. Subjects were asked to log onto the study website when they experienced a gout attack. Risk factors, including cherry fruit and cherry products (i.e. cherry extract) intake, occurring each day over the two-day period prior to an acute gout attack (case-period) were assessed using an online questionnaire. The same questionnaire was used over each of the two days during an intercritical period (control-period). We examined the relation of cherry fruit and cherry products intake over the 2-day period to the risk of recurrent gout attacks using conditional logistic regression, adjusting for alcohol consumption, purine intake, and diuretic use.

Results: Included in this analysis were 633 subjects who experienced recurrent gout attacks during the study period. Participants were predominantly white (88%), men (78%), and 58% had a college education. Of the 468 medical records obtained to date, 82% fulfilled the ACR Classification Criteria for Gout. The median time between the onset of a gout attack and logging on to the website was 3 days. Compared with no cherry fruit intake over the 2-day period, the odds ratios (OR) of recurrent gout attacks were 1.0, 0.5, 0.4, and 0.6, respectively, for 1, 2, 3 and ≥4 servings (one serving is one-half cup or 10 cherries) over the past two days (p for trend <0.001). Intake of cherry products over the past 2 days was also associated with a decreased risk of recurrent gout attacks (OR=0.6, 95% CI: 0.3–1.0) (Table).

Conclusions: Intake of cherry fruit and cherry products over the past 2 days were associated with a reduction in risk for recurrent gout attacks. Cherry consumption may provide a safe, non-pharmacologic option that can help prevent recurrent gout flares among patients with preexisting gout.

Intake over past 2 days	No. of Case-periods	No. of Control-periods	Crude OR	Adjusted OR* (95% CI)
# Servings of cherry fruit				
0	1074	1318	1.0	1.0
1	53	71	0.9	1.0 (0.6–1.4)
2	56	98	0.6	0.5 (0.3–0.8)
3	16	35	0.5	0.4 (0.2–0.8)
≥4	48	67	0.7	0.6 (0.4–1.0)
Use of cherry product				
No	1212	1520	1.0	1.0
Yes	35	69	0.6	0.6 (0.3–1.0)

* Adjusted for diuretic use, purine and alcohol intake

Disclosure: Y. Zhang: None; **C. Chen:** None; **D. J. Hunter:** None; **C. E. Chaisson:** None; **H. K. Choi:** None; **T. Neogi:** None.

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Serum Urate Levels in Young Adults Are Associated with the Risk of Incident Hypertension: Findings from the Coronary Artery Risk Development in Young Adults (CARDIA) Cohort. Angelo L. Gaffo[1], David R. Jacobs[6], Femke Sijtsma[5], Cora E. Lewis[3], Ted R. Mikuls[2] and Kenneth G. Saag[4]. [1]Birmingham VAMC and University of Alabama at Birmingham, Birmingham, AL, [2]Univ of Nebraska Med Ctr, Omaha, NE, [3]University of Alabama at Birmingham, [4]University of Alabama-Birmingham, Birmingham, AL, [5]University of Minnesota, [6]University of Minnesota and University of Oslo

Purpose: to determine if serum urate concentrations in young adults are associated with the subsequent development of hypertension.

Methods: Women and men were analyzed separately because of intrinsic differences in their serum urate levels at the ages studied. Blood pressure (BP) was measured at cohort baseline (1985–1986) and at years 2, 5, 7, 10, 15, and 20 of follow-up. Using Cox-proportional hazard regressions, the associations between sex-specific categories of serum urate at baseline with subsequent development of hypertension (defined as BP ≥ 140/90 or being on blood pressure medication) were examined. Baseline covariates included in the models were age, race/ethnicity, body mass index, physical activity scores, total alcohol intake, smoking status, HDL and LDL cholesterol levels, serum triglyceride levels, serum insulin levels, education completed, and center of recruitment.

Results: 4933 participants free of hypertension at baseline were included in the longitudinal analysis. Mean age (standard deviation) at initiation of follow-up was 24.8 (3.6) years for men and 24.9 (3.7) years for women. The cumulative incidence of hypertension at 20 years of follow-up was 28.5% for men and 30.2% for women. Categories cutpoints of serum urate were higher in men than in women. After multivariable adjusted analyses men showed consistent dose-dependent increases in the risk of developing hypertension with higher levels of serum urate at the beginning of follow-up.

Figure 1. Table showing the multivariable adjusted risk of developing hypertension over 20 years of follow-up by baseline serum urate among men

Serum urate category	Hazard ratio	95% CI
1: <5.4 (REF) (n=521)	1.00	REF
2: 5.4–6.09 (n=533)	1.64	1.22–2.21
3: 6.1–6.79 (n=568)	1.87	1.39–2.50
4: 6.8–7.49 (n=312)	1.62	1.16–2.28
5: ≥ 7.5 (n=290)	2.40	1.73–3.32
Linear HR (p<0.001)	1.19	1.10–1.27

For women the increases in risk were inconsistent and did not conform with a linear trend, but the risk of incident hypertension did increased across all but the relatively small highest serum urate category.

Figure 2. Table showing the multivariable adjusted risk of developing hypertension over 20 years of follow-up by baseline serum urate among women

Serum urate category	Hazard ratio	95% CI
1: <3.8 (REF) (n=630)	1.00	REF
2: 3.8–4.39 (n=693)	1.25	0.97–1.60
3: 4.4–5.09 (n=696)	1.37	1.08–1.75
4: 5.1–5.59 (n=332)	1.54	1.16–2.04
5: ≥ 5.6 (n=358)	1.09	0.81–1.47
Linear HR (p=0.21)	1.04	0.98–1.11

Conclusions: We demonstrated an association between higher urate concentrations in young men and the subsequent risk for incident hypertension, even at concentrations considered to be within the normal range for serum urate (< 6.8 mg/dl). Lack of a consistent trend among women could relate to their comparatively low concentrations of serum urate. Our findings are consistent with previous reports generated in populations followed later in life and provide additional support to the hypothesis that higher levels of serum urate play a role in the development of hypertension.

Disclosure: A. L. Gaffo: None; **D. R. Jacobs:** None; **F. Sijtsma:** None; **C. E. Lewis:** None; **T. R. Mikuls:** None; **K. G. Saag:** Savient Pharmaceuticals, 5, Takeda Pharmaceuticals North America, 5.

ACR Concurrent Abstract Sessions
Imaging of Rheumatic Disease: X-ray and MRI
Tuesday, November 9, 2010, 2:30 PM–4:00 PM

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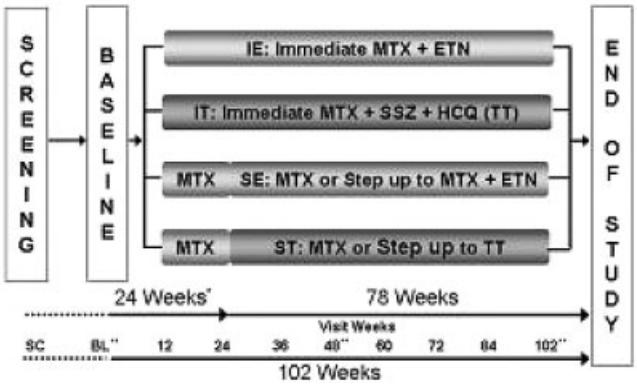
Two-Year Radiographic Results from the TEAR Trial. Larry W. Moreland[7], James R. O'Dell[9], Harold E. Paulus[1], Jeffrey R. Curtis[8], Joan M. Bathon[3], E. William St Clair[2], S. Louis Bridges[6], Xiao Zhang[5], George Howard[5], Desiree M. Van Der Heijde[4], Stacey S. Cofield[5] and for the TEAR Trial Investigators. [1]Encino, CA, [2]Duke University, Durham, NC, [3]Johns Hopkins Univ Ste, Baltimore, MD, [4]Leiden University Medical Center, Meerssen, The Netherlands, [5]The University of Alabama at Birmingham, [6]Univ of Alabama-Birmingham, Birmingham, AL, [7]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [8]University of Alabama-Birmingham, Birmingham, AL, [9]University of Nebraska Medical Center, Omaha, NE

Statement of Purpose: To describe radiographic results of the Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) Trial, two-year, longitudinal, multi-center, randomized clinical trial that enrolled 755 early rheumatoid arthritis (RA) participants, comparing immediate combination treatment groups versus step-up from methotrexate (MTX) alone.



*For SE: ETN or ST: SSZ + HCQ added at week 24 if DAS ≥ 3.2.
**X-Rays of hands and feet at BL = Baseline, Weeks 48 and 102.

Figure 1. TEAR Study Protocol

Methods: Participants that were enrolled in TEAR from 2004–2007 with early RA (≤3 years). In addition to demographic and clinical measures, hand/foot radiographs were obtained at weeks 0, 48 and 102 and scored using the modified Sharp/van der Heijde scoring system.

Results: A total of 755 participants were enrolled in TEAR with 476 (63%) completing 102 weeks. As of June 2010: 474 (99.6%) baseline films and 297 completed films sets have been scored (62% of all completers). At baseline, the mean radiographic score was 6.2±15.0 units (median 2, IQR 0.5–6.0) and 22.2% had no damage (p = 0.30 by treatment group); 25.7% had no erosions, 66.9% had no joint space narrowing (p = 0.15 by group). The 297 with week 0 and 102 scores had a mean baseline score 5.4±12.7 (median 2, IQR 0.5–6.0, similar to entire cohort, p = 0.11); 19.5% had no damage.

Table 1. Mean Radiographic Scores for Completers Cohort (N=297)

		Observed Mean ± SD (% without damage)		Baseline Adjusted Change, Week 102-0		
Group	N	Week 0	Week 102	Mean ± SD	95% CI	p-value
IE	105	7.2 ± 19.8 (21.9)	7.9 ± 20.5 (11.5)	0.6 ± 4.2	−0.6, 1.7	0.6884
IT	45	4.4 ± 5.5 (17.8)	7.1 ± 14.8 (11.4)	2.7 ± 12.6	0.9, 4.5	
SE	106	4.1 ± 5.8 (20.8)	4.7 ± 6.1 (8.0)	0.6 ± 2.1	−0.8, 1.8	
ST	41	5.3 ± 7.2 (12.2)	7.4 ± 10.1 (4.0)	2.1 ± 6.4	0.2, 4.0	
By Treatment Only						
ETN + MTX	211	5.7 ± 14.5 (21.3)	6.2 ± 15.2 (9.7)	0.6 ± 3.3	−0.2, 1.4	0.0180
TT	86	4.9 ± 6.3 (15.1)	7.3 ± 12.7 (7.7)	2.4 ± 10.1	1.1, 3.7	
By Timing Only						
Immediate	150	6.4 ± 16.8 (20.7)	7.6 ± 19.0 (11.5)	1.6 ± 7.7	0.6, 2.6	0.8059
Step-Up	147	4.5 ± 6.1 (18.4)	5.4 ± 7.5 (6.7)	1.4 ± 3.9	0.4, 2.5	
All	297	5.4 ± 12.7 (19.5)	6.5 ± 14.5 (14.5)	1.1 ± 6.1	0.4, 1.8	NA

At week 102, the completers cohort had a mean score 6.5±14.5 (median 3, IQR 1.0–7.5), 9.1% had no damage; 10.8% with no erosions, 40.3% with no joint space narrowing. The mean increase from week 0 to 102 was 1.1±6.1 (median 0, IQR 0–1.0) and was not different across the four groups (p=0.69). When only treatment is considered, pooling the two etanercept (ETN) groups and the two triple therapy (TT) groups, to assess main effects, there was a significant difference between those receiving ETN + MTX and TT (increase of 0.6 vs 2.4, respectively; p=0.02). There was no difference by the timing of treatment (immediate versus step-up, p=0.81). The difference between ETN + MTX and TT was also observed in the subgroup of individuals with baseline radiographic damage score > 0 (increase of 0.6 vs 2.8, p=0.02). There was no change at week 102 among patients with no damage at week 0. In addition, 71.4% of participants achieved radiographic remission (change ≤ 0.5), which was not different by the timing or type of treatment. The remaining 38% of x-rays for trial completers are in the process of being scored.

Conclusions: While prior TEAR results showed no significant differences in clinical findings as assessed by DAS28, this preliminary analysis

showed that treatment with ETN + MTX resulted in statistically significant radiographic benefit over TT, regardless of timing of treatment. All results to be updated to the full 476 completion cohort.

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Development and Validation of an MRI Joint Space Narrowing Score for Use in Rheumatoid Arthritis: A Potential Adjunct to the OMERACT RA MRI Scoring System. Mikkel Østergaard[4], Pernille Bøyesen[5], Iris Eshed[10], Frédérique Gandjbakhch[7], Siri Lillegraven[5], Paul Bird[6], Violaine Foltz[8], Annelies Boonen[9], Marissa N. Lassere[12], Kay-Geert Hermann[2], Allen Anandarajah[16], Uffe Møller Døhn[3], Jane Freeston[15], Charles G. Peterfy[11], Harry K. Genant[14], Espen Haavardsholm[5], Fiona M. McQueen[13] and Philip G. Conaghan[1]. [1]Chapel Allerton Hospital, Leeds, United Kingdom, [2]Charité University Hospital, Berlin, Germany, [3]Copenhagen University Hospitals at Hvidovre and Glostrup, Denmark, [4]Copenhagen University Hospitals at Hvidovre and Glostrup, Hvidovre, Denmark, [5]Diakonhjemmet Hospital, University of Oslo, Oslo, Norway, [6]Division of Medicine, St. George Hospital, University of NSW, Sydney, Australia, [7]Hôpital Pitié-Salpétrière, Université PARIS VI-UPMC, Paris, France, [8]Hôpital Pitié-Salpétrière, Université PARIS VI-UPMC, Paris, France, [9]Maastricht University Hospital, Maastricht, [10]Sheba Medical Centre, Tel Aviv University, Tel Aviv, Israel, [11]Spire Sciences LLC, Kentfield, CA, [12]St. George Hospital, University of NSW, Sydney, Kogarah, Australia, [13]University of Auckland School of Medicine, Auckland, New Zealand, [14]University of California San Francisco, Tiburon, CA, [15]University of Leeds, Leeds, UK, [16]University of Rochester, Rochester

Background: Magnetic resonance imaging (MRI) is now frequently being used as an outcome measure in rheumatoid arthritis (RA) clinical trials. The OMERACT RA MRI score (RAMRIS), evaluating bone erosions, bone oedema and synovitis, is generally used in such trials.

Cartilage damage is an important aspect of structural joint damage in RA, and a reliable MRI assessment system of joint space narrowing (JSN), reflecting cartilage damage, would further improve the usefulness of MRI in RA clinical trials.

Objective: The aim of the present initiative was to develop and validate an OMERACT MRI assessment method of JSN in RA, which may be a useful adjunct to the current OMERACT RAMRIS.

Methods: The project, which was undertaken by the OMERACT MRI in inflammatory arthritis group, had 3 phases:

Phase A: Exercise 1 (pilot study): Coronal T1weighted gradient echo MR images of unilateral wrist and MCP-joints from 5 RA patients and 3 controls were scored for JSN at 15 sites in the wrist and each of the 2nd-5th metacarpophalangeal (MCP), without reader pre-training or calibration, by 8 readers (7 readers read once, 1 reader twice), after circulation by DVD.

Phase B: Discussion, review of images and consensus on exact definition and scoring system.

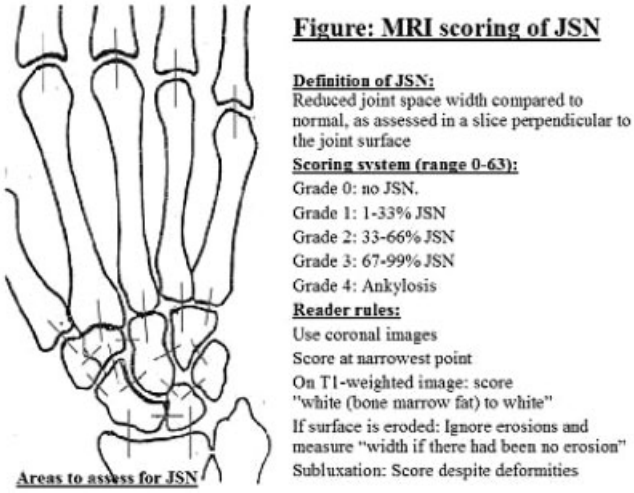
Phase C (Exercise 2): Coronal T1-weighted 3D gradient echo images (voxel size 0.4×0.4×0.4 mm) MR-images of unilateral wrist and 2nd-5th MCP-joints of 15 RA (80% female; age: median 51 (33–78) y, disease duration 7 (4–22) y and 4 controls (75% female; age: median 36 (34–57) y) were scored using a revised score sheet (22 sites, Figure). MRI results were compared with radiographic JSN scores from the same hand (Sharp-van der Heijde method).

Intraclass correlation coefficients (ICCs; single/average measure used for intraobserver/interobserver agreements), and smallest detectable differences (SDDs, for mean of readings) were calculated.

Results: Phase A: Interobserver agreement: ICC 0.93 and SDD 6.4 JSN units (9.9% of observed max). Intraobserver agreement: ICC 0.99 and SDD 2.8 JSN units (4.9% of observed max).

Phase B: Based on experiences from Phase A, agreement was reached on definition, scoring system, and reader rules (Figure).

Phase C: Interobserver agreement: ICC 0.92 and SDD 6.2 JSN units (8.7% of observed max). Intraobserver agreement: ICC 0.90 and SDD: 6.8 JSN units (11.0% of observed max). The correlation (ICC) with the Sharp-van der Heijde radiographic score of JSN in the same hand (which includes MCP-joints, PIP- joints and selected joint areas in the wrist, i.e. not exactly the same joints as the MRI score) was 0.77.



Conclusion: An MRI scoring system of JSN in RA wrist and MCP joints was developed and showed good intra- and interreader agreements. The system may, after further validation in longitudinal data sets, be useful as an outcome measure of cartilage damage in RA, and may thereby further improve the usefulness of MRI in RA clinical trials.

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1370

Patterns of MRI Bone Erosion in Rheumatoid Arthritis—Which Bones Are Most Frequently Involved and Show Most Change? Mikkel Østergaard[3], Uffe Møller Døhn[4], Anne Duer-Jensen[3], Merete L. Hetland[3], Kim Hørslev-Petersen[5], Kristian Stengaard-Pedersen[1], Peter Junker[6], Jan Pødenphant[2] and Bo Ejbjerg[7]. [1]Århus University Hospital, Åarhus, Denmark, [2]Copenhagen University Hospitals at Gentofte, Copenhagen, Denmark, [3]Copenhagen University Hospitals at Hvidovre and Glostrup, Copenhagen, Denmark, [4]Copenhagen University Hospitals at Hvidovre and Glostrup, Copenhagen, Denmark, [5]KIng Christian X's Rheumatism Hospital, University of Southern Denmark, Gråsten, Denmark, [6]Odense University Hospital, Odense C, Denmark, [7]Slagelse Hospital, Denmark

Background: Magnetic resonance imaging (MRI) has been shown to be more sensitive for early bone damage than conventional radiography, and MRI of unilateral wrist and 2nd- 5th metacarpophalangeal (MCP) joints is more sensitive to change for erosive progression than radiography of both hands, wrists and forefeet. However, data on the exact distribution of bone erosions, i.e. the pattern of bone involvement are minimal.

Objective: To investigate which bones in RA wrists and MCP-joints that most frequently show bone erosion and which bones most frequently show erosive progression, in early as well as established RA and during disease-modifying anti-rheumatic drug (DMARD) as well as anti-tumor necrosis factor (TNF) therapy.

Patients and Methods: MRI datasets from 258 RA patients (126 with early RA (disease duration <6 months)) were analysed. 223 patients (126 early RA) had 1-year follow-up MRIs. All patients had MRI of one wrist, whereas 86 had additional MCP-joint images, and 46 had additional images of the contralateral wrist. MRIs were evaluated according to the OMERACT RA MRI scoring system (RAMRIS) for erosions, and presence/absence of erosion at baseline was noted in each bone, as was presence/absence of erosive progression.

Results: The distribution of baseline erosions per wrist bone is shown in Figure 1a, whereas the distribution of bones with progression at year 1 is seen in Figure 1b. The capitate, ulna, lunate, triquetrum and scaphoid were the 5 bones with both most frequent baseline erosion and most frequent erosive progression, whereas metacarpal (M) base 3–4–5 were rarely involved. The patterns were similar in early RA and established RA.

In patients with bilateral wrist MRI available, no apparent major difference between dominant and non-dominant was found (269 versus 277 bones

with baseline erosion; 73 versus 85 bones with erosive progression). In the patients in which both wrist and MCP-joint images were available, baseline erosions were still most frequently found in the 5 previously mentioned wrist bones, whereas the 2nd metacarpal head was the most frequently involved MCP-joint bone.

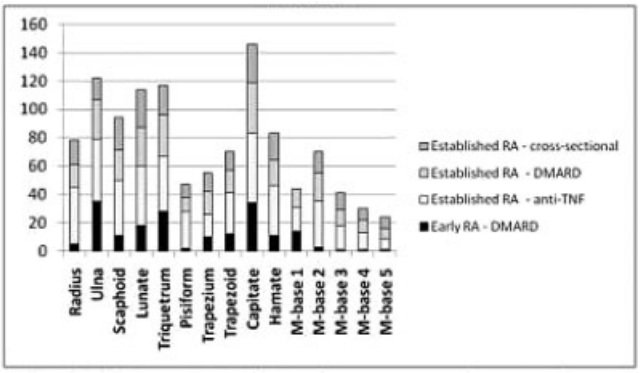

Fig. 1A. Presence of baseline erosion, per bone (n=258).

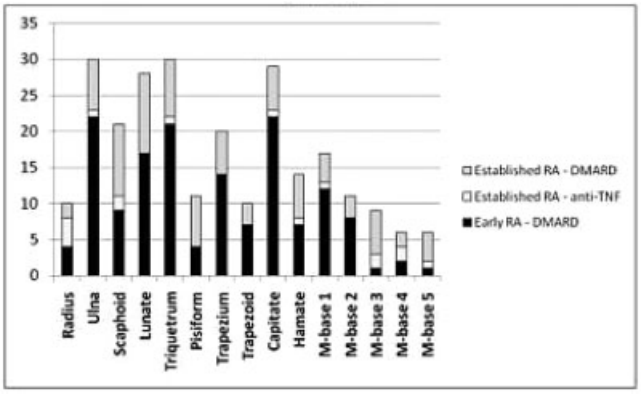

Fig. 1B. Presence of erosive progression, per bone (n=223).

Conclusion: Based on data from 223 RA patients, patterns of MRI bone erosion in RA wrists and MCP joints could be identified. The ulna, scaphoid, lunate, triquetrum and capitate were the most frequently involved bones and showed most change over time. No obvious differences between dominant and non-dominant wrists were identified. Bone involvement patterns should be considered, when joints are selected for MR imaging protocols for clinical trials and practice.

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1371

MRI-Proven Bone Edema of Wrist and Finger Joints at Entry Is the Strongest Predictor toward Further Radiografic Progression in Patients with Undifferentiated Arthritis: Results from the Prospective Cohort at Nagasaki University. Junko Kita[7], Atsushi Kawakami[7], Mami Tamai[1], Naoki Iwamoto[7], Shin-ya Kawashiri[8], Kazuhiko Arima[2], Akitomo Okada[7], Tomohiro Koga[7], Satoshi Yamasaki[7], Hideki Nakamura[7], Tomoki Origuchi[5], Kiyoshi Aoyagi[3], Masataka Uetani[4] and Katsumi Eguchi[6]. [1]Center for Health & Community Medicine, Nagasaki University, Nagasaki, Japan, [2]Department of Medical Gene Technology, Atomic Bomb Disease Institute, Nagasaki University Graduate School of BIomedical Sciences, [3]Department of Public Health, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan, [4]Department of Radiology and Radiation Research, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan, [5]Nagasaki University School of Health Sciences, Nagasaki University, Nagasaki, Japan, [6]Sasebo City General Hospital, Sasebo, Nagasaki, [7]Unit of Translational Medicine, Department of Immunology and Rheumatology, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan, [8]Unit of Translational Medicine, Department of Immunology and Rheumatology, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan

Purpose of Study: We have published the importance of autoantibodies and MRI-proven joint damages of wrist and finger joints toward the prediction of development of rheumatoid arthritis (RA) from undifferentiated arthritis (UA) in Arthritis Rheum 2009: 65; 751–8. By using the same patients population, we have tried to find what variables at entry are able to predict the further plain radiografic progression in patients with UA.

Methods: Our cohort included 129 patients of UA. In the present study, we have focused on the 75 out of 129 patients who developed RA at 1 year. Among 75 patients, all of the follow-up data, including serial plain radiography of both hands, were completed in 58 patients. We have examined, by univariate and multivariate analyses, to determine what variables at entry predict the plain radiographic progression at 2 years calculated by Modified Genant Sharp score. Annual progression value greater than 1 was considered as plain radiografic progression.

Results: After the follow-up of 2 years, eighteen patients were classified as having plain radiografic progression (progression group) whereas 40 were not (non-progression group). The multiple logistic regression analysis was conducted to determine the independent effects of variables on radiographic progression. The variables were included in the model if the p value was less than 0.20 in univariate analyses. Duration of morning stiffness, CRP, DAS28-CRP, MMP-3, anti-CCP antibodies, RF, MRI-proven symmetrical synovitis and MRI-proven bone edema were selected. Logistic regression analysis have revealed that MRI-proven bone edema is the first (p=0.023, Odds ratio 13.84) and RF is the second (p=0.049, Odds ratio 6.65) predictors toward plain radiografic progression.

Conclusions: Our data suggest that bone edema of wrist and finger joints at entry is the strongest predictor toward further radiografic progression in patients with UA.

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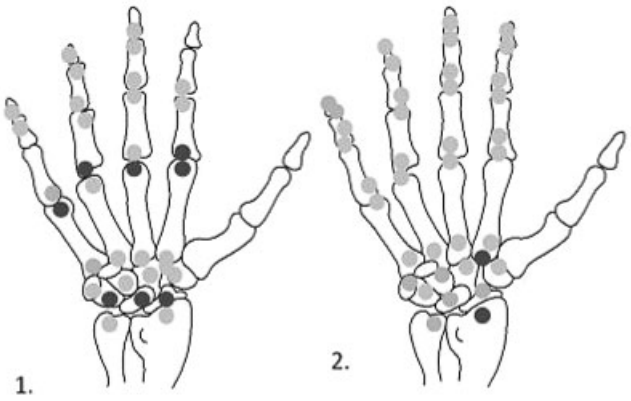
1372

Zoledronic Acid Does Not Reduce Erosive Progression in PsA but May Suppress MRI Bone Oedema. Richard Lloyd[3], Anthony Doyle[3], Nicola Dalbeth[3], Maria Lobo[1], Elizabeth Robinson[5], William Taylor[6], Peter Jones[2] and Fiona M. McQueen[4]. [1]Auckland District Health Board, [2]QEHealth, [3]Univ of Auckland, [4]Univ of Auckland Sch of Med, Auckland, New Zealand, [5]University of Auckland, [6]University of Otago

Magnetic resonance imaging (MRI) can reveal bone pathology in psoriatic arthritis (PsA). Zoledronic acid (ZA) inhibits osteoclast maturation, recruitment to sites of bone resorption and mature osteoclast function. We sought to investigate its effect on bone pathology in PsA using MRI scanning.

Methods: 26 PsA patients (mean age 49 yrs, disease duration 15 yrs) received either 4mg of zoledronic acid (ZA) IV 3 monthly for 1 year or placebo in a blinded manner. A second control group received MRI scans alone (no drug/placebo due to patient concern about risk of side-effects). Paired baseline and 1 year 1.5T MRI scans of the dominant wrist and fingers, using sequences as published (1), were available in 6 ZA and 16 non-ZA (6 placebo) patients for further analysis.

Results: Median MRI erosion scores increased over 12 months but did not differ between groups (ZA group, 35.0 to 39.5; non-ZA group 44.5 to 45.5). However, bone edema scores decreased in the ZA group (15.5 to 8.5) but increased in the non-ZA group (14.0 to 18.0) (p= 0.0056). A site-by-site analysis (maximum of 38 sites for bone oedema and erosion per patient) revealed regression of bone edema at 13.5% of sites in the ZA group compared with 1.3% of sites in the non-ZA group (p = 0.0073) and progression in 1.3% ZA patients compared with 6.9% non-ZA patients (p = 0.072). For bone erosion there was progression at 5.5% of sites in the ZA patients compared with 5.3% in non-ZA patients and regression in 2.6% and 0% of sites respectively (p = NS for all). Bone sites are shown coded as follows: bone edema regression (red), progression (green) and no change (yellow) in 1) a ZA patient and 2) a non-ZA patient.



Conclusions: In this pilot study, there was no evidence that ZA influenced the progression of bone erosions in PsA. However, bone edema scores and number of involved sites fell over 1 year in ZA-treated patients, indicating potential suppression of osteitis. Further studies may be indicated to explore the therapeutic effect of ZA in PsA.

1) Tan et al. Arthritis Research & Therapy. 11(1):R2, 2009.

Disclosure: R. Lloyd: None; **A. Doyle:** None; **N. Dalbeth:** None; **M. Lobo:** None; **E. Robinson:** None; **W. Taylor:** None; **P. Jones:** None; **F. M. McQueen:** None.

1373

Cartilage Damage and Osteophytes: MRI-Defined Atrophic and Hypertrophic Phenotypes of Knee Osteoarthritis in the Framingham Cohort.
Frank Roemer, Ali Guermazi, Jingbo Niu, Yuqing Zhang and David Felson, Boston University

Purpose: Osteophytes (OPs) are a common feature of moderate to advanced radiographic osteoarthritis (OA). It is not known to what extent advanced cartilage damage detected by magnetic resonance imaging (MRI) correlates with severity of osteophyte formation. On the other hand, it is not known if knees without severe cartilage damage exhibit large osteophytes t.

Our purpose was to describe the prevalence of osteophytes and concomitant cartilage damage in a population-based cohort using semi-quantitative MRI assessment. Focus of the investigation were a.) knees with severe cartilage damage and no or tiny concomitant osteophytes and b.) knees without substantial cartilage damage but with large OPs in order to characterize the atrophic and hypertrophic phenotypes of knee OA respectively.

Methods: Participants of the Framingham Knee Osteoarthritis Study were examined with a 1.5 T MRI system. Cartilage and OPs were assessed according to the WORMS scoring system. "Severe" cartilage damage was defined as cartilage morphology (CM) scores of 5 or 6 in at least 2 of 10 TF subregions. "Without substantial" cartilage damage was defined as none of 10 TF subregions exhibiting CM scores ≥3. Large OPs were defined as OPs grade 5–7. Absent or tiny OPs were defined as OP scores 0–2.

We first calculated the overall prevalence of knees with severe cartilage damage and described concomitant OP status. The odds ratios (OR) of severe cartilage damage according to OP size were estimated using a logistic regression model. Further the association of large OPs according to ROA status was analyzed. In addition we focused on knees with absent or only tiny osteophytes in all 10 TF subregions but with severe cartilage damage as defined above (atrophic phenotype) and knees with large osteophytes and without substantial cartilage damage (hypertrophic phenotype).

Results: 1597 knees of 1248 subjects were included. Mean age was 63.9 years, mean BMI 28.9, 58.3% were women. 197/246 (80.1%) knees with severe cartilage damage exhibited large OPs. The risk of severe cartilage damage increased in a linear fashion with increasing OP size when using the knees without or only tiny osteophytes as the reference. 21 knees showed an atrophic phenotype. Only 3 knees exhibited a hypertrophic phenotype.

Table 1. Association of osteophyte size with risk of severe cartilage damage

Osteophyte status	Subregions with severe cartilage damage[1] n/N (%)	Crude model Odds ratio [95% CI]	Model adjusting age, sex, BMI, race, TF radiographic OA Odds ratio [95% CI] p-value
OPs absent (max. OP size 0–1)	1/498 (0.2)	1.0 (reference)	1.0 (reference)
OPs present (max OP size 2–7)	172/1099 (15.7)	92.9 [16.3, 528.9]	10.6 [1.8, 63.8] <.001*
Maximum OP size: 0 (reference)	1/498 (0.2)	1.0 (reference)	1.0 (reference)
2	20/704 (2.8)	17.1 [1.9, 157.2]	4.2 [0.6, 28.4] 0.15
3–4	98/328 (29.9)	247.3 [27.7, 2208.5]	14.6 [2.2, 98.2] 0.006*
5–7	54/67 (80.6)	2378.1 [249.8, 22,643.4]	108.8 [14.2, 834.9] <0.0001*
p-value for linear trend			<0.0001*

* statistically significant, defined as $p<0.05$
† severe cartilage damage defined as WORMS cartilage morphology scores of 5–6 in ≥2 of 10 TF subregions

Conclusion: The majority of knees with severe TF cartilage damage exhibit moderate to large TF OPs. A linear increase in risk of severe cartilage damage was observed with increasing OP size. A minority of knees exhibits the so-called atrophic phenotype, which also includes knees without ROA. The hypertrophic phenotype is extremely rare. MRI-based prevalence data on the different types of OA phenotypes contributes to understanding disease pathology.

Disclosure: F. Roemer: Boston Imaging Core Lab, 4; **A. Guermazi:** Boston Imaging Core Lab, 2, 4, 5, Facet Solutions, 2, 4, 5, General Electric, 2, 4, 5, Genzyme Corporation, 5, Merck Serono, 2, 4, 5, Novartis Pharmaceuticals Corporation, 5, Stryker, 2, 4, 5, Synarc, Inc., 1; **J. Niu:** None; **Y. Zhang:** None; **D. Felson:** None.

ACR Concurrent Abstract Sessions
Muscle Biology, Myositis and Myopathies: Insights into the Pathogenesis and Outcomes of Myositis
Tuesday, November 9, 2010, 2:30 PM–4:00 PM

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The Influence of Regulatory T-Cell Deficiency and Endogenous Muscle Tissue Antigens on the Development of Inflammatory Myopathy in Mice.
N. A. Young, R. Sharma, B. Kaffenberger, A. Friedman and W. N. Jarjour, The Ohio State University Medical Center, Columbus, OH

Background: Myositis is characteristically associated with an inflammatory process that results in pronounced muscle weakness. Myositis is observed in some regulatory T-cell (Treg) deficient mouse models. Scurfy mice lack Treg due to mutation in the X-linked forkhead box P3 (Foxp3) and develop multi-organ inflammation with little inflammation involving muscle tissue. Multiorgan inflammation but not muscle inflammation could be induced in RagI knockout (KO) recipient mice upon intravenous (IV) or intraperitoneal (IP) adoptive transfer of Scurfy lymph node (LN) cells. However, injecting scurfy cells intramuscularly (IM) induces severe inflammation in skeletal muscle suggesting that release of muscle antigen due to injury is a predisposing factor in triggering of muscle inflammation. To investigate the role of muscle antigens and Treg deficiency in the development of muscle inflammation, we crossed scurfy mice with synaptotagmin (Syt) VII deficient mice. The Syt VII mutation results in impaired membrane resealing and has been shown to lead to limited inflammation of muscle.

Methods: Syt VII KO mice were bred with scurfy mice to produce Syt VII/Foxp3 double KO males. Genotyping was performed by PCR analysis of tail clippings and tissue was collected to analyze by H&E staining. LN cells from double KO or Foxp3 single mutant mice were used for injection into RagI KO males through IM and/or IP routes. In conjunction with the IP injection, some mice received muscle cell extract along with LN cells from scurfy mice. Skeletal muscle tissue was collected and analyzed as above.

Results: Double KO mice with Syt VII/Foxp3 mutations developed more severe myositis compared to mice with either mutation alone. Furthermore, IP adoptive transfer of double KO LN cells induced dramatic myopathology in RagI KO recipients. Conversely, a notably limited infiltrate was seen in the skeletal muscle of Rag1 KO mice that received LN cells from Syt VII

sufficient scurfy mice. The muscle antigen effect was then examined through IP adoptive transfer of scurfy LN cells into RagI KO recipients with and without muscle tissue cell extract. These results were compared to RagI KO recipients of scurfy LN cells by IM injection, which readily exhibit severe muscle inflammation. Inflammatory myopathy could only be induced in the RagI KO recipients through IP injection of scurfy LN cells if the mice were co-injected with muscle extract.

Conclusions: This mouse model of myositis illustrates the interplay between two genetic defects in establishing a robust inflammatory process involving the muscle and that regulatory T cells are critical in limiting inflammation in muscles. The results suggest that endogenous muscle tissue antigen exposure either through injection of muscle extract or through leakage of endogenous antigen due to Syt VII mutation is essential in priming autoreactive cells. We have established a novel, reproducible model to study myositis that will be useful to define new autoantigens. Furthermore, extensions of this model can be used to investigate autoimmune phenomena that are triggered by extrinsic factors such as ultraviolet light or exposure to certain drugs.

Disclosure: N. A. Young: None; **R. Sharma:** None; **B. Kaffenberger:** None; **A. Friedman:** None; **W. N. Jarjour:** None.

1375

Blockade of TNFα or IL-1 Ameliorates Established C-Protein Induced Myositis of Mice. Takahiko Sugihara[2], Naoko Okiyama[2], Naoto Watanabe[2], Nobuyuki Miyasaka[1] and Hitoshi Kohsaka[1]. [1]Department of Medicine and Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan, [2]Department of Medicine and Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Japan

Objective: Histological studies of the muscle biopsy specimens suggest that inflammatory cytokines are involved in pathology of inflammatory myopathy. Therapeutic effects of their blockade are controversial with anecdotal reports of clinical efficacy. Systematic pre-clinical studies can be performed by use of animal models. In this regards, C-protein induced myositis (CIM) was established recently as a murine model of polymyositis (PM). Unlike previous models, it represents pathology of PM closely since cytotoxic CD8 T cells are responsible for muscle injury. Using this model, significance of two inflammatory cytokines, interleukin (IL)-1 and tumor necrosis factor (TNF)α was studied as therapeutic targets of the myositis.

Methods: C57BL/6 mice were immunized with recombinant C protein fragments. IL-1 and TNF expression in the CIM muscles was evaluated with immunohistochemistry and real-time PCR. After onset of the myositis, CIM mice were treated with IL-1 receptor antagonist (IL-1ra), anti-IL-1 receptor monoclonal antibody (IL-1R mAb) and TNF receptor (p75)-fused with IgFc (TNFRFc), provided by Amgen as well as with anti-TNFα monoclonal antibody (TNFα mAb), provided by Centocor. Following completion of treatment, the muscles from the treated animals were examined for histological scoring.

Results: IL-1 and TNFα mRNA was expressed in the muscles as early as 7 days after the immunization. This was when mononuclear infiltration and muscle necrosis became appreciable. Their expression was up-regulated at the peak of the myositis. These cytokines were expressed primarily by infiltrating macrophages. To inhibit them in vivo, IL-1ra (0.24, 0.8 and 2.4 mg/day/mouse) was administered continuously with mini-pumps implanted subcutaneously for a week, starting 7 days after the immunization. These treatments suppressed pathology of CIM. While the continuous IL1ra delivery of 0.8 mg/day/mouse was effective (a total of 5.6 mg/mouse), intermittent intraperitoneal injections (three times a week) of a total of 7.2 mg/mouse were not. In contrast, intraperitoneal injections of anti-IL-1R mAb (100 mg and 50 mg/mouse) with the same intermittent protocol succeeded in ameliorating CIM. Next, anti-TNFα mAb (50, 200 and 500 mg/mouse) and TNFRFc (100 mg/mouse) were administered intraperitoneally three times a week for 2 weeks. Both of anti-TNF biological reagents suppressed pathology of CIM.

Conclusions: IL-1 and TNF blockade ameliorated ongoing CIM. Blockade of TNFα or IL-1 may be new strategies for treatment of PM. Previously, we reported that CIM developed in TNFα null mice but not in IL-1α/β null mice. Cytotoxic activity of anti-TNFα mAb does not account for this difference because TNFRFc treatment was also effective. TNFα null mice are reportedly susceptible to collagen-induced arthritis, which can be treated with anti-TNFα mAb. This paradoxical sensitivity of TNFα deficient mice to autoimmunity holds true in CIM, which is driven by autoaggressive CD8 T cells. As for the IL-1 blockade, anti-IL-1R mAb appeared clinically more feasible than IL-1ra presumably because of differences in affinity and pharmacokinetics.

Disclosure: T. Sugihara: None; **N. Okiyama:** None; **N. Watanabe:** None; **N. Miyasaka:** None; **H. Kohsaka:** None.

1376

UPR Activation and IFNb Production in Myocytes in Adult and Juvenile Myositis. Ann M. Reed[1], Molly S. Hein[1] and Robert A. Colbert[2]. [1]Mayo Clinic, [2]NIH, NIAMS

Background: The unfolded protein response (UPR) to endoplasmic reticulum (ER) stress in myocytes may contribute to skeletal muscle damage and dysfunction in Inflammatory Myositis (IM). Overexpression of Interferon b (IFNb) has been demonstrated in immune cells in Adult and Juvenile Dermatomyositis (DM JDM), and to a lesser extent in Polymyositis (PM) and Inclusion Body Myositis (IBM), and is hypothesized to contribute to the UPR through upregulation of MHC class I. Since the UPR can contribute to IFNb upregulation in other cell types, we hypothesized that UPR activation in autoimmune myositis might correlate with IFNb expression in myocytes in active disease.

Methods: Intracellular staining of BiP (Grp78/HSPA5), a marker of UPR activation, and IFNb were assessed in muscle biopsy tissue from new onset IM subjects (n=5 each of DM, JDM, PM, IBM and control subjects). Myocyte regeneration marker (MYH3) expression was assessed using immunofluorescence (IF) staining. Co-localization of these proteins and inflammatory cell phenotyping, including CD3 (T cells), CD123 (plasmacytoid dendritic cells (pDCs)), CD4 (T cells and pDCs) and CD19 (B cells), was performed by cell surface staining. Direct comparisons of the number of IF positive cells were normalized per 10X field.

Results: Co-localization of BiP and IFNb expression was seen in 10–25% of the myocytes per high power field (HPF) in all IM subgroups and 20–50% of the mononuclear (MN) cells compared with rare <1% of myocytes and MN cells in control tissue ($p=0.017$ and 0.004). BiP staining in myocytes was seen rarely without IFNb. The IFNb levels were increased in all forms of myositis (JDM 25%, DM 8%, PM 7% and IBM 15%) versus 3% of controls with JDM having the highest values. Regenerating fibers express BiP in 80% of cases. MYH3 co-localized with BiP and IFNb in ~80% of myocytes, with 20% staining for MYH3 alone. BiP+ pDCs were also greater in JDM (average of 44 cells/HPF vs. 6 in controls ($p<0.0001$) and 7 cells/HPF in DM/PM/IBM). IFNb co-localized with pDCs (72 JDM, 23 DM, 25 PM, 15 IBM and 8 control cells per HPF (all groups vs controls $p<0.003$)). The co-localization of BiP and IFNb in myocytes suggests that non-immune cell production of IFNb including regenerating cells, may be important in IM pathogenesis, and that the UPR may contribute to its production, possibly creating a positive feedback loop.

Conclusions: The UPR is associated with Type-I IFN (IFNb) expression in myocytes in several forms of IM.

Disclosure: A. M. Reed: None; **M. S. Hein:** None; **R. A. Colbert:** None.

1377

A New ELISA System for Detecting Autoantibodies to aminoacyl-tRNA Synthetases: Usefulness in Myositis and Interstitial Pneumonia. Ran Nakashima[2], Yoshitaka Imura[4], Shio Kobayashi[3], Yuji Hosono[4], Naoichiro Yukawa[4], Daisuke Kawabata[4], Takaki Nojima[4], Koichiro Ohmura[2], Takashi Usui[4], Takao Fujii[1], Minae Seto[6], Akihiro Murakami[5] and Tsuneyo Mimori[2]. [1]Department of Rheumatology and Clinical Immunology, Kyoto University Graduate School of Medicine, Sakyo-ku Kyoto, Japan, [2]Department of Rheumatology and Clinical Immunology, Kyoto University Graduate School of Medicine, Kyoto, Japan, [3]Department of Rheumatology and Clinical Immunology, Kyoto University Graduate School of Medicine, Kyoto, Japan, [4]Department of Rheumatology and Clinical Immunology, Kyoto University Graduate School of Medicine, [5]Medical and Biological Laboratories CO., LTD, [6]Medical and Biological Laboratories Co., Ltd., Nagano, Japan

Purpose: Autoantibodies to aminoacyl-tRNA synthetases (ARS) are the most frequent myositis-specific antibodies and patients with anti-ARS antibodies show a spectrum of common clinical manifestations known as anti-synthetase syndrome. Detecting anti-ARS antibodies is useful in diagnosis, classification and management of polymyositis (PM)/dermatomyositis (DM) and interstitial pneumonia (IP). Immunoprecipitation assay is utilized currently to detect anti-ARS antibodies but can be

done only in limited numbers of laboratories. For easy detection of anti-ARS antibodies, we established enzyme-linked immunosorbent assay (ELISA) system using a mixture of five known recombinant ARS antigens for detecting anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ and anti-KS antibodies at once.

Methods: We prepared 6 recombinant ARS antigens; GST-Jo-1, His-PL-12, His-EJ and GST-KS expressed in *E. coli*, and His-PL-7 and His-OJ expressed in *Trichoplusia* Hi-5 cells. After confirming antigenic activity of all recombinant proteins except His-OJ using immunoblot and ELISA, we made an ELISA system using mixture of the five recombinant ARS. In order to confirm the efficiency of this newly established ELISA, we screened a total of 241 sera from patients with various connective tissue diseases (PM 57, DM 46 and other diseases 138), 62 from idiopathic IP (IIP) and 30 from healthy controls. The results of ELISA were compared with those of standard RNA immunoprecipitation assay.

Results: Except for one false-negative and two false-positive samples, all of the results on anti-ARS positivity by ELISA were consistent with those by RNA immunoprecipitation. Sensitivity and specificity of the ELISA compared with RNA immunoprecipitation were 97.5% and 99.3%, respectively. Anti-ARS antibodies were detected in 33% (19/57) of PM, 28% (13/46) of DM, 2% (1/49) of SLE, 2% (1/49) of RA and 11% (7/62) of IIP. None of healthy controls was positive for anti-ARS antibodies. Among 32 anti-ARS-positive PM/DM patients, 30 (94%) had IP, 18 (56%) arthralgia, 12 (38%) fever, 12 (38%) Raynaud's phenomenon and 8 (25%) mechanic's hand. Two anti-ARS-positive patients either with SLE or RA revealed IP but no evidence of myositis.

Conclusion: We established the new anti-ARS ELISA system using a mixture of five recombinant ARS antigens and demonstrated that it detected anti-ARS antibodies as efficiently as RNA immunoprecipitation. This system will make possible to detect anti-ARS antibodies in patients with PM/DM and IP more easily and be used widely in daily practice.

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Atherosclerotic Cardiovascular Disease among Hospitalized Dermatomyositis Patients in the US. Eleni Linos[3], David Fiorentino[3], Bharathi Lingala[3], Eswar Krishnan[2] and Lorinda Chung[1]. [1]Stanford Univ Medical Center, Palo Alto, CA, [2]Stanford University, Palo Alto, CA, [3]Stanford University School of Medicine

Purpose: Increasing evidence suggests that atherosclerotic cardiovascular disease is more prevalent among patients with rheumatologic diseases, including rheumatoid arthritis and systemic lupus erythematosus, compared with the general population. Cardiac involvement in patients with dermatomyositis (DM) has been reported and is associated with a poor prognosis, but the prevalence of atherosclerotic cardiovascular disease is unknown. Our aim was to evaluate the prevalence of atherosclerotic cardiovascular comorbidities and their associated mortality risk among hospitalized DM patients in the US.

Methods: We examined the in-hospital frequency and mortality rates of specific diagnoses and procedures associated with atherosclerotic cardiovascular disease among hospitalized adult patients with DM using data from the Nationwide Inpatient Sample (NIS) from 1993 to 2007. The NIS is a national, annual, representative survey of hospitalized patients in the US. The following diagnoses and procedures were identified by ICD-9 codes: coronary artery disease, congestive heart failure, angina, myocardial infarction, and cerebrovascular accidents; coronary artery bypass grafts, coronary catheterization, and percutaneous transluminal coronary angioplasty. We compared the odds of death among hospitalized DM patients with each cardiovascular diagnosis or procedure to those without using logistic regression. Analyses were weighted so results are standardized to the US population as a whole.

Results: A total of 50,323 hospitalizations of DM patients occurred in the US between 1993 and 2007. The mean patient age was 58 years, and 73% of patients were female. Of all DM hospitalizations, 20% were associated with a concurrent atherosclerotic cardiovascular diagnosis or procedure. The overall in-hospital mortality rate was 57 per 1000. DM patients with any of the specified atherosclerotic cardiovascular diagnoses or procedures were twice as likely to die during the inpatient stay compared to DM patients who did not have atherosclerotic cardiovascular disease (OR=2.0 95% CI 1.7–2.5, $p<0.0001$). The highest odds of death were noted for patients with congestive heart failure (OR=2.3 95% CI 1.9–2.8, $p<0.001$) and cerebrovascular accidents (OR=2.3 95% CI 1.7–3.3, $p<0.001$).

Conclusions: In this large US-based hospitalization database, approximately one fifth of hospitalizations in DM patients were associated with an atherosclerotic cardiovascular diagnosis or procedure. These patients have double the risk of in-hospital death, making identification of these groups important for both prognostic purposes and clinical care. Further prospective studies are necessary to confirm our findings and to analyze the relative contribution of disease activity, concomitant risk factors, and corticosteroid treatment.

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Predictors of Response to B Cell Depleting Therapy in Adult and Juvenile Myositis. Ann M. Reed[1], Kelly T. McNallan[1], Cindy S. Crowson[1] and Chester V. Oddis[2]. [1]Mayo Clinic, [2]University of Pittsburgh

Background: Idiopathic inflammatory myopathy (IIM) is associated with significant morbidity and mortality. There are no curative therapies and markers to predict therapeutic response are lacking. Type I interferon (IFN) regulated genes and cytokines/chemokines are known biomarkers of disease activity in IIM and predict response to therapy while autoantibody production and B cell survival factors including BAFF are hypothesized as important biomarkers in IIM. The Rituximab (Rtx) in Myositis (RIM) Study collected longitudinal patient (pt) samples and assessed the efficacy of Rtx in refractory adult polymyositis (PM) and dermatomyositis (DM) and juvenile DM (JDM) pts. We investigated if a biological signature predicts disease responsiveness to B cell depletion (BCD) therapy in the RIM Study.

Methods: Peripheral blood samples and clinical/laboratory data were collected at baseline and 16 and 24 weeks after Rtx in 75 RIM Study pts to: (a) determine biomarkers of disease activity, (b) predict treatment response, and (c) determine whether biomarkers predict disease flare. Multiplexed sandwich immunoassays (Meso Scale Discovery) quantified serum levels of IFN-regulated chemokines and other pro-inflammatory cytokines. B cell regulating factor transcripts were determined by quantitative PCR. Cytokines (IL-1β, IL-2, IL-12, IFNα, MIP1α, MIG and TNF-α), chemokines (MCP-1, MCP-2, ITAC and IP-10) and B cell regulating factors (BAFF, ΔBAFF, APRIL, BAFFR, BCMA, and TACI) were measured. Clinical response and disease activity were assessed utilizing a consensus-driven definition of improvement (DOI) in IIM and the Physician's Global Activity (PGA). Spearman's rank correlation coefficient (r) described the relationship between biomarkers and disease activity/response.

Results: Changes in serum biomarkers correlated with disease activity and response to Rtx. Disease activity measured by PGA at week 16 correlated with IL-12 at week 0 ($r=-0.22$ $p=0.018$), and with change from week 0 to 16 in IL-12 ($r=0.33$; $p<0.001$), IL-1β ($r=0.21$; $p=0.023$), MIG ($r=0.21$; $p=0.025$), and TNF-α ($r=0.20$; $p=0.028$). Predictive treatment responses were detected in pts with higher IL-2 levels at week 0 who had an 80% likelihood of achieving DOI (hazard ratio: 1.84; 95% CI: 1.04, 3.27; $p=0.036$). Serum levels of IFN regulated cytokines and chemokines declined from week 0 to 16 and correlated with change in PGA from week 0 to 16 and predicted responsiveness to Rtx [IL-12 ($r=0.19$; $p=0.04$), IL-1β ($r=0.21$; $p=0.02$), MIP-1α ($r=0.21$; $p=0.02$), TNFα ($r=0.19$; $p=0.03$), ITAC ($r=0.26$; $p=0.007$) and IP-10 ($r=0.24$; $p=0.01$)]. Peripheral blood RNA levels of BAFFR, BCMA, CD20, and TACI decreased significantly between week 0 and 24 and clinical improvement (decrease in PGA) was significantly correlated with change in DBAFF ($r=0.26$; $p=0.01$) and full length BAFF ($r=0.25$; $p=0.022$). Markers of disease worsening, defined by a 10% increase in PGA between weeks 0 and 24, included BCMA/BAFFR ratio ($p=0.04$) and BAFFR/TACI ratios ($p=0.06$).

Conclusion: These studies show that cytokine and chemokine levels correlate with disease activity and physician-assessed worsening and predict response to BCD in adult and juvenile myositis.

Disclosure: A. M. Reed: None; **K. T. McNallan:** None; **C. S. Crowson:** None; **C. V. Oddis:** None.

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Clinical Improvement and Structural Tissue Repair by Joint Distraction, in Treatment of End-Stage Knee Osteoarthritis. F. Intema[2], K. Wiegant[3], P. M. van Roermund[3], A. C. A. Marijnissen[3], S. Cotofana[1], F. Eckstein[1], S. C. Mastbergen[3] and F. P. J. G. Lafeber[3]. [1]Institute of Anatomy and Muscoskeletal Research, Paracelsus Medical University, Salzburg, Austria, [2]Rheumatology & Clinical Immunology, University Medical Center Utrecht, Utrecht, The Netherlands, [3]Rheumatology & Clinical Immunology, University Medical Center Utrecht, The Netherlands

Background: End-stage knee osteoarthritis (OA) is frequently treated by total knee replacement (TKP). In 40% of the cases this expensive treatment is performed under the age of 65 years, while the procedure has a higher risk of failure in younger patients, due to higher physical demands.

Knee joint distraction (KJD) is an experimental treatment for end-stage knee OA, aimed at unloading the joint cartilage and subchondral bone by use of a 'fixateur externe'. The technique proved to be clinically effective for end-stage ankle OA. The present study describes an exploratory, open, uncontrolled trial to verify whether KJD has the potency to postpone a TKP by inducing clinical improvement and cartilage repair.

Methods: Twenty patients, under 60 years of age, with end-stage knee OA were treated with KJD for 2 months. Two monotubes with internal coil springs were placed parallel (medial and lateral) bridging the knee joint and were distracted for 5 mm. Patients were encouraged to load the knee during distraction, in order to achieve intermittent intra-articular fluid pressures. During the treatment most patients (n=17) suffered from single or multiple pin tract infections, all being successfully treated with antibiotics.

After 2 months, tubes and pins were removed, and function was actively practiced.

The primary clinical outcome was pain and function by use of the WOMAC questionnaire. For secondary clinical outcome VAS pain was documented. Primary structural outcome was cartilage thickness by use of quantitative MRI and digital analyses of standardized X-rays. Secondary outcome parameters were MRI determined decrease in area of denuded bone, increase in cartilage area and volume as well as biochemical markers of cartilage. All structural parameters were analyzed blinded.

Results: One year after distraction, the total WOMAC score improved significantly from 45% at baseline to 77% ($p<0.001$). This improvement is supported by a decrease in VAS pain score from 73 to 31 mm ($p<0.001$).

Complementary, quantitative MRI analysis showed an increase in cartilage thickness of the affected compartment from 2.4 to 3.0 mm ($p<0.01$), both femur and tibia. The total area of denuded bone decreased from 22% to 5% ($p<0.01$). Cartilage area and volume increased from 15.6 to 18.9 cm^2 and 2.3 to 2.8 cm^3 (both $p<0.05$).

X-ray analysis corroborated the MRI findings by an increased mean, as well as minimum JSW from 2.7 to 3.6 mm ($p<0.05$) and 1.0 to 1.9 mm ($p<0.01$), respectively.

Increase in cartilage area and thickness and decrease in denuded bone area correlated with the increase in the mean radiographical JSW ($r=0.571$, $r=0.553$, $r=-0.613$ resp. all $p<0.05$)

Long term changes in biomarkers showed a decrease of collagen type II breakdown marker CTXII (−11%; $p=0.04$) and an increase of collagen type II synthesis marker PIIANP (+103%; $p=0.03$). The average change in the ration of PIIANP/CTXII of each patient was in favor of synthesis ($p<0.03$).

Conclusion: In treatment of end-stage knee OA it is proven to induce significant intrinsic joint cartilage repair by use of joint distraction, based on MRI, X-ray and biochemical marker analyses. These significant tissue structure changes are accompanied by clinical improvement in pain and function.

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TNF Blockade during Elective Orthopaedic and Hand Surgery in Arthritis Patients: Friend or Foe? Elisabet Pettersson, Pierre Geborek and Anders Gülfe. Lund University, Dept of Clinical Sciences, Lund, Section for Rheumatology, Lund, Sweden

Background: Data on the risk for surgical site infections (SSI) in patients with inflammatory arthritis who continue TNF blockade perioperatively, compared to those who stop treatment, is sparse and contradictory. Patients withholding treatment may experience a flare in their arthritis, hampering postoperative mobilisation.

Methods: Patients with inflammatory arthritis, admitted to the Dept of Rheumatology, Lund University Hospital, Jan 1st, 2003–Sep 30th, 2009, were evaluated 1–4 weeks preoperatively. Demographic data, previous and current treatment and core set variables of disease activity were recorded. In 2003–2005, infliximab, etanercept and adalimumab were discontinued for 8, 1 and 4 weeks preoperatively and reintroduced 1 week after surgery if there were no infection signs (group A). After Jan 1st, 2006, TNF blockers were continued before and during surgery (group B). Patients were followed up for at least 6 months. Infections were recorded according to the Centers for Disease Control 1992 criteria. Surgical procedures were classified as Foot, Hand, Implant or Other.

Results: There were 312 and 515 procedures in group A and B, respectively. 67% had rheumatoid arthritis, and about 5% each had spondyloarthritis including ankylosing spondylitis, psoriatic arthritis and juvenile idiopatic arthritis in both group A and B. 49 and 48% were on prednisolone, 43 and 51% were on methotrexate, 30 and 37% on biologics, whereof 14 and 21% on biologics + methotrexate in groups A and B, respectively.

Total SSI rate were 12 (3.8%) in group A and 33 (6.4%) in group B. The difference was not statistically significant. When analysed by type of procedure, there were no significant differences, except higher SSI for foot surgery in group B. Total number of infections in the various medication groups were also similar, except higher rates in patients on methotrexate monotherapy in group B; 3.0 vs 8.7%, $p=0.027$. In a multivariate regression model, correcting for various baseline variables, methotrexate without biologics was the only predictor of SSI in groups A and B combined (OR 2.66, 95% CI 1.18–6.02).

Conclusion: We found no overall increased risk for SSI in patients continuing TNF blockade in the perioperative period in our cohort. Higher SSI rates in foot surgery in group B owed to extremely low rates in group A. Methotrexate without biologics was the only medication group with an elevated SSI rate, while biologics and prednisolone were not. However, low event rates preclude firm conclusions.

Disclosure: E. Pettersson: None; **P. Geborek:** None; **A. Gülfe:** None.

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Guided Mesenchymal Stem Cell Layering Technique for Treatment of Osteoarthritis of the Knee. Nathan Wei[1], Sheila Beard[1], Sheila K. Delauter[1], Carla Bitner[1], Rebecca Gillis[1], Laura Rau[1], Colleen Miller[1] and Thomas B. Clark[2]. [1]Arthritis Treatment Center, Frederick, MD, [2]Musculoskeletal Ultrasound, Vista, CA

Current treatments for osteoarthritis of the knee (OAK) relieve pain and improve function somewhat, but do not restore articular cartilage.

While described in animal models, the use of autologous stem cells has not been extensively studied in humans.

We have employed an ultrasound-guided procedure using autologous mesenchymal stem cells, growth factors, and fat matrix (GMSCL) in patients with severe OAK.

Twenty-two patients underwent GMSCL for OAK. They ranged in age from 36 to 84 years. There were 16 men and 6 women. BMI for the patients ranged from 21 to 36.1. Kellgren-Lawrence status was 6 grade II, 10 grade III, and 6 grade IV.

Bone marrow (60 mls) was harvested from the posterior iliac crest and centrifuged to isolate marrow stem cells. In addition, peripheral blood (60 mls) was obtained in order to isolate growth factors in a platelet-rich plasma sample. In addition, 15 mls of subcutaneous fat was also harvested from the flanks.

Ultrasound guided fenestration at joint capsule sites including the joint line, adductor tubercle and medial patellar facet was conducted. Stem cells, platelet-rich plasma subcutaneous fat, and calcium chloride and thrombin were injected into the fenestrated areas and also into the joint.

Post-procedure, patients were placed at both a non-weight-bearing as well as limited weight-bearing protocol using a brace to unload the narrowed compartment for four-six weeks.

There were three treatment failures defined as patients who did not improve above baseline.

The following is a summary of results at baseline, six months, and twelve months in evaluable patients at the time of abstract submission.

Patient Pain VAS
Baseline - (22 pts) 36.1 6 Months - (11 pts) 15.6 12 Months - (8 pts) - 11.7
Patient Global Assessment of Disease
Baseline - (22 pts) 34.4 6 Months - (11 pts) 21.4 12 Months - (8 pts) - 13.1
Physician Global Assessment
Baseline - (22 pts) 72.3 6 Months - (11 pts) 28.6 12 Months - (8 pts) - 16.1
50 Foot Walk Pain
Baseline - (22 pts) 27.7 6 Months - (11 pts) 14.6 12 Months - (8 pts) - 8.4
WOMAC
Baseline - (22 pts) 27.1 6 Months - (11 pts) 13.7 12 Months - (8 pts) - 8.0

Ultrasound measurement of patellofemoral cartilage thickness at 7 standardized points (medial to lateral) was performed. Reproducibility error was reduced by confirming the original site and repeating measurements three times. Measurements showed:

Mean improvement from baseline to 6 months (11 pts) - 0.4 mm
Mean improvement from baseline to 12 months (8 pts) - 0.8 mm

While it is an uncontrolled study, GMSCL demonstrates some promise as a treatment for OAK. Further study is recommended.

Disclosure: N. Wei: None; **S. Beard:** None; **S. K. Delauter:** None; **C. Bitner:** None; **R. Gillis:** None; **L. Rau:** None; **C. Miller:** None; **T. B. Clark:** None.

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Increased Fat Mass Is Associated with High Levels of Low Back Pain Intensity and Disability. Donna Urquhart[4], Patricia Berry[4], Anita Wluka[4], Boyd Strauss[3], Yuanyuan Wang[4], Joseph Proietto[5], Graeme Jones[2], John Dixon[1] and Flavia Cicuttini[4]. [1]Baker IDI Heart and Diabetes Institute, [2]Menzies Research Institute, [3]Monash Medical Centre, [4]Monash University, [5]University of Melbourne

Background: The relationship between obesity and low back pain and disability is unclear. No study has examined the role of body composition in low back pain and disability. The aim of the study was to determine whether body composition is associated with low back pain intensity and/or disability in a cross sectional study.

Methods: 135 participants (25 to 62 years), with a range of body mass indicies (BMI) (18 to 55 kg/m^2), were recruited for a study examining the relationship between obesity and musculoskeletal disease. Participants completed the Chronic Back Pain Grade Questionnaire, which examines individuals' levels of low back pain intensity and disability. Body composition was assessed using dual x-ray absorptiometry.

Results: BMI was associated with higher levels of back pain intensity (Odds ratio (OR) 1.35, 95% CI 1.09, 1.67) and disability (OR 1.66, 95% CI 1.31, 2.09). Higher levels of pain intensity were positively associated with total (1.19, 95% CI 1.04, 1.38) and lower limb fat mass (OR 1.51, 95% CI 1.04, 2.20), independent of lean tissue mass. There were also positive associations between higher levels of low back disability and total (OR 1.41, 95% CI 1.20, 1.67), upper (OR 1.67, 95% CI 1.27 2.19) and lower limb (OR 2.29, 95% CI 1.51, 3.49) fat mass. Similar relationships were observed with trunk, android and gynoid fat mass. After adjusting for confounders, no measures of lean tissue mass were associated with higher pain intensity or disability ($p>0.10$).

Conclusions: Greater fat, but not lean tissue mass, was associated with high levels of low back pain intensity and disability. While this needs to be confirmed in longitudinal studies, it suggests that weight loss strategies aimed at reducing fat mass may be important in the prevention of low back pain and disability. Understanding the mechanism for these relationships may provide novel approaches to managing low back pain.

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Creatine Supplementation Associated to Resistance Training in Post-Menopausal Women with Knee Osteoarthritis Improves Physical Function: A Randomized, Double-Blinded, Placebo-Controlled Clinical Trial. Manoel Tavares Neves Junior[1], Bruno Gualano[2], Hamilton Roschel[2], Marcelo Tatit Sapienza[2], Fernanda Rodrigues Lima[2], Ana Lucia de Sa Pinto[2], Ricardo Fuller[2], Rosa Maria Rodrigues Pereira[2], Antonio Herbert Lancha Junior[2] and Eloisa Silva Dutra de Oliveira Bonfa[2]. [1]Universidade de Sao Paulo, Sao Paulo, SP, Brazil, [2]Universidade de Sao Paulo

Background: Quadriceps muscle strength is associated with functional impairment in osteoarthritis (OA), reinforcing the relevance of strategies to optimize muscle strength in this disease. Creatine supplementation has been found to significantly increase muscle strength and hypertrophy in adults, particularly when associated with a resistance training regime.

Methods: We conducted a randomized, double-blinded, placebo-controlled trial investigating the efficacy and safety of creatine (CR) supplementation in sedentary post-menopausal women (50–65 years old) with knee osteoarthritis (grades II and III) submitted to resistance training. Subjects ($n=16$) were randomly allocated to receive treatment with either CR (5 g day-1 over 3 months) or placebo (PL) (dextrose). All of the subjects undertook moderate intensity resistance training, three times a week for three months. The patients were submitted to a physical function test (timed-stands test - measured by the number of repetitions performed over time), lower limb maximum dynamic strength test (1RM), body composition using a dual energy X-ray absorptiometry and renal function assessed by 51Cr-EDTA clearance before and after the training period. Data were analyzed by a mixed model for repeated measures.

Results: Functional testing revealed a significant improvement (pre to post) in the timed-stands test for the CR group (16.6 $\pm$ 1.06 vs. 19.1 $\pm$ 1.83 repetitions, $p=0.02$) while no change was observed for the PL group (15.1 $\pm$ 1.45 vs. 16.7 $\pm$ 1.11 repetitions, $p=0.17$). Additionally, between-group comparison revealed a statistically significant difference for CR when compared to PL ($p=0.03$). Body composition data showed a significant increase over time (pre to post) in total body weight (64.7 $\pm$ 7.65 vs. 67.1 $\pm$ 7.15 kg, $p=0.02$) and lean mass (39274.78 $\pm$ 5384.17, vs. 40595.16 $\pm$ 4932.96 g, $p=0.01$) for the CR group, whereas the PL group showed no alteration in any of the body composition parameters ($p=0.95$ and $p=0.99$, respectively). Moreover, 1RM significantly improved in both, CR (81.25 $\pm$ 16.71 vs. 98.83 $\pm$ 16.22 kg, $p=0.02$) and PL (85.98 $\pm$ 19.43 vs. 106.10 $\pm$ 27.43 kg, $p=0.01$) groups, thus indicating the efficacy of the training protocol in improving strength. Finally, renal function remained stable throughout the study (pre to post) for CR (88.00 $\pm$ 17.11 vs. 88.65$\pm$16.45 mL/min/1.73 m2, $p=0.89$) and PL (83.43$\pm$6.62 vs. 83.0$\pm$5.29 mL/min/1.73 m2, $p=0.99$) groups, with no between-group differences. Creatine supplementation had no side-effects.

Conclusion: Our findings highlight that creatine is a promising treatment to help OA patients to perform daily living tasks since it safely improves lean mass and function. The underlying mechanism probably involves an additive effect of the CR supplementation and resistance training on the increase in muscle mass and work capacity, thus ameliorating muscle function. Clinical Trial Identification-NCT00749983

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Role of Central Sensitization in Persistent Pain Post-Knee Replacement: The MOST Study. Tuhina Neogi[3], Jingbo Niu[4], Laura Frey-Law[9], Lars Arendt-Nielsen[1], Jasvinder Singh[8], Joachim Scholz[2], Clifford Woolf[2], Irina Tolstykh[7], Jessica L. Maxwell[4], Barton Wise[6] and David T. Felson[5]. [1]Aalborg University, Denmark, [2]Boston Childrens Hospital, [3]Boston Univ Schl of Med, Boston, MA, [4]Boston Univ School of Medicine, Boston, MA, [5]Boston University School of Medicine, Boston, MA, [6]UCDavis, Sacramento, CA, [7]UCSF, [8]University of Alabama at Birmingham, Minneapolis, MN, [9]University of Iowa

Purpose: Pain persists post-knee replacement (KR) in ~20–30% of patients. The reason for this pain persistence is unclear. One possibility is that long-standing mechanical and inflammatory stimuli in osteoarthritis (OA) can lead to changes in the peripheral and central nervous system, with subsequent peripheral and central sensitization resulting in heightened pain sensitivity. We hypothesized that central sensitization may be associated with persistent pain post-KR.

Methods: The Multicenter Osteoarthritis (MOST) Study is cohort study of persons with or at high risk of knee OA. This analysis was limited to those with KR at any time during the study, confirmed by medical records and/or x-ray. At the 60-month clinic visit, participants had knee x-rays, answered a knee-specific WOMAC pain questionnaire, and had temporal summation (TS) assessed at the wrist. TS is an augmented pain response to repetitive mechanical stimuli thought to reflect central sensitization. TS was defined as being present when, after touching the skin with a 60g monofilament repeatedly at a frequency of 1Hz for 30 seconds, the subject reported increased pain at the site being tested. For cross-sectional analyses, we defined

presence of knee pain (of the KR knee) as moderate or greater pain vs none/mild based on the maximal score of any of the 5 WOMAC pain questions. For longitudinal analyses, we defined knee pain improvement post-KR as a decrease of ≥5.6/20 in WOMAC pain (of the KR knee) from pre- to post-KR (Escobar, OA&C, 2007) using the closest clinic visits to those time-points. We examined the relation of presence of TS with presence of knee pain among all persons with KR, and with having pain improvement post-KR among those with a new KR during follow-up, using Poisson regression with GEE to obtain prevalence ratios (cross-sectional) and risk ratios (longitudinal). All analyses were adjusted for age, sex, BMI, depressive symptoms, race, clinic site, and time since KR. Only the cross-sectional analysis could be adjusted for catastrophizing due to unstable estimates in the longitudinal analysis.

Results: There were 114 subjects with 151 knees that had a KR at baseline (22) or during follow-up (129) who also had TS measured at the 60-month visit (mean age 71.2, mean BMI 32.9, 74.6% female, mean time since KR 3.7 yrs (range <1–15 yrs)). Maximal WOMAC knee pain was rated as ≥moderate in 26.5% of KR knees. Cross-sectionally, presence of TS was associated with 2.06 times higher prevalence of knee pain compared with no TS (95% CI 1.12–3.79, p=0.02). Pain improvement from pre- to post-KR occurred in 42% of KR knees. In the longitudinal analysis, presence of TS was associated with a 67% lower chance of having a pain improvement post-KR (RR 0.33, 95% CI 0.17–0.63, p=0.0009).

Conclusions: Temporal summation was associated with presence of, and less improvement in, post-KR pain. Central sensitization may therefore partially explain why some individuals have pain persistence post-KR. These findings suggest that consideration for performing KRs earlier in the course of OA, when central sensitization is still potentially reversible, may be warranted.

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ACR Concurrent Abstract Sessions
Rheumatoid Arthritis - Human Etiology and Pathogenesis: RA Human Etiology and Pathogenesis
Tuesday, November 9, 2010, 2:30 PM–4:00 PM

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Thrombin-Activatable Carboxypeptidase B (CPB) Plays a Central Role in Down-Regulating Inflammatory Responses in Rheumatoid Arthritis by Cleaving C5a. Jason J. Song[3], Inyong Hwang[3], Tiffany Wang[4], Annette T. Lee[1], S. Louis Bridges[5], Peter K. Gregersen[1], Lawrence Leung[4] and William Robinson[2]. [1]North Shore-LIJ Research Institute, Manhasset, NY, [2]Stanford Univ School of Med, Stanford, CA, [3]Stanford University, Palo Alto, CA, [4]Stanford University, [5]Univ of Alabama-Birmingham, Birmingham, AL

Purpose: Thrombin-activatable CPB is known to play an anti-fibrinolytic role by removing C-terminal lysine residues from fibrin, thereby preventing the cleavage of fibrin by plasmin. Recently, C3a, C5a, thrombin-cleaved osteopontin, and bradykinin have been identified as additional substrates of CPB. CPB removes arginine residues from the C-terminus of these inflammatory mediators, thereby altering their biological functions. Here we investigate the molecular mechanisms underlying the anti-inflammatory role of CPB in rheumatoid arthritis (RA).

Methods: We evaluated arthritis in CPB−/− mice, osteopontin−/− mice, C5−/− mice, and bradykinin B2 receptor−/− mice after injection of anti-collagen antibody. Arthritis was assessed visually and by caliper measurement of paw thickness daily for 10 days after injections. To determine the effect of CPB on C5a-mediated chemotaxis in vivo, we injected intact C5a or CPB cleaved C5a into mouse peritoneum and assessed neutrophil migration. To study the role of CPB in human RA, CPB and C5a levels were measured in synovial fluids derived from RA and osteoarthritis (OA) patients using commercial ELISA kits. To investigate the role of CPB genetic variants in RA, we genotyped two nonsynonymous CPB2 SNPs (rs1926447 and rs3742264) and evaluated the association with modified Sharp score (MSS) in the SONORA cohort (n=109, 70% female, 100% Caucasian) and the CLEAR Registry (n=118, 100 % female, 100% African-American).

Results: We found that anti-collagen antibody-induced arthritis was much more severe in CPB−/− mice than in wild-type mice. In contrast, C5−/− mice were protected from arthritis, while bradykinin B2 receptor−/− mice and osteopontin−/− mice developed arthritis equivalent in severity to that in wild-type mice. In vivo studies showed that C5a chemotactic effect is decreased with CPB incubation (peritoneal neutrophil of intact C5a vs CPB cleaved C5a; 15.66% vs 5.14%, p<0.01). We found that levels of CPB and C5a are increased in RA synovial fluid compared to OA synovial fluid (CPB 644.2 vs 374.1%, p<0.0001; total C5a 24.0 vs 9.6 ng/ml, p <0.05). CPB level is correlated with C5a level (p<0.01, r=0.41). CPB SNP rs1926447 is associated with radiologic progression of RA: (MSS for CT/TT vs CC; SONORA (year 2), 4.5 vs 8.4, p=0.03; CLEAR I (year 3), 1.8 vs 5.9 p<0.01).

Conclusions: These results suggest that thrombin-activatable CPB plays a critical role in down-regulating inflammatory responses in anti-collagen antibody-induced arthritis, and that CPB exerts its anti-inflammatory effects by cleaving, and thereby inactivating, C5a. We also demonstrate that CPB is elevated in RA synovial fluid, and is associated with synovial C5a level. Our SNP analysis results suggest that CPB variant 1064T (minor allele of rs1926447) that has been reported to produce a CPB protein with a two-fold longer half-life, results in less radiographic damage in Caucasians and African-Americans with RA, further suggesting that CPB plays a central role in down-regulating inflammatory responses in RA.

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1387

The Liver × Receptor (LXR) Regulates Arthritis Fibroblast-Like Synoviocyte NFκB Activity, IL-6 Production and Cell Invasion. Carl Petrus Linge[2], Teresina Laragione[3] and Percio S. Gulko[1]. [1]Feinstein Institutue Med Rsch, Manhasset, NY, [2]The Feinstein Institute for Medical Research, Manhasset, NY, [3]The Feinstein Institute for Medical Research

Background: Fibroblast-like synoviocytes (FLS) produce several pro-inflammatory cytokines, chemokines, and proteases that mediate the development of synovial hyperplasia, inflammatory infiltration, and pannus invasion and destruction of cartilage and bone in rheumatoid arthritis (RA). We have recently determined that the expression and transcriptional activity of the anti-inflammatory nuclear receptor LXRα is down-regulated in the synovial tissues of arthritis-susceptible and erosive DA rats, compared with resistant strains. Furthermore, two recent studies demonstrated that LXR agonists ameliorate rodent models of RA and reduce cytokine levels and joint erosions. Those observations led us to hypothesize that a state of deficient LXRα activity in the arthritic FLS could favor the increased production of pro-inflammatory cytokines such as IL-6 as well as the increased FLS invasive and destructive properties. We tested this hypothesis using an LXR agonist to modulate these cellular functions in FLS from DA rats and RA.

Methods: FLS were isolated from synovial tissues obtained from DA rats 21 days after the induction of pristane-induced arthritis (PIA), and from RA patients. Cells were passaged at least three times before use. The effect of the LXR agonist T0901317 (10 μM) was determined in a) IL-1β-induced (10 ng/ml) IL-6 production (ELISA) using FLS culture supernantants; b) IL-1β-induced NFκB activation using DA FLS transfected with a NFκB luciferase reporter construct; c) FLS invasion using a well-established in vitro model through Matrigel-coated chambers; d) actin cytoskeleton distribution (phalloidin staining), lamellipodia formation and phospho-FAK expression and localization.

Results: T0901317 significantly increased LXR activity as evidenced by a 42-fold up-regulation of SCD1 expression, a known LXR target gene. T0901317 reduced the IL-1β-induced IL-6 production in DA FLS (n=7) by 61% (P≤0.001, Mann-Whitney test). The reduction in IL-6 production also correlated with a significant reduction in the NFκB reporter activity. T0901317 nearly completely blocked DA FLS invasion, reducing it by 99% (P≤0.001, n=8). A nearly identical major effect was observed in RA FLS where a 96% inhibition of invasion was detected (P≤0.001, n=7), compared with control vehicle. The reduced invasion caused by T0901317 was associated with reduced levels of active MMP-2, reduced actin distribution and reduced polarized formation of lamellipodia (including reduced levels of phospho-FAK) both in DA and RA FLS.

Conclusion: This is the first time that LXR is implicated in the regulation of FLS production of IL-6 and FLS invasion. Our data show that this inhibitory effect is mediated, at least in part by NFκB, and suggest that LXR agonists have the potential to become useful therapies aimed at reducing both inflammation and FLS-mediated invasion and destruction in RA.

Disclosure: C. P. Linge: None; **T. Laragione:** None; **P. S. Gulko:** None.

1388

Cadherin-11 Engagement Increases Matrix Metalloproteinase Production by Rheumatoid Arthritis Fibroblast-Like Synoviocytes. Erika H. Noss, Sook-Kyung Chang and Michael B. Brenner. Brigham and Women's Hospital, Boston, MA

Background: Cadherin-11 is expressed on fibroblast-like synoviocytes (FLS) and mediates homophilic cell-to-cell adhesion by binding of cadherin-11 on one cell to cadherin-11 on an adjacent cell. Absence of cadherin-11 in mouse rheumatoid arthritis (RA) models led to a striking reduction of cartilage erosion independent of bone erosion, suggesting this molecule modulates the ability of FLS to degrade cartilage. Matrix metalloproteinases (MMPs) are a family of enzymes produced by FLS important in cartilage erosion. The aim of this study was to determine if FLS MMP production is regulated by cadherin-11, providing a possible mechanism to explain diminished cartilage erosion in the absence of cadherin-11 in RA models.

Methods: To test whether cadherin-11 engagement increases MMP production, human RA FLS were incubated with chimeric constructs containing human IgG1 Fc linked to the cadherin-11 extracellular domain (cad-11-Fc) in the presence or absence of tumor necrosis factor-a (TNF-a). MMP-1 and MMP-3 production were assessed by enzyme-linked immunosorbent assay (ELISA) and quantitative reverse transcription-polymerase chain reaction (qRT-PCR). Both mutagenesis to reduce cad-11-Fc binding affinity and lentiviral short-hairpin RNA infection to silence cadherin-11 were used to test the specificity of cad-11-Fc stimulation for surface cadherin-11. Immunoblotting with phospho-specific antibodies was used to determine signaling protein activation, and specific chemical inhibitors of these proteins were used to examine their role in cad-11-Fc MMP activation.

Results: Human cad-11-Fc upregulated protein production of MMP-1 and MMP-3 in RA FLS culture supernatants both alone and in synergy with TNF-a. MMP upregulation by cad-11-Fc was specific for engagement of cell cadherin-11, as a cad-11-Fc mutant construct lacking two tryptophan residues important for cadherin binding induced significantly less MMP production. Also, cadherin-11 silencing by lentiviral shRNA infection almost completely reduced the ability of cad-11-Fc to stimulate MMP expression compared to control-infected cells. Cad-11-Fc stimulation increased MMP transcription as measured by qRT-PCR. Since mitogen-activated protein kinase (MAPK) signaling pathways are important for induction of MMP synthesis, the ability of cad-11-Fc to activate these pathways was tested. Phosphorylation of the MAPKs jun N-terminal kinase (JNK) and extracellular signal-related kinase (ERK) was induced upon cad-11-Fc stimulation of RA FLS. Inhibitors of JNK and ERK phosphorylation partially blocked RA FLS MMP-3 expression by cad-11-Fc, providing evidence that these pathways help transduce the signal to upregulate MMP synthesis after surface cadherin-11 engagement.

Conclusions: Cadherin-11 binding by cad-11-Fc induced production of MMP-1 and MMP-3 by increasing MMP synthesis in RA FLS. Since MMPs are important mediators of cartilage degradation, these results point to a novel pathway by which cadherin-11 may influence joint destruction in RA.

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1389

Rheumatoid Synovial Fibroblasts Support Aid Expression and IG Class-Switching in B Cells Via a BAFF-Dependent TLR3-Stimulated Pathway. Michele Bombardieri[1], Yvone N. W. Kam[1], Fabia Brentano[1], Ken Choi[1], Diego Kyburz[3], Steffen Gay[3], Iain B. McInnes[2] and Costantino Pitzalis[1]. [1]Queen Mary University London, London, United Kingdom, [2]University of Glasgow, Glasgow, United Kingdom, [3]University of Zurich, Zurich, Switzerland

Background and Aims: Rheumatoid arthritis (RA) is characterized by the presence of synovial niches of autoreactive B cells which express activation-induced cytidine deaminase (AID), the enzyme initiating Ig class-switching (CSR), and sustain in situ autoantibody production. Importantly, B cell niches remain functional in the RA-SCID model in the absence of recirculating cells, suggesting that autocrine mechanisms support ongoing B cell activation in the RA synovium. Here we investigated whether RA synovial fibroblasts (RASF), which are known to contribute to RA synovitis, are capable of directly regulating B cell activation, AID expression and CSR. In addition, we dissected the molecular basis of stromal cell/B cell interactions with particular emphasis on the role of Toll-like receptors (TLRs) signaling and B cell survival/proliferating factors.

Methods: mRNA and protein expression of B cell survival factors BAFF and APRIL in RASF and OASF stimulated with TLR2, TLR3 and TLR4 ligands was assessed by Taqman PCR (QT-PCR) and ELISA, respectively. Un-switched IgD+ B cells were isolated from human tonsils using magnetic cell sorting. Isolated B cells were co-cultured via transwell or cell-cell contact with RASF/OASF for 24h and 72h in the presence or absence of TLR ligands and with or without blocking of soluble BAFF/APRIL. AID mRNA expression and IgM/A/G production were measured to assess functional activation of B cells. In addition, Iγ-Cμ and Iα-Cμ circular transcripts (CT, molecular by-products of ongoing CSR from IgM to IgG and IgM to IgA, respectively) were assessed by rt-PCR.

Results: In vitro stimulation of TLR3, and to a significantly lesser extent TLR4, but not TLR2 on RASF led to strong induction of BAFF (~1,000-fold increase with TLR3) and APRIL mRNA expression. In response to TLR3, BAFF was time-dependently released in the supernatant of RASF (~600pg/ml) and, to a lesser extent, OASF. TLR3 stimulation of RASF in co-culture with B cells strongly enhanced AID expression, ongoing CSR to IgG, but not IgA, as shown by detection of Iγ-Cμ CT and release of IgG. In contrast, TLR3 stimulation alone had no direct effect on B cells. Conversely, blockade of soluble BAFF/APRIL inhibited TLR3-induced RASF-dependent production of AID mRNA, Iγ-Cμ CT as well as the secretion of IgG.

Conclusions: Here we demonstrated that RASF are able to release high levels of B cell survival factors upon TLR3 stimulation at both mRNA and protein level. The release of these factors was functional, as demonstrated by the capacity of RASF to directly modulate AID expression, CSR and production of class-switched antibodies in co-cultured un-switched B cells. This effect was abrogated by blockade of soluble BAFF and APRIL. Overall, these data strongly support a fundamental role for TLR3-dependent release of BAFF and APRIL by RASF in sustaining functional B cell activation and antibody production in the RA synovium.

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Characteristic Oral and Intestinal Microbiota in Rheumatoid Arthritis (RA): A Trigger for Autoimmunity? Jose U. Scher[7], Carles Ubeda[3], Michael H. Pillinger[2], Walter Bretz[6], Yvonne Buischi[6], Pamela B. Rosenthal[7], Soumya M. Reddy[7], Jonathan Samuels[4], Peter M. Izmirly[7], Rennie N. G. Howard[7], Gary Solomon[8], Yusuf Yazici[8], Mukundan Attur[8], Michele Equinda[3], Nicholas Socci[3], Agnes Viale[3], Eric Pamer[1], Dan R. Littman[9], Gerald Weissmann[5] and Steven B. Abramson[10]. [1]Lucille Castori Center for Microbes, Inflammation, and Cancer/MSKCC, [2]Manhattan VA Med Hospital, New York, NY, [3]Memorial Sloan-Kettering Cancer Center (MSKCC), [4]New York University Hospital for Joint Disease, New York, NY, [5]New York University Medical Center, New York, NY, [6]NYU College of Dentistry, [7]NYU Hospital for Joint Diseases, New York, NY, [8]NYU Hospital for Joint Diseases, [9]NYU School of Medicine, [10]NYU School of Medicine, NYU Hospital for Joint Diseases, New York, NY

Purpose: The etiology of RA remains unknown, but genetic and environmental factors have been implicated. An infectious trigger has been sought but conventional microbiologic techniques have been uninformative. The human intestine contains a dense, diverse and poorly characterized (≥80% uncultured) bacterial population whose collective genome (microbiome) is ≥100 times larger than its human host. We (DRL) have recently shown in mice that gut-residing bacteria drive autoimmune arthritis via Th17 cell activation (*Immunity* 2010). Multiple lines of investigation also suggest a link between RA and oral microbes.

Methods: As part of an NIH ARRA grant, the NYU Microbiome Center for Rheumatology and Autoimmunity was established to study gut and oral microbiota in RA and related conditions. A cross-sectional study and prospective proof-of-concept antibiotic intervention trial are ongoing. Fecal samples are collected, periodontal status assessed and oral samples obtained by subgingival biofilm collection. To date, oral/intestinal microbiomes have been analyzed in 8 RA patients, 3 psoriatic arthritis (PsA) patients and 9 healthy controls. Periodontal status was characterized in 30 RA, 4 PsA and 8 controls. DNA was purified and variable 16s rRNA gene regions amplified. PCR products were pyrosequenced (454 Life Sciences), and DNA sequences compared to the RDP and BLAST catalogs. rDNA-based phylogenetic trees were created, and the UNIFRAC metric used to compare bacterial communities across individuals. Sera from all subjects were evaluated for anti-citrullinated peptide antibodies (ACPA).

Results: Prevotellaceae family was significantly overrepresented in fecal microbiota from ACPA+ RA patients (range 13%-85%; mean=38%) vs ACPA- individuals (mean=4.3%); p=0.003. One ACPA+ healthy individual and 1 ACPA+ PsA patient shared similar microbiomes with ACPA+ RA. Subgingival microbiomes in patients with new-onset drug-naive RA exhibited overabundance of the Spirochetaceae/Prevotellaceae/Porphyromonaceae families (mean=53%) compared to chronic-active RA and healthy controls (mean=18.5%). Periodontal assessment revealed 78% of examined sites bled upon probing in RA patients (mean age 39; 73% female), significantly more than controls (38% PsA, 12% healthy; p<0.001 vs RA); 66% of RA patients also presented with moderate periodontitis compared to PsA (25%) and controls (12%).

Conclusions: This is the first study using high-throughput technologies to assess oral and intestinal microbiota in RA. Our data corroborate prior reports demonstrating an underappreciated high prevalence of periodontal disease at a young age in patients with RA. Moreover, our preliminary data suggest that ACPA generation may be associated with larger populations of Prevotellaceae in both oral and intestinal microbiomes. In response to such altered microbial flora, certain predisposed individuals may develop auto-inflammatory disease, through mechanisms that may include the generation of cyclic citrullinated peptides or Th17 cell activation in the intestinal mucosa. Thus, the oral and intestinal microbiota merit further investigation as potential triggers for autoimmunity and clinical RA.

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Toll-Like Receptor 2 Activation Induces Angiogenesis, ICAM-1 Expression and EC Invasion in Rheumatoid Arthritis. Tajvur P. Saber[2], Sinead NicUltaigh[3], Jennifer McCormick[2], Douglas J. Veale[4], Mary Connolly[2] and Ursula Fearon[1]. [1]Dublin, Ireland, [2]Dublin Academic Medical Centre, Dublin, Ireland, [3]Dublin Academic Medical Centre, Dublin, Ireland, [4]St Vincents Univ Hospital, Dublin, Ireland

Background: Angiogenesis is a critical early event in inflammatory arthritis, facilitating leukocyte migration into the synovium resulting in invasion and destruction of articular cartilage and bone. This study investigates the effect of TLR2 on angiogenesis, EC adhesion and invasion using microvascular endothelial cells and RA whole tissue synovial explants *ex-vivo*.

Methods: Microvascular endothelial cells (HDEC) and RA synovial explants *ex vivo* were cultured with the TLR2 ligand, Pam3CSK4 (1μg/ml). HDEC tube formation was assessed using Matrigel matrix assays. Angiopoietin 2 (Ang2) was measured by ELISA. ICAM-1 cell surface expression was assessed by flow cytometry. Cell migration was assessed by wound repair scratch assays. ECM invasion, MMP-2 and 9 expression were assessed using transwell invasion chambers and zymography.

Results: Pam3CSK4 significantly increased angiogenenic tube formation (p<0.05). Pam3CSK4 significantly upregulated Ang2 production in HDEC (p<0.05) and RA synovial explants (p<0.05). Pam3CSK4 induced cell surface expression of ICAM-1, from basal level of 149 ± 54 (MFI) to 617±103 (p<0.01). TLR-2 activation induced an 8.8 ± 2.8 fold increase in cell invasion compared to control (p<0.05). Pam3CSK also induced cell migration and induced MMP-2 and -9 from RA synovial explants. Neutralisation of TLR2 with a blocking monoclonal antibody (OPN 301, 1μg/ml) inhibited Pam3CSK4-induced wound repair and EC tube formation.

Conclusion: Pam3CSK4 activation of TLR2 promotes angiogenesis, cell adhesion and invasion, key mechanisms involved in the pathogenesis of RA.

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1392

Radiological Progression in Patients with Early RA and a Good Clinical Response to MTX Monotherapy: Predictors and Clinical Implications. Hamed Rezaei[3], Ronald Van Vollenhoven[2], Kristina Forslind[1], Kristina Albertsson[3], Helena Wallin[3], Pierre Geborek[4], Sofia Ernestam[3], Ingemar Petersson[5] and Johan Bratt[3]. [1]Helsingborgs Hospital, [2]Karolinska University Hospital, Stockholm, Sweden, [3]Karolinska University Hospital, [4]Lund University Hospital, [5]Spenshult Hospital

Background: In patients with early RA, several randomized trials have demonstrated the superiority of methotrexate (MTX) + anti-TNF over MTX alone. However, these trials also showed that some patients did have excellent responses to MTX monotherapy. In the SWEFOT trial, all patients were given an initial 3–4 months trial period with MTX alone; patients achieving a low disease activity state with this treatment were not randomized in the controlled portion of the trial. We previously demonstrated that this was the case for appr. 30% of the patients. In a separate report (Wallin et al, abstract submitted) we showed that these patients had an excellent clinical course during the first two years, but that some radiological progression did nonetheless occur. Here, we investigated specific details of and predictors for radiological progression in this cohort.

Objective: To analyze in detail the radiological course in patients from the SWEFOT study who responded adequately to initial MTX monotherapy and who were not included in the randomized trial.

Methods: A total of 487 patients with early RA (symptom duration <1 year) were started on MTX at a rapidly escalating dosage up to at least 20 mg/week. After 3–4 months, the 147 patients who had a DAS28<3.2 were not randomized but continued on MTX and followed in "regular care", including 3-monthly assessments. These patients were analyzed here. Van der Heijde modified Sharp scores (SvdH) were done by two experienced readers. Scores at different times were compared by Wilcoxon paired test. Complete x-ray data were available for 114 patients.

Results: At baseline, the mean±SEM total SvdH score (median, IQR) was 3.8±0.7 (1, 0–5). After 1 year, it had increased to 6.0±0.8 (4, 0–8; p<0.0001 vs. baseline) and after 2 years to 7.9±0.9 (4, 0–8; p<0.0001 vs both BL and 1 year). Highly significant progression was seen for both erosion score and joint space narrowing score. The increase in total score after 2 years was 3.9±0.7 (2, 0–6). At baseline, 48.1% of patients had no x-ray damage (total score= 0); at 1 year 26.9%, and at 2 years 20.2%. An increase in total score ≥ 10, was seen in 15% of patients. RF positive patients had a trend towards greater progression than RF-negative ones: 4.78±0.91 (2, 0–7) vs. 1.90±0.78 (0, 0–5; p=0.067). For ACPA positive vs. negative, a smaller, non-significant difference was seen. Double-positive patients had the highest progression: 5.27±1.21 (2, 0–9). Single-positive RF had significantly higher progression than single-positive ACPA. Men had numerically more progression than women (5.00±1.05 (2, 0–9) vs 3.08±0.88 (1, 0–3; p=0.119).

Conclusions: Patients who responded to an initial 3–4 months trial of MTX monotherapy with a DAS28<3.2 showed statistically significant (but on average numerically modest) radiological progression during the first 2 years of disease. Progression was associated with RF- and double-positivity. About half of all patients had no damage at baseline but the majority of these did develop damage over 2 years.

An initial good clinical response to MTX does not preclude a less favorable radiological course.

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In Early RA, Patients with a Good Initial Response to MTX Monotherapy Have Excellent Clinical Outcomes over Two Years of Therapy, but Radiological Progression Is Not Completely Prevented. Helena Wallin[4], Ronald Van Vollenhoven[2], Kristina Albertsson, Kristina Forslind, Sofia Ernestam, Ingemar F. Petersson[3], Pierre Geborek, Hamed Rezaei, Johan Bratt[1] and The SWEFOT Study Group, [1]Karolinska Univ Hosp Huddinge, Stockholm, Sweden, [2]Karolinska University Hospital, Stockholm, Sweden, [3]Lund University Hosp, Lund, Sweden, [4]The Karolinska Institute, Stockholm, Sweden

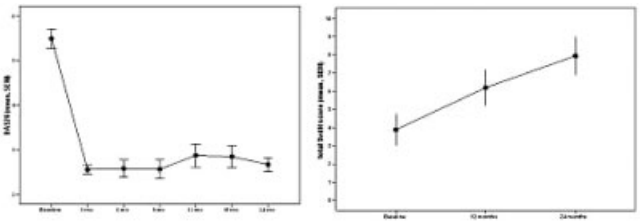
Background: In the SWEFOT trial, all patients were initially given MTX monotherapy for 3–4 months; patients achieving a DAS28≤3.2 were not randomized in the controlled portion of the trial. We previously demonstrated that this was the case for 30% of the patients, most of whom maintained remission during the first year. Here, we investigated the clinical and radiological results in these patients over two years of follow-up.

Objectives: To analyze the clinical and radiological course in patients from the SWEFOT study who responded adequately to initial MTX monotherapy and were not included in the randomized trial.

Methods: A total of 487 patients with early RA (symptom duration <1 year) were started on MTX at a rapidly escalating dosage up to at least 20 mg/week. After 3–4 months, the 147 patients who had a DAS28≤3.2 were not randomized but continued on MTX and were followed in "regular care", including 3-monthly assessments. These patients were analyzed here. Complete data at 24 months were available for 65% of patients.

Results: The majority of patients continued on MTX monotherapy. In 15 patients MTX was replaced by or complemented with another DMARD or a biologic. DAS28 values in all patients are shown in the figure, and demonstrate low values throughout. At the 6, 12, 18 and 24 months time-points, 61.1%, 61.0%, 64.2%, and 72.7% of patients, respectively, were in DAS28 remission, and 82.1 – 87.6% had a low disease activity state.

The mean (SEM) progression in total Sharp-vdHeijde score at 24 months was 3.90 (0.68). For the subset of patients who had been in sustained remission at each time point from 3 to 24 months (n=18) the progression was 4.06 (1.85). Progression in patients on MTX monotherapy throughout follow-up was 3.97 (0.85).



Conclusion: Patients who respond to an initial 3–4 month trial of MTX monotherapy with a DAS28≤3.2 continue to have very good clinical responses for two years, and additional treatment is needed infrequently. However, radiographic progression does occur and is seen even in those patients who have sustained remission and/or stay on MTX monotherapy. An initial good response to MTX appears to portend a good clinical prognosis but close monitoring of radiological disease is warranted.

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1394

Genetic Polymorphisms in Key Methotrexate (MTX) Pathway Genes Associated with Response to MTX Treatment in Rheumatoid Arthritis. Sally-Anne Owen[2], Stephen Eyre[2], Paul Martin[2], Samantha Hider[1], Ian N. Bruce[2], Anne Barton[2] and Wendy Thomson[2]. [1]ARC National Primary Care Centre, Keele University, Staffordshire, United Kingdom, [2]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom

Background: Methotrexate (MTX) is the cornerstone of treatment for rheumatoid arthritis (RA). However, up to a third of individuals will fail to respond to MTX treatment or suffer adverse events (AE). The main determinates of MTX response in RA remain unclear although evidence suggests that part of this variability is genetic. Genes within the MTX metabolic pathway represent good candidates as predictors of response. We investigated SNPs spanning 11 MTX pathway genes on the efficacy and occurrence of AE in MTX treated patients with RA.

Methods: Subjects included 309 RA patients with a defined response to MTX. Patients were included if they were (i) good responders (n=147) (with an ESR <20 and/or normal CRP and on a stable dose of MTX for at least 6mths) (ii) inefficacy failures (n=101) (physician statement and failure to reduce ESR/CRP by 20%) or (iii) AE failures (n=61) (verified by medical record review). Tagging SNPs were selected for genes: *AMPD1, ATIC, DHFR, FPGS, GGH, ITPA, MTHFD1, MTHFR, SHMT1, SLC19A1* (RFC) and *TYMS* using an r^2 cutoff ≥ 0.8 and MAF ≥ 0.05 within 10kb up and down stream of each gene. Genotyping was performed using the Sequenom iPlex® MassARRAY platform. Three different analyses were conducted: 1) responders vs inefficacy failures 2) responders vs AE failures and 3) responders vs inefficacy and AE failures combined. Genotype frequencies were compared between the groups using the trend test implemented in PLINK and allelic odds ratios with 95 % confidence intervals (CI) calculated in STATA 9.2.

Results: Of the 150 SNPs tested, 9 were found to be significantly associated (p-trend ≤ 0.05) with MTX response and 2 with MTX related AE. Interestingly 3 of these (rs12995526, rs7563206 and rs16853834) were found in the 5-aminoimidazole-4-carcoxamide ribonucleotide transformylase (*ATIC*) gene which encodes an enzyme that is important in the de novo purine synthesis pathway. Individuals carrying these SNPs had an increased risk of poor response to MTX (OR 1.48, 95%CI (1.01–2.17), OR 1.47, 95%CI (1.00–2.17) and OR 1.47 95% CI (1.01–2.76) respectively). Other associations included 6 SNPs in the *SLC19A1* gene (rs11702425, rs2838956, rs7499, rs2274808, rs9977268, rs7279445) all conferring an increased risk of poor response to MTX and two SNPs in the *DHFR* gene (rs12517451, rs10072026) were associated with AE. In addition there were a further 2 SNPs in the *FPGS* gene associated with AE under a recessive model (rs1054774, rs4451422) and 1 additional SNP in the *ATIC* gene approaching statistical significance (rs4673990) (p-trend<0.1) warranting further investigation.

Conclusion: Genetic variations in a number of key MTX pathway genes have been found to be significantly associated with MTX response and AE in RA patients. Further studies will be required to validate these findings. If confirmed these results could contribute towards a better understanding of and ability to predict MTX response in RA.

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1395

Observational Study To Evaluate the Relationship of Methotrexate to Interstitial Lung Disease in Rheumatoid Arthritis. Liron Caplan[7], Anne E. Hines[15], Jay R. McDonald[10], Angelique L. Zeringue[10], Alyse Mann[6], Paul H. Sufka[13], Kevin G. Osgood[2], Ted R. Mikuls[14], Jasvinder Singh[3], Itziar Quinzanos[5], Lela Mansoori[11], Chrysoula Pappa[12], Leah M. Haverhals[6], Andre Barkhuizen[8], Douglas Phelps[1], Roderick S. Hooker[4], Hong Xian[10], Prabha Ranganathan[9], Fran Cunningham[17] and Seth Eisen[16]. [1]Albancy VAMC, [2]Austin Diagnostic Clinic, Austin, TX, [3]Birmingham VAMC, Minneapolis, MN, [4]Dallas VAMC, Dallas, TX, [5]Denver Health, [6]Denver VAMC, [7]Denver VAMC, Aurora, CO, [8]Portland Rheum Clinic LLC, Lake Oswego, OR, [9]St. Louis VAMC, St. Louis, MO, [10]St. Louis VAMC, [11]Univ of Colorado, [12]Univ of Florida Jacksonville, Saint Augustine, FL, [13]Univ of Minneapolis, Minneapolis, MN, [14]Univ of Nebraska Med Ctr, Omaha, NE, [15]University of Colorado, [16]VA HSR&D, [17]VA PBM

Purpose: The relationship of methotrexate (MTX) to interstitial lung disease (ILD) remains controversial, with some studies supporting an association, while others dispute this association. We sought to identify risk factors for incident ILD in a population of veterans with rheumatoid arthritis (RA), with special attention on the disease modifying anti-rheumatic drug (DMARD) methotrexate (MTX).

Methods: We used a retrospective case-control study design where controls consist of subjects with RA and cases consist of subjects with both RA and ILD. We identified subjects based on ICD-9-CM diagnostic codes and prior DMARD or glucocorticoid treatment (n=442). Validation of ICD-9-CM codes for ILD relied upon medical records, as well as radiographic and pulmonary function results. All demographics, putative risk factors, and pharmaceutical data were abstracted using a detailed review of the medical record and defined abstraction algorithms. We performed unconditional multivariate logistic regression, controlling for multiple RA and ILD risk factors. Methotrexate was forced into the final model as the variable of

interest. All analyses were performed using Stata software version 10.2. Confidence intervals were established at 95%.

Results: In the multivariate regression adjusting for all covariates, patients with ILD were no more likely to have been exposed to MTX than patients without MTX exposure. Conversely, rheumatoid factor, C reactive protein and history of emphysema were all associated with presence of ILD (see table).

Conclusions: Though markers of RA disease severity and activity are associated with ILD in patients with RA, MTX exposure does not demonstrate this relationship in our observational study. There is a strong relationship between prior emphysema and subsequent ILD in RA patients.

Table 1. Factors associated with the odds of interstitial lung disease in rheumatoid arthritis patients

		Multivariate Model				Final Model			
Conceptual Block/ Domain	Variable	Odds Ratio	p	Lower 95% CI	Upper 95% CI	Odds Ratio	p	Lower 95% CI	Upper 95% CI
Generic Confounders	Age at Cohort Entry, years	0.96	0.274	0.89	1.03				
	Gender, male	0.96	0.978	0.07	12.91				
Rheumatoid Arthritis-associated Variables	Biologic Therapy	0.50	0.388	0.10	2.41				
	Rheumatoid Factor level*	1.03	0.044	1.00	1.07	1.02	0.012	1.00	1.04
	C Reactive Protein, mg/dL**	1.21	0.001	1.08	1.36	1.19	<0.001	1.08	1.31
ILD-associated Variables	History of Emphysema	17.14	0.009	2.06	142.31	14.37	0.002	2.56	80.62
	History of Previous Pneumonia	0.50	0.452	0.08	3.02				
	History of Recurrent Pneumonia	15.78	0.144	0.39	639.37				
	History of COPD	3.41	0.143	0.66	17.58				
	History of Bronchitis	2.89	0.200	0.57	14.68				
	Currently smoking	0.56	0.526	0.09	3.38				
DMARD exposure	Methotrexate Exposure	0.48	0.386	0.09	2.53	0.62	0.563	0.12	3.11

Chi^2 (df3) = 23.9; Pseudo R^2 = 0.24 for final model

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Induction Therapy with Methotrexate and Prednisone in Rheumatoid or Very Early Arthritic Disease: IMPROVED Study. K. V. C. de Boer[5], K. Visser[6], H. K. Ronday[4], A. A. Schouffoer[3], J. H. L. M. Groenendael[2], A. J. Peeters[9], I. Speyer[1], G. Collée[7], P. B. J. Sonnaville[8], B. A. M. Grillet[10], T. W. J. Huizinga[6] and C. F. Allaart[5]. [1]Bronovo Hospital, The Hague, [2]Franciscus Hospital, Roosendaal, [3]Groene Hart Hospital, Gouda, [4]Haga Hospital, The Hague, [5]LUMC, Leiden, The Netherlands, [6]LUMC, Leiden, [7]MCH, the Hague, [8]Oosterschelde Hospital, Goes, [9]Reinier de Graaf Gasthuis, Delft, [10]Zorgsaam, Terneuzen

Aim: To assess the rate of remission after 4 months of treatment with methotrexate (MTX) and a tapered high dose prednisone in patients with recent onset rheumatoid or undifferentiated arthritis (RA and UA), in relation to clinical and demographic baseline criteria.

Methods: IMPROVED is a multicenter single blind clinical study in patients with recent onset RA and UA, with an open label induction phase with MTX 25 mg/wk and prednisone 60 mg/day tapered to 7.5 mg/day in 7 weeks, aimed at achieving DAS < 1.6, which will be followed by tapering to drug free if remission persists, or randomization to multi-DMARD or MTX + adalimumab if DAS ≥ 1.6 after 4 months. To date, 161 patients with UA (arthritis > 1 joint, at risk for developing RA by estimation of a rheumatologist) and 261 patients with recent onset RA (ACR 1987 criteria, symptom duration $<$ two years) were included. Clinical outcomes (% remission DAS <1.6) and functional ability measured with the Dutch Health Assessment Questionnaire (HAQ) after 4 months of treatment were compared between RA and UA patients. Independent predictors at baseline for achieving remission after 4 months were established by univariable followed by multivariable regression analysis.

Results: At baseline, UA patients were younger, less often RF positive and had lower DAS, HAQ and ESR values, than RA patients (table 1). After four months of treatment, clinical remission was achieved in 107/161 UA patients (66.5%) and in 153/261 RA (58.6%) ($P = 0.12$). Improvement in mean DAS was 1.32 (0.95) in the UA patients and 1.90 (1.05) in the RA patients ($P < 0.001$), improvement in mean HAQ was 0.57 (0.65) and 0.81 (0.65), respectively ($P < 0.001$) (table 1). Low baseline DAS was predictive for achieving remission after 4 months in both UA and RA (OR 0.36, 95% CI 0.18–0.67). In UA patients, but not in RA patients, other predictors for achieving clinical remission were male sex (OR 2.76, 95% CI 1.13–6.73) and ACPA-positivity (OR 2.83, 95% CI 1.07–7.51)

Conclusion: After 4 months of treatment with MTX and a tapered high dose of prednisone in patients with recent onset RA or UA, clinical remission (DAS < 1.6) was achieved in 63% of all patients, with similar outcomes for mean DAS and HAQ. Only in UA patients, ACPA positivity is an independent predictor for achieving remission. This suggests that ACPA negative UA patients, who did not benefit from treatment with MTX monotherapy in the PROMPT study, also benefit less from prednisone. ACPA negative UA may be a different disease that requires different therapy than ACPA positive UA.

Table 1. Baseline characteristics, and clinical outcomes after 4 months of treatment of patients with UA or recent onset RA.

Baseline	UA N = 161	RA N = 261	P-value
Age, years (mean, SD)	**48.3 (13.3)**	**53.5 (14.2)**	**<0.001**
% Female	64.6	66.3	0.72
Symptom duration, months (median, IQR)	4.0 (2.0–7.0)	4.0 (2.0–7.0)	0.57
% RF positive	33.1	61.1	<0.001
% ACPA positive	48.4	59.7	0.47
ESR mm/hr (median, IQR)	17.0 (8.0–30.0)	29.0 (13.0–42.5)	<0.001
CRP mg/l (median, IQR)	7.0 (3.0–19.0)	12.5 (6.0–34.0)	<0.001
DAS (mean, SD)	2.74 (0.74)	3.44 (0.91)	<0.001
HAQ (mean, SD)	0.96 (0.62)	1.24 (0.64)	<0.001
Follow up (4 months)			
DAS (mean, SD)	1.43 (0.90)	1.54 (0.88)	0.57
HAQ (mean, SD)	0.40 (0.49)	0.43 (0.52)	0.13
Improvement DAS (mean, SD)	1.32 (0.95)	1.90 (1.05)	<0.001
Improvement HAQ (mean, SD)	0.57 (0.65)	0.81 (0.65)	<0.001
% Remission	66.5	58.6	0.12

Disclosure: K. V. C. de Boer: Abbott Laboratories, 2; **K. Visser:** None; **H. K. Ronday:** None; **A. A. Schouffoer:** None; **J. H. L. M. Groenendael:** None; **A. J. Peeters:** None; **I. Speyer:** None; **G. Collée:** None; **P. B. J. Sonnaville:** None; **B. A. M. Grillet:** None; **T. W. J. Huizinga:** None; **C. F. Allaart:** None.

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The Role of Low-Dose Oral Prednisone Treatment in Early Rheumatoid Arthritis: Effects on Clinical and Ultrasonographic Remission and Functional Outcome. Garifallia Sakellariou[1], Monica Todoerti[2], Carlo A. Scirè[2], Serena Bugatti[2], Carlomaurizio Montecucco[2] and Roberto Caporali[2]. [1]Chair and Division of Rheumatology, Università degli Studi di Pavia, Fondazione IRCCS Policlinico San Matteo, Pavia, Lombardia, Italy, [2]Chair and Division of Rheumatology, Università degli Studi di Pavia, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Background: Glucocorticoids are widely used in treating patients with rheumatoid arthritis (RA), providing rapid clinical improvement, reduction of radiographic progression and higher rates of clinical remission. Nevertheless, there is evidence of persistent subclinical synovitis even in clinical remission, and ultrasonography (US) is considered a sensitive tool to detect it. In this study we investigated the effect of low-dose oral prednisone co-medication on the occurrence of clinical and US remission, and the impact of these statuses on the development of future disability in a cohort of patients with early RA.

Methods: 210 patients with early RA (symptom duration$<$1 year) were assigned to receive (P) or not (no-P) low-dose oral prednisone in association with a DAS-driven DMARD therapeutic protocol. Patients started with a dosage of 12.5 mg/day of prednisone, tapered to 6.25 mg/day after two weeks. Disease Activity Score 28 (DAS28) was assessed at the beginning of the study and after 12 months. A DAS28$<$2.6 identified patients in clinical remission. The US assessment of patients included 12 joints (MCPs and wrists). A single operator unaware of the clinical findings carried out all scans

with a GE Logiq 9 scanner, using a multi-frequency linear array transducer (8–15MHz), under standardized settings. Grey-scale (GS) and power Doppler (PD) synovitis were subjectively scored (0 to 3) for each joint. US remission was defined as absence of intra-articular PD signal (PD grade 0). Health Assessment Questionnaire (HAQ) was completed at the beginning of the study, at 12 and 24 months; disability (mild) was defined as a value of HAQ>0.5. Patients with complete data both on clinical and US variables were included in the analyses.

Results: Out of 210 patients, 105 were on prednisone plus DMARDs (P) and 105 on DMARDs alone (no-P). Age, disease duration, DAS28, HAQ, ESR, CRP, US findings did not differ between P and no-P at baseline. At 12 months, 44% of P patients, and only 28% of no-P patients were in DAS28 remission (p=0.018). US remission occurred in 71.2% of P patients, and in only 55.4% of no-P patients (p=0.041). At 24 months, the odds ratio of progression to disability in patients who were in DAS 28 remission, compared to those with active disease, was 0.18 (95% confidence interval, CI, 0.063–0.55, p=0.001). In this subgroup, patients who were also in PD remission carried the lowest risk of development of disability (OR 0.16, 95% CI 0.01–0.62, p=0.008).

Conclusions: low-dose oral prednisone co-medication gave an advantage over DMARD monotherapy in terms of higher rates of clinical and US remission. Patients in clinical and US remission showed the lowest rate of progression to disability at two years. These findings suggest a more complete suppression of joint inflammation in patients with early RA receiving glucocorticoids, resulting in a positive influence on functional outcome.

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ACR Concurrent Abstract Sessions
Systemic Lupus Enrythematosus - Clinical Aspects and Treatment: Renal
Tuesday, November 9, 2010, 2:30 PM–4:00 PM

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Repeat Kidney Biopsies Fail To Detect Differences between Azathioprine and Mycophenolate Mofetil Maintenance Therapy for Lupus Nephritis: Data from the MAINTAIN Nephritis Trial. Maria Stoenoiu[1], Selda Aydin[1], Carlos Vasconcelos[4], Maria Tektonidou[5], Isabelle Ravelingien[6], Véronique le Guern[2], Geneviève Depresseux[1], Ricard Cervera[3], Jean-Pierre Cosyns[1] and Frédéric A. Houssiau[1], [1]Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Bruxelles, Belgium, [2]Hôpital Cochin, Paris, France, [3]Hospital Clinic, Barcelona, Spain, [4]Hospital Santo Antonio, Porto, Portugal, [5]National University of Athens, Athens, Greece, [6]O.L. Vrouwziekenhuis, Aalst, Belgium

Introduction: In the MAINTAIN Nephritis Trial, an investigator led randomized study, azathioprine (AZA) and mycophenolate mofetil (MMF) were compared as maintenance immunosuppressive treatment of proliferative lupus nephritis (LN) after a short course of low-dose (6 × 500 mg q2w; Euro-Lupus) intravenous cyclophosphamide. Although more renal flares were observed in AZA (25%) compared to MMF patients (19%), time to renal flare by Kaplan-Meier analysis did not statistically differ. Per protocol repeat kidney biopsies were available in 26 patients. Here we compare the pathological findings between the two groups.

Methods: 105 lupus patients with biopsy-proven proliferative nephritis were included in the MAINTAIN Nephritis Trial. Per protocol repeat renal biopsies were performed between month 18 and 30 in 26 patients (all females; 15 AZA and 11 MMF). All 26 patients had been treated exactly according to the protocol, i. e. had stayed on the same immunosuppressant and had tapered the steroids as requested. Biopsies were classified according to the ISN/RPS classification. The activity index (AI, max 42) and the chronicity index (CI, max 6) were calculated using the semi-quantitative scoring system of Morel-Maroger. Statistics were by non-parametric tests.

Results: Baseline and follow-up renal parameters of AZA and MMF patients did not differ. Time (SD) to repeat renal biopsy was 24.7 (1.7) and 25.1 (2.1) months in AZA and MMF patients, respectively. In both groups, the activity index dramatically and statistically decreased at follow up compared to baseline, while the chronicity index slightly but statistically increased. No between groups differences could be detected. In a second analysis, we added 4 patients for whom a repeat renal biopsy was also available, within the same time frame, but who had been switched to another immunosuppressant due to a renal flare which had occurred before the second biopsy. Baseline and follow up AI and CI on these 30 (26+4) paired renal biopsies were exactly comparable to the data obtained on the 26 patients.

Conclusion: No differences were observed on repeat kidney biopsies between patients treated with AZA or MMF.

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1399

C4d on Circulating Cells and Renal Tissues in Lupus Nephritis as Novel Biomarkers. Kelly V. Liang[4], Ibrahim Batal[2], Sheldon Bastacky[4], Lawrence Kiss, Theresa McHale, Nicole Wilson, Barbara Paul, Apinya Lertratanakul, Joseph M. Ahearn[1], Susan Manzi[5] and Amy H. Kao[3]. [1]Wexford, PA, [2]Pittsburgh, PA, [3]Allegheny Singer Research Institute, Pittsburgh, PA, [4]University of Pittsburgh, Pittsburgh, PA, [5]West Penn Allegheny Health System, Pittsburgh, PA

Background: Immune complex deposition and complement activation via the classical pathway play a key role in the pathogenesis of lupus nephritis (LN), a severe manifestation of systemic lupus erythematosus (SLE). Traditional serologic tests such as anti-double stranded DNA titers and serum complement levels (C3 and C4) are inconsistent predictors of renal pathology in LN. The complement activation product C4d bound to circulating erythrocytes (E-C4d), reticulocytes (R-C4d) and platelets (P-C4d) has been shown to reflect disease activity in SLE but has not been systematically studied in LN. The aims of this study were to: 1) compare C4d deposition on circulating cells and in renal tissues between LN subjects and two control groups (non-SLE renal disease and SLE subjects without LN), and 2) determine the association of C4d deposition with LN disease activity.

Methods: We prospectively evaluated C4d on circulating cells in 15 LN subjects and two control groups: 13 non-SLE renal subjects (control A) and 239 SLE subjects without LN (control B). Circulating cell-bound C4d levels were measured by flow cytometry. C4d deposition in different anatomic renal compartments was semiquantitatively assessed in LN and control A using immunoperoxidase staining performed on formalin-fixed, paraffin-embedded renal tissue.

Results: LN renal tissues had higher glomerular C4d scores than those of control A (p=0.003). Glomerular C4d stain was detected in the majority (12/13, 92%) of LN samples and was associated with more frequent granular glomerular immunofluorescence staining and electron-dense, immune complex deposits (p<0.001). C4d score in other anatomic compartments showed no differences. Compared to controls A and B, LN subjects had higher levels of E-C4d (p=0.002 and p=0.005) and R-C4d (p=0.002 and p=0.008), respectively. LN subjects were also more likely to have positive P-C4d compared to control A (p=0.016) but not control B. In LN samples, E-C4d, but neither serum complement (C3, C4) nor renal tissue C4d, correlated with NIH activity index (r=0.55, p=0.04).

Conclusions: Glomerular C4d staining was associated with immune complex deposits in LN biopsies. LN subjects also had higher levels of E-C4d and R-C4d when compared to non-SLE renal subjects and non-LN SLE subjects. E-C4d levels correlated significantly with the NIH activity index. Larger prospective studies are needed to validate our findings and further investigate the role of C4d on circulating cells and renal biopsy tissues as biomarkers for LN.

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1400

Are the Current Thresholds for SLE Proteinuric Flare Set Too High? Determining the 99% Confidence Intervals for Spontaneous Variation in Urine Protein/Creatinine Ration in SLE GN Patients Who Are Clinically Stable (Not Flaring). Stacy P. Ardoin[1], Dan J. Birmingham[2], Brad H. Rovin[2], P. Hebert[3], C.-Y. Yu[2] and Lee A. Hebert[2]. [1]Ohio State University, Columbus, OH, [2]Ohio State University, [3]University of Washington

Statement of Purpose: Proteinuria is the most common manifestation of a moderate or severe flare of SLE glomerulonephritis (GN). However, there is no general consensus on the threshold for proteinuric flare and the proposed criteria are based largely on expert opinion. The criteria that have been proposed can be categorized as having low, medium or high thresholds, depending upon the minimum increase in proteinuria deemed necessary to constitute a proteinuric flare. This study provides an evidence-based approach to validate the magnitude of proteinuria increase that should constitute a proteinuric flare.

Methods: This work involved analysis of data collected as part of the Ohio SLE Study (OSS), a prospective observational study of 106 SLE patients with recurrently active disease, 72 of whom had moderate or severe renal disease. Patients were managed by pre-specified protocols. Median follow up was > 46 months with over 2400 visits. >90% of visits occurred bimonthly, within pre-specified windows of ± 1 week. The renal OSS patients provided 24 hour urine collections at 84% of OSS visits and random spot urine collections at remaining visits. At each visit it was determined, using pre-specified criteria (JASN 16: 467–473, 2005), whether a renal or non-renal SLE flare had occurred at the previous OSS visit.

To assess spontaneous variation in protein/creatinine (P/C) ratio in patients with SLE under no-flare conditions, P/C ratios measured within 4 months of a renal flare were excluded. "P/C ratio datasets" were developed and required a minimum of 3 bimonthly consecutive urine collections spanning 4 months. At least 50% of the P/C ratios were required to be measured by 24 hour urine collection. The P/C ratio datasets were stratified into groups according to the mean P/C ratio of the dataset: group 1 (mean P/C ratio <0.15), group 2 (mean P/C ratio ≥0.15 to ≤0.38), group 3 (mean P/C ratio >0.38 to ≤0.77), group 4 (mean P/C ratio >0.77 to ≤1.54), group 5 (mean P/C ratio >1.54). For each group, 99% confidence intervals were developed.

Summary: Of 1168 urine collections in the OSS study, 895 met the above criteria. These were provided by 58 of the 72 SLE GN patients (mean age 34 ± 11 years, 91% female, 38% African American, 58% European American, 4% Other). Mean P/C ratio was 1.5 ± 2.4. 91% were taking prednisone and 88% an immunosuppressant. Confidence intervals (CI) for each group are displayed in Figure 1.

Conclusions: Most of the current thresholds for SLE GN proteinuric flare are set well above the 99% CI for spontaneous variation in P/C ratios under no-flare conditions. This suggests that SLE GN patients by be exposed to unnecessarily prolonged periods of increasing proteinuria before flare is declared and treated. This work is hypothesis generating and needs to be confirmed in a prospective randomized trial to determine whether lowering proteinuric flare threshold would benefit SLE patients.

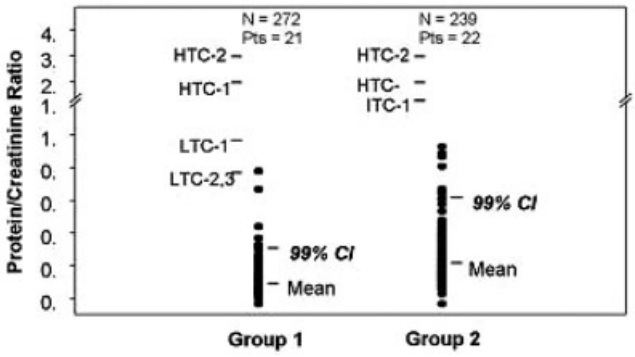

Figure 1.

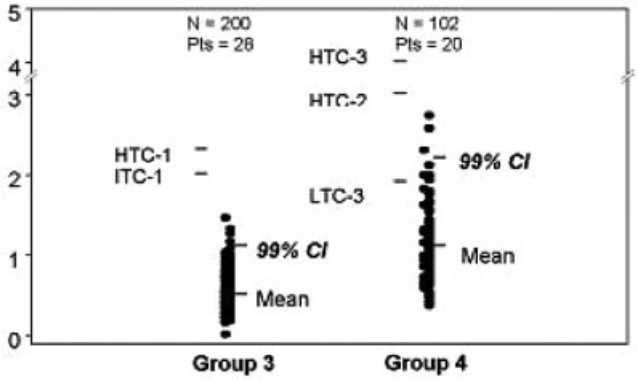

Figure 2.

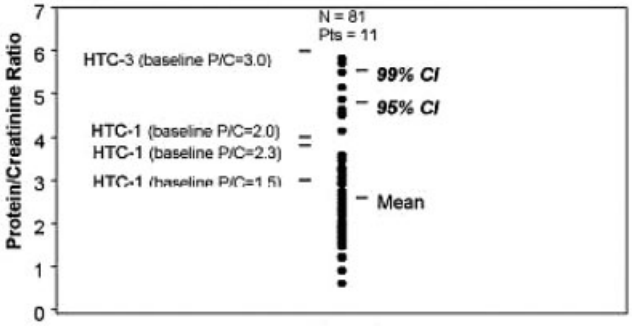

Figure 3.

Figures 1–3. Individial urine protein/creatinine (P/C) ratios measured under non-flare conditions for P/C ratio groups 1 to 5. These ratios are shown in relation to the currently published low (LCT), intermediate (ICT), and high threshold (HTC) criteria for proteinuria flare. The 99% CI for the given P/C ratio group is provided.

Disclosure: S. P. Ardoin: None; **D. J. Birmingham:** None; **B. H. Rovin:** None; **P. Hebert:** None; **C.-Y. Yu:** None; **L. A. Hebert:** None.

1401

Systematic Review and Meta-Analysis of Immunosuppressant Therapy Clinical Trials in Membranous Lupus Nephritis. Vikas Majithia[2], Josh T. Swan[1] and Daniel Riche[3]. [1]Methodist Hospital, Houston, [2]University of Mississippi Medical Center, Jackson, MS, [3]University of Mississippi Medical Center

Background: There is no current consensus on a standard treatment for patients with class V membranous lupus nephritis. Clinical trial data are typically inconsistent in design, small in number of patients, and lacking in control groups.

Objective: The primary objective was to compare remission rates for immunosuppressant therapy to steroid therapy through meta-analysis of currently available data.

Methods: A literature review was conducted from June 2010 by querying PubMed, MEDLINE, and EMBASE databases. Inclusion criteria were trials containing remission data for confirmed pure class V (Va & Vb) membranous lupus nephritis patients. The primary analysis evaluates any immunosuppressant treatment, while subgroup analyses isolate adult patients, azathioprine (AZA), cyclosporine A (CSA), cyclophosphamide (CYP), mycophenolate mofetil (MMF), and steroids only therapies. A proportion meta-analysis using a DerSimonian-Laird random-effects model was performed. Data are reported as pooled proportions in percentages with 95% confidence intervals [CI]. Significant heterogeneity and publication bias was compensated for by trial exclusion.

Results: Of 396 trials in initial search, 92 trials were reviewed for full text analysis. Twenty-three studies met inclusion criteria for meta-analysis, which yielded 34 groups of patient data. Upon meta-analysis, the response rate (complete and partial remission) for immunosuppressant pharmacotherapy is much higher than for steroids alone (81% versus 60%) {shown in figure 1}, even when compensating for significant heterogeneity and publication bias (76% versus 60%). Any response rate is similar amongst azathioprine (88% [95% CI 81–94%]), cyclophosphamide (75% [95% CI 60–88%]), mycophenolate mofetil (81% [95% CI 67–92%]), and cyclosporine A (84% [95% CI 67–96%]). Patients were twice as likely to have no response to steroids alone vs immunosuppressant therapy (39% versus 19%).

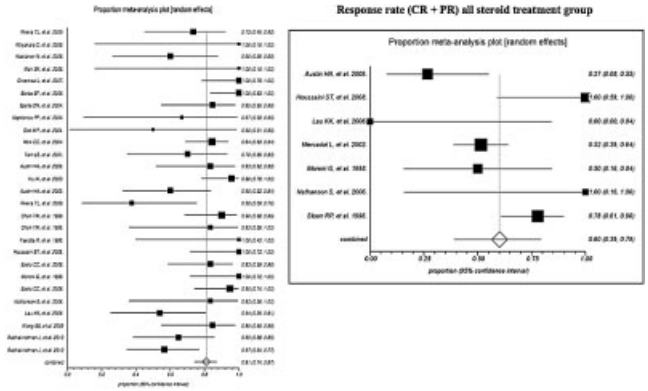

Figure 1. Response rate (CR + PR) for all immunosuppressant therapy.

Discussion: There is a wide range of variation between immunosuppressant studies including: study design (retrospective versus prospective), patient-selection, racial variation, and lack of standard steroid regimens. With all these factors in mind, this pooled analysis was extremely challenging, but important. Our results indicate that treatment with an immunosuppressive agent (e.g., CYP, MMF, AZA, and CSA) should be strongly considered in MLN patients. Subgroup analyses demonstrate a much better response with AZA, CSA, CYP, or MMF when compared to the steroid alone group. The results of this analysis are corroborated by the recently published randomized controlled trials of MLN patients.

Conclusion: Overall, conventional immunosuppressant therapies appears to be more effective than steroids alone for inducing partial or complete remission in patients with MLN and should be considered in treatment of nephritis in lupus MLN patients.

Disclosure: V. Majithia: None; **J. T. Swan:** None; **D. Riche:** None.

1402

Treatment of Lupus Nephritis with Enteric-Coated Mycophenolate Sodium (EC-MPS)—MyLupus Exploratory Study. Andrea Doria. For the MyLupus Study Group, Padova, Italy

The MyLupus study was designed to compare the non-inferior efficacy and safety of EC-MPS using two different oral prednisolone regimens (standard SD or reduced dose RD) for the induction of remission of a lupus nephritis (LN) flare.

Methods: A 24-week (W) exploratory, multi-center, open-label study was conducted in patients with a LN flare (ISN/RPS Class III or IV documented by renal biopsy within 24 months of study entry). All patients received EC-MPS 1440 mg/day for the first 2W, followed by 2160 mg/day for the remaining 22W, and methylprednisolone iv. (0.5 g/day) for the first 3 days. Patients were randomized to either SD or RD (starting dose of 1.0 mg/kg/day and 0.5 mg/kg/day for 2W, respectively, followed by pre-specified dose reduction). Primary end-point was the proportion of patients with complete response (urine protein/creatinine [P/C] ratio <0.5, urine sediment normalized, and serum creatinine $<10\%$ normal value) of LN after 24W. Partial response was defined as urine P/C ratio reduced by at least 50% from baseline and serum creatinine stable ($<10\%$ of baseline value) or improved.

Results: 81 patients were enrolled, 42 in SD and 39 in RD group. Baseline characteristics were comparable between groups. After 24 W, a similar proportion of patients achieved complete response in both groups (19% SD vs. 18% RD), although non-inferiority was not demonstrated. A higher proportion of patients achieved partial response in SD (48% SD vs. 33% RD). Index scores decreased in both groups from 4 to 24W (British Isles Lupus Assessment Group [BILAG] index: mean change from baseline -8.6 SD vs. -9.4 RD, Systemic Lupus Erythematosus Disease Activity Index [SLEDAI]: -10.4 SD vs. -9.4 RD). There was greater improvement in glomerular filtration rate (mL/min/1.73m^2) in RD (mean change from baseline 9.0 SD vs. 15.2 RD). There were 2 deaths, both in SD group. The incidence of serious adverse events was 16.7% (SD) vs. 10.3% (RD).

Conclusions: This exploratory study suggests that EC-MPS in combination with steroids is a viable therapy for LN. The overall clinical results indicate that RD of CS may offer benefits in terms of tolerability compared to SD of CS while maintaining efficacy.

Disclosure: A. Doria: None.

1403

Machine Learning Models Using Multiple Low Abundance Protein Biomarker Levels Are Superior to Those Using Clinical Laboratory Values in Diagnosing ISN/RPS Class of Lupus Nephritis. Jim C. Oates[2], Michelle A. Petri[1], Jonas S. Almeida[4], Thomas W. Fleury[3], Janech G. Michael[3] and John M. Arthur[3]. [1]Timonium, MD, [2]Medical University of South Carolina, Charleston, SC, [3]Medical University of South Carolina, [4]The University of Texas M. D. Anderson Cancer Center

Objectives: Treatment in lupus nephritis (LN) is often driven by renal biopsy findings, and traditional biomarkers are not predictive of renal pathology. We hypothesized that levels of multiple candidate low abundance urine proteins, when analyzed my multivariable machine learning techniques, would create more effective models of International Society of Nephrology/Renal Pathology Society class of nephritis (ISN/RPS Class) than traditional biomarkers now available to clinicians.

Methods: Subjects from the Charleston and Baltimore LN inception cohorts and the Rituxan in LN (LUNAR) study population were recruited. ISN/RPS Class was determined prior to induction therapy. Urine samples were collected at entry for analysis. Urine levels of 12 candidate low abundance proteins (chemokines, growth factors, cytokines, and renal damage markers) were determined by the multiplex bead array, ELISA or activity assay for all patients. Levels of individual markers were used to create multivariable models of LN Class at baseline. Diagnostic models were trained using machine learning (artificial neural network (ANN) and nearest related neighbor (NRN) algorithms). The diagnostic power of models was reported as the receiver operating characteristics curve area under the curve (ROC AUC), with AUC values for perfect and non-diagnostic tests being 1 and 0.5 respectively. Input variables were traditional biomarkers (anti-double stranded DNA antibodies (DNA), C3, C4, serum Cr) and/or the selected biomarker panel. The output variables were the individual biopsy classes.

Input variables	Number of subjects	Outcome (ISN/RPS Class)	NRN ROC AUC	ANN ROC AUC
Novel biomarkers	99	II	0.91	0.95
		III	0.82	0.68
		IV	75	0.92
		Proliferative	0.84	0.94
		V	0.59	0.94
Traditional Biomarkers	66	II	0.82	0.97
		III	0.64	0.78
		IV	0.62	0.68
		Proliferative	0.63	0.96
		V	0.64	0.57
Novel and traditional biomarkers	66	II	0.84	0.82
		III	0.79	0.85
		IV	0.82	0.96
		Proliferative	0.73	0.89
		V	0.86	0.74

Results: Biomarker data were available for 99 subjects. Combined biomarker clinical data were available for a subset of 66 subjects. In general, ANN and NRN models using biomarkers either alone or in combination with traditional biomarkers were superior to models with clinical variables alone. ANN models tended to have greater diagnostic power than NRN models. 93% of the predictive power from the ANN model of proliferative disease came from GM-CSF, IFNα2 MCP1, NGAL, IL-6, and IL-12 levels.

Conclusions: This study suggests that multiple biomarkers representing diverse pathogenic mechanisms by machine learning modeling techniques are effective in diagnosing ISN/RPS class of nephritis. It demonstrates that when markers of multiple types of cell activation, migration, and damage are combined into a single model, diagnostic power is improved over models using traditional biomarkers alone.

Disclosure: J. C. Oates: None; **M. A. Petri:** None; **J. S. Almeida:** None; **T. W. Fleury:** None; **J. G. Michael:** None; **J. M. Arthur:** None.

ACR/ARHP Combined Abstract Session

ACR/ARHP Combined Pediatric Rheumatology - Clinical and Therapeutic Aspects Abstracts: Quality of Life in Children and Adolescents with Arthritis

Tuesday, November 9, 2010, 2:30 PM–4:00 PM

1404

Investigating Medication Adherence in Pediatric Rheumatology Using a Medical Claims Database. Caitlin M. Sgarlat[3], Jorge M. Lopez-Benitez[2], Emily Cox[1] and Ira B. Wilson[4]. [1]Express Scripts Inc. Research and Analysis, St. Louis, MO, [2]Tufts Medical Center and Floating Hospital for Children: Division of Pediatric Rheumatology, Boston, MA, [3]Tufts Medical Center and Floating Hospital for Children: Division of Pediatric Rheumatology; Tufts University Sackler School of Graduate Biomedical Sciences, Boston, MA, [4]Tufts Medical Center and Floating Hospital for Children; Tufts University Sackler School of Graduate Biomedical Sciences

Background: Juvenile Idiopathic Arthritis (JIA) or Juvenile Rheumatoid Arthritis (JRA) is the most common pediatric rheumatologic disease. Pharmacologic therapy use in this population is important at the onset of disease as well as throughout its course and adherence to the planned treatment is critical for good outcomes. Adherence to treatment in these conditions and in

this population has not been well studied and little is known about an association between age and adherence. We hypothesized that medication adherence would be better in a younger pediatric population with JRA compared with an adolescent pediatric population with JRA because of parental medication administration and supervision and because of problems reported with medication adherence in adolescents with other chronic conditions.

Methods: We used The MarketScan® Commercial Claims and Encounters Database, a nationwide pharmaceutical database with 12 million enrollees that includes both medical and pharmacy claims. Pediatric patients were identified by ICD-9 codes for a medical claim of JRA from 7/1/07 to 12/31/07. Pharmacy claims were obtained for these patients up to 1 year after the medical claim was made. Claims included the following medications: non-steroidal anti-inflammatory agents, cytotoxic agents, corticosteroids, and biologic agents. For each medication a possession ratio (MPR) was calculated. The denominator for the MPR was the number of days between the first and last prescription in that year, and the numerator was the number of dispensed days of medication between those dates. For patients on more than one medication, the average of the MPRs of the individual medications was used. Age was dichotomized into patients aged 0 to 12 years and 13 to 18 years. T-tests were used to compare the MPR in the different age groups. The data was analyzed using statistical software SAS 9.2.

Results: Of 5,452 patients with a medical claim of JRA, 1,946 patients, or 36%, were on one or more medications. Of those on medication, 64.5% were females and 34.5% were males. 40.6% were 0 to 12 years old and 59.5% were between 13 and 18 years old. The overall MPR of all patients was 0.67 (SD 0.46). The mean MPR for the patients ages 0 to 12 years was 0.77 (SD 0.47) and the mean MPR for the patients ages 13 to18 years was 0.60 (SD 0.44), p-value <0.0001. Adjusting for gender in a multivariable linear regression model did not change these results.

Conclusion: Adherence was significantly worse in teenagers with JRA than in younger children, but even in younger children whose medication taking is presumably supervised by an adult, it was surprisingly low. These low levels of adherence are a potentially serious problem for patients who are likely to have suboptimal clinical outcomes as a result. Pediatric rheumatologists need to be aware of the extent of nonadherence that these data reveal, and endeavor to communicate more effectively with their patients about the issues and problems that they are having taking medications as prescribed. While the challenges to taking care of adolescent patients are not unique to JRA or rheumatologic diseases in general, the need to address poor medication adherence in these patients appears particularly pressing.

Disclosure: C. M. Sgarlat: None; **J. M. Lopez-Benitez:** None; **E. Cox:** Express Scripts Inc., 3; **I. B. Wilson:** None.

1405

Development of a Vision Related Quality of Life Instrument for Children with Juvenile Idiopathic Arthritis-Associated Uveitis. Sheila Angeles-Han[4], Kenneth Griffin[7], Melanie J. Harrison[5], Kerrie Fields[2], Lori Ponder[2], Rachel Reeves-Robb[3], Marla Shainberg[3], Phoebe Lenhart[3], Amy Hutchinson[3], Sunil Srivastava[3], Sampath Prahalad[1], Scott Lambert[3] and Carolyn Drews-Botsch[6]. [1]Emory Children's Center, Atlanta, GA, [2]Emory Children's Center, [3]Emory Eye Center, [4]Emory University, Atlanta, GA, [5]Pfizer, Blue Bell, PA, [6]Rollins School of Public Health, [7]Weill Cornell Medical College

Purpose: Studies on quality of life (QOL) in JIA-associated uveitis (JIA-U) focus on visual acuity (VA) and the presence of flare and cells during the ophthalmologic exam as a measure of visual function. However, these measures do not adequately assess the impact of disease activity on daily life from a child's perspective. Assessment of QOL in JIA-U could improve by including both objective measures of visual function and subjective assessments of the impact of disease activity on daily functioning. However, there are no validated instruments that measure vision related QOL in children 8–18 years old. Hence, we developed a new instrument to evaluate the performance of activities that rely on vision in home and school – Effects of Youngsters' Eyesight on QOL (EYE-Q).

Methods: We interviewed experts in the field and children regarding how vision affects a child's daily activities. In addition to developing new items, we selected relevant items from existing instruments and adapted them to increase their relevance to a U.S.-based sample of children. We administered preliminary versions of the EYE-Q to normal sighted children and those with JIA-U. We then recruited 82 children, 8–18 years old, with various (or no) ocular conditions that affect vision. We measured VA and contrast sensitivity (CS). Patient-based questionnaires were administered -the EYE-Q to measure vision related QOL, and the Pediatric Quality of Life Inventory (Peds QL) to measure overall QOL. The EYE-Q was again completed 10 days after the visit. VA was converted to logmar VA values which are a linear scale for statistical analysis. Test-test reliability over a 10 day period was calculated, and validity was determined by examining associations between the EYE-Q and VA, CS, and QOL using Pearson's correlation.

Results: Of 82 patients, 42.4% were female, 65.9% were Caucasian, 22.4% were African American, and 76.5% had eye disease. Mean age was 11.1 years (range 8–18). Mean scores of the instruments, VA, and CS are shown in Table 1.

Table 1. Mean Scores of Visual Function Measures

	Mean (SD)
EYE-Q[1] score	3.51 (0.52)
2nd EYE-Q[1] score	3.54 (0.52)
PedsQL[2] Physical score	85.91 (15.04)
PedsQL[2] Psychosocial score	75.56 (17.66)
PedsQL[2] Total score	79.18 (15.49)
Logmar VA[3], left eye	0.245 (0.357)
Logmar VA[3], right eye	0.220 (0.510)
Contrast Sensitivity	1.74 (0.18)

[1] Effects of Youngsters' Eyesight on QOL; [2]Pediatric Quality of Life Inventory; [3] Visual Acuity

Correlations between EYE-Q and measures of validity and reliability are shown in Table 2.

Table 2. Correlation Between the EYE-Q and PedsQL With Measures of Validity and Reliability

Measures	R	P value
EYE-Q[1] repeat	0.943	0.00**
PedsQL[2] Physical	0.489	0.00**
PedsQL[2] Psychosocial	0.427	0.00**
PedsQL[2] Total	0.489	0.00**
Logmar Far VA[3], left eye	−0.546	0.000**
Logmar Far VA[3], right eye	−0.609	0.00**
Contrast Sensitivity	0.366	0.019**
PedsQL[2] and Logmar VA[3], left eye	−0.299	0.018**
PedsQL[2] and Logmar VA[3], right eye	−0.197	0.122

[1] Effects of Youngsters' Eyesight on QOL; [2]Pediatric Quality of Life Inventory; [3]Visual Acuity; **$p < 0.05$

There were significant associations between the EYE-Q and standardized measures.

Conclusions: Our study confirms the validity and reliability of our EYE-Q and the contribution of visual function to overall QOL. Studies on QOL in JIA-U should incorporate all components of disability in their analysis and not rely only on objective measurements of vision or measures of overall QOL. Our EYE-Q may be an important instrument in the assessment of vision related QOL in children with JIA-U and a better measure than VA or measures of overall QOL alone.

Disclosure: S. Angeles-Han: Emory Egleston Children's Research Center Seed Grant, 2, Knights Templar Eye Foundation, Inc, 2; **K. Griffin:** None; **M. J. Harrison:** Pfizer Inc, 3; **K. Fields:** None; **L. Ponder:** None; **R. Reeves-Robb:** None; **M. Shainberg:** None; **P. Lenhart:** None; **A. Hutchinson:** None; **S. Srivastava:** None; **S. Prahalad:** None; **S. Lambert:** None; **C. Drews-Botsch:** None.

1406

Sleep in Polyarticular Juvenile Idiopathic Arthritis: An Electronic Daily Diary Study. Maggie H. Bromberg[5], Cecelia R. Valrie[4], Mark Connelly[1], Kelly K. Anthony[3], Lindsey Franks[3], Karen M. Gil[6] and Laura E. Schanberg[2]. [1]Children's Mercy Hospital and Clinics, [2]Duke Univ Medical Center, Durham, NC, [3]Duke University Medical Center, Durham, NC, [4]East Carolina University, [5]University of North Carolina at Chapel Hill, Carrboro, NC, [6]University of North Carolina at Chapel Hill

Purpose: In addition to joint pain and stiffness, children with arthritis may experience sleep problems. Recently, researchers have used electronic surveys to track symptom and behavior fluctuations, including sleep, in home settings. This study compares child- and parent- reported daily electronic surveys describing children's sleep quality.

Methods: The sample consisted of 31 children with active polyarticular arthritis (27 girls; 80.7% Caucasian; mean age 12.7 years, 45% with moderate

to severe disease severity) and their parents (87% mothers; mean age 41.7 years). As part of a larger study, all participants recorded symptoms on an electronic survey via a smartphone three times each day for one month, including ratings of child sleep each morning. Physicians completed disease severity ratings at baseline. Sleep quality was rated on an electronic visual analog scale with the anchors "Did not sleep well" and "Slept very well." Daily sleep quality reports were aggregated, descriptive statistics were performed on all sleep variables, and compliance rates were calculated. Dependent sample t-tests were used to compare average parent and child sleep quality ratings.

Results: Children completed 65% and parents completed 72% of all possible electronic morning reports. Averaging all reports, children in the sample reported moderate to high sleep quality (m = 70.09, SD = 27.77). Parent ratings of child sleep quality were not significantly different (t = −0.59, p >.05). Children and parents' individual sleep quality entries spanned the full range of 0–100mm. Poor sleep quality (>1SD below the mean) was reported by children on 18% and parents on 25% of all morning reports. Self-reported sleep quality did not vary by gender (t=−1.58, p>.05). Neither child nor parent-reported average sleep quality scores correlated with physician-rated disease severity (r =.27, p >.05; r=.22, p >.05) or age (r = −.25, p >.05; r=−.18, p >.05). However, average self-reported pain (m = 28.6, SD =21.9) and self-reported sleep quality were significantly correlated (r = −.45, p <.05), as were parent-reported average pain (m = 28.42, SD = 20.66) and parent-reported average sleep quality (r = −.41, p <.05). Children reported sleeping 4–8 hours on 55.7% of nights and 8–10 hours on 33.4% of nights, and reported mild difficulty with sleep onset and few night wakenings.

Conclusions: Parents and children completed comparable numbers of morning electronic diary surveys, suggesting that children can adequately complete independent entries using this new technology. Self- and parent-ratings of child sleep quality were similar, supporting the use of child self-reported sleep ratings in future studies. Children generally reported adequate sleep duration and few sleep disruptions during the night. Although disease and demographic variables were not related to sleep quality scores, pain intensity reports correlated to sleep quality. Despite adequate sleep quality on average, children reported experiencing poor sleep quality on 18% of morning reports, suggesting daily variability. Additional research is needed to identify factors effecting daily sleep quality and to determine the clinical impact of sleep quality variability.

Disclosure: M. H. Bromberg: None; **C. R. Valrie:** None; **M. Connelly:** None; **K. K. Anthony:** None; **L. Franks:** None; **K. M. Gil:** None; **L. E. Schanberg:** None.

1407

Clinically Meaningful Improvements in Health-Related Quality of Life, Pain and Sleep Quality in Children with Polyarticular Juvenile Idiopathic Arthritis Treated with Abatacept over the Long Term. Daniel J. Lovell[3], Nicolino Ruperto[15], Pierre Quartier[19], Eliana Paz[13], Nadina Rubio-Perez[10], Clovis A. Silva[5], Carlos Abud-Mendoza[6], Ruben Burgos Vargas[7], Valeria Gerloni[16], José A. Melo-Gomes (Andre Dos Santos)[14], Claudia S. Magalhães[18], Flavio Sztajnbok[12], Claudia Goldenstein-Schainberg[17], Morton Scheinberg[8], Inmaculada Calvo Penadés[11], Michel Fischbach[4], Javier Orozco[9], Lisa Rosenblatt[1], Monica Mody[1], Marleen Nys[2], Edward H. Giannini[3] and Alberto Martini[15]. [1]Bristol-Myers Squibb, NJ, [2]Bristol-Myers Squibb, Braine-l'Alleud, Belgium, [3]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [4]Hôpital Universitaire Hautepierre, Strasbourg, France, [5]Hospital Das Clinicas, Sao Paulo, Brazil, [6]Hospital General "Dr Ignacio Morones Prieto", San Luis Potosì, Mexico, [7]Hospital General de México and Universidad Nacional Autónoma de México, Mexico City, Mexico, [8]Hospital Israelita Albert Einstein, Research Institute, São Paulo, Brazil, [9]Hospital San Javier, Rheumatology, Guadalajara, Jalisco, Mexico, [10]Hospital Universitario "Dr. J. E. Gonzalez", Monterrey, Mexico, [11]Hospital Universitario La Fe, Valencia, Spain, [12]Hospital Universitario Pedro Ernesto, Rio de Janeiro, Brazil, [13]Instituto de Salud del Nino, Lima, Peru, [14]Instituto Portugues de Reumatologia, Lisbon, Portugal, [15]IRCCS G Gaslini, Pediatria II-PRINTO, Università di Genova, Genova, Italy, [16]Istituto Gaetano Pini, Milan, Italy, [17]Universidade de São Paulo, São Paulo, Brazil, [18]Universidade Estadual Paulista, Botucatu, Brazil, [19]Universite Paris-Descartes and Centre de Reference National Pour les Arthrites, Paris, France

Background: Systemic inflammation, chronic arthritis and possible joint damage can lead to functional impairment and diminished health-related quality of life (HRQoL) in children and adolescents with juvenile idiopathic arthritis (JIA). In a double-blind (DB), placebo-controlled, randomized withdrawal trial (RWT)[1] in subjects with polyarticular JIA, abatacept significantly improved multiple aspects of HRQoL, pain and sleep quality[2]. Here we report follow-up data on these variables for up to 31 months of treatment, including 21 months of the long-term extension (LTE) of this trial.

Methods: Subjects in the RWT treated with abatacept who achieved an ACR Pedi 30 response in a 4-month open-label lead-in were randomized 1:1 to DB abatacept or placebo for 6 months or until flare[2]. Subjects eligible to enter the open-label LTE (10 mg/kg abatacept) included ACR Pedi 30 non-responders (NR) from the lead-in who did not enter the DB period, and subjects randomized into the DB phase who either flared or completed the 6-month DB period. HRQoL was assessed by the Child Health Questionnaire (CHQ), which includes 15 health concepts, sleep quality by the Children's Sleep Habits Questionnaire (CSHQ) (score 0–100) and parent global assessment of pain by 0–100 mm VAS. Mean CHQ component scores are also presented for healthy children[3]. Data up to Month 21 of the LTE are presented for subjects who entered the LTE (either NR from the open-label lead-in or subjects treated with abatacept during the DB period), and who had data available at the visit of interest (as-observed).

Results: At study entry, subjects had considerably lower HRQoL than the general population[1]. Mean changes in CHQ components from baseline to Month 31 generally indicated improvements in both patient cohorts, with greater changes seen for DB abatacept patients compared with open-label NRs (Table). Mean scores at Month 31 for each CHQ component were generally comparable to scores for healthy children. Reductions from baseline in CSHQ scores and pain also were comparable by Month 31 for the DB abatacept versus NR cohorts: mean (95% CI) changes in CHSQ total scores were –3.5 (–6.5, –0.5) versus –2.9 (–6.3, 0.6), and in parent global assessment of pain were –31.2 (–37.8, –24.6) versus –20.6 (–30.2, –10.9) (n=28, n=16, n=50 and n=22, respectively).

	Healthy children	DB abatacept N = 58‡		Open-label NR N = 36‡	
	Mean (SD) scores	Mean (SD) score at Month 21	Mean change to Month 21	Mean (SD) score at Month 21	Mean change to Month 21
CHQ components*					
Global health	86.7 (16.6)	73.8 (22.1)§	31.2 (22.9, 39.4)§	65.2 (27.4)	25.9 (12.3, 39.6)
Physical function	97.2 (10.8)	79.6 (28.1)	24.4 (16.9, 31.8)	78.3 (27.8)	20.2 (7.7, 32.7)
Role/Social Emotional	96.7 (12.8)	86.7 (25.2)	17.2 (7.3, 27.1)	82.3 (28.8)	4.0 (−8.4, 16.4)
Role/Social Physical	96.3 (12.6)	87.3 (25.5)	20.9 (10.7, 31.3)	78.0 (31.0)	5.3 (−7.3, 17.9)
Pain/discomfort	89.7 (16.4)	80.6 (20.5)‖	31.6 (23.4, 39.8)‖	68.6 (25.7)	19.6 (10.5, 28.6)
Behaviour	79.5 (14.5)	82.2 (12.7)	12.2 (6.7, 17.6)	82.1 (15.0)	12.9 (6.8, 19.0)
Global behaviour	80.0 (18.8)	78.0 (19.9)	13.3 (5.8, 20.9)	75.7 (22.4)	15.0 (0.3, 29.7)
Mental health	78.5 (14.1)	78.3 (18.5)	12.7 (7.2, 18.1)	75.0 (19.0)**	7.7 (−2.1, 17.5)**
Self esteem	81.8 (16.6)	79.4 (20.1)	11.8 (6.2, 17.4)	81.9 (18.4)**	14.1 (2.5, 25.7)**
General health	77.7 (15.4)	62.7 (15.5)	11.9 (7.0, 16.8)	59.9 (17.1)	12.5 (4.8, 20.2)
Change in health†	59.4 (19.0)	4.5 (0.8)	1.0 (0.7, 1.4)	4.4 (1.0)**	1.1 (0.5, 1.7)**
Parental emotional impact	79.7 (23.0)	65.0 (32.6)	22.2 (12.8, 31.7)	70.1 (30.4)	18.2 (5.1, 31.3)
Parental time impact	90.9 (18.3)	88.2 (21.0)	20.7 (12.4, 29.0)	79.3 (27.7)	3.0 (−7.2, 13.3)
Family activity	89.7 (14.4)	89.6 (15.9)	13.0 (7.8, 18.3)	79.7 (27.3)	5.7 (−7.9, 19.3)
Family cohesion	75.3 (20.4)	76.5 (19.7)	10.9 (3.6, 18.2)	71.8 (24.9)	3.6 (−9.8, 17.1)

*Higher scores on the CHQ indicate better HRQoL; †Note that change in health scores for subjects in this study are on a 1–5 scale, whereas those for healthy children have been transformed to a 0–100 scale; ‡N is the number of patients who entered the LTE from each group, and data shown are for patients with data available at baseline and the visit of interest, with n = 51 for DB abatacept and n = 22 for open-label NRs, except §n = 48, ‖n = 50; **n = 21

Conclusions: Treatment with open-label abatacept for up to 31 months resulted in improvements in multiple aspects of HRQoL, to within the range of healthy children, for subjects with JIA, including those who were ACR Pedi 30 non-responders in the lead-in period. These data suggest that long-term abatacept treatment can provide real-life tangible health-related benefits to children with polyarticular JIA.

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1408

Jointly Managing Arthritis: Information Needs of Children with Juvenile Idiopathic Arthritis (JIA) and Their Parents. Jennifer Stinson[4], Brian M. Feldman[5], Ciaran Duffy[3], Adam Huber[2], Lori Tucker[1], Patrick McGrath[2], Shirley M. Tse[5], Ross Hetherington[5], Lynn Spiegel[5], Sarah Campillo[3], Susanne Benseler[5], Navreet Gill[5], Meghan E. White[5] and Abi Vijenthira[5]. [1]BC Children's Hospital, [2]IWK Health Centre, [3]Montreal Children's Hospital, [4]The Hospital for Sick Children, Toronto, ON, Canada, [5]The Hospital for Sick Children

Purpose: This study explores the information needs of children with JIA and their parents in order to develop a web-based program of disease-specific information, management skills, and social support aimed at improving their quality of life.

Methods: A qualitative study design was used. A purposive sample of children (n=41, 73% female) between 8 and 11 years of age diagnosed with JIA and one of their parents (n=48), was recruited from four Canadian tertiary care centers (Vancouver, Toronto, Montreal, Halifax). Parent-child dyad interviews (n=29) and 4 separate child and parent focus group interviews were conducted using semi-structured interview guides. Audiotaped interviews were transcribed verbatim. Nvivo 8.0 (QSR, 2009) was used to assist with sorting, organizing and coding data. The thematic analysis was a collaborative and iterative process. Data were organized into categories that reflected the emerging themes.

Results: Preliminary findings uncovered two major themes: "Living with Arthritis" and "Jointly Managing Arthritis". Major subthemes for "Living with Arthritis" were: pain, maintaining friendships, communicating about the disease, and worry/distress. Two further sub-themes were found under worry/distress: parents expressed concern about their child's future, and children wondered "why me?" Two sub themes were identified under "Jointly Managing Arthritis" where managing JIA was viewed as being a joint responsibility between the parent and child. The first sub theme, "desire for information and disease management strategies", highlighted the need for further information on JIA, medications, tests and procedures, managing pain and emotions, and advocacy and communication strategies. The second sub theme was staying strong and seeking social support. Participants explained that staying strong as a family was essential, and they also wanted the opportunity to connect with others with JIA to help them feel that they are not alone. Finally, children and their parents felt that a web-enabled program of JIA information, disease management strategies and opportunities for social support would be the ideal way to meet their information needs.

Conclusions: In order to jointly manage JIA, children and their parents expressed the need for disease-specific information, management strategies, and social support. Web-enabled treatments are a promising avenue to improve the accessibility and availability of JIA information and disease management strategies for children and their parents. Findings from this study will be used to develop and test an on-line program to help children and their parents jointly manage arthritis.

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1409

Follow-Up Survey on Adolescent Rheumatology Patients' Online Activities and Social Support Systems: Opportunities for Transition Program Development. Peter Chira. Stanford University, Palo Alto, CA

Purpose: To evaluate current trends of social support systems and online behaviors of teen patients attending Stanford pediatric rheumatology clinic at Lucile Packard Children's Hospital (LPCH) and to assess opportunities for a transition intervention

Methods: We administered a written survey to consecutive teen rheumatology patients ages 13–22 during routine LPCH rheumatology clinic visits from April-June 2010. Informed consent and assent were obtained from parents (and participants ≥18) and teens <18, respectively. Stanford University's IRB approved the study. The survey is based on one administered in 2003. Descriptive statistics are presented. Trends are compared between surveys.

Results: 120 patients completed the survey (Table 1). Most have discussed their disorder with another, typically parent (95%) or friend (81%); few had spoken to a peer with a similar rheumatic disease (22%), and this is an increase from 2003. Computer and internet use are pervasive: 89% use email but only 38% check daily, and 74% use social networking sites, with 54% checking daily. Online communications such as chat room and IM are used less often than in 2003 (16%, 51% vs 33%, 69%, respectively), with a drop in daily IM from 33% to 24%. 90% have cellphones, and calling (87%), texting (78%), and taking pictures (73%) are the most common uses. 44% send >50 text messages daily.

Teens go online to learn about their rheumatic condition more frequently than in 2003 (73% vs 44%) but still seek a reliable website to find this information as well as an online personal record of their own medical/health information (83% and 80%).

Table 1. Teen Patient Characteristics, Computer and Internet Use, Social Support Systems

		2010 survey (N = 120) n	%	*2003 survey (N = 101) n*	*%*
Gender					
	Male		29.2	*28*	*27.8*
	Female	85	70.8	*73*	*72.2*
Age					
	Years (Mean, S.D)	17.0 ± 2.1		*15.7 ± 2.3*	
Race/Ethnicity					
	Caucasian/White	44	36.7	*34*	*33.6*
	Hispanic/Latino	32	26.7	*24*	*23.8*
	Asian-American/ Pacific Islander	26	21.7	*23*	*22.8*
	African-American/Black	2	1.6	*1*	*1.0*
	Multi-racial, other	16	13.3	*19*	*18.8*
Diagnoses					
	JIA	50	41.7	*37*	*36.6*
	SLE	40	33.3	*28*	*27.7*
	Other (includes vasculitis, JDM, systemic sclerosis, MCTD)	30	25.0	*36*	*35.7*
Media use					
	Home computer	113	94.2	*94*	*93.1*
	Internet access (any source)	116	96.7	*92*	*91.1*
	Home computer internet access	104	86.7	*81*	*80.2*
	Cellphone	108	90.0	*N/A*	*N/A*
	Cellphone internet access	42	35.0	*5*	*5.0*
	Looked up condition online	87	72.5	*47*	*46.5*
	Looked up any teen issues online	38	31.7	*12*	*11.9*
Social support					
	Spoken about illness with someone	117	97.5	*94*	*93.1*
	Want to meet peers with condition	74	61.7	*79*	*78.2*
	Want online contact with peers	75	62.5	*89*	*88.1*

Discussion: The Pew Survey on Social Media in Young Adults in March 2010 revealed changing trends of teen internet practices. Our survey demonstrates that teen rheumatology patients have similar online habits, but they are more likely to go online for health information and for sensitive teen topics than the general adolescent population. We note increasing use of cellphones for communication and internet access, which have affected other interactive online modalities. Interest in online meetings with teens with similar conditions is declining, but our teens prefer website development and tools to collect their personal health information that also can be a reliable resource for medical information about their condition. While many teens commonly use online social networking sites, overall interest of their use as a social support resource may be limited.

Conclusion: Technology and social media use by teens with rheumatic diseases are evolving and follow the general young adult population. Further development of programs, especially those using mobile technologies such as cellphones, will help teens to learn about and track their rheumatic conditions, as well as to assist in peer communication– all potential opportunities in the creation of a teen transition program.

Disclosure: P. Chira: None.

1410

TLR7 and IFNα Influence B Cell Selection in the Germinal Center. Ioana Moisini[1], Weiqing Huang[1], Tony Marion[3] and Anne Davidson[2]. [1]Feinstein Institute, [2]Feinstein Institute for Medical Research, Manhasset, NY, [3]University of Tennessee

Background: Male NZW/BXSB.Yaa (W/B) mice express two copies of the TLR7 gene and develop pathogenic autoantibodies whereas females with only one copy of TLR7 have attenuated disease. V_H3H9 is an autoreactive Ig heavy chain that can pair with a variety of light chains generating both autoreactive and non-autoreactive antibodies. Our goal was to analyze the regulation of the autoantibody response in male and female 3H9.W/B mice.

Methods: 3H9.W/B mice were bred and monitored for proteinuria. Some female mice received IFNα adenovirus at 3 months of age. Sera were analyzed for autoantibodies by ELISA. Mice were sacrificed at 8, 24 and 56 weeks of age and single cell PCR and sequencing of heavy and light chain Ig genes performed for all B cell subsets. Selected germline light chains were coexpressed with the 3H9 heavy chain and transfectant supernatants screened for autoreactivity by ELISA.

Results: IgM and IgG anti-CL antibodies appeared in the serum by 12 weeks of age in both males and females. Anti-dsDNA antibodies appeared in the serum of males at 12 weeks and most had high titer IgG anti-CL and anti-dsDNA antibodies and developed >300mg/dl proteinuria and thrombocytopenia by 8 months. Females had only low titer IgG anti-CL antibodies and none developed proteinuria by 1 year.

Using flow cytometry and single cell PCR of 3H9 associated light chains we showed that males had a much smaller marginal zone (MZ) with a repertoire that was distinct from the follicular repertoire, indicating that the loss of MZ B cells was not due to diversion to the follicular compartment. The germinal center (GC) repertoire was more diverse in males than in females. Vk5–45 and Vk5–48 were overrepresented in the GC repertoire of both males and females but the VJ junctions were different between males and females. For example Vk5–48 junctional diversity generated Leu at position 116 of the light chain in 88% of female sequences compared with only 22% of male sequences. In contrast there was a Phe at position 116 in 52% of male sequences but only 5% of female sequences ($p < 0.0001$). Germline 3H9/Vk5–48 with Phe116 had anti-cardiolipin, anti-histone and anti-dsDNA activity whereas 3H9/Vk5–48 with Leu116 did not bind dsDNA or cardiolipin and retained binding only to histones, a specificity associated with low renal pathogenicity. Administration of IFNa to female mice induced anti-cardiolipin and anti-DNA autoantibodies and proteinuria and was associated with a diverse GC repertoire and a male pattern of junctional diversity in Vk5–45 and Vk5–48.

Conclusions: Tolerance to cardiolipin is broken in W/B mice as they age and is regulated independently of anti-DNA reactivity. Analysis of the naïve repertoire suggests a shift in the threshold for negative selection in males resulting in deletion of MZ B cells. In contrast, selection into or expansion in the germinal center is a major checkpoint for regulation of autoreactivity, and female germinal centers are regulated more stringently than those of the males. Our studies are consistent with the hypothesis that TLR7 overexpression or exogenous IFNα relaxes the stringency for selection in the germinal centers resulting in increased autoreactivity of the antigen driven B cell repertoire.

Disclosure: I. Moisini: None; **W. Huang:** None; **T. Marion:** None; **A. Davidson:** None.

1411

Impaired Somatic Hypermutation in Pre-Switch Memory B Cells and Modulation of Mutational Targeting in Memory B Cells during Tocilizumab Treatment in RA Patients. Khalid Muhammad[1], Petra Roll[1], Stefan Kleinert[2], Thomas Seibold[2], Martin Feuchtenberger[2], Thomas Dörner[3] and Hans-Peter Tony[2]. [1]Department of Medicine II, Rheumatology/Clinical Immunology, University of Würzburg, Würzburg, Bayern, Germany, [2]Department of Medicine II, Rheumatology/Clinical Immunology, University of Würzburg, Würzburg, Germany, [3]Dept. of Medicine/Rheumatology and Clinical Immunology Charite Universitätsmedizin Berlin and DRFZ Berlin, Berlin, Germany

Purpose: Tocilizumab, a humanized anti-IL-6R antibody, is a novel anti-inflammatory drug with documented clinical effects in rheumatoid arthritis. Since IL-6 is a key differentiation factor of B cells, we analysed molecular effects of tocilizumab on pre- (IgD+CD27+) and post- switch (IgD-CD27+) memory B cells in vivo.

Methods: Memory B cell subsets were analyzed from 10 RA patients by using single B cell sorting technique followed by nested PCR and Ig-VH3/VH4 sequencing. 6/10 received tocilizumab (8 mg/kg every 4 weeks) and 4/10 received as a control population anti-TNFα therapy with etanercept.

Results: Pre-therapy analysis of 344 rearranged IgR sequences from 10 RA patients revealed a diversified mutational pattern of pre-switch memory B cells containing mutated and non-mutated sequences. Patients receiving tocilizumab (n=6) showed a reduced mutational frequency in Ig-receptors of pre-switch memory B cells along with a marked reduction of the highly mutated Ig-receptor population at week 12 and 24 after tocilizumab. In detail, the mutational frequency of pre-switch memory B cells decreased from 4.1±0.2 %(mean±SEM) to 2.9± 0.1 % (P=0.0001) at week 12 and 2.5±0.2 %(P=0.0001) at week 24, respectively. Pre-switch memory B cells contained 50.6±2.3% highly mutated sequences (>9 mutations/sequence) before treatment which declined to 28.5±2.0% and 22.5± 4.5% at week 12 and week 24 (P=0.0001), while low mutated sequences (≤9 mutations/sequence) increased significantly from 43.1±2.7% to 65.1±1.8% and 63.6±4.0 (P=0.0001). This included a significant increase of unmutated sequences at week 24(6.3±1.8 vs. 13.9±4.2, P=0.0001) after tocilizumab. The mutational frequency within post-switch memory B cells was unaffected. Analysis of the mutational hotspot RGYW/WRCY(R= A/G, Y=T/C, W=A, T) motifs indicated significantly decreased targeting in pre-switch memory B cells (24.3± 14% before therapy versus 17± 1.0% and 16± 0.6%, P<0.025) as well as in post-switch memory B cells (30.2±3.2% before therapy versus 17.2±2.0% and 16.0±0.5%, P<0.025) at week 12 and week 24 under tocilizumab.

In contrast, anti-TNFα therapy (n=4) had no effect on both, mutational frequency and mutational targeting of hotspot motifs in pre- and post-switched memory B cells.

Conclusions: Our data suggest that pre- and post-switch memory B cells are susceptible to IL-6R inhibition in vivo. Particularly, acquisition of mutations was substantially altered in pre-switch memory B cells, while targeting of mutational hotspots affected both pre- and post-switch memory B cells. The results indicate that pre- and post-switch memory B cells have a differential dependence on the IL6/IL6R system for differentiation in vivo which can be influenced by anti-IL6R therapy.

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1412

IL-17 Downregulates NF-κB1/p50 and Upregulates BCL6 To Promote Germinal Center B Cell Differentiation in Autoimmune BXD2 Mice. Shutao Xie[2], Hui-Chen Hsu[2], Jun Li[2], Qi Wu[2], PingAr Yang[2] and John D. Mountz[1]. [1]Univ Alabama at Birmingham, Birmingham, AL, [2]Univ Alabama at Birmingham

Background: Suppression of NF-κB1/p50 by transcription factor BCL6 has been shown to be associated with early germinal center (GC) B cell differentiation. BXD2 mice express high levels of IL-17 and spontaneously develop lupus and erosive arthritis. We previously showed that IL-17 can regulate the migration behavior of B cells *via* the canonical NF-κB P-p65 signaling pathway to facilitate the close contact of B and T cells in spontaneous GCs. This study is to determine if IL-17 can promote GC B cell differentiation through its effects to modulate the expression of BCL6 and NF-κB1/p50.

Methods: Purified splenic B cells from BXD2, BXD2-*Il17ra*$^{-/-}$, B6 or B6-*Il17ra*$^{-/-}$ mice were incubated with or without IL-17 or IL-21 *in vitro*. NF-κB proteins were analyzed by western blot using antibodies against P-p65, p50, p105. Adenovirus (Ad)-IL-17RA:Fc, AdIL-17A, AdLacZ, an anti-IL-17 neutralization antibody and an isotype control antibody were administered into BXD2 mice. Expression of *Rgs, Irf4, Bcl6* and *Nfkb1* were determined by qRT-PCR. Expression of BCL6 in GC B cells was determined by FACS. B cells were stimulated *in vitro* with anti-CD40 (2 mg/ml) + anti-mouse Ig (4 mg/ml) in vitro.

Summary of the Results: IL-17 by itself upregulated the expression of *Bcl6* and downregulated nuclear expression of p50 in BXD2 B cells *in vitro*. IL-17 also acted synergistically with IL-21 to upregulate the expression of *Bcl6* in BXD2 B cells. *In vivo* blockade of IL17Rα signaling by administration of anti-IL-17 decreased BCL6 in BXD2 GC B cells. Consistent with this,

administration of AdIL-17RA:Fc, which blocks IL-17/IL17Rα signaling, to BXD2 mice also resulted in signficantly decreased BCL6, increased p50 and p105, and decreased P-p65 in B cells. Administration of AdIL-17A to BXD2 mice induced opposite effects. Both p50 and p105 in IL-17RA intact B cells were significantly lower than those in *Il17ra*$^{-/-}$ B cells from both B6 and BXD2 mice. BXD2-*Il17ra*$^{-/-}$ B cells also exhibited higher nuclear localization of p50, and when induced with anti-CD40 + anti-IgG, they showed dramatically lower expression of classical NF-κB responsive genes including *Rgs* (>10.0-fold, $p<0.001$) and *Irf4* (>4.0-fold, $p<0.01$), compared with anti-CD40 + anti-IgG stimulated BXD2-*Il17ra*$^{+/+}$ B cells.

Conclusion Reached: Our results reveal a novel mechanism for IL-17 to regulate the development of GC B cells in autoimmune BXD2 mice in that: (i) IL-17 can directly upregulate BCL6 to facilitate GC B cell differentiation; and (ii) IL-17 suppresses the NF-κB1/p50 to promote a global canonical NF-κB P-p65 pathway facilitating GC formation and GC B-cell development.

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1413

Targeting the Splicing of mRNA in Autoimmune Diseases: BAFF Inhibition in Sjögren's Syndrome as a Proof of Concept. Nienke Roescher[5], Jelle L. Vosters[2], Ghada Al Saleh[6], Patrick Dreyfus[7], Sebastien Jacques[4], Luis Garcia[7], Gilles Chiocchia[4], Antoine Francois[6], Jean Sibilia[6], Paul P. Tak[1], Jay A. Chiorini[5], Xavier Mariette[3] and Jacques-Eric Gottenberg[6]. [1]Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, [2]Academic Medical Center/University of Amsterdam, [3]Bicetre Hospital, [4]Cochin Hospital, [5]National Institutes of Health, National Institute of Dental and Craniofacial Research, [6]Strasbourg Hospital, EA 4438, [7]UMR 7215 CNRS, Institut de Myologie

Background: B-cell activating factor of the TNF family (BAFF) is a relevant target in autoimmunity. BAFF is increased in various animal models of autoimmunity and in patients with autoimmune diseases, including Sjögren's syndrome (SjS). Moreover, inhibition of BAFF using monoclonal antibodies or soluble receptors improves the course of arthritis, diabetes, and systemic lupus erythematosus in animal models of autoimmunity. There are as yet no data available regarding the efficacy of BAFF inhibition on salivary gland (SG) inflammation and dysfunction in animal models of SjS.

Delta BAFF is a physiological non-secreted inhibitor of BAFF. It prevents the intracellular binding of BAFF to other monomers of BAFF and APRIL, another important factor in the activation and survival of B cells, and inhibits BAFF secretion. Delta BAFF is a splice variant of BAFF and lacks a single exon compared with full length BAFF (exon 3 in humans, exon 4 in mice), which is naturally more abundant than delta-BAFF.

The use of exon skipping to promote the expression of one shorter variant over the predominant full length mRNA has shown encouraging effects for the treatment of the monogenic disease Duchenne's myopathy and offers exciting therapeutic opportunities for many other diseases. We hypothesized that targeting the splicing of BAFF mRNA using exon skipping and thereby decreasing BAFF may improve features of SjS.

Methods: Adeno-associated virus (AAV) and lentiviral vectors were constructed encoding U7 RNA with an antisense sequence targeting the exon of BAFF, which is absent in delta-BAFF. The expression of BAFF and delta-BAFF mRNA was assessed by PCR after infection of U937 and human lymphoma cell lines.

Exon skipping-inducing AAV (AAV 161) or an AAV control vector encoding for beta galactosidase (LacZ) were administered by retrograde canulation of the submandibular glands of 19 NOD mice at the age of 10 weeks. Salivary gland function was assessed and expression of BAFF and SG inflammation was determined by quantitative immunohistochemistry 10 weeks post-treatment.

Results: In vitro transfection of U937 and human lymphoma cell lines with an exon skipping inducing lentivirus resulted in a marked decrease of BAFF and an increase of delta-BAFF mRNA and decreased BAFF protein in the supernatant.

In vivo, BAFF expression in the SG was significantly decreased (48% decrease in optical density per mm2, $p<0.05$) in mice treated with AAV161. Stimulated saliva flow increased with almost 100% from 2.0 (control LacZ mice) to 3.8 (AAV161) ul/20min/gram body weight, $p<0.01$. In addition, treatment with AAV161 decreased the average number of salivary gland lymphocytic infiltrates per cross sectional surface area of the SG (3.9 vs 2.4, $p<0.05$) and reduced the number of B (Δ87%, $p<0.05$) and plasma cells (Δ69%, $p<0.01$), compared with control mice.

Conclusion: These results demonstrate the efficacy of BAFF inhibition on features of SjS in NOD mice and offer a rationale to evaluate BAFF inhibition in patients with SjS. This study also represents a proof of concept of the efficacy of modulating mRNA splicing in autoimmune diseases.

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1414

Adoptive Transfer of Long-Lived Plasma Cells from NZB/W Mice Causes Immune Complex Nephritis in Recipient Rag1−/− Mice. Quingyu Cheng[3], Imtiaz M. Mumtaz[1], Bimba F. Hoyer[1], Andreas Radbruch[4] and Falk Hiepe[2]. [1]Charité - Universitätsmedizin, Berlin, Germany, [2]Charité - Universitätsmedizin, Berlin, Berlin, Germany, [3]Charité - Universitätsmedizin Berlin, Berlin, Germany, [4]German Rheumatism Research Center, Berlin, Germany

Background: Previously, we showed that long-lived plasma cells refractory to immunosuppression significantly contribute to autoantibody production in NZB/W mice used as a model of lupus nephritis. Since immunosuppressive and B cell depletion therapy affecting only short-lived plasmablasts and plasma cells can induce remission of the disease, the role of surviving long-lived plasma cells in the pathogenesis of the disease is not well-defined.

Objectives: To elucidate the role of autoreactive long-lived plasma cells in the pathogenesis of lupus nephritis.

Methods: CD138+ plasmablasts and plasma cells were isolated by MACS technology from the spleens of >6-month-old NZB/W mice with high levels of anti-dsDNA antibodies and adoptively transferred to immunodeficient Rag1−/− mice (3 million cells/mouse). Contamination with B cells was about 2% and with T cells 0.02%. To exclude a contribution of these contaminated B cells, the corresponding number of B cells was transferred in a control experiment. Serum antibody levels in recipient mice were measured using ELISA. The recipient mice were sacrificed 21 weeks after adoptive transfer for analysis of plasma cells, including anti-DNA-secreting cells, by flow cytometry and ELISPOT as well as for renal immunohistology.

Results: Total IgG, total IgM and IgG and IgM anti-dsDNA antibody levels were measured in recipient mice starting one week after transfer and remained constant for the entire observation (21 weeks), even after cyclophosphamide treatment. Mature non-dividing plasma cells but not plasmablasts were detected in bone marrow, spleen, and kidneys of the recipient mice. Adoptive transfer of B cells in numbers corresponding to the B-cell contamination levels within the transferred plasmablast fraction did not result in significant antibody (autoantibody) levels. Proteinuria developed 21 weeks after plasma cell transfer. Renal immunohistology showed immune complex nephritis with deposition of IgG, IgM and C3.

Conclusions: Adoptive transfer of plasmablasts results in homing of long-lived plasma cells in spleen and bone barrow. Autoantibodies secreted by long-lived plasma cells can cause nephritis. This supports the suggestion to consider long-lived plasma cells refractory to conventional immunosuppression and B cell depletion as candidate targets for future therapeutic strategies.

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1415

B Cells Induced Proteinuria and Glomerulopathy in Absence of Immune Complexes Similar to Minimal Change Disease. Alfred H. Kim[1] and Andrey S. Shaw[2]. [1]Washington Univ School of Med, St. Louis, MO, [2]Washington Univ School of Med

Purpose: B cell depletion therapies have been efficacious in several immunopathologic glomerulopathies, such as minimal change disease. The contributions of B cells to proteinuria and podocyte foot process effacement remain unknown though. Here, we test whether the glomerular localization of antigen, followed by adoptive transfer of antigen-specific B cells, can induce proteinuria and glomerular disease. This would enhance our understanding of immune-based kidney diseases.

Methods: The well-characterized B cell model antigen hen egg lysozyme (HEL) was biotinylated and complexed to avidin. Following intravenous injection in mice, purified naive HEL-specific B cells were adoptively transferred and proteinuria was assessed at various timepoints post-transfer.

Kidneys were processed for immunofluorescence, H&E staining, and transmission electron microscopy. Intravital two-photon microscopy was performed on exteriorized kidneys from live, anesthetized mice.

Results: HEL was found to be embedded within the glomerular basement membrane (GBM) within 30 minutes following intravenous injection as visualized with immunofluorescence microscopy. Induction of proteinuria occurred only after the transfer of HEL-specific B cells, as compared to wild-type polyclonal B cell transfer. The presence of HEL alone in the GBM did not induce proteinuria, nor did the transfer of HEL-specific B cells in the absence of HEL injection. The proteinuria is associated with podocyte foot process effacement as visualized on transmission electron microscopy. The absence of periglomerular infiltrates on H&E stained sections were noted in both proteinuric and control mice, indicating the absence of inflammation. There was no immune complex or complement deposition within the glomeruli during proteinuria. Intravital two-photon microscopy demonstrated that HEL-specific B cells were retained only within the antigen-bearing glomeruli and became activated in situ as measured by calcium flux.

Conclusion: We have demonstrated that B cells were activated within antigen-bearing glomeruli, and induced proteinuria and podocyte foot process effacement in the absence of immune complex deposition, complement deposition, or inflammation. These are observations similar to those found in minimal change disease. These data provide additional evidence that B cells can generate pathophysiologic conditions seen in immune-based diseases in the absence of immune complexes. We hypothesize that B cell-derived cytokines are directly responsible for this phenotype, and this is currently being tested.

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Cell-Cell Adhesion, Cell Trafficking and Angiogenesis
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1416

Nuclear Factor-κB Inducing Kinase Is Preferentially Expressed in Rheumatoid Arthritis Synovial Tissue Containing Ectopic Lymphoid Neogenesis. Ae-Ri Noort[2], Katinka P. M. van Zoest[3], Mariagrazia Modesti[4], Sander W. Tas[2] and Paul P. Tak[1]. [1]Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, [2]Academic Medical Center/University of Amsterdam, The Netherlands, [3]Academic Medical Center/University of Amsterdam, [4]University of Rome

Background: Approximately 30% of synovial tissues derived from rheumatoid arthritis (RA) patients is characterized by ectopic lymphoid neogenesis (ELN). This results in structures that may resemble germinal centers, containing dendritic cells and aggregates of B and T cells. This process also occurs in other chronic inflammatory diseases. Nuclear factor-κB (NF-κB) transcription factors are essential for the expression of pro-inflammatory cytokines, but can also induce regulatory pathways. These regulatory circuits are thought to be modulated by the non-canonical NF-κB pathway of which NF-κB-inducing kinase (NIK) is a key mediator. Non-canonical NF-κB signaling can be triggered by stimuli like CD40L and lymphotoxin that are abundantly present in ELN. Therefore, the non-canonical NF-κB pathway might play an important role in ELN.

Objectives: To investigate the expression and distribution of NIK in RA synovial tissue (ST) in relation to ELN and to study the functional role of non-canonical NF-κB signaling.

Methods: ST was obtained via mini-arthroscopy from inflamed knee or ankle joints of RA patients with active disease. RA ST samples were analyzed by microarray analysis. Next, we evaluated the expression of NIK in ST of 40 RA patients using immunohistochemistry. NIK expression was scored on a semiquantitative 5-point scale (0–4) by 2 independent observers. Furthermore, we analyzed NIK and von Willebrand Factor (vWF) expression using immunofluorescence microscopy, not only in RA ST, but also in Grawitz tumour tissue and breast cancer tissue.

Results: Microarray analysis showed increased relative expression of non-canonical NF-κB pathway associated genes in ST containing ELN compared to tissue samples without ELN ($p<0.05$). Next, we confirmed these findings by immunohistochemistry. ELN was present in 15 out of 40 RA ST. NIK expression was significantly higher in ST with ELN and more abundantly present within lymphocyte aggregates (1.53 ± 0.32 vs 0.62 ± 0.19; $p<0.05$). Of interest, in the tissue away from the lymphocyte aggregates, NIK was expressed by vascular structures. Further analysis revealed that NIK positive cells were negative for the lymphatic vessel markers LYVE-1 and podoplanin. Immunofluorescence microscopy demonstrated that NIK co-localised with the endothelial cell marker vWF. We observed co-expression of NIK and vWF not only in RA ST, but also in Grawitz tumor and breast cancer tissue. Functional studies on the role of non-canonical NF-κB signaling in endothelial cells are currently being performed.

Conclusion: NIK is preferentially expressed in RA ST containing ectopic lymphoid aggregates. NIK expression in RA ST co-localised with vWF, indicating that NIK is expressed by blood vessel endothelial cells. These findings point towards an important role of the non-canonical NF-κB pathway in either blood vessel formation or in the activation of endothelial cells to attract immune cells. This could be exploited for the development of future new therapies, which would not only be applicable for RA but also for other diseases.

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1417

CXCL16 as an Early Response Chemokine in Rat Adjuvant and K/BxN Serum Induced Arthritis Models. Jeffrey H. Ruth[2], Chrisitian S. Haas[1], M. Asif Amin[2], G. Kenneth Haines III[4] and Alisa E. Koch[3]. [1]University of Luebeck - Department of Medicine I, Luebeck, Germany, [2]University of Michigan Medical School, Ann Arbor, MI, [3]University of Michigan, Ann Arbor, MI, [4]Yale University Medical School

Purpose: We and others have previously shown that the transmembrane chemokine CXCL16 and its counterpart CXCR6 are important in the pathogenesis of rheumatoid arthritis (RA) predominantly via recruitment and stimulation of mononuclear cells. However, the expression pattern of CXCL16 during the development of RA and the optimal time point for therapeutic targeting remain unclear. In the present study we determined the spatiotemporal expression of CXCL16-CXCR6 in rat adjuvant induced arthritis (AIA), a rodent model for RA. We also examined joint swelling in CXCR6 deficient ($CXCR6^{-/-}$) and wild-type (Wt) mice administered K/BxN serum, an acute model of RA.

Method: Rat AIA synovial tissues (STs) were immunostained to determine the percentage of cells expressing CXCL16 and CXCR6. CXCL16 levels were also determined in serum and ankle homogenates using ELISA assays. CXCR6 expression was evaluated on rat macrophages and tested to induce rat macrophage migration towards soluble CXCL16 using a modified Boyden chemotaxis system. Lastly, $CXCR6^{-/-}$ and Wt C57BL/6 mice were primed to develop K/BxN serum induced arthritis and evaluated for joint swelling.

Results: CXCL16 showed constitutive expression on endothelial cells in rat AIA, and was upregulated on both lining cells (LCs) and macrophages on day 14, prior to arthritis onset ($p<0.05$). CXCR6 was virtually absent in normal ST but was expressed on LCs and macrophages on day 14. CXCL16 levels in serum and joints were increased on day 4 of rat AIA, suggesting that CXCR6 positive inflammatory cells migrate very early to the ST in rat AIA. Rat macrophages constitutively expressed CXCR6 *in vitro* and migrated in response to the ligand in a dose-dependent manner. Finally, using the K/BxN serum induced arthritis model, $CXCR6^{-/-}$ mice showed significantly reduced joint swelling compared to Wt mice at day 5 after serum induction.

Conclusion: CXCL16 and CXCR6 are upregulated in the early course of rat AIA. CXCL16 positive macrophages and LCs are found predominantly prior arthritis onset. Rat macrophages express CXCR6 and migrate in response to CXCL16 *in vitro*. In addition, $CXCR6^{-/-}$ mice show significantly less joint swelling using in an acute model of RA, suggesting that CXCL16 and CXCR6 function early in disease development to recruit inflammatory cells to the joint. Our findings may help guide *in vivo* targeting strategies for the CXCL16-CXCR6 pathway in RA.

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1418

Angiogenic Potential of HMECs Is Driven by HIF-2α Overcoming the Effects of HIF-1α. Martin Hahne[2], Steffi Luetkecosmann[1], Cam Loan Tran[1], Ferenz Lohanatha[1], Manuela Jakstadt[6], Grit Kasper[4], Georg Duda[4], Paula Kolar[4], Timo Gaber[1], Gerd R. Burmester[3] and Frank Buttgereit[5]. [1]Berlin-Brandenburg Center for Regenerative Medicine, [2]Berlin-Brandenburg School for Regenerative Medicine, Germany, [3]Charite - University Medicine, Berlin, Germany, [4]Charite - University Medicine, [5]Charite University Med-Berlin, Berlin, Germany, [6]German Rheumatism Research Center

Background: Hypoxia and angiogenesis are features of inflamed tissues. For the development of the rheumatoid pannus, subsequent synovial inflammation and joint destruction, the growth of new vessels is necessary. Inhibition of angiogenesis is one potential therapeutic approach to manage inflammatory diseases like rheumatoid arthritis (RA). In this regard the transcription factors Hypoxia inducible factor (HIF)-1α and (HIF)-2α control cellular response to decreased oxygen tension thereby promoting angiogenesis. Although HIF-1α and HIF-2α share structural similarities, they are supposed to have distinct transcriptional targets with implications on the pathogenesis of RA.

Objective: We focused on the effects of HIF-2α in the process of angiogenesis. Therefore, we developed a stable human microvascular endothelial cells (HMEC) lentiviral based knockdown system for HIF-2α. This model allowed us to analyze the ability of HMECs to perform angiogenesis under hypoxia in the absence of HIF-2α.

Methods: Specific knockdown of HIF-2α was achieved using lentiviral-based shRNA technology. Absence of HIF-2α and presence of HIF-1α was proved on transcriptional level by realtime RT-PCR as well as on translational level via Western blot. Angiogenic potential of HMECs was studied using an angiogenesis assay by investigating both tubuli and node formation under hypoxia (<1% O_2). Furthermore, realtime RT-PCR was carried out for expression analysis of hypoxia driven genes *HIF1A*, *HIF2A*, *GAPDH, PGK, GLUT1, LDHA* and angiogenesis related genes *VEGFA* and *IL8*.

Results: Evidencing the successful knockdown of HIF-2α, the gene expression levels of *HIF2A* were reduced by 69% under normoxia (scr vs. HIF2shRNA; p=0.0045) with the same reductive effect of 69% under hypoxia. Moreover, strongly reduced HIF-2α protein levels were detected by Western blot. HIF-1α levels were not affected by HIF-2α knockdown. Targeting HIF-2α led to a significantly decreased node formation by factor 2 under normoxia (Nox) and factor 4.5 under hypoxic (Hox) incubation (Nox scr vs. Nox HIF2shRNA, p=0.0255 and Hox scr vs. Hox HIF2shRNA, p=0.0002). Similar effects were observed at tubuli formation with a reduction by 70% in HIF-2α targeted cells (Nox scr vs. Nox HIF2shRNA, p=0.0128 and Hox scr vs. Hox HIF2shRNA, p=0.0053). Furthermore, targeting of HIF-2α gave rise to reduced levels of *VEGFA* and *IL8* expression, whereas the expression of metabolic relevant genes *GAPDH, PGK, GLUT1, LDHA* were not affected by HIF-2α knockdown under hypoxia.

Conclusions: Our findings show for the first time in a functional assay HIF-2α (i) to be responsible for the angiogenic potential of endothelial cells and (ii) to overcome HIF-1α's impact on angiogenesis. These findings provide new insights into basic principles of angiogenesis in inflamed tissues and therefore could be of clinical importance.

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1419

Soluble Junctional Adhesion Molecule-A Promotes Angiogenesis in Rheumatoid Arthritis. Bradley J. Rabquer[1], George Boychev[2], Jeffrey H. Ruth[2], Thilo Stehle[3] and Alisa E. Koch[4]. [1]University of Michigan, Ann Arbor, MI, [2]University of Michigan, [3]University of Tubingen, [4]Unversity of Michigan, Ann Arbor, MI

Purpose: Angiogenesis is a highly regulated process of new blood vessel formation that may occur from pre-existing blood vessels. Rheumatoid arthritis (RA) is characterized by synovial hyperplasia, inflammatory cell infiltration, and neovascularization. In RA, angiogenesis is regulated by the expression of angiogenic and angiostatic growth factors, cytokines, and adhesion molecules. Junctional adhesion molecule-A (JAM-A) is a novel member of the immunoglobulin supergene family expressed by epithelial cells and endothelial cells (ECs) and mediates EC permeability, leukocyte adhesion and migration, and angiogenesis. Interestingly, JAM-A was recently found in soluble form (sJAM-A). The aim of this study was to determine if sJAM-A is present in RA synovial fluid, if it mediates angiogenesis, and which signaling pathways sJAM-A utilizes to promote angiogenesis.

Methods: We designed and performed an ELISA to determine if sJAM-A was present in normal serum and synovial fluid from patients with RA and osteoarthritis (OA). To determine if sJAM-A mediates specific angiogenic events *in vitro*, human microvascular endothelial cell (HMVEC) chemotaxis assays and Matrigel EC tube formation assays were performed. To determine if sJAM-A mediates *in vivo* angiogenesis, we performed a Matrigel plug angiogenesis assay. HMVECs were stimulated with sJAM-A to determine which signaling pathways were activated.

Results: Our results indicate that sJAM-A is present in RA synovial fluid and that sJAM-A promotes angiogenesis. sJAM-A was detectable in normal serum (n=the number of patients=8, 0.9 (mean) ± 0.2 (SEM) ng/ml) and was significantly elevated in OA (n=9, 3.0 ± 0.5 ng/ml) and RA (n=10, 2.3 ± 0.5 ng/ml) synovial fluid (both $p<0.05$). sJAM-A stimulated HMVEC migration in a dose dependent manner that was significantly greater than phosphate buffered saline (PBS, negative control) from 5 nM to 500 nM (n=4 experiments, $p<0.05$). In addition, at 50 nM sJAM-A induced significantly more EC tubes compared to PBS (n=3 experiments, $p<0.05$) in a Matrigel *in vitro* EC tube formation assay. In an *in vivo* Matrigel plug angiogenesis assay, plugs containing sJAM-A had significantly more hemoglobin than those with PBS ($p<0.05$). Lastly, sJAM-A stimulated the phosphorylation of Mek1/2 and Erk1/2 kinases in HMVECs in a time dependent manner.

Conclusions: Our results show that sJAM-A is upregulated in RA and OA synovial fluid compared to normal serum. In addition, we show that sJAM-A promotes *in vitro* and *in vivo* angiogenesis. These results suggest that modulation of sJAM-A may provide a novel route for controlling angiogenesis in RA.

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1420

Invasiveness of Rheumatoid Arthritis Synovial Fibroblasts Is Affected by Extracellular RNA and DNA. Birgit Zimmermann[3], Silvia Fischer[1], Stephanie Lefèvre[4], Angela Lehr[6], Jürgen Steinmeyer[5], Henning Stürz[2], Thomas Umscheid[7], Ulf Müller-Ladner[3], Klaus T. Preissner[1] and Elena Neumann[3]. [1]Dept of Biochemistry, Justus-Liebig-University Giessen, [2]Dept of Experimental Orthopedics, University Hospital Giessen and Marburg, [3]Dept of Internal Medicine and Rheumatology, Justus-Liebig-University Giessen, Kerckhoff-Klinik, Bad Nauheim, Germany, [4]Dept of Internal Medicine and Rheumatology, Justus-Liebig-University Giessen, Kerckhoff-Klinik, Bad Nauheim, [5]Dept of Orthopedics and Orthopedic Surgery, University Hospital Giessen and Marburg, [6]Dept of Orthopedics and Trauma Surgery, Markuskrankenhaus Frankfurt, Germany, [7]Dept of Vascular Surgery, Helios William Harvey Klinik

Background: Activated synovial fibroblasts (SF) are one of the main cell populations in the inflamed joints of patients with rheumatoid arthritis (RA). RASF contribute to synovial neoangiogenesis and are cells central for cartilage destruction. In the SCID mouse model, we could recently show the potential of RASF to migrate out of a primary implantation site, to transmigrate through vessel walls, and to leave the vasculature again at a distant implanted cartilage site. Extracellular RNA has been shown to induce neoangiogenesis, increase endothelial cell (EC) permeability and to contribute to inflammation. Extracellular DNA is also known to induce inflammation. We therefore analyzed the effects of RNA/RNase and DNA/DNase on the invasiveness, migratory, and endothelial transmigratory potential of RASF.

Methods: RASF were treated for 15 h with RNase, DNase or control medium. Monolayers of different human EC were cultured on transwell chambers (umbilical venous and primary venous EC, EC of varicose veins). For the transmigration assay, 10% FCS served as chemoattractants. After 8 h, transmigrated cells were counted. Attachment of RASF and OASF to EC was measured in a cell-to-cell binding assay. As control cells, SF from osteoarthritis (OA) patients were used. In the SCID mouse model, healthy cartilage was coimplanted subcutaneously with RASF at the ipsilateral site (I). At the contralateral site (C), cartilage without RASF was implanted. Before implantation and every other day the animals received i.v. injections and were divided in 3 groups: (1) 42 μg DNase/kg body weight (2) 42 μg RNase/kg body weight; (3) saline. After 45 days, implants were removed and scored for cartilage invasion.

Results: Stimulation of RASF with RNase and DNase resulted in reduced synthesis of pro-inflammatory, pro-destructive and pro-angiogenic factors (e.g. IL-6, IL-8, MMP-3, VEGF). RASF showed an increased medium-dependent adherence to EC monolayers in comparison to OASF. RASF were able to pass all investigated EC monolayers. The invasion of RASF at the ipsilateral cartilage was significantly inhibited by RNase as well as DNase in comparison to saline (I saline, 2.3 +/−0.7, I RNase: 1.2 +/−0.6, p=0.048; I DNase: 0.8 +/−0.3, p=0.007). In contrast, the invasion of the contralateral cartilage was not affected by RNase or DNase (Inv C saline, 1.3 +/−0.7 vs. C RNase: 1.2 +/−1.2, p=0.74; C DNase: 1.1 +/−0.6, p=0.73). RNase or DNase did not inhibit the migration of RASF to and invasion into the contralateral implant (Inv I RNase vs. C RNase: p=0.77; I DNase vs. C DNase: p=0.35).

Conclusion: RASF are able to attach to EC and to pass different EC monolayers, reflecting the ability for vascular transmigration. Extracellular DNA and RNA reduce the secretion of pro-inflammatory and pro-destructive factors by RASF. In the SCID-mouse model, the migration to the contralateral implantation site and the invasive behavior of RASF was not influenced by RNase or DNase treatment, whereas RASF at the primary implantation site showed a significant decrease in their invasiveness. Interestingly, the results show different properties in the response to RNase and DNase treatment of migratory and non-migratory RASF in the SCID mouse model.

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Citrullination of Extracellular Matrix Proteins Inhibits Synovial Fibroblast Invasion and Migration. Miriam A. Shelef[1], David A. Bennin[3] and Anna Huttenlocher[2]. [1]Department of Medicine, University of Wisconsin, Madison, WI, [2]Medical Microbiology & Immunology and Pediatrics, University of Wisconsin, Madison, WI, [3]Medical Microbiology & Immunology and Pediatrics, University of Wisconsin, Madison, WI

Purpose: The inflamed joint in rheumatoid arthritis (RA) has elevated levels of citrullinated proteins including fibronectin and collagen type II. RA patients make antibodies against citrullinated proteins, which are associated with more severe disease. However, how citrullinated proteins affect synovial cells and the development of erosive arthritis remains unknown. Since synovial fibroblasts (SFs) can migrate in the bloodstream and invade cartilage and bone, we examined how citrullinated extracellular matrix affects the migratory and invasive behavior of SFs.

Method: SFs were harvested from mouse ankle joints or synovial fluid from patients with RA or osteoarthritis and cultured. After 4–9 cell passages, SFs were analyzed for appropriate surface marker expression by flow cytometry. We then assessed invasion through citrullinated and normal Matrigel Invasion Chambers, migration across citrullinated fibronectin versus normal fibronectin coated transwells, and speed of adhesion on citrullinated versus normal fibronectin using time-lapse microscopy. Citrullination was accomplished by incubating Matrigel Invasion Chambers or fibronectin with peptidyl arginine deiminase type 2, isolated from rabbit skeletal muscle. To determine if citrullination alters integrin-mediated signaling, phosphorylation of focal adhesion kinase (FAK) and paxillin was examined by western blot analysis.

Results: SFs had dramatically impaired invasion through citrullinated invasion chambers compared to normal invasion chambers. They also displayed defective migration, slower adhesion, and reduced spreading on citrullinated fibronectin compared to normal fibronectin. SF cell lysates revealed decreased phosphorylation of FAK and paxillin after attachment to citrullinated fibronectin compared to normal fibronectin.

Conclusion: Citrullination of extracellular matrix proteins impairs SF invasion. The defects in migration, adhesion, and spreading on citrullinated fibronectin suggest abnormal integrin-mediated signaling. This idea is supported by the observed decrease in phosphorylation of FAK and paxillin, downstream targets of integrin signaling. Since fibronectin is thought to facilitate the adhesion of rheumatoid SFs to articular cartilage, potentially an initial step in joint destruction, citrullination may be a protective mechanism to halt invasion of SFs into cartilage and impede joint destruction in RA. This work supports the novel hypothesis that citrullination of extracellular matrix proteins seen in RA may be a protective response leading to decreased invasion of SFs.

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The Role of miR-155 in the Activation of RA and PsA Synovial Fluid Monocytes. Mariola S. Kurowska-Stolarska[2], Lucy Ballantine[2], Bartosz E. Stolarski[2], John Hunter[2], Foo Y. Liew[2], J. Alastair Gracie[2] and Iain B. McInnes[1]. [1]Gartnavel General Hospital, United Kingdom, [2]University of Glasgow, United Kingdom

Purpose: MicroRNA (miR) network has emerged recently as an important post transcriptional regulator of immune response. Each individual miRNA species is capable of targeting a large number of distinct mRNA transcripts often belonging to one pathway. In our previous study we identified miR-155 to be strongly up-regulated in RA and PsA synovial fluid (SF) CD14+ cells compared to matched peripheral blood (PB) CD14+ cells suggesting that this miR may be involved in regulation of inflammatory pathways in arthritic joints. The aim of our study was to investigate the impact of miR 155 on the cytokine production and transcriptomic signature of RA and PsA SF monocyte and macrophage.

Methods: CD14+ cells from SF or PB of RA patients (n=14), PsA patients (n=13) and CD14+ cells from PB of healthy controls (n=6) were purified using CD14 MACS MicroBeads. PB CD14+ cells were transfected with miR-155 or scramble mimics (20 nM). Total RNA was isolated by miRNeasy kit. TaqMan miRNA and mRNA assays were used for semi-quantitative determination of the expression of miR-155 and its targets. The expressions of U6B small nuclear RNA or beta-actin were used as endogenous controls. Target prediction program and mRNA transcriptomic signature of RA and PsA SF CD14+ cells were employed to identify the cellular targets of miR-155 in SF CD14+ cells.

Results: Overexpression of miR-155 in PB CD14+ monocytes and PB CD14+ derived macrophages triggered TNF production suggesting that miR-155 may indeed be involved in post-transcriptional control of inflammatory pathways in SF monocyte. A computational target ranking system (TargetScan human 5.1, aggregate Pct above 4.0) predicted 127 mRNA targets for miR-155. To identify mRNAs that are specifically targeted in SF monocytes we cross-referenced TargetScan predictions with a list of 2312 mRNAs that were differentially expressed in SF CD14+ cells compared to PB CD14+ cells of RA (n=8) and PsA (n=7) patients (GeneChip Affymetrix U133 plus 2). This approach produced a list of 26 miR-155 targets that were relevant to SF CD14+ activation. Among them, 24 genes were up-regulated and 2 genes were down-regulated in SF CD14+ cells compared to PB CD14+ cells. Since miRs exert their function by mRNA degradation, we focused on genes that were down-regulated in SF CD14+ cells, namely SHIP1 (Src homology-2 domain-containing inositol 5-phosphatase 1) and ZNF652 (zinc finger DNA-binding protein). Expression of SHIP1 was down-regulated by 9 and 3.9 fold in SF CD14+ cells from RA (n=8) and PsA (n=7) patients, respectively. ZNF652 was decreased by 4.43 and 2.97 fold in SF CD14+ cells from RA and PsA patients, respectively. The decrease of SHIP1 and ZNF652 expression in SF monocyte was confirmed by QPCR on additional patient samples. Experimental validation revealed that the expression of SHIP1 and ZNF652 was inhibited in PB CD14+ cells transfected with miR-155 mimic compared to control mimic transfected cells (48 ± 10% and 43± 7%, respectively).

Conclusion: This study identified functional miRNA-mRNA networks that may be responsible for pro-inflammatory activation of synovial fluid monocyte and macrophage in RA and PsA patients.

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Rapid Improvement in Health-Related Quality of Life (HRQoL) in Gouty Arthritis Patients Treated with Canakinumab (ACZ885) Compared to Triamcinolone Acetonide. A. So[6], M. De Meulemeester[4], A. Pikhlak[2], A. E. Yücel[1], U. Arulmani[3], D. Richard[3], K. Stricker[3], A. Ferreira[3], V. Murphy[3], P. Sallstig[3] and N. Schlesinger[5]. [1]Baskent University, Ankara, Turkey, [2]Moscow State University of Medicine and Dentistry, Moscow, Russian Federation, [3]Novartis Pharma AG, Basel, Switzerland, [4]Private PracticeGozée, Gozée, Belgium, [5]UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, [6]University of Lausanne, Lausanne, Switzerland

Background: Gouty arthritis is a painful inflammatory disease with a significant impact on patients' HRQoL. In gouty arthritis, the inflammatory response is initiated by interleukin-1β (IL-1β) release, due to activation of the NALP3 inflammasome by MSU crystals. Canakinumab, a fully human anti-IL-1β antibody has a long half-life and has been shown to control inflammation in gouty arthritis. This study evaluated changes in HRQoL in gouty arthritis patients following treatment with canakinumab or triamcinolone acetonide (TA).

Methods: This was an 8-week, dose-ranging, multi-center, active controlled, single-blind study. Patients ($\geq$18 to $\leq$80 years) experiencing an acute gouty arthritis flare, refractory to or contraindicated to NSAIDs and/or colchicine, were randomized to canakinumab 10, 25, 50, 90, 150 mg sc or TA 40 mg im. HRQoL was assessed as an exploratory endpoint at baseline and different pre-specified time-points using patient reported outcomes evaluating general mental and physical component summary scores and subscale scores of SF-36® (acute version 2) and functional disability (HAQ-DI©). We report HRQoL results for canakinumab 150 mg, the dose that was selected for the Phase III studies.

Results: Baseline assessments showed a major impact on the HRQoL during acute gouty arthritis. Compared to TA, canakinumab 150 mg showed greater improvements in SF-36® physical and mental component summary and subscale scores at 7 days post-dose.

In the canakinumab 150 mg group, the most severe impairment at baseline was reported for physical functioning and bodily pain; levels of 41.5 and 36.0, respectively, which improved within 7 days to 80.0 and 72.2 (mean increases of 39.0 and 35.6) approaching levels of the general US population (84.2 and 75.2). 8 weeks post-dose patients reached levels of 86.1 and 86.6 (mean increases of 44.6 and 50.6 for physical functioning and bodily pain, respectively) and these were higher than levels seen in the general US population. This was in contrast to patients treated with TA, who showed less improvement within 7 days (mean increases of 23.3 and 21.3 for physical function and bodily pain, respectively). None of the scores reached levels of the general US population 8 weeks post-dose. Functional disability scores, as measured by the HAQ-DI© decreased in both treatment groups (Table).

Table. Comparison of HRQoL scores of gouty arthritis patients treated with canakinumab and triamcinolone acetonide

Component	General US population†	Canakinumab 150 mg s.c. Baseline N = 27	Canakinumab 150 mg s.c. 7 days post-dose N = 26†	Canakinumab 150 mg s.c. Change from baseline	Triamcinolone acetonide 40 mg i.m. Baseline N = 56	Triamcinolone acetonide 40 mg i.m. 7 days post-dose N = 54†	Triamcinolone acetonide 40 mg i.m. Change from baseline
		Score	Score		Score	Score	
SF-36 scores (0–100)							
Physical component summary score	50.0* (10.0)	36.4 (8.2)	48.3 (8.6)	12.0 (10.0)	33.5 (9.2)	41.9 (9.4)	8.5 (10.4)
Mental component summary score	50.0* (10.0)	46.7 (13.6)	50.7 (11.2)*	3.4 (11.0)	44.7 (15.1)	47.9 (12.4)	2.9 (13.5)
SF-36 subscale scores							
Physical functioning	84.2 (23.3)	41.5 (30.2)	80.0 (25.5)	39.0 (30.9)	38.4 (26.5)	61.5 (29.3)	23.3 (34.6)
Role-physical	80.9 (34.0)	53.0 (32.5)	71.2 (26.8)	18.3 (28.7)	43.2 (25.4)	60.5 (29.0)	17.4 (32.4)
Bodily Pain	75.2 (23.7)	36.0 (26.6)	72.2 (22.0)	35.6 (38.8)	32.4 (25.7)	53.7 (28.6)	21.3 (35.3)
General health	71.9 (20.3)	65.4 (18.0)	71.2 (18.5)	4.6 (8.6)	56.0 (20.2)	61.8 (20.7)	5.5 (18.3)
Vitality	60.9 (20.9)	53.9 (20.5)	66.6 (18.5)*	12.3 (19.5)	48.9 (25.3)	58.6 (25.5)	9.8 (24.7)
Social functioning	83.3 (22.7)	61.6 (32.1)	81.7 (23.5)	18.8 (28.3)	52.5 (29.9)	70.1 (28.3)	17.1 (32.5)
Role-emotional	81.3 (33.0)	63.9 (32.6)	80.8 (25.0)	16.3 (32.1)	66.5 (31.5)	72.1 (27.4)	6.2 (33.3)
Mental health	74.7 (18.1)	67.4 (21.1)	78.1 (18.2)*	9.6 (14.4)	60.5 (25.1)	68.5 (22.8)	8.5 (23.3)
HAQ-DI (0–3)	NA	0.8 (0.7)	0.3 (0.4)	−0.5 (0.7)	1.1 (0.7)	0.6 (0.6)	−0.5 (0.5)

Mean (SD) values are presented through-out; †for some scores evaluations were missing for up to 3 patients of the group; *normalized scores representing an average US person with no chronic disease; *reached general population levels; NA, not available

Reference: 1. Adapted from Ware J et al. SF-35 Physical and Mental Health Summary Scales: A User's Manual, Boston, MA: The Health Institute, 1994

Conclusions: All canakinumab doses showed a rapid improvement in physical and mental well-being of gouty arthritis patients based on SF-36® scores, in particular the 150 mg dose. In contrast to the TA group, patients treated with canakinumab showed improvement within 7 days in physical function and bodily pain approaching levels of the general population. The 150 mg dose of canakinumab was selected for further development in Phase III studies.

Disclosure: A. So: Abbott Laboratories, 5, Bristol-Myers Squibb, 5, Essex, 5, MSD, 5, Novartis Pharma AG, 5, Pfizer Inc, 5, Roche, 5, UBC, 5, Wyeth Pharmaceuticals, 5; **M. De Meulemeester:** None; **A. Pikhlak:** Novartis Pharma AG, 2; **A. E. Yücel:** None; **U. Arulmani:** Novartis Pharma AG, 1, 3; **D. Richard:** Novartis Pharma AG, 1, 3; **K. Stricker:** Novartis Pharma AG, 1, 3; **A. Ferreira:** Novartis Pharma AG, 1, 3; **V. Murphy:** Novartis Pharma AG, 1, 3; **P. Sallstig:** Novartis Pharma AG, 1, 3; **N. Schlesinger:** EnzymeRx, 8, 9, Novartis Pharmaceuticals Corporation, 2, 5, 9, Savient Pharmaceuticals, 9, Takeda, 8, 9, URL Pharma, 9.

1424

Toll-Like Receptor Signals Modify the ER Stress Response. Jane C. Goodall[1], Louise McNeill[2], Lou Ellis[2] and J. Hill Gaston[2]. [1]Cambridge University, Cambridge, Cambs, United Kingdom, [2]Cambridge University

During cellular stress, the decrease in protein translation caused by eIF2α phosphorylation reduces protein load in the endoplasmic reticulum (ER) which allows the cell a window of time to instigate a program of gene expression coined as the unfolded protein response (UPR). To allow the recovery of protein translation, GADD34 is activated in a negative feedback loop which dephosphorylates eIF2α and enables more efficient protein translation and recovery from cellular stress. We have previously shown that ER stress signals are induced following bacterial infection and that these signals synergise with Toll-like-receptor (TLR) signals to enhance the expression of cytokines such as IL-23.

The aim of this study was to determine if TLR signals have a reciprocal activity and modify the ER stress response and in particular the expression of GADD34, the molecule involved in translation recovery from ER stress. Monocyte derived dendritic cells (mDC) were subjected to ER stress using thapsigargin (TP) or tunicamycin (TM) in the presence or absence of different pattern recognition receptor (PRR) agonists. The expression of GADD34 mRNA and protein was induced by the ER stress stimuli, but was substantially enhanced by costimulation with LPS (TLR4), Curdlan (dectin 1) or peptidoglycan (TLR2 and NOD2) agonists.

MyD88 knockdown in the monocyte cell line THP-1, abrogated the ability of LPS to enhance GADD34 expression induced by ER stress stimuli, this effect was not seen in THP-1 cells expressing a control shRNA. This suggests that Myd88 dependent signals are required for LPS upregulation of GADD34 in the presence of ER stimulation. Using specific inhibitors for defined signalling pathways we identified that upregulation of GADD34 by LPS was dependent on the activity of p38Map kinase and ERK but not JNK and NF-κB. These inhibitors did not inhibit the upregulation of GADD34 by ER stress stimuli alone, suggesting that ER stress and LPS stimuli provide independent signals that synergise to enhance GADD34 expression.

ER stress and substantial upregulation of GADD34 expression was detected in mDC and THP-1 following infection with the intracellular bacterium, *Chlamydia trachomatis* (CT). To determine if the upregulation of GADD34 following intracellular bacterial infection was dependent on MyD88, THP-1 cells expressing MyD88 or a control shRNA were infected with CT and GADD34 expression was analysed. The upregulation of GADD34 was substantially reduced in THP-1 cells expressing MyD88 shRNA suggesting that MyD88 dependent TLR signals were required for this effect.

These data show that the regulation of protein translation has not only the potential to be modulated via ER stress but also via the stimulation of PRR pathways. This may have significant implications for the expression of pro-inflammatory or regulatory cytokines. We hypothesize that changes in GADD34 expression induced by TLRs will contribute significantly to the ability of myeloid cells to secrete pro-inflammatory cytokines in response to bacterial infection.

Disclosure: J. C. Goodall: None; **L. McNeill:** None; **L. Ellis:** None; **J. H. Gaston:** None.

1425

Canakinumab (ILARIS®) Improves Health-Related Quality of Life (HRQoL) in Patients with Cryopyrin-Associated Periodic Fever Syndrome (CAPS): Results of a Phase III, Open-Label Study in a Large Cohort of CAPS Patients. I. Kone-Paut[4], H. J. Lachmann[12], J. B. Kuemmerle-Deschner[6], E. Hachulla[3], R. Cartwright[1], J. Hoyer[2], P. Quartier[11], J. Smith[13], M. Gattorno[5], K. Leslie[10], J. Braun[9], A. Widmer[7], A. Ferreira[7], N. Patel[8], R. Preiss[8] and P. N. Hawkins[12]. [1]Allergy Center at Brookstone, Columbus, GA, [2]Department of Internal Medicine and Nephrology, Universitaetsklinikum Giessen und Marburg GmbH, Marburg, Germany, [3]Hôpital Claude Huriez CHRU, Lille Cedex, France, [4]Hôpital Kremlin Bicetre, CEREMAI, Le Kremlin Bicetre, France, [5]Istituto Giannina Gaslini, Genova, Italy, [6]Klinik fuer Kinder-und Jugendmedizin, Universitaetsklinikum, Tuebingen, Germany, [7]Novartis Pharma AG, Basel, Switzerland, [8]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [9]Rheumazentrum Ruhrgebiet, Herne, Germany, [10]UCSF School of Medicine, San Francisco, CA, [11]Unit'e d'Immunologie, Hematologie et Rhumatologie Pediatrique, Hopital Necker-Enfants Malades, Paris, France, [12]University College London Medical School, London, United Kingdom, [13]University of Wisconsin Hospital and Clinics, Madison, WI

Background: Canakinumab (a fully human anti-interleukin-1β monoclonal antibody) has been recently approved by the FDA for the treatment of familial cold auto-inflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS) and by the EU for the treatment of cryopyrin-associated periodic syndrome (CAPS). This spectrum of autoinflammatory disease is caused by overproduction of IL-1β and is associated with rash, constitutional inflammatory symptoms and marked fatigue. Health-related quality of life (HRQoL) was assessed during a phase III, open-label, multi-center study to evaluate the direct impact of the disease on patients' well-being and to assess the long-term maintenance of HRQoL.

Methods: The 119 adult CAPS patients in this study were canakinumab-naive (n=71) or rolled-over from earlier Phase II/III studies (n=48). They received canakinumab 150 mg s.c. every 8 weeks and HRQoL was assessed using the following domains: general physical and mental health (SF-36® physical and mental component summary [PCS and MCS]), fatigue (FACIT-Fatigue©) and functional disability (HAQ-DI).

Results: Median duration of exposure to canakinumab in the study was 414 days (range 29–687 days). Of the 119 adult CAPS patients there were 25 FCAS, 80 MWS, 14 MWS/NOMID [6 NOMID] patients. In canakinumab-naive patients the baseline scores (mean [SD]) for physical function (SF-36® PCS: 41.2 [10.9]) and mental health (SF-36® MCS: 45.5 [10.7]) and fatigue (FACIT-F: 32.8 [11.7]) were considerably lower than those expected in the general population (50 [10] for SF-36® PCS and MCS and 43.6 [9.4] for FACIT-F), which demonstrates the significant impact that CAPS has on patients' well-being. The scores improved rapidly after one single dose of canakinumab and approached levels of the general population after 8 weeks (SF-36® PCS, 48.4 [8.7] and MCS, 52.8 [7.7]; FACIT-F, 41.7 [9.3]). This improvement was maintained at one year, as shown by the SF-36® PCS (49.8 [8.6]) and MCS (51.2 [9.9]) and FACIT-F (42.9 [10]) scores. For patients who continued the study beyond one year for up to two years HRQoL scores remained within the range of general population at the final visit. An improvement in functional disability was also observed as shown by HAQ-DI scores, although the level of functional disability in these patients as measured by the HAQ was not marked. Patients who rolled-over from previous studies while maintaining the 8 weeks dosing schedule already had HRQoL scores close to general population levels at baseline and these levels were maintained throughout the study.

Conclusions: Canakinumab administration improved the HRQoL scores to levels seen in the general population in a large cohort of CAPS patients across all severity phenotypes.

Disclosure: I. Kone-Paut: Novartis Pharmaceuticals Corporation, 5; **H. J. Lachmann:** EU framework 7grant, 2, Novartis Pharmaceuticals Corporation, 5; **J. B. Kuemmerle-Deschner:** Novartis Pharmaceuticals Corporation, 2, 5; **E. Hachulla:** Novartis Pharmaceuticals Corporation, 5; **R. Cartwright:** Dey Pharmaceuticals, 5, GlaxoSmithKline, 8, Novartis Pharmaceuticals Corporation, 5, Pfizer Inc, 8, sanofi-aventis, 8, UCB, Inc., 8; **J. Hoyer:** None; **P. Quartier:** None; **J. Smith:** None; **M. Gattorno:** Novartis Pharmaceuticals Corporation, 9; **K. Leslie:** None; **J. Braun:** Novartis Pharmaceuticals Corporation, 2; **A. Widmer:** Novartis Pharma AG, 1, 3; **A. Ferreira:** Novartis Pharma AG, 1, 3; **N. Patel:** Novartis Pharmaceuticals Corporation, 1, 3; **R. Preiss:** Novartis Pharmaceuticals Corporation, 1, 3; **P. N. Hawkins:** Novartis Pharmaceuticals Corporation, 5.

1426

Osteoarthritis-Associated Basic Calcium Phosphate Crystals Activate the NLRP3 Inflammasome in a Syk Kinase Dependent Manner. Aisling Dunne[2], Lisa Mielke[2], Jurg Tschopp[3], Kingston H. G. Mills[2] and Geraldine M. McCarthy[1]. [1]Royal College of Surgeons, Ireland & Mater Hospital, Ireland, [2]Trinity College Dublin, Ireland, [3]University of Luasanne, Switzerland

Background: Basic calcium phosphate (BCP) crystals which were traditionally considered markers of osteoarthritis-associated (OA) tissue damage are now themselves considered potent drivers of pro-inflammatory cytokine production. In this study we investigated the ability of BCP crystals to drive IL-1β and IL-18 production through activation of the NLRP3 (NOD-like Receptor (NLR) Protein 3) inflammasome complex. In addition we assessed the ability of these crystals to induce neutrophil influx in an *in vivo* peritonitis model and to skew T cell responses towards a Th17 phenotype.

Methods: Murine and human dendritic cells (DC) were stimulated with BCP crystals, with or without priming with a Toll-like receptor (TLR) agonist and IL-1β and IL-18 production was quantified by enzyme linked immunosorbent assay (ELISA). Specific inhibitors of caspase-1 and NLRP3-deficient cells were used to determine the role of caspase-1 and the NLRP3 inflammasome complex while a role for Syk and PI3 kinase was determined with the use of the inhibitors piceatannol and LY294002, respectively. BCP-activated DC were tested for their ability to promote T cell responses using FACS analysis following treatment of splenocytes or purified $CD4^+$ T cells with supernatants from BCP-treated DC. Finally, BCP-induced neutrophil infiltration was assessed using an *in vivo* peritonitis model.

Results: Physiological concentrations of BCP crystals (50μg/ml) induced robust IL-1β and IL-18 production in a caspase-1 and NLRP3 dependent manner. IL-1β was produced at an average concentration of 2 ng/ml following a 2 hour treatment of LPS-primed DC while IL-18 production averaged at 200 pg/ml under the same conditions. This activity is dependent on lysosomal acidification and potassium efflux as pre-incubation with sub-optimal doses of bafilomycin and quinidine, the potassium channel blocker, caused a 2-fold reduction in IL-1β levels. In addition, pre-incubation with specific Syk and PI3 kinase inhibitors abrogated both IL-1β and IL-18 production. In addition to IL-1β, BCP crystals greatly enhanced the production of the Th17 skewing cytokines IL-1α and IL-23 and incubation of splenocytes or purified CD4+ T cells with supernatants from BCP treated DC promoted Th17 cell differentiation. Finally, BCP crystals promoted robust neutrophil influx in a model of crystal induced peritonitis after 6 hours.

Conclusion: Our findings demonstrate that BCP crystals induce the pro-inflammatory cytokines IL-1, IL-18 and IL-17 via activation of the NLRP3 inflammasome and identify the inflammasome, Syk kinase and PI3 kinase as potential targets for the treatment of BCP crystal-induced inflammation and tissue destruction seen in OA patients.

Disclosure: A. Dunne: None; **L. Mielke:** None; **J. Tschopp:** None; **K. H. G. Mills:** None; **G. M. McCarthy:** None.

1427

Lipid-Cytokine-Chemokine Cascade Drives Neutrophil Recruitment in a Murine Model of Inflammatory Arthritis. Nancy D. Kim[3], Richard C. Chou[1], Christian Sadik[2], Edward Seung[2], Yinan Lan[2], Yoichiro Iwakura[4] and Andrew Luster[2]. [1]Dartmouth-Hitchcock Medical Center, Lebanon, NH, [2]Massachusetts General Hospital, [3]Massachusetts General Hospital, Boston, MA, [4]University of Tokyo

Purpose: A diverse array of chemoattractants control leukocyte trafficking, but how these apparently redundant signals collaborate *in vivo* is still unknown. We previously demonstrated an absolute requirement for the lipid chemoattractant leukotriene B_4 (LTB_4) and its receptor BLT1 for neutrophil recruitment into the joint in the development of immune complex-induced arthritis. The purpose of these studies was to further dissect the sequential roles of LTB_4, IL-1β, and chemokine signaling in neutrophil recruitment in this model of inflammatory arthritis.

Methods: Using the K/BxN serum transfer arthritis mouse model, K/BxN serum was injected into C57Bl/6, BLT1−/−, CXCR2−/−, CCR1−/−, and CXCR2−/−/CCR1−/− mice, and arthritis was assessed by hind paw measurement and clinical scoring. Bone marrow neutrophils from IL-1α/β−/− mice were purified and injected for neutrophil adoptive transfer studies. On designated days, synovial fluid leukocytes and neutrophils and synovial tissue were isolated, and chemokine, chemokine receptor, and

cytokine transcription and production were analyzed by quantitative PCR and ELISA. Primary murine fibroblast-like synoviocytes (FLS), endothelial cells, and macrophages were stimulated *in vitro* with recombinant murine IL1-1β or TNF-α, and neutrophil-active chemokine expression was measured by qPCR.

Results: Synovial fluid analysis demonstrated that CCR1 was the predominant neutrophil chemokine receptor in the early phase of disease, and CXCR2 was the predominant neutrophil chemokine receptor in established disease. Synovial fluid neutrophils produced IL-1β and the neutrophil-active chemokines CCL3/MIP-1α and CXCL2/MIP-2. In contrast, synovial tissue expressed greater proportions of the neutrophil-active chemokines CXCL1/KC and CXCL5/LIX. Adoptive transfer of IL-1$\alpha/\beta-/-$ neutrophils into BLT1$-/-$ mice was not able to restore disease or chemokine expression. *In vitro* IL-1β-stimulated FLS and endothelial cells expressed primarily CXCL5/LIX and CXCL1/KC, respectively. Finally, upon induction of K/BxN serum transfer arthritis, CCR1$-/-$ mice had delayed and attenuated disease compared with wild-type mice, while CXCR2$-/-$ mice had normal onset of disease that quickly waned. Importantly, deletion of both CCR1 and CXCR2 in the mice completely abrogated arthritis development.

Conclusions: In this model of acute autoantibody-induced arthritis, we uncovered a sequence of events in which a lipid receptor (BLT1) initiates disease by promoting the influx of neutrophils producing IL-1β, which then induces CXCL1/KC and CXCL5/LIX from surrounding synovial tissue. Synovial fluid leukocytes themselves also produce CCL4/MIP-1β and CXCL2/MIP-2, promoting further neutrophil trafficking into the joint. CCR1 and CXCR2 operate in series to mediate all chemokine-dependent neutrophil recruitment. Thus, we have demonstrated that neutrophil trafficking into the joint is a tightly regulated process requiring the sequential involvement of multiple cytokine and chemoattractant pathways.

Disclosure: N. D. Kim: None; **R. C. Chou:** None; **C. Sadik:** None; **E. Seung:** None; **Y. Lan:** None; **Y. Iwakura:** None; **A. Luster:** None.

ACR Concurrent Abstract Sessions
Education

Tuesday, November 9, 2010, 4:30 PM–6:00 PM

1428

The Impact of Patient-Physician Relationship Components on Physician Trust and Treatment Adherence in Patients with Rheumatic Disease. Sofia de Achaval[1], Michael A. Kallen[1], Vanessa L. Cox[1], Marsha N. Richardson[1] and Maria E. Suarez-Almazor[2]. [1]The University of Texas M. D. Anderson Cancer Center, Houston, TX, [2]University of Texas, MD Anderson Cancer Center, Houston, TX

Background: Treatment adherence plays a significant role in the successful management of rheumatic disease. Adherence itself may be influenced by patient-physician relationship factors and a patient's overall physician trust.

Purpose: We investigated whether specific components of the patient-physician relationship were directly associated with the more global concept of physician trust; we then assessed the extent to which these relationship components influenced treatment adherence via their impact on overall physician trust.

Methods: We performed a cross-sectional study of outpatient clinic patients with rheumatic disease, i.e., Rheumatoid Arthritis (RA) or Systemic Lupus Erythematosus (SLE). Six specific components of the patient-physician relationship were measured: doctor informativeness, sensibility to concerns, reassurance and support, patient centeredness, participatory decision-making, and patient disclosure of information. Patient's physician trust was evaluated using the Wake Forest Physician Trust Scale, while treatment adherence was measured via the Compliance Questionnaire Rheumatology (CQR). A conceptual model was developed, with the relationship component variables predicting trust, and trust predicting adherence. We statistically assessed bivariate relationships across all model variables, using Pearson product-moment correlations. We then conducted a path analysis to test our conceptual model and identify statistically significant direct, indirect, and total effects of the conceptual model's patient-physician relationship variables on physician trust and treatment adherence. Path analysis' particular strength lies in its capacity to model and then simultaneously estimate a number of regression equations when exploring complex relationships. For the path analysis we analyzed the model variable covariance structure.

Results: Our sample included 311 patients (201 with RA and 110 with SLE). Eighty percent of patients were female; mean patient age was 46 years. Bivariate correlations were all positive and statistically significant ($p<0.05$) and ranged from 0.25–0.79. In the path analysis, 4 of 6 relationship component variables (doctor informativeness, reassurance and support, patient centeredness and participatory decision-making) were found to have statistically significant direct effects on trust and indirect effects on treatment adherence; trust had a statistically significant direct effect on adherence. The overall path analytic model displayed good fit to the data (chi-square$=2.56$, $p=0.63$, RMSEA<0.01).

Conclusion: Patients' perceptions of multiple specific components of their relationship with their physician are associated with patient trust in their physician, which is strongly related to treatment adherence, with greater trust enhancing adherence. Modifications to specific components of the patient-physician relationship, namely doctor informativeness, reassurance and support, patient centeredness and participatory decision-making, could potentially improve treatment adherence by increasing physician trust.

Disclosure: S. de Achaval: None; **M. A. Kallen:** None; **V. L. Cox:** None; **M. N. Richardson:** None; **M. E. Suarez-Almazor:** None.

1429

Development of an ACMGE Core Competency-Based Electronic Portfolio at the USC-LAC Rheumatology Fellowship Program. Karina Marianne D. Torralba[2], Francisco P. Quismorio[3], Beatrice A. Boateng[1] and Shylaja Rachabattula[4]. [1]Arkansas Children's Hospital-University of Arkansas for Medical Sciences, [2]University of Southern California-Los Angeles County Medical Center, Pasadena, CA, [3]University of Southern California-Los Angeles County Medical Center, Los Angeles, CA, [4]University of Southern California-Los Angeles County Medical Center

Portfolios have been utilized in health sciences education over the past 10 years to document and assess progress in training, and as a vehicle for reflection on lifelong learning. The Accreditation Council for Graduate Medical Education (ACGME) has encouraged the use of core-competency based portfolios for postgraduate training, but current and convenient formats have not been widely available. The objectives of this study are to assess the effectiveness of paper-based portfolios in our program in demonstrating achievement of ACGME core competencies, and to develop an electronic portfolio that would conveniently document evidences according to these competencies. We conducted a systematic review of paper-based fellow portfolios over the past 7 years using the following parameters: evidence management, demonstration of fulfillment of core competency criteria, ability to show reflections of lifelong learning. Our fellowship program has 2–3 fellows at each training year level. Our review revealed that evidences of education and performance (eg. conference presentations, letters to patients and insurance companies, Mini-CEX, 360 degree evaluations) were not organized according to competency mainly due to 1) physical limitations of paper portfolios to adequately show that certain evidences had applicability to more than one competency, and 2) lack of perception by learners of what educational activities and evidences were pertinent to specific competencies. There was also a lack of reflection on self-assessment of educational progress. An institution-based software for residency management (Verinform©) which is mainly used by faculty and fellows to access evaluations and procedure logs was inadequate to assess achievement of competencies. As a result, over the past 2 years, a Microsoft© Word-based portfolio was developed and implemented at our institution. We initially asked fellows and key faculty to identify the applicability of core competencies according to the various educational activities and evidences in the program. Activity/evidence-based and competency-based rubrics were then developed to help establish levels of achievement that could help fellows understand criteria for improvement and allow faculty raters criteria for evaluation. The electronic format permitted filing of evidences under multiple competencies using hyperlink and cross-referencing functions. Self-assessments using reflection were also developed. Our MS Word portfolio adequately demonstrates achievements of ACGME competencies. We seek to further evaluate the effectiveness of this portfolio and the evaluation rubrics as mentorship and career development tools.

Disclosure: K. M. D. Torralba: None; **F. P. Quismorio:** None; **B. A. Boateng:** None; **S. Rachabattula:** None.

1430

An Updated Immunology Curriculum for Rheumatology Fellows. Rahul K. Patel[1], Lisa Hodge[1], Jerry Simecka[1] and Bernard R. Rubin[2]. [1]UNT Health Science Center, Fort Worth, TX, [2]UNT Health Science Center, Birmingham, MI

Purpose: Basic immunology is a rapidly advancing area, with numerous clinical advances stemming from basic immunologic insights. Educating rheumatology fellows in training on basic immunology topics remains a challenge. Residents begin rheumatology programs having matriculated in widely different medical school and internal medicine environments. Balancing basic immunology concepts, experimental methods, and review of classic and recent immunology literature is a challenge, while maintaining a clinically relevant approach to the topic.

In an attempt to improve the basic immunology curriculum for our rheumatology fellows in training, we updated the immunology course to incorporate a clinically oriented text, lectures from clinical and basic research faculty, journal club style presentation of papers by fellows, and lectures by clinicians and basic researchers from industry.

Exam scores from a pre-test and post course test are compared.

Methods: 4 fellows (two 2nd year fellows, two 1st year fellows) completed the course. The course is taught from January to April. It consisted of 2 weekly sessions, 2 hours each, for 13 weeks. The text chosen for the course was Chapel et al Essentials of Clinical Immunology, 5th edition, 2006. Fellows were given weekly reading assignments from the text. One weekly session consisted of didactic lectures by immunology and clinical rheumatology faculty, covering key chapters from the text. The second weekly session consisted of discussion of journal papers from immunology literature. Papers were picked by rheumatology fellows to cover recent topics discussed in didactic lectures. Finally, clinical science liaisons and basic researchers from industry were invited to present unbranded talks covering basic immunology topics relevant to therapeutics in rheumatology. Participating fellows in training were given a pre-test at the start of the course, as well as a post-test at the conclusion of the course., with 30 multiple choice questions, written by immunology faculty. The pre and post tests included different questions, covering similar topics in basic immunology.

Results: Pre and post-test results were available for 3 fellows (1 fellow was absent on the pre and post test date). Results for the pre-test were 33 and 33% for both first year fellows, and 73% for 2nd year fellow with post-test results of 73 and 67% for first year fellows, and 87% for 2nd year fellow. All fellows showed an increase between pre to post test results, ranging from absolute increases of 15% to 34%.

Conclusions: Our experience suggests that rheumatology fellows' understanding of immunologic topics, as reflected by increases between pre and post test exam results, showed improvement. Further longer term data, including measuring outcomes from the rheumatology in-service exams and board certification scores, would help support whether this approach can lead to long term successful education of fellows in training on immunologic topics.

Disclosure: R. K. Patel: None; **L. Hodge:** None; **J. Simecka:** None; **B. R. Rubin:** None.

1431

A Case-Controlled Study of a Multimodal Rheumatology Elective for Medical Residents. Deana M. Lazaro[4], Sheen Yee Lim[2], David R. Blumenthal[3], Joshua Scheers-Masters[1], Jeanne Macrae[1] and Matthew Avitable[1]. [1]SUNY Downstate Medical Center, [2]SUNY Downstate-Brooklyn, Brooklyn, NY, [3]VA New York Harbor Healthcare System, Short Hills, NJ, [4]VA New York Harbor Healthcare System and SUNY Downstate Medical Center, Brooklyn, NY

Background: Training medical residents to treat patients with musculoskeletal complaints is highly desirable because of the aging United States population and relative shortage of rheumatologists. To address this concern, we tested whether first year medical residents who have clinical experience in Rheumatology clinic and an enhanced curriculum will perform better than residents without such experience on a multiple choice examination and an objective structured clinical examination (OSCE). We also surveyed the residents on their confidence and attitudes regarding musculoskeletal diseases.

Methods: Thirty-five SUNY Downstate first-year medical residents were randomized to participate in the ambulatory Rheumatology elective or another subspecialty experience for four weeks. All residents reviewed the MedStudy guide for Rheumatology and several Hopkins modules and received a copy of the Primer on the Rheumatic Diseases. The residents assigned to Rheumatology clinic were given access to 12 case-based learning modules with questions based upon the material, a video on the musculoskeletal physical examination, instruction on arthrocentesis and injection techniques using simulators, approximately 3 out-patient Rheumatology clinic sessions each week and weekly journal club. All residents completed a 45 question pre- and post-test, 4 OSCE stations focused on the evaluation and treatment of musculoskeletal diseases and completed a pre- and post-questionnaire to gather information on the confidence of the residents in their knowledge of Rheumatology.

Summary of the Results: All residents improved performance on the multiple choice examination after the clinical rotations, however, there was no significant difference in the improvement rate pre- and post- rotation between the groups ($p=0.18$). Likewise performance on the OSCE was similar with the exception of the station on arthrocentesis. The residents who received a training session on arthrocentesis and injection technique and had the opportunity to interact with patients in the rheumatology clinic performed significantly better ($p=0.02$). The residents assigned to the rheumatology clinic reported greater confidence in their ability to treat patients with arthritis ($p=<0.001$).

Conclusions: Exposure of medical residents to an enhanced curriculum and experience in rheumatology clinic improved performance of arthrocentesis as demonstrated on a simulator and increased their perception of their abilities. Rate of improvement on the multiple choice examination and the other OSCE stations were not significantly different between the two groups.

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1432

Effect of Internal Medicine Resident Participation in Team-Based Learning on In-Training Exam Scores in Rheumatology. Karina Marianne D. Torralba[2], Beatrice A. Boateng[1], Ron Ben-Ari[3] and Francisco P. Quismorio[2]. [1]Arkansas Children's Hospital-University of Arkansas for Medical Sciences, [2]University of Southern California-Los Angeles County Medical Center, Los Angeles, CA, [3]University of Southern California-Los Angeles County Medical Center

Objective: Team-based learning (TBL) has been utilized as a teaching strategy for Rheumatology core curriculum learning sessions (CCLSs) of residents at the University of Southern California-Los Angeles County Internal Medicine Residency program since 2008. TBL is an interactive small group learning technique that encourages accountability, teamwork and has been demonstrated to improve board scores and patient care. This study seeks to examine if there is a correlation between attendance and participation in TBL sessions on the Rheumatology component of the Internal Medicine In-training exam (IM-ITE) scores.

Method: There have been 13 TBL-CCLSs over a two-year period (2008/09 and 2009/10) on various connective tissue diseases including rheumatoid arthritis, osteoarthritis, myopathies and spondyloarthropathies. Resident attendance of TBL sessions and their ITE scores were recorded. Data was collected on two groups: group 1 represents residents who were in their year 1 of residency when the TBL sessions started and group 2 are those who were in year 2. Of 129 residents, 117 participated in the TBL-CCLSs over the 2-year period. Twelve residents did not participate in any TBL session; however their ITE scores are included in the analysis. ANOVA, T-test and Scheffe's post-hoc analysis were used to analyze the data.

Results: TBL-CCLSs were required for residents however they are not always able to attend due to other responsibilities. Data were stratified into quartiles based on total attendance: no attendance; low, $\leq$4 times; medium, 5–9 times, high, $>$9. The average attendance was 3.17 $\pm$2.22 (SD). There was an increase in ITE scores over the two-year period. TBL participation had no significant effect on ITE scores (ANOVA). Scheffe's post-hoc analysis was conducted to determine if there were any significant differences among the three levels of attendance in TBL. There was a significant difference in the mean ITE scores of residents with medium attendance (5–9 sessions) when compared to those with low attendance (1–4 sessions) ($p<.05$). This implies that residents that participated in 5–9 TBL-CCLSs over a two-year period were more likely to have significantly higher Rheumatology ITE scores than those who participated in less than 5 sessions.

Conclusions: There was no statistically significant increase in the overall ITE scores over the two-year period. However, residents participating in 5–9 TBL-CCLSs were more likely to have significantly higher Rheumatology ITE scores when compared to those that did not participate or participated in less than five sessions.

Disclosure: K. M. D. Torralba: None; **B. A. Boateng:** None; **R. Ben-Ari:** None; **F. P. Quismorio:** None.

1433

"Rheumapalooza": An Intensive Rheumatology Curriculum for Second Year Medical Students. Helen Emery[1] and Gregory Gardner[2]. [1]Seattle Children's Hospital, [2]University of Washington

Background: Medical students at our institution have little exposure to rheumatology in their preclinical years. The musculoskeletal curriculum included only two hours on arthritis, taught by an orthopedic surgeon. When students scored poorly on rheumatic disease topics in standardized tests, we introduced a course at the beginning of the second year to increase their knowledge and stimulate interest in rheumatic diseases. The course was given in 2008 and 2009 with some adjustments in response to faculty and student input.

Goals: Develop a curriculum to provide exposure to rheumatology

Evaluate students' rheumatology knowledge before and after this curriculum

Review students' assessment of the course

Prepare a manual as a guide for future courses here and at other medical schools.

Methods: The program is divided into two half days.

The first half day is didactic (concepts of inflammation, introduction to adult rheumatology; introduction to pediatric rheumatology; imaging techniques, and laboratory studies in the rheumatic diseases).

The second half day, the students are divided into groups of 14 groups and rotate through fifteen minute stations. Two demonstrate normal knee and shoulder exam; eight have a preceptor and a patient to elicit history and physical findings (adult rheumatoid arthritis, juvenile idiopathic arthritis, lupus, scleroderma, gout, ankylosing spondylitis, juvenile dermatomyositis, and osteoarthritis,) and four stations discuss osteoporosis, bone density interpretation, crystals, and characteristic x-ray, CT and MR images.

A twenty question pretest and post test was administered to evaluate increase in student knowledge from the course, and a student evaluation was completed at the end of the course.

Results: students showed a marked increase in knowledge as assessed by the pre and post tests. Paired t-test is highly statistically significant, with very large effect size (2.7 of the pooled SD). Student evaluations were 4.0/5, (179 respondents/216 participants) and offered useful suggestions for future programs A manual has been prepared to guide others in adapting this curriculum to their own setting.

Conclusions: The one day "Rheumapalooza" program has been effective in providing an intensive exposure to rheumatology, increasing rheumatology knowledge in second year medical students, and establishing a curriculum reproducible to other settings.

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Disclosure: H. Emery: None; **G. Gardner:** None.

ACR Concurrent Abstract Sessions
Pediatric Rheumatology - Clinical and Therapeutic Aspects - Therapeutics

Tuesday, November 9, 2010, 4:30 PM–6:00 PM

1434

Tocilizumab in Patients with Systemic Juvenile Idiopathic Arthritis: Efficacy Data from the Placebo-Controlled 12-Week Part of the Phase 3 TENDER Trial. Fabrizio De Benedetti[1], Hermine Brunner[4], Nicola Ruperto[9], Inmaculada Calvo[5], Ruben Cuttica[10], Clara Malattia[11], Rayfel Schneider[2], Patricia Woo[7], Carine H. Wouters[8], Ricardo Xavier[6], Lawrence S. Zemel[3], Stephen Wright[12], Andrew Kenwright[12], Alberto Martini[9] and Daniel J. Lovell[4]. [1]IRCCS Ospedale Pediatrico Bambino Gesu, Rome, Italy, [2]PRCSG, Toronto, ON, Canada, [3]PRCSG, Hartford, CT, [4]PRCSG, Cincinnati, OH, [5]PRINTO, Valencia, Spain, [6]PRINTO, Porto Alegre, Brazil, [7]PRINTO, London, United Kingdom, [8]PRINTO, Leuven, Belgium, [9]PRINTO, Genova, Italy, [10]PRINTO, Buenos Aires, Argentina, [11]PRINTO, [12]Roche, Welwyn, UK, Welwyn, United Kingdom

Purpose: Systemic juvenile idiopathic arthritis (sJIA) is the most severe form of JIA and is characterized by arthritis and prominent systemic manifestations. Interleukin-6 (IL-6) plays a pivotal role in sJIA pathogenesis. Tocilizumab (TCZ), an anti-IL-6 receptor antibody, was shown to be effective in a Japanese phase 3, placebo-controlled, withdrawal-design trial in patients with sJIA. We report 12-week efficacy data from the global phase 3 TENDER trial in patients with sJIA.

Methods: Patients with active sJIA (age range, 2–17 years; disease duration, ≥6 months; inadequate response to previous NSAIDs and corticosteroids) were randomly assigned 2:1 to receive TCZ every 2 weeks (8 mg/kg for patients ≥30 kg body weight; 12 mg/kg for patients <30 kg) or placebo (control). Stable doses of NSAIDs and methotrexate were continued, and corticosteroid tapering was allowed from week 6. Patients who qualified for rescue therapy received standard of care, were offered open-label TCZ, and were considered nonresponders. Primary end point was the proportion of patients with JIA ACR30 response plus absence of fever at week 12 (ITT analysis).

Results: The ITT population consisted of 112 patients (37 controls, 75 TCZ). Baseline characteristics were similar between groups. By week 12, 3% of patients in both arms (1 control, 2 TCZ) withdrew from the study, and more control than TCZ patients required rescue therapy (54% vs 3%). Significantly more TCZ patients experienced JIA ACR30 response plus absence of fever at week 12 compared with controls (85% vs 24%; $p<0.0001$). Additionally, significantly more TCZ patients than controls achieved JIA ACR50/70/90 response (Table A). Of the patients who had fever at baseline, significantly more TCZ patients than controls had no fever at week 12. Similarly, of those patients with anemia or thrombocytosis at baseline, significantly more patients treated with TCZ than control had normal hemoglobin levels or normal platelet counts, respectively (Table A). A considerable proportion of TCZ patients achieved ACR70/90 responses, even in subgroups whose baseline characteristics included a high number of active joints, fever, or a high platelet count, and in those treated with prior biologic therapy (Table B). Four serious adverse events were reported in 3 TCZ patients—angioedema and urticaria (1), varicella (1), and bacterial arthritis (1)—all of which resolved without sequelae.

Conclusions: These results show that TCZ is highly effective in treating sJIA, as shown by the clinically relevant JIA ACR70 and ACR90 responses, irrespective of baseline characteristics such as active joint disease, fever, high platelet count, and previous biologic therapy.

Table A. Efficacy Outcomes at Week 12

	Control, n = 37	TCZ, n = 75
JIA ACR50 responses, n (%)	4 (11)	64 (85)[a]
JIA ACR70 responses, n (%)	3 (8)	53 (71)[a]
JIA ACR90 responses, n (%)	2 (5)	28 (37)[a]
No fever after having a fever at baseline, n/n (%)	5/24 (21)	35/41 (85)[a]
Normal hemoglobin after having anemia at baseline, n/n (%)	2/29 (7)	40/50 (80)[a]
Normal platelet count after having thrombocytosis at baseline, n/n (%)	1/26 (4)	47/52 (90)[a]

Table B. Efficacy Outcomes at Week 12 by Select Baseline Characteristics, n/n (%)

		TCZ, n = 75		
		ACR 30 + absence of fever	ACR70	ACR90
No. of active joints	0–9	18/20 (90)	13/20 (65)	7/20 (35)
	10–29	32/39 (82)	30/39 (77)	18/39 (46)
	30–71	14/16 (88)	10/16 (63)	3/16 (19)
Fever status (last 7 d)	Fever present	27/32 (84)	24/32 (75)	11/32 (34)
	Fever free	37/43 (86)	29/43 (67)	17/43 (40)
Platelet count[b]	≤ULN	13/20 (65)	11/20 (55)	9/20 (45)
	> ULN	48/52 (92)	39/52 (75)	18/52 (35)
Previous anakinra use	Yes	35/41 (85)	29/41 (71)	16/41 (39)
	No	29/34 (85)	24/34 (71)	12/34 (35)
Previous TNF-α inhibitor use	Yes	45/55 (82)	35/55 (64)	19/55 (35)
	No	19/20 (95)	18/20 (90)	9/20 (45)

TNF = tumor necrosis factor.
ITT analysis; analysis adjusted for randomization stratification factors applied at baseline.
* $p < 0.0001$.
[b] Data missing for 3 patients.

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1435

Canakinumab (ILARIS®) Provides Rapid Response and Sustained Remission in Children across Different Disease Severity Phenotypes of Cryopyrin Associated Periodic Syndrome (CAPS). P. Quartier[13], E. Hachulla[2], M. Gattorno[5], R. Cartwright[1], I. Kone-Paut[4], F. Zulian[15], E. Weisbarth-Riedel[6], L. Lepore[10], J. Hoyer[12], I. Foeldvari[16], E. Ramos[3], P. N. Hawkins[14], K. Leslie[11], G. Krammer[8], R. Preiss[9], A. Widmer[8] and J. B. Kuemmerle-Deschner[7]. [1]Allergy Center at Brookstone, Columbus, GA, [2]Department of Internal Medicine, Hôpital Claude Huriez CHRU, Lille Cedex, France, [3]Department of Pediatrics, Hospital Central de Asturias, Oviedo, Spain, [4]Hôpital Kremlin Bicetre, CEREMAI, Le Kremlin Bicetre, France, [5]Istituto Giannina Gaslini, Genova, Italy, [6]Kinderklinik, Rheum. Ambulanz, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany, [7]Klinik fuer Kinder-und Jugendmedizin, Universitaetsklinikum, Tuebingen, Germany, [8]Novartis Pharma AG, Basel, Switzerland, [9]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [10]S.C.U. Clinica Pediatrica, IRCCS Burlo Garofolo, Trieste, Italy, [11]UCSF School of Medicine, San Francisco, CA, [12]Universitaetsklinikum Giessen und Marburg GmbH, Marburg, Germany, [13]Universite Paris-Descartes and Unite d'Immuno-Hematologie et Rhumatologie Pediatrique, Necker-Enfants Malades, Assistance Publique Hopitaux de Paris, Paris, France, [14]University College London Medical School, London, UK, [15]University of Padova School of Medicine, Padova, Italy, [16]Zentrum für Reumatologie, Hamburger Zentrum fuer Kinder-und Jugendrheumatologie, Hamburg, Germany

Background: Canakinumab provides sustained interleukin-1β (IL-1β) blockade and is effective in the treatment of CAPS (comprising of familial cold auto-inflammatory syndrome [FCAS], Muckle-Wells syndrome [MWS], chronic infantile neurologic, cutaneous and articular syndrome [CINCA]/neonatal-onset multisystem inflammatory disease [NOMID]). Herein we report the long-term safety, tolerability, and efficacy of canakinumab in the subgroup of pediatric CAPS patients who were enrolled as part of an open-label, single-treatment arm, Phase III study.

Methods: Patients enrolled in this study were canakinumab-naive or rolled-over from earlier Phase II/III studies. Patients received canakinumab 150 mg s.c. or 2 mg/kg s.c. (body weight ≤40 kg) every 8 weeks. Complete response was assessed for canakinumab-naive patients, while roll-over patients entered the study allowing continuous treatment every 8 weeks. In case of an incomplete response patients could be changed to a more intense dosing regimen (received an additional dose of canakinumab 300 mg s.c. or 4 mg/kg s.c. [body weight ≤40 kg]). Adjustment of the dosing frequency was also permissible. Complete response was defined as: physician's global assessment of disease activity and skin assessment score ≤minimal and normal CRP and/or SAA values (<10 mg/L). Relapse was defined as: serum levels of CRP and/or SAA >30 mg/L and (a) physician's global assessment of disease activity >minimal or (b) physician's global assessment of disease activity minimal along with the assessment of skin disease >minimal.

Results: Of 47 pediatric patients (3–17 years) (1 patient did not have CAPS and was discontinued [protocol violation] and of the remaining 46 patients there were 5 FCAS, 23 MWS, 18 MWS/NOMID [includes 8 NOMID] patients), 38 were canakinumab-naive, while 9 had been pre-treated with canakinumab. 43 (92%) completed the study and 3 patients discontinued the study (1 due to adverse event [AE]). The median duration of exposure to study drug was 290 days (range: 29–625 days). Complete response was achieved in most (n=26, 68%) of canakinumab-naive pediatric patients. The majority of canakinumab treated pediatric patients were relapse free (29 out of 35 [83%]) and 6 patients experienced a relapse. Dose adjustments were required in 16 patients (34%). Amongst all NOMID patients (including MWS/NOMID overlap) 15 (47%) received at least one dose or frequency adjustment. In canakinumab-naive patients median CRP and SAA levels rapidly decreased within 7 days (2.5 and 7.4 mg/L [baseline levels were 14.8 and 40.6 mg/L, respectively]) and these levels were maintained at normal levels (<10 mg/L) during the study (both in naive and roll-over patients). The most frequent AEs were rhinitis, nasopharyngitis and headache. Serious AEs were reported in 6 pediatric patients. Most patients (n=43, 91%) had no injection site reactions.

Conclusions: Canakinumab s.c. every 8 weeks induced rapid and sustained clinical and biochemical remission in pediatric patients across all severity of CAPS phenotypes. Adjustment of dose appears to be predominantly applied in pediatric and/or NOMID patients. Long-term tolerability and safety was good.

Disclosure: P. Quartier: None; **E. Hachulla:** Novartis Pharmaceuticals Corporation, 5; **M. Gattorno:** Novartis Pharmaceuticals Corporation, 9; **R. Cartwright:** Dey Pharmaceuticals, 5, GlaxoSmithKline, 8, Novartis Pharmaceuticals Corporation, 5, Pfizer Inc, 8, sanofi-aventis, 8, UCB, Inc., 8; **I. Kone-Paut:** Novartis Pharmaceuticals Corporation, 5; **F. Zulian:** None; **E. Weisbarth-Riedel:** None; **L. Lepore:** None; **J. Hoyer:** None; **I. Foeldvari:** Novartis Pharmaceuticals Corporation, 5; **E. Ramos:** None; **P. N. Hawkins:** Novartis Pharmaceuticals Corporation, 5; **K. Leslie:** None; **G. Krammer:** Novartis Pharma AG, 1, 3; **R. Preiss:** Novartis Pharmaceuticals Corporation, 1, 3; **A. Widmer:** Novartis Pharma AG, 1, 3; **J. B. Kuemmerle-Deschner:** Novartis Pharmaceuticals Corporation, 2, 5.

1436

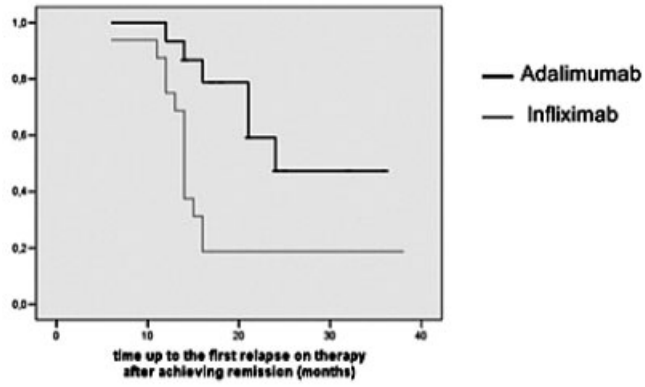
Prevention of Flare Recurrences in Childhood Refractory Chronic Uveitis: An Open-Label Comparative Study of Adalimumab Versus Infliximab. GABRIELE Simonini[5], Andrea Taddio[1], Marco Cattalini[4], Roberto Caputo[3], Cinzia De Libero[2], Cecilia Bresci[5], Monica Lorusso[5], Samuele Naviglio[1], Loredana Lepore[1] and Rolando Cimaz[5]. [1]Department of Sciences of Reproduction and Development, Institute of Child Health, IRCCS Burlo Garofolo, University of Trieste, Trieste, Italy, [2]Opthalmology Unit, A.Meyer's Children's Hospital, Firenze, Italy, [3]Opthalmology Unit, A.Meyer's Childrens Hospital, Firenze, Italy, [4]Pediatric Clinic, University of Brescia, Brescia, Italy, [5]Rheumatology Unit, Dpt of Pediatrics, University of Florence, A.Meyer's Childrens Hospital, Firenze, Italy

Background: Up to now, no data are available about the comparison in efficacy and safety of Adalimumab versus Infliximab in treating chronic, refractory uveitis in childhood.

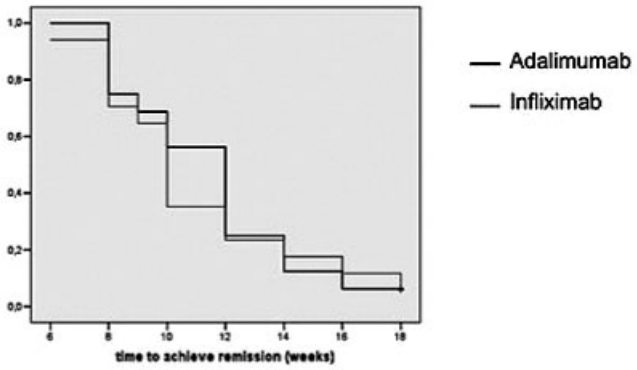
Objective: To compare the efficacy and safety of Adalimumab versus Infliximab in an open-label prospective, comparative, multi-centre, cohort study of childhood non-infectious chronic uveitis.

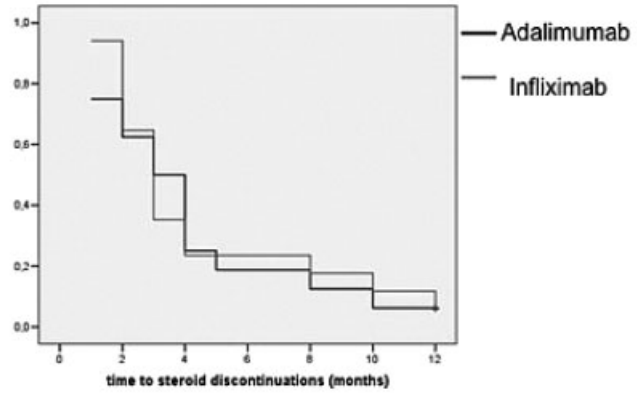
Methods: 33 patients (22 F, 11 M; median age: 9,17 years) with refractory vision threatening non-infectious uveitis, were enrolled, over 28 months, to receive, for at least 1 year, Infliximab (5 mg/kg at weeks 0, 2, 6 and then every 6–8 weeks) or Adalimumab (24 mg/sq.mt, every 2 weeks). Primary outcome was to assess, once remission was achieved, the time of a first relapse during time treatment. Time to remission, time to steroid discontinuation and the number relapses, were also considered.

Results: 16 children (12 with Juvenile Idiopathic Arthritis [JIA], 3 with idiopathic uveitis, 1 with Behçet's disease) were recruited in the Adalimumab cohort; 17 children (10 with JIA, 5 with idiopathic uveitis, 1 with early-onset sarcoidosis, 1 with Behçet's disease) into the Infliximab group. Cox-regression analysis did not show statistical significant differences between the two groups with regard to time to achieve remission, and time to steroid discontinuation, whilst showed a higher probability of uveitis remission on Adalimumab during the time of treatment entered for each cohort (Mantel-Cox $\chi 2$ 6.83, $p<0.001$).



At 40 months follow-up, 9/15 children on Adalimumab (60%) compared to 3/16 children on Infliximab (18.8%) were still on remission on therapy ($p<0.02$).Considering the secondary outcomes, at mean on the above reported covariates, survival Cox-regression analysis did not show statistical significant differences between the two treatment groups with regard to time to remission, and time to steroid discontinuation.





Among children who relapsed, at 40 months follow-up, the median number of relapses resulted statistically significantly higher in Infliximab group than in Adalimumab group: 3, range 1–5, versus 1, range 1–3 respectively, $p<0.001$.

Conclusion: Even if limited to a relatively small group, our study suggests that, at 3 year treatment, Adalimumab is more efficacious than Infliximab in maintaining remission of chronic childhood uveitis.

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1437

Safety and Low Seroprotection/Seroconversion Rates of Pandemic Influenza A Vaccine (Anti-H1N1/2009) in Juvenile Systemic Lupus Erythematosus. Lucia M. Campos[3], Clovis A. A. Silva[3], Nadia Aikawa[3], Eloisa Bonfa[5], Guilherme Trudes[3], Ana Cristina M. Ribeiro[5], Carla Gonçalves Saad[5], Vilma Trindade Viana[5], Maria do Carmo Timenetsky[1], Alexander R. Precioso[2] and Rosa M. R. Pereira[4]. [1]Instituto Adolpho Lutz, [2]Instituto Butantã, [3]Paediatric Rheumatology Unit, Faculdade de Medicina da Universidade de São Paulo, [4]Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil, [5]Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo

Purpose: To assess immunogenicity and safety of pandemic influenza A (H1N1) 2009 virus vaccine in juvenile systemic lupus erythematosus (JSLE) patients.

Methods: 75 JSLE patients and 64 age-matched healthy controls were vaccinated with the strain influenza A/California/7/2009 (H1N1) vaccine. All participants were older than 9 years and were evaluated pre and 21 days post-vaccination. Anti-H1N1 antibody titer in serum samples was determined by influenza hemagglutination-inhibition (HI) assay. Appropriate endpoints included the percentage of subjects achieving an HI antibody titer $\geq$1:40 (seroprotection) and rates of seroconversion, defined as the percentage of subjects with either a pre-vaccination HI titer $<$1:10 and a post vaccination HI titer $\geq$1:40 or a pre-vaccination HI titer $>$1:10 and a minimum four-fold rise in post-vaccination HI antibody titer.

Results: The mean age was similar in JSLE and controls (16.52$\pm$3.34 vs. 15.92$\pm$4.81 years, $p=0.39$). Among JSLE patients 74.6% were female, the mean follow up was 5.4 $\pm$ 3.6 years and treatments included: antimalarial in 74.7%, glucocorticoids in 68% and immunosuppressors in 60% of patients. Before immunization seroprotection was comparable in JSLE and controls (21.3 vs. 21.9%, $p=1.00$). After vaccination these percentages increased significantly to 74.6% ($p<0.0001$) in JSLE and to 95.3% ($p<0.0001$) in the control group. The percentage of seroprotection was, however, significantly lower in JSLE after immunization (74.6% vs. 95.3%, $p=0.0009$). Seroconversion rates were also inferior in JSLE compared to controls (62.7% vs. 89.1%, $p<0.001$) with a lower median titers in JSLE (160 vs. 320, $p=0.008$). The comparison of 47 seroconverters patients with the remaining 28 nonresponders revealed a similar mean age and disease duration, female predominance, frequency of immunomodulators and prednisone use. Nevertheless, the prednisone dose was lower in seroconverters vs. nonresponders (8.66$\pm$10.81 vs. 16.84$\pm$18.51 mg/day, $p=0.018$). Concerning vaccine safety in JSLE patients, no difference in SLEDAI scores was observed before and after immunization (6.03$\pm$6.10 vs. 5.23$\pm$5.45, $p=0.12$). Nonresponders group had a higher SLEDAI before the vaccination compared to seroconverters (8$\pm$6.13 vs. 4.98$\pm$5.86, $p=0.037$) whereas the post-vaccine SLEDAI was alike in both group (5.36$\pm$4.03 vs. 5.21$\pm$6.15, $p=0.91$). No serious vaccine adverse events were observed during 2 months follow-up.

Conclusions: The pandemic influenza A (H1N1) 2009 virus vaccine is safe in JSLE patients; however the seroprotection/seroconversion rates were lower than healthy controls. This finding suggests the need of a boost, particularly in active lupus patients and those under high dose of glucocorticoid therapy. ClinicalTrials.gov Identifier: NCT01151644

Disclosure: L. M. Campos: None; **C. A. A. Silva:** Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPQ) 300248/2008-3, 2; **N. Aikawa:** None; **E. Bonfa:** Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPQ) 301411/2009-3, 2; **G. Trudes:** None; **A. C. M. Ribeiro:** None; **C. G. Saad:** None; **V. T. Viana:** None; **M. Timenetsky:** None; **A. R. Precioso:** None; **R. M. R. Pereira:** Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPQ) 300559/2009-7, 2.

1438

Mortality/Morbidity in Cardiac Neonatal Lupus and Associated Maternal/Fetal Risk Factors. Peter M. Izmirly[1], Amit Saxena[1], Zoey Smith[2] and Jill P. Buyon[1]. [1]NYU School of Medicine, New York, NY, [2]NYU School of Medicine

Purpose: The classic cardiac manifestations of neonatal lupus (cardiac-NL) include a spectrum of conduction dysfunction (1st, 2nd, or 3rd degree heart block (CHB)) and more rarely cardiomyopathy which can be absent any conduction disease. This study was undertaken to update the mortality data of cardiac-NL in a large US based cohort and identify associated risk factors to further understand the pathogenesis of anti-SSA/Ro mediated injury and provide evidence based data for counseling women with these antibodies.

Methods: Three hundred and one children with cardiac-NL (295 with CHB and 6 with isolated cardiomyopathy) enrolled in the Research Registry for Neonatal Lupus (RRNL) had sufficient medical records for review. The RRNL database was analyzed for the following potential mortality maternal risk factors: age at pregnancy, race/ethnicity, anti-SSB/La antibody status, health status and fetal risk factors: time of diagnosis, exposure to maternal non-fluorinated and fluorinated steroids during pregnancy, method of delivery, and gender. In addition, morbidity was assessed by the frequency of pacemaker placement and cardiac transplant.

Results: Follow up of the children ranged from in utero death to adulthood. Of the 301 children with cardiac-NL, 53 (17.6%) died. Thirty percent died in utero or at birth, 41% died prior to six months of postnatal life and the remaining 29% died after 6 months. Mortality was higher among children born to non-Caucasian mothers compared to Caucasian mothers (33% vs 15% $p=.0003$). Maternal age was equivalent between the groups (29.1 dead vs 29.7 live). The maternal presence of anti-SSB/La antibodies was 74% for those whose children died and 63% for those whose children survived, which was not significant. A maternal diagnosis of Sjorgen's

Syndrome and/or Systemic Lupus Erythematosus was not significantly associated with cardiac-NL death (53% in death vs 44%) suggesting that prior knowledge of maternal antibody status did not influence mortality. With regard to fetal factors, 86% of those who died were diagnosed with cardiac-NL during pregnancy compared to 85% who survived. For those diagnosed during pregnancy there was a trend towards early gestational diagnosis for those children that died compared to those that survived (21 vs 23.5 weeks p=.09). There was also a trend toward higher exposure to maternal fluorinated steroids after the diagnosis in children that died (53% vs 40% p=.09), however there was no difference in maternal use of non-fluorinated steroids in those that died vs those that survived (19% vs 16%). Most fetuses were delivered by C-section and this was not significantly associated with death (70% dead vs 75% live). Female gender was also not associated with outcome (49% who died were female vs 52% live). Eighty-five percent of children received a pacemaker, 43% within 9 days of birth, 20% between 9 days and one year. Five children (2%) received a heart transplant.

Conclusion: Based on data from this large cohort, 17.6% of children born with cardiac-NL die from complications of the disease. Eighty-five percent required pacing and two percent required cardiac transplantation. Mortality was more prevalent in children born to non Caucasian mothers.

Disclosure: P. M. Izmirly: None; **A. Saxena:** None; **Z. Smith:** None; **J. P. Buyon:** NIAMS-NIH, 2, NIH, 2.

1439

Methotrexate in Children with Juvenile Localized Scleroderma: A Randomized, Double-Blind, Placebo-Controlled Trial. Francesco Zulian[7], Cristina Vallongo[8], Giorgia Martini[8], Fernanda Falcini[5], Annalisa Patrizi[4], Maria Alessio[3], Francesco La Torre[6], Mario Cutrone[1], Anna Belloni-Fortina[8], Mauro Paradisi[2], Silvana Martino[9], Fabio Vittadello[8] and Giorgio Perilongo[8]. [1]Children's Hospital of Mestre, [2]Dermatology, IDI IRCCS, Rome, [3]University Federico II Naples, [4]University of Bologna, [5]University of Florence, Florence, Italy, [6]University of Messina, [7]University of Padua, Padua, Italy, [8]University of Padua, [9]University of Turin

Background: Juvenile localized scleroderma (JLS) is a chronic progressive fibrotic process of the skin causing permanent disability and aesthetic damage. Although no universally accepted effective treatment is available, recent studies seem to support the use of methotrexate (MTX).

Objectives: We aimed to assess the safety and efficacy of methotrexate in patients with JLS.

Methods: We performed a double-blind, randomised controlled trial. Patients with active JLS, with linear, generalized or deep subtypes, were randomly assigned to receive oral MTX, at a dose of 15 mg/m^2 once a week (max 20 mg), for 12 months or until flare of the disease (MTX arm), or placebo at the same dose and timing (placebo arm). Oral prednisone (1 mg/Kg/day, max 50 mg), in a single morning dose for 3 months then tapered down until stopping in one month, was added to both groups. The randomization rate MTX/PLAC was 2:1. The extension of the skin lesions was evaluated by a computerized scoring system[1] and changes were quantified by the skin score rate (SSR) (skin score at time$_n$/skin score at time$_0$). Clinical examination and serial thermographies monitored the changes of active lesions[2]. The primary endpoint was the rate of response to treatment. Responders were defined those patients who satisfied the following 3 criteria: SSR≤1; decrease of the temperature at thermography of at least 10% compared to baseline; absence of new lesions. Disease relapse was defined when was present at least one of the following: SSR>1; unchanged or increased lesion temperature; appearance of new lesions. All analyses were intention-to-treat.

Results: 85 patients entered the screening phase and 70, aged 6–17 years, from 13 centres in Italy, were enrolled. 46 patients were randomized in the MTX arm and 24 in the placebo arm. Groups were homogeneous as far as clinical and immunological features, mean disease duration was 2,1 years in both groups. After an initial response in all patients, disease relapse occurred in 15 MTX patients (32,6%) and 17 placebo patients (70,8%) (p<0.005), mean SSR value decreased from 1 to 0.79 with MTX vs 1,1 with placebo. The mean target lesion temperature decreased 44% vs 12.1%. New lesions appeared in 3 MTX patients (6.5%) vs 4 on placebo (16.7%). 26 patients (56,5%) of MTX group and 11 patients of the placebo group (45,8%) presented mild side effects related to treatment. None was severe enough to stop treatment.

Conclusion: MTX is an effective and well tolerated treatment for patients with JLS.

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ACR Concurrent Abstract Sessions
Rheumatoid Arthritis - Clinical Aspects: Outcomes Associated with Biologic Therapy for RA
Tuesday, November 9, 2010, 4:30 PM–6:00 PM

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Methotrexate but Not TNF-Blockers Reduces Immune Response Following Pneumococcal Vaccination Using 7-Valent Conjugate Pneumococcal Vaccine (Prevenar®) in Adult Patients with Established Arthritis. Meliha C. Kapetanovic[5], Carmen Roseman[5], Göran Jönsson[1], Lennart Truedsson[4], Tore Saxne[3] and Pierre Geborek[2]. [1]Dept of Clinical Sciences Lund, Section of Infectious Diseases, Lund University, Lund, Sweden, [2]Dept of Clinical Sciences Lund, Section of Rheumatology, Lund University, Lund, Sweden, [3]Dept of Clinical Sciences Lund, Section of Rheumatology, Lund University, Sweden, [4]Dept of Laboratory Medicine, Section of Microbiology, Immunology and Glycobiology, Lund University, Lund, Sweden, [5]Section of Rheumatology, Lund University, Lund, Sweden

Aim: To study the influence of anti-inflammatory treatments including methotrexate (MTX) and TNF-blockers on serological response following pneumococcal vaccination using 7-valent conjugate vaccine (Prevenar®) in adult patients with established arthritis.

Patients and Methods: Altogether 506 patients with rheumatoid arthritis (RA) or spondylarthropathy (SpA) including psoriatic arthritis were vaccinated. All patients were stratified into 6 prespecified groups based on diagnosis and type of anti-rheumatic treatment: 1. RA patients treated with methotrexate + in some cases other DMARDs (n=85; 79 % female; mean age 62 years); 2. RA patients on TNF blockers as monotherapy (n=80; 88% female; mean age 60 years); 3. RA patients on anti-TNF +MTX + possibly other DMARDs (n=89; 78% female; mean age 60 years); 4. SpA patients on anti-TNF drugs as monotherapy (n=83; 34% female; mean age 49 years); 5. SpA patients on anti-TNF drugs +MTX (n=83; 53% female; mean age 50 years) and 6. SpA patients on NSAIDs and/or analgesics (n=86; 45% female; mean age 52 years). Group 5 served as a control group. All patients received one dose of 0,5 ml Prevenar intramuscularly. Levels of IgG antibodies against two pneumococcal serotypes (23F and 6B) were measured prior to and 4–6 weeks following vaccination using standardised ELISA.

Results: Postvaccination geometric mean IgG levels increased significantly for both serotypes in all groups compared to baseline (p=0.000). Immune response (IR); i.e ratio between post- and prevaccination antibody levels differed significantly between the groups. Patients with spondylarthropathy on NSAIDs and/or analgesics (controls) had better IR compared to groups treated with MTX or MTX combined with TNF blockers (group 1, 3 and 5). Patients treated with TNF-blockers as monotherapy (group 2 and 4) had numerically somewhat lower IR but not significantly different compared to controls for both serotypes.

Positive immune response (posIR) was defined as ≥ 2 times increase in antibody levels compared to baseline. Patients with RA exhibited reduced responsiveness compared to patients with SpA in univariate analysis. In multivariate analysis only older age and MTX treatment predicted reduced response while ongoing systemic prednisolone treatment elicited better posIR, table1.

Conclusion: Higher age and treatment with methotrexate predicted an impaired immune response to the 7-valent conjugate pneumococcal vaccine in this cohort of patients with chronic arthritis. Concomitant prednisolone treatment was associated with better IR. TNF-blockers did not affect the immune responses significantly.

Table 1. Predictors of positive immune response (pos IR) for both 23F and 6B.

	B	p-value	Exp(B)	95% C.I. for EXP (B) Lower	Upper
Age (years)	**−0.024**	**0.024**	**0.977**	**0.957**	**0.997**
Gender (male/female)	0.248	0.360	1.282	0.753	2.181
Disease duration (years)	0.015	0.208	1.015	0.992	1.039
RA diagnosis (yes/no)	−0.283	0.335	0.753	0.424	1.340
Swollen join count (SJC28)	−0.037	0.618	0.963	0.832	1.115
Tender join count (TJC28)	0.001	0.979	1.001	0.928	1.079
ESR (mm/h)	0.011	0.098	1.011	0.998	1.025
HAQ (0–3)	−0.316	0.179	0.729	0.460	1.155
Methotrexate (yes/no)	**−0.726**	**0.003**	**0.484**	**0.297**	**0.787**
Anti-TNF (yes/no)	0.039	0.882	1.039	0.625	1.729
Prednisolone (orally: yes/no)	**0.689**	**0.017**	**1.991**	**1.131**	**3.505**
Pneumovax vaccination previously (yes/no)	−0.221	0.630	0.802	0.327	1.969
Smoking (yes/no)	−0.268	0.394	0.765	0.413	1.416

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Lipid and Inflammation Parameters: A Translational, Randomized Placebo-Controlled Study To Evaluate Effects of Tocilizumab: The MEASURE Study. Iain B. McInnes[7], Janet S. Lee[6], Wen Wu[6], Jon T. Giles[5], Joan M. Bathon[5], Jane E. Salmon[4], Andre D. Beaulieu[2], Christine E. Codding[3], Christian Delles[1] and Naveed Sattar[1]. [1]British Heart Foundation, Glasgow, United Kingdom, [2]Centre de Rhumatologie St-Louis, Montreal, QC, Canada, [3]Health Research of Oklahoma, Oklahoma City, OK, [4]Hospital for Special Surgery, New York, NY, [5]Johns Hopkins University, Baltimore, MD, [6]Roche, Nutley, NJ, [7]University of Glasgow, United Kingdom

Purpose: Mechanistic data describing changes in lipid parameters upon IL-6R inhibition with tocilizumab (TCZ) are lacking. We report initial results from a randomized, double-blind, placebo-controlled study to evaluate the impact of TCZ on lipid particle subclasses and markers potentially relevant to cardiovascular (CV) risk.

Methods: Serum lipid subclasses characterized by nuclear magnetic resonance (NMR) and a range of inflammatory biomarkers were measured in patients with active rheumatoid (RA) with an inadequate response to MTX. Changes from baseline (BL) to wk 12 were compared between TCZ 8 mg/kg + MTX (N=69) and PBO+MTX (N=63) arms. The data were analyzed using nonparametric analysis of variance, not corrected for multiplicity.

Results: Baseline values and changes from baseline for each parameter by treatment arm are shown in the Table. Within lipid parameters, the largest changes occurred in the VLDL/triglyceride and large VLDL. Within LDL, increases occurred almost exclusively in large, more buoyant particles whereas small, dense LDL particles remained stable. Within HDL, increases occurred primarily in small HDL particles. Among inflammatory markers, Hs-CRP, HDL-associated SAA, and sPLA2-IIA were reduced with TCZ treatment; the prothrombotic marker D-dimer was also reduced. The HDL-associated antioxidative enzyme, paraoxonase I was increased with TCZ treatment.

Conclusion: Small LDL particles, thought to be proatherogenic, did not increase with TCZ treatment, in contrast to large VLDL particles and in small HDL particles with statistically significant increases. The changes in lipid parameters that occur with TCZ treatment, coupled with reductions in a wide range of inflammatory markers, demonstrate the intrinsic linkage of inflammation and metabolic regulation in the context of RA. Furthermore, reductions in HDL-associated SAA and sPLA2-IIA along with increases in paraoxonase reflect qualitative changes in lipoproteins that may favor improvements in CV risk-benefit.

	TCZ 8MG/KG + MTX N = 69		PBO + MTX N = 63		
	Median BL (n)	Median Cfb to Wk 12 (n)	Median BL (n)	Median Cfb to Wk 12 (n)	P Value
VLDL Triglycerides (mg/dL)	56.0 (63)	39.0 (55)	63.0 (59)	2.5 (56)	<0.0001
Large VLDL/Chylomicrons (nmol/L)	1.3 (63)	1.1 (55)	1.1 (59)	0.0 (56)	0.0026
Small LDL Particle (nmol/L)	693 (63)	−14 (55)	843 (59)	29.5 (56)	>0.1
Small HDL (μmol/L)	17.4 (63)	3.9 (55)	19.9 (59)	0.6 (56)	0.0001
Hs-CRP (mg/dL)	0.9 (69)	−0.8 (60)	0.9 (63)	0.1 (61)	<0.0001
HDL SAA (mg/L)	9.3 (60)	−6.0 (53)	6.7 (57)	0.6 (54)	<0.0001
Paraoxonase (U/L)	27.4 (64)	3.3 (56)	14.3 (58)	0.0 (55)	<0.0001
D-Dimer (ng/mL)	1032 (68)	−639 (62)	806 (63)	−60.0 (60)	<0.0001
sPLA2-IIA (ng/mL)	6.7 (66)	−4.3 (58)	6.9 (62)	0.1 (59)	<0.0001

BL = Baseline; Cfb = change from baseline

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Tumor Necrosis Factor-α Inhibitors and Reduced Risk of Developing Diabetes in Patients with Rheumatoid Arthritis. Jana Antohe[1], Androniki Bili[1], Jennifer A. Sartorius[2], H. Lester Kirchner[2], Stephanie J. Morris[1], Sorina Dancea[1] and Mary Chester Wasko[3]. [1]Geisinger Health System, Danville, PA, [2]Geisinger Health System, [3]Univ of Pittsburgh, Pittsburgh, PA

Background: Tumor necrosis factor-alpha (TNF-α) inhibitors may improve insulin sensitivity and thus would be expected to reduce the risk of diabetes mellitus (diabetes) in patients with rheumatoid arthritis (RA). This study examined the association of TNF-α inhibitor use and the risk of developing diabetes in an RA inception cohort in a rural, tertiary health system using Electronic Health Records (EHR).

Methods: All adult individuals diagnosed with RA between 1/1/2001 – 3/31/2008 were identified (n=1539). RA was defined as ICD-9 code 714.0 at ≥ 2 outpatient encounters with a rheumatologist, and diagnosis was validated against the American College of Rheumatology criteria by manual review of 100 random charts (97% concordance). Prevalent cases of diabetes, defined as 1 or more outpatient visits with ICD-9 250, a non-fasting blood glucose ≥ 200 mg/dl, hemoglobin A1C ≥ 7, or a hypoglycemic medication order, were excluded (n=252). Information on demographic data, medical history, body mass index (BMI), laboratory measures and medications were collected at office visits. Patients were classified as ever (n=352) or never (n=935) users of a TNF-a inhibitor (etanercept, adalimumab, or infliximab). Incident diabetes cases were identified using 2010 American Diabetes Association criteria. Time-varying Cox Proportional Hazard regression models were used to adjust for gender, age, race, hypertension, BMI, positive rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP), erythrocyte sedimentation rate, C-reactive protein (CRP), non-steroidal anti-inflammatory drug (NSAID), glucocorticoid, hydroxychloroquine and methotrexate use. Medication use was considered continuous for lapses ≤ 90 days.

Results: 1287 non-diabetic incident RA patients were included in the analysis. Patients were predominantly women (63%), and 97% were Caucasian, with median age of 61 y and BMI 28.6 kg/m^2. RF and anti-CCP were positive in 80% and 53%, respectively. Patients in the ever TNF-α inhibitor use group had a higher median BMI and CRP levels and were more likely to have positive RF and anti-CCP and to have taken NSAIDs, glucocorticoids or methotrexate. Median follow-up time (last visit or diabetes diagnosis date) for the ever- and never-TNF-α inhibitor users was 34.7 months and 23.1 months, respectively (p<.001).The median duration of TNF-α inhibitor exposure was 33.5 months. Of the 56 cases developing diabetes during observation, 13 wereever and 43 were never TNF-α inhibitor users, yielding incidence rates of 10.5 and 22.0 per 1000 person-years (p=0.019), respectively. Adjusting for covariates, the hazard ratio for incident diabetes among TNF-α inhibitor users was 0.40 (95% confidence interval 0.16–0.98, p=0.046) compared to non-users.

Conclusions: In this inception RA cohort, the use of TNF-α inhibitors was associated with a 60% reduction in risk of developing diabetes after controlling for confounders. These findings need to be confirmed by additional studies in this group of patients at high risk of cardiovascular disease.

Disclosure: J. Antohe: None; **A. Bili:** Amgen Inc., 2, Wyeth Pharmaceuticals, 2; **J. A. Sartorius:** None; **H. L. Kirchner:** Amgen Inc., 2, Wyeth Pharmaceuticals, 2; **S. J. Morris:** None; **S. Dancea:** None; **M. C. Wasko:** Amgen Inc., 2, Centocor, Inc., 2, 5, UCB, Inc., 5, Wyeth Pharmaceuticals, 2.

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Superior Protection Against "Vulnerable" Coronary Plaque in Asymptomatic TNFi-Responders vs. DMARD Responders with Rheumatoid Arthritis (RA). George A. Karpouzas[1], Naser Ahmadi[2], Tae-Young Choi[2], Fereshteh Hajsadeghi[2], Silvia Munoz[2] and Mathew Budoff[2]. [1]Harbor-UCLA, Long Beach, CA, [2]Harbor-UCLA

Background: A lower risk of myocardial infarction (MI) was recently reported in patients (pts) with RA exposed to Tumor necrosis factor-a inhibitors (TNFi). It is unclear, however, whether a good disease response is necessary for the observed benefit. Additionally, the mechanisms, as well as sequalae of disease response on coronary plaque quantity and composition are unknown. We prospectively evaluated the presence, total burden, and differences in the quality of coronary plaque in asymptomatic RA pts treated with TNFi vs. DMARDs alone.

Methods: We report on 74 RA pts recruited from a single center. Pt characteristics, including disease response, coronary risk factors and treatments are shown in table 1. Good EULAR response (DAS28≤3.2 and DAS28 change>1.2) distinguished responders (R) from non-responders (NR). Pts underwent 64+ slice cardiac Computed Tomography Angiography (CTA); this non-invasive modality includes an initial non-contrast phase assessing coronary calcium, followed by a contrast scan that detects plaque with equal accuracy to conventional angiography, and is superior in the assessment of non-calcified, lipid-rich, non-obstructive or "vulnerable" plaque. Individual coronary trees were evaluated for plaque volume and composition by standard methods (American Heart Association). Non-parametric tests were used for data analysis; regression models for plaque prevalence ratios (PR) and relative risk (RR) for plaque burden in TNFi R vs. NR and DMARD R vs NR, adjusted for conventional risk factors were constructed.

Results: No differences in coronary risk factors were present in DMARD vs. TNFi treated pts. Both TNFi and DMARD responders (R) had significantly less plaque prevalence than NR of both categories (table). Both R groups had lower numbers of diseased coronary segments vs. NR (p=0.008 for DMARD and TNFi respectively), and less total plaque burden (p=0.04 for DMARD and p=0.005 for TNFi vs. NR respectively). More importantly, R groups had less NC/mixed plaque (p=0.001 for DMARD and p=0.0001 for TNFi vs. NR respectively). TNFi R had 61% lower risk of having "vulnerable" plaque, and 23% less burden of it compared to DMARD R, after adjustment for age, sex and traditional risk factors. Interestingly, TNFi NR also had 38% lower risk of NC/mixed plaque and 21% less burden, insinuating a superior protective effect of TNFi against plaque progression, independent of RA disease response.

Conclusion: Good EULAR response to TNFi affords superior protection against total, but more importantly, "vulnerable" coronary plaque progression compared to good response to DMARDs. TNFi seem to have an independent- to RA clinical response- protective effect against plaque as evidenced by significantly lower volume and vulnerable plaque features in the TNFi NR group.

Table 1. Patient Features

	DMARD-treated = 27			TNFi-treated = 47		
Age (yrs)	53 ± 12			53 ± 10		0.9
Gender (% female)	85			91		0.5
Disease duration (yrs)	7 ± 5.6			12 ± 7.6		***0.0004***
Time on TNFi (mon)	–NA			51.8 ± 25.9		–
	R = 16	**NR = 11**	**p**	**R = 28**	**NR = 19**	**p**
DAS28-3v-ESR (M ± SD)	2.2 ± 0.6	3.7 ± 0.2	***<0.0001***	2.6 ± 0.5	4.3 ± 0.9	***<0.0001***
ESR (mm/hr)	16 ± 8	38 ± 21	***0.001***	23 ± 15	30 ± 17	***0.009***
CRP (mg/dl)	0.6 ± 1.2	0.9 ± 0.8	0.4	0.8 ± 1.9	1.4 ± 1.2	0.3
n (%) with plaque	9 (56)	8 (73)	0.4	15 (53.5)	14 (73)	0.2
n (%) assessed segments	64 (100)	44 (100)	–	112 (100)	76 (100)	–
n (%) diseased segments	16 (25)	18 (40.9)	***0.008***	13 (11.6)	20 (25.4)	***0.008***
Non-calcified/mixed	12 (18.8)	15 (34.1)	***0.001***	8 (7.1)	16 (21.1)	***0.0001***
calcified	4 (6.3)	3 (5.9)	0.3	5 (4.4)	4 (4.3)	0.8
Total plaque burden score	3.5 ± 3	4.4 ± 3.3	***0.04***	1.6 ± 2.5	3.4 ± 4.1	***0.005***
Non-calcified/mixed	2.8 ± 3.2	4.4 ± 3.3	***0.04***	1.4 ± 2.4	2.8 ± 3.8	***0.01***
calcified	2.3 ± 3.8	2.1 ± 3	0.2	2.1 ± 2.6	4 ± 2.6	0.1

Model	DMARD-Responders	TNFi-Responders	
Prev Ratio-any plaque	1 (ref)	0.89 (CI = 0.38–2.78)	0.61
non-calcified/	1 (ref)	0.39 (CI = 0.1–0.6)	***0.02***
mixed calcified	1 (ref)	0.78 (CI = 0.2–1.3)	0.25
RRisk-total burden score*	1 (ref)	0.78 (CI = 0.6–0.9)	***0.03***
Non-calcified/	1 (ref)	0.77 (CI = 0.6–0.9)	***0.01***
mixed calcified	1 (ref)	1.12 (CI = 0.9–1.3)	0.3

Model	DMARD-Non Responders	TNFi-Non Responders	
Prev Ratio-any plaque	1 (ref)	0.99 (CI = 0.97–1.03)	0.9
non-calcified/	1 (ref)	0.62 (CI = 0.1–0.7)	***0.02***
mixed calcified	1 (ref)	0.74 (CI = 0.1–1.5)	0.3
RRisk-total burden score*	1 (ref)	0.87 (CI = 0.6–0.9)	0.09
Non-calcified/	1 (ref)	0.79 (CI = 0.6–0.98)	***0.04***
mixed calcified	1 (ref)	1.75 (CI = 0.9–1.96)	0.07

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Discontinuation of TNF-Inhibitor Treatment in Clinical Practice Has a Negative Impact on Radiographic Progression 2 Years after Initiation of Therapy. Results from the Nationwide Danish DANBIO Registry. Lykke M. Ørnbjerg[1], Mikkel Østergaard[1], Pernille Bøyesen[13], Anja Thormann[1], Ulrik Tarp[6], Wolfgang Böhme[14], Ditte Dencker[14], Hanne Lindegaard[16], Uta Poulsen[15], Anette Hansen[2], Vibeke Ringsdal[5], Anette Schlemmer[5], Niels Graudal[10], Anne R. Andersen[12], Jakob Espesen[4], Gina Kollerup[7], Torben G. Christensen[11], Randi Pelck[3], Bente Glintborg[3], Ole R. Madsen[2], Dorte V. Jensen[8], Ole Majgaard[9] and Merete L. Hetland[1]. [1]DANBIO Registry and Depts. of Rheumatology, Copenhagen University Hospitals at Hvidovre and Glostrup, Denmark, [2]Dept. of Internal Medicine and Rheumatology, Gentofte University Hospital, Denmark, [3]Dept. of Internal Medicine, Copenhagen University Hospital at Holbæk, Denmark, [4]Dept. of Internal Medicine, Hospital Lillebaelt at Vejle, Denmark, [5]Dept. of Rheumatology, Arhus University Hospital at Alborg, Denmark, [6]Dept. of Rheumatology, Arhus University Hospital, Denmark, [7]Dept. of Rheumatology, Copenhagen University Hospital at Frederiksberg, Denmark, [8]Dept. of Rheumatology, Copenhagen University Hospital at Hørsholm, Denmark, [9]Dept. of Rheumatology, Copenhagen University Hospital at Næstved, Denmark, [10]Dept. of Rheumatology, Copenhagen University Hospital at Rigshospitalet, Denmark, [11]Dept. of Rheumatology, Copenhagen University Hospital at Slagelse, Denmark, [12]Dept. of Rheumatology, Copenhagen University Hospitals at Hvidovre and Glostrup, Denmark, [13]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [14]Dept. of Rheumatology, Hospital of South West Jutland at Esbjerg, Denmark, [15]Dept. of Rheumatology, King Christian Xth Hospital, Gråsten, Denmark, [16]Dept. of Rheumatology, Odense University Hospital, Denmark

Background: Randomised controlled trials have shown that tumour necrosis inhibitor (TNF-I) treatment halts erosive progression in rheumatoid arthritis (RA). In clinical practice, patients often withdraw from or switch TNF-I treatment. The impact of discontinuation or change of TNF-I treatment on radiographic progression in RA clinical practice is unknown.

Objectives: To investigate and compare the annual radiographic progression rates on conventional radiographs (CR) 2 years before and after TNF-I initiation in three subgroups of an observational cohort of RA patients, who

(1) stayed on their first TNF-I,
(2) withdrew from TNF-I treatment or
(3) switched to another TNF-I drug.

Methods: Conventional radiographs (CR) of hands and wrists were obtained ~2 years before start of TNF-I (time-point A), at the start of TNF-I (B) and ~ 2 years after start of TNF-I (C). Clinical data from the DANBIO registry and the patientfiles were collected. The CRs were scored blinded to chronology (modified Sharp score). Annual radiographic progression rates during DMARD (delta A-B)

and TNF-I (delta B-C) treatments were calculated, stratified according to treatment status at timepoint C (Group 1–3, see above). Data were analysed with non-parametric analyses due to a skewed distribution.

Result: 522 patients (76% women, 80% rheumatoid factor positive, age 54(21–86) years (median(range)); disease duration 5 (0–67) yrs) had complete A-B-C series. At time-point B, patients who stayed on TNF-I had a higher rate of concomitant methotrexate (MTX) treatment, while patients who switched TNF-I had a higher DAS28. At time-point A, patients received DMARDs (90%) or no DMARDs (10%). At time-point B, patients started treatment with infliximab (61%), etanercept (15%), or adalimumab (24%). The TNF-I were given in combination with MTX(78%); other DMARDs(10%); or in monotherapy (12%). The duration of Period A-B was median 736 (Interquartile range, IQR 486–1006) days and of period B-C 562 (405–766) days. Patients who withdrew from treatment were treated in 68% (mean) of the follow-up period, and withdrew due to lack of effect (LOE) (46%), adverse events (AE)(37%) or remission (2%), while patients who switched did so due to LOE(68%) and AE(26%), and were treated 99% of the follow-up period.

Radiographic data demonstrated significantly reduced progression rates during TNF-I therapy in all subgroups (Table), and that patients who continued treatment progressed less than patients who stopped.

Timepoint C treatment status	TSS A median (IQR)	TSS B median (IQR)	TSS C median (IQR)	Delta TSS a-b/yr median (IQR)	Delta TSS b-c/yr median (IQR)	P value	Patients progressing A-B (%)	Patients progressing B-C (%)	P value
(1) 1st TNF-I (312 patients)	10 (1–34)	15 (3–42)	15 (3–46)	0.64 (0–2.9)	0.0 (0–0.5)	<0.0001[3]	58	7	<0.002[2]
(2) Withdrawn (60 patients)	7 (0–29)	11 (2–34)	14 (3–34)	1.47 (0–2.9)	0.0 (0–1.2)	0.0007[3]	63	43	0.001[2]
(3) Switched (150 patients)	4.5 (0–23)	9 (2–34)	13 (1–36)	0.71 (0–3)	0.0 (0–1)	<0.0001[3]	58	34	<0.0001[2]
P value	0.01[1]	0.10[1]	0.23[1]	0.72[1]	0.03[1]		0.76[2]	0.03[2]	

[1] Kruskal Wallis
[2] Chi-square
[3] Paired Wilcoxon tests

Conclusion: In this observational study of 522 RA patients, initiation of TNF-I treatment reduced the rate of radiographic progression in the following 2 years, compared to the preceding 2 years of DMARD treatment, irrespective of treatment status after 2 years. The lowest level of radiographic progression was found in patients who continued treatment.

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1445

Immunogenicity in a 3-Year Follow-Up Cohort of Adalimumab Treated Rheumatoid Arthritis Patients. Geertje M. Bartelds[1], Charlotte L. Krieckaert[1], Michael T. Nurmohamed[1], Pauline van Schouwenburg[2], Ben A. Dijkmans[3] and Gerrit J. Wolbink[1]. [1]Jan van Breemen Institute, [2]Sanquin Research, [3]VU Medical Center

Background: Short term data regarding the immunogenicity of adalimumab in adalimumab treated rheumatoid arthritis (RA) patients have been reported. After approximately 6 months follow-up anti-adalimumab antibody frequencies ranged from 17 to 44% in different studies, and were associated with low to undetectable serum adalimumab levels and non-response to treatment. [1–3] However, thus far long-term immunogenicity data for adalimumab have not been reported.

Objectives: To examine the course of anti-adalimumab antibody formation during long-term (3 year) follow-up and its effect on treatment.

Methods: Two-hundred-seventy-two consecutive RA patients with active disease were treated with adalimumab in a prospective observational cohort study. All patients were monitored at baseline and 4, 16, 28, 40, 52, 78, 104, 130 and 156 weeks. Trough serum samples were obtained at all visits. Serum adalimumab concentrations and anti-adalimumab antibody titres were determined retrospectively at the end of follow-up using an ELISA and RIA, respectively, designed by Sanquin Research Amsterdam. Patients were defined as positive for anti-adalimumab antibodies if titres were above 12 AU/ml on at least one occasion, in combination with serum adalimumab levels below 5.0 mg/L. A survival analysis including Cox regression analysis was performed.

Results: After three years 76 out of 272 patients (28%) developed anti-drug antibodies (ADA) against adalimumab. Figure 1 shows that 51 patients (19%) developed ADA during the first 28 weeks of treatment. One hundred twenty four patients dropped out of the study before the end of follow-up: 57 (46%) due to treatment failure, 30 (24%) due to adverse events, 11 (9%) due to a combination of failure and adverse events, and 26 (21%) due to other reasons. Patients with ADA significantly more often dropped out of the study due to treatment failure compared to patients without ADA in univariate analysis (figure 2, $p<0.0001$) and after adjustment for confounders MTX use, number of previous DMARDs and C-reactive protein (HR:3.0; 95%CI:1.6–5.5, $p<0.0001$).

Conclusions: Discontinuation of adalimumab treatment due to treatment failure was observed more frequently in patients who developed ADA compared to patients without ADA. The majority of the ADA positive patients developed ADA during the first 28 weeks of treatment. This suggests that monitoring immunogenicity is most effective during the first six months of treatment.

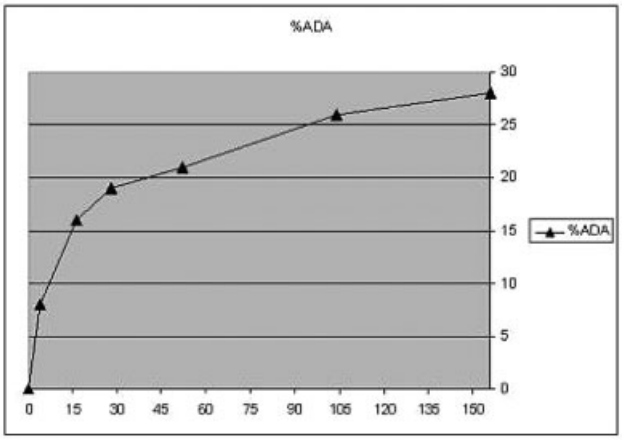

Figure 1. Development of AAA in percentages over 156 weeks follow-up.

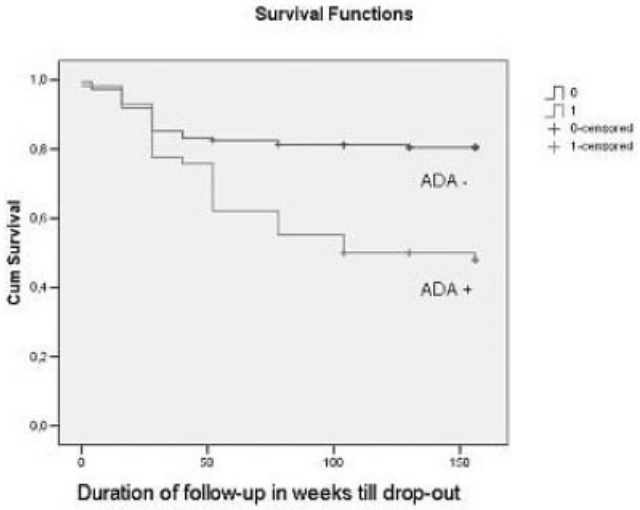

Figure 2. Discontinuation of treatment due to failure for patients with and without ADA ($P<0.0001$).

1. Bartelds, G. M. et al. *Ann Rheum Dis* 2007;**66:**921–926.
2. Radstake, T. R. et al. *Ann Rheum Dis* 2009;**68:**1739–1745
3. Miyasaka, N. *Mod.Rheumatol* 2008;**18:**252–262.

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1446

Fungal beta-Glucan Triggers Spondyloarthropathy and Crohn's Disease in SKG Mice. Merja Ruutu[4], Bijesh Yadav[4], Gethin Thomas[4], Roland Steck[2], Geoffrey Strutton[3], Ai Tran[4], Jared Velasco[4], Mariapia Degli Esposti[1], Martin Zinkernagel[1], Matthew A. Brown[4] and Ranjeny Thomas[4]. [1]Lions Eye Institute, [2]Queensland University of Technology, [3]Queenslande Health Pathology, [4]University of Queensland Diamantina Institute

Background: Recent genome-wide association studies reveal candidate genes for ankylosing spondylitis, psoriatic arthritis and Crohn's disease associated with proinflammatory cytokine production promoting T-helper 17 cells, including IL1R2, IL12B, IL23R, CCR6, JAK2, STAT3 and Card9. However, the functional correlates of these polymorphisms are unclear. This pathway is activated after dectin-1 signaling during fungal infection. Since skg ZAP70 mutant mice over-express these cytokines, and were reported as a model of rheumatoid arthritis triggered by fungal infection, we investigated whether skg mice develop spondyloarthropathy after systemic administration of fungal beta-glucan.

Methods: Skg mice and control BALB/c mice were injected i.p. or s.c. once with 3 mg 1,3-beta-glucan (curdlan). Arthritis, general appearance and weight loss were scored for 10 weeks. Organ pathology was determined by H&E staining of paraffin-embedded tissue sections at sacrifice between 1 and 10 weeks after injection of curdlan. Paws and spines were examined after sacrifice by radiography and micro-CT.

Results: After curdlan administration, BALB/c mice developed mild self-limiting arthritis of the ankles and wrists. By contrast, in skg mice, conjunctivitis, and progressive inflammatory arthritis of ankles and wrists, swelling of the soft tissue of the feet and typical sausage digits were evident from 3 weeks after injection. Over time, the mice developed hunching of the upper body, tail deformity, weight loss and abdominal bloating, but no diarrhea. Histologically and by imaging, we observed severe inflammation and progressive destruction of sacroiliac and vertebral facet joints, longitudinal ligaments and intervertebral discs with new bone formation, as well as enthesitis of Achilles tendon and plantar fascia in curdlan-treated but not naïve skg mice. Analysis of tissues over time showed that inflammation first appeared in ankles, wrists and para-vertebral ligaments from 1 week after injection. Around 6 weeks later, mice began to develop unilateral uveitis and Crohn's-like ileitis with granulomas and crypt abscesses. In contrast, the colon was not inflamed.

Conclusions: These characteristic features indicate that after systemic exposure to beta-glucan, skg mice develop a disease closely resembling human spondyloarthropathy. Since the zap70 mutation decreases T cell receptor signaling and required for disease perpetuation, these data strongly suggest that polymorphisms enhancing signaling of the beta-glucan molecular pattern (present in pollens, fungi and many bacteria), coupled with defects in antigen presentation or T cell response, may increase spondyloarthropathy risk in humans.

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Deficiency in IFNγHas Markedly Different Effects on Uveitis Versus Arthritis in the Aggrecan-Induced Mouse Model of Spondyloarthropathy. Holly L. Rosenzweig[3], Jelena M. Kezic[2], Tibor T. Glant[5], Stephen R. Planck[2], Tammy M. Martin[1], Michael P. Davey[6] and James T. Rosenbaum[4]. [1]Oregon Health & Science University, Portland, OR, [2]Oregon Health & Science University, [3]Oregon Health & Science University/VA Medical Ctr, Portland, OR, [4]Oregon Health Science Univ, Portland, OR, [5]Rush Med Ctr Cohn Bldg Rm 708, Chicago, IL, [6]VA Medical Ctr/Oregon Health & Science University, Portland, OR

Purpose: Uveitis, or intra-ocular inflammation, is a commonly associated extra-articular manifestation of spondyloarthropathies such as Behcet's disease or ankylosing spondylitis. However, the mechanisms regulating the eye's susceptibility to ocular inflammation in these diseases remain unknown. Here, we expanded on our initial finding that uveitis occurs in mice in the presence of increased auto-reactive T cells recognizing the proteoglycan (PG) aggrecan in order to elucidate the onset and severity of eye disease as it relates to the joint and spine. We further tested the functional contribution of the Th-1 cytokine (IFNγ) versus the Th-2 cytokine (IL-4).

Methods: BALB/c mice transgenic for the T cell receptor specific for a dominant epitope of aggrecan (TCR-Tg mice) or TCR-Tg mice lacking IFNγ or IL-4 were immunized with PG. Ocular inflammation was assessed by intravital microscopy and histological analysis. Corresponding joint and spine inflammation was examined using an established clinical scoring system, histology and NIR-fluorescence imaging. Immunofluorescence staining of eye tissue was performed to further identify the cellular mediators and the presence of PG in the eye.

Results: Immunofluorescence staining of whole mounts revealed the presence of PG on nerve fibres in the cornea, retina, iris and optic nerve. Upon immunization with PG, a progressive mild uveitis was observed. Intravital microscopic imaging revealed an increased number of rolling, adhering and infiltrating leukocytes within the iris vasculature within 3 weeks post immunization, whilst deficiency in IL-4 significantly impaired the severity of uveitis. By comparison, mice lacking IFNγ expression showed a marked exacerbation of eye disease with a higher number of rolling and adherent cells within the iris. Histological analysis revealed a florid cellular infiltrate in the absence of IFNγ for both the anterior and posterior segments of the eye, with cells in the vitreous, iris, ciliary body, and choroid; along with retinal vasculitis, retinal folding and photoreceptor damage. Immunofluorescence studies have identified a predominance of neutrophils and mononuclear MHC-II-positive cells within the eye. Interestingly, the protective role for IFNγ in the eye is in direct contrast with the joint and spine, wherein we find IFNγ KO mice have reduced severity of arthritis/spondylitis.

Conclusions: We present a newly described model of ocular disease that occurs in the context of murine arthritis/spondylitis. IFNγ and IL-4 appear to play opposing roles within the eye disease. IFNγ promotes joint disease, yet somewhat surprisingly our findings demonstrating exacerbated uveitis in the absence of IFNγ supports a protective role for IFNγ the eye. The disparity in mechanisms between the eye and joint may have potential implications for the treatment of systemic diseases accompanying uveitis.

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1448

Autoimmunity to Sperm and Testicular Antigens Precedes Onset of Spondyloarthritis in HLA-B27/Hu-β2-Microglobulin Transgenic Rats. Joel D. Taurog[1], Claudia Rival[3], Martha Dorris[2], Nimman Satumtira[2], Margaret Sun[3] and Kenneth S. K. Tung[3]. [1]U-Texas SW Med Ctr, Dallas, TX, [2]U-Texas SW Med Ctr, [3]U-Virginia HSC

Purpose: In all lines of rats transgenic (TG) for HLA-B27 and human β2m that develop spondyloarthritis (SpA), epididymo-orchitis (EO) develops in nearly all males. In the B27/Huβ2m TG (21-3×283-2)F1 rats (A&R 54:1317, 2006), in which only males develop SpA, EO is evident as scrotal swelling at a median age of 100 d, which is 50 d and 90 d, respectively, before the median time of onset of arthritis and spondylitis,. We have previously found that castration (i.e., bilateral resection of testis and epididymis) by 91 d of age prevents subsequent SpA (A&R 60s:1168, 2009). Here, we sought to investigate the pathogenesis of the EO and to characterize the autoimmune response to sperm and testis antigens.

Methods: B27/Huβ2m TG 21-3×283-2 F1 males underwent either castration, unilateral castration, or sham castration between ages 36 d and 125 d. Castrated rats were given testosterone replacement. Rats were observed for > 300 d for EO, arthritis, and spondylitis. Resected tissue was examined for histopathology and by immunohistology. Serum was examined for anti-sperm and anti-testis cell antibodies by IF and ELISA.

Results: As a rule, inflammation was first evident in the ductuli efferentes (DE, small ducts that link the rete testis to the epididymis) adjacent to the testis. As early as age 36 d, focal periductal neutrophils and mononuclear cells were detected, some penetrating the basal lamina. By 62 d, there was extensive mononuclear cell granulomatous inflammation in the DE. This was more severe by age 77 d, when aspermatogenesis was evident, coinciding with the appearance of anti-sperm and anti-testis cell antibodies in serum. Rats castrated after onset of orchitis showed a decline in these antibodies, even when arthritis developed later.

Immunohistological examination identified massive infiltration of activated macrophages and activated T cells surrounding the granulomatous lesions in the testis, but not elsewhere. In addition, granular deposition of rat IgG, presumed to reflect immune complexes, were deposited at the periphery

of the seminiferous tubules. Indirect IF showed that the serum autoantibodies bind to antigens in the testis cell cytoplasm, sperm acrosome, and sperm tail. Thus both T cell and antibody-mediated mechanisms participate in the autoimmune EO, but the T cell-mediated processes appear first and are primary.

Conclusion: The B27/Huβ2m transgenes initiate characteristic T cell-mediated inflammation in the ductus efferentes that becomes granulomatous. Orchitis appears later, coinciding with the appearance of anti-sperm and anti-testis cell antibodies in serum, presumably as a result of an ongoing autoimmune response to sperm and other testicular antigens. As previously shown, bilateral castration prevented subsequent development of SpA if carried out before the age of onset of arthritis, even if advanced EO was already present. The data therefore suggest that the process of prolonged inflammation and antigenic stimulation within the testis and epididymis is an essential precursor of SpA in (21-3×283-2) F1 B27/Huβ2m TG rats. More generally, persistent autoimmune inflammation in one site seems linked causally to autoimmunity targeting a second site.

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1449

Mast Cells Contribute to Synovial Inflammation in Non-Psoriatic and Psoriatic Spondyloarthritis. Troy Noordenbos[1], Nataliya Yeremenko[1], Tineke Cantaert[1], Christine Teitsma[1], Marleen van de Sande[1], Paul P. Tak[1], Juan Canete[2] and Dominique Baeten[1]. [1]Academic Medical Center/University of Amsterdam, [2]University Hospital Barcelona

Objective: We recently observed a striking synovial infiltration with cells positive for C-kit, a marker for mast cells, in psoriatic arthritis (PsA). As mast cells have potent inflammatory functions, including the production of pro-inflammatory cytokines, we performed a systematic analysis of mast cells infiltration in different forms of chronic inflammatory arthritis.

Materials and Methods: Synovial tissue biopsies from active rheumatoid arthritis (RA)(n=21), non-psoriatic spondyloarthritis (SpA)(n=16), and PsA (n=23) was stained by immunohistochemistry and double immunofluorescence. Synovial fluid (SF) from RA (n=18), SpA (n=19), and PsA (n=16) was analyzed by ImmunoCap and ELISA. The effect of C-kit inhibition by imatinib mesylate on proinflammatory cytokine production was tested in vitro on fresh SpA synovial biopsies.

Results: C-kit positive mononuclear cells were found in the synovial sublining in all disease groups. Double stainings with tryptase confirmed that C-kit indeed identified mast cells. C-kit positive mast cells were significantly increased in SpA ($p=0.010$) and PsA ($p=0.001$) versus RA despite similar levels of global inflammation as reflected by CD3, CD20, and CD68 staining. This was confirmed in an independent cohort of early untreated SpA and RA. The synovial infiltration by mast cells was not purely inflammation-driven as it persisted in SpA synovial biopsies taken after 12 weeks of successful treatment with TNF blockers. SF levels of factors involved in chemotaxis and differentiation of mast cells such as SCF, IL-3, and IL-33 were similar in all groups but sST2, the soluble decoy receptor for IL-33, was significantly decreased in SpA. As to the function of mast cells in synovial inflammation, double staining of the c-kit positive cells with toluidine blue and anti-tryptase and SF analysis for mast cell products did not show evidence for enhanced degranulation in SpA versus RA synovitis. Preliminary data, however, show IL-17 signal in the synovial mast cells. Accordingly, C-kit inhibition in ex-vivo synovial cultures strongly reduced the production and secretion of pro-inflammatory cytokines.

Conclusion: There is an increased synovial infiltration with C-kit positive mast cells in non-psoriatic and psoriatic SpA. Inhibition of C-kit in vitro leads to a reduction of proinflammatory cytokine production by synovial biopsies. These data suggest a role for mast cells in driving and/or sustaining the synovial inflammation in SpA.

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Gene Silencing of *ERAP1 and ERAP2* Displays Differential Effects on Intracellular Free Heavy Chain Accumulation and Peptide Presentation in B*27 Subtypes Associated with Ankylosing Spondylitis (AS). Nigil Haroon, Florence W. Tsui and Robert D. Inman, Toronto Western Hospital and Research Institute. University of Toronto, Toronto, Canada

Introduction: Ankylosing spondylitis (AS) demonstrates differential association with different HLA subtypes: *B*2704* and *B*2705* are associated with AS while *B*2706* and *B*2709* are not. With the recognition that *ERAP* polymorphisms are associated with AS, we investigated the interaction of AS-associated genes *ERAP1* and *ERAP2* with *HLA B*27* subtypes.

Methods: C1R cells stably transfected with the respective B*27 subtypes (B*2704, *2705, *2706 and *2709) were used. For gene silencing, two duplexes each of Stealth RNAi™ for ERAP1 and ERAP2 or a negative control (NC) siRNA were nucleofected into the respective transfected cells. For flow cytometry, ME1, HC10, W6/32 and MARB4 antibodies were used respectively for intact B27, MHC-I free heavy chains (FHC), intact MHC-I and B27 presenting abnormally long peptides (B27_lp). For intracellular FHC (iFHC) HC10 was used after cell permeabilization. The change in MFI was calculated as a ratio of the MFI with specific siRNA to NC for each antibody. Western blot showed more than 80% suppression of ERAP with specific siRNAs but no suppression with NC.

Results: Silencing of ERAP1/2 was associated with a significant increase in iFHC in B*2704 and *2705 cells compared to *2706 and *2709 cells ($p=0.002$). The median (IQR) increase in IFHC (ΔiFHC) in the B*2704 and *2705 cells was 2.5 (1.8, 4.2) compared to 1.3 (1.1, 1.5) in the *2706 and *2709 cells. There was no significant difference in the level of surface FHC, B27 or MHC-I expression. The median ΔB27_lp expression with ERAP1/2 silencing in B*2704 and *2705 cells was 1.2 (1.1, 1.4) and was significantly higher ($p=0.03$) than the median ΔB27_lp of 0.9 (0.8, 1.0) in *2706 and *2709 cells. There was no significant difference in the results whether ERAP1 or ERAP2 was suppressed.

Conclusion: ERAP1/2 silencing causes accumulation of more iFHC and higher B27_lp in AS-associated B*27 subtypes cells compared to non-associated subtypes. This suggests that interaction of B*27 with ERAP1/2 could be a key determinant underlying the B*27 subtype specific associations with AS.

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Multiplex Assay of a Panel of 58 Biomarkers in Ankylosing Spondylitis: Identification of High Priority Candidates for Prediction of Structural Damage. Walter P. Maksymowych[4], Nathalie Morency[4], Stephanie Wichuk[4], Proton Rahman[1], Dafna D. Gladman[2] and Robert D. Inman[3]. [1]Memorial University Newfoundland, St. Johns, NL, Canada, [2]Toronto Western Hospital, Toronto, ON, Canada, [3]Toronto Western Hospital, Toronto, ON, Canada, [4]University of Alberta, Edmonton, AB, Canada

Purpose: Radiographic progression in ankylosing spondylitis (AS) requires 2 years before it can be reliably detected and prospective studies have consistently identified only baseline radiographic damage as an independent predictor of radiographic progression in AS. This presents a major challenge to the study of disease modifying therapies and to the identification of patients at risk for damage progression. We aimed to simultaneously analyze a large panel of serologic biomarkers reflecting pathophysiological processes in AS as potential predictors of radiographic progression.

Method: We used multiplexed sandwich immunoassays (Eve Technologies) to simultaneously quantify a panel of 58 biomarkers that comprised 8 markers reflecting bone turnover, calcium homeostasis and osteoclasis, 8 metalloproteinases (MMP), 6 joint tissue growth factors, 23 cytokines known to regulate inflammation, 9 chemokines, and 4 factors reflecting miscellaneous immunological processes such as T-cell co-stimulation and enthothelial activation. Serum was obtained at a single time point from 60 patients with AS and 60 age- and sex-matched controls. Selection of 30 AS patients was based on phenotypic characterization of their progression status as measured by the modified Stoke AS Spine Score (mSASSS) after patients had been followed for at least 2 years. Progressors were defined as those patients where the baseline mSASSS was at least 10 units, progression over 2 years was at least 5 units, and included at least one new syndesmophyte. Non-progressors were patients meeting all 3 of the following: disease duration at baseline of at least 10 years, baseline mSASSS of less than 5 units, and no change in mSASSS over 2 years. Unpaired t-test analyses were stratified according to radiographic phenotype.

Results: A total of 23 biomarkers demonstrated significant differences between AS patients and controls, the most significant being osteocalcin and Rantes (both $p<0.0001$). Ten biomarkers only demonstrated significant differences from controls when analysis was stratified according to radiographic phenotype: in the progressor subgroup MMP-9, transforming growth factor alpha, and tumor necrosis factor alpha were significantly elevated compared to controls (all $p<0.0001$) while eotaxin, interferon alpha-2, and

monocyte chemotactic protein-3 were significantly increased in the non-progressor subgroup. Three biomarkers, interleukin-17, interferon-gamma, and macrophage inhibitory protein-beta, demonstrated significantly increased levels in AS patients that were further increased in the progressor subgroup. Six biomarkers were significantly increased only in male patients and particularly the progressor subgroup, especially macrophage derived chemokine and CD40 ligand (both $p<0.0001$).

Conclusion: Multiplexed assay of an extensive panel of biomarkers reflecting pathophysiological processes implicated in AS has identified several biomarkers as high priority candidates for prospective validation studies aimed at predictors of structural damage in AS.

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ACR Concurrent Abstract Sessions
Systemic Lupus Enrythematosus - Clinical Aspects and Treatment: New Therapies
Tuesday, November 9, 2010, 4:30 PM–6:00 PM

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Epratuzumab Demonstrates Clinically Meaningful Improvements in Patients with Moderate to Severe Systemic Lupus Erythematosus (SLE): Results from EMBLEM™, a Phase IIb Study. Daniel J. Wallace[1], Kenneth C. Kalunian[5], Michelle A. Petri[2], Vibeke Strand[3], Brian Kilgallen[4], Lexy Kelley[4] and Caroline P. Gordon[6]. [1]West Hollywood, CA, [2]Timonium, MD, [3]Division of Immunology and Rheumatology, Stanford University School of Medicine, Palo Alto, CA, [4]UCB, Smyrna, GA, [5]UCSD School of Medicine, La Jolla, CA, [6]University of Birmingham, Birmingham, United Kingdom

Background: Epratuzumab is a humanized anti-CD22 monoclonal antibody under development for the treatment of patients with moderate to severe SLE. This 12-week, double-blind, Phase IIb study (NCT00624351) was designed to evaluate the efficacy and safety of epratuzumab in SLE, and identify an optimal dose and regimen.

Methods: Patients with moderate/severe SLE (≥1 BILAG 2004 A or ≥2 Bs) were randomized to 1 of 6 intravenous regimens: placebo (PBO, standard of care) or cumulative dose (cd) epratuzumab (200, 800, 2400 or 3600 mg in equal divided doses using 2 every other week [EOW] infusions or 2400 mg cd as 4 equal infusions 1 week apart). Both 2400 mg cd groups (600 mg weekly and 1200 mg EOW) were also combined for analysis. Primary end point was a combined responder index of clinical disease activity at Week 12, defined as reduction of all baseline BILAG A to B/C/D and BILAG B to C/D in all body systems, no BILAG worsening in other organ systems, and no deterioration in SLEDAI or physician's global disease activity assessment, with no increase in corticosteroids, immunosuppressives or anti-malarials over baseline. The combined responder index was analyzed using logistic regression. All drop-outs were counted as nonresponders.

Results: At baseline, in the entire population (N=227) mean age was 38.8 years, 94% were female; with high disease activity (71% with ≥1 BILAG A, mean total scores: BILAG 15.2, SLEDAI 14.8). Combined responder index rates were higher in all epratuzumab groups than in the placebo group (Table), reaching statistical significance in the epratuzumab 600 mg weekly group (2400 mg cd) and the combined group of all 74 patients who received a cd of 2400 mg (600 mg weekly and 1200 mg EOW). In both groups, responder rates were twice those of placebo. Differences in responder rates between the epratuzumab 600 mg weekly and 1200 mg EOW groups, and the placebo group were observed at Week 8, with further improvement to Week 12 (epratuzumab 600 mg weekly vs 1200 mg EOW vs PBO; Week 8: 37.8% vs 35.1% vs 21.1%; Week 12: 45.9% vs 40.5% vs 21.1%). By Week 12, 37.9% and 35.3% of patients in the epratuzumab 600 mg weekly and 1200 mg EOW groups, respectively, achieved enhanced BILAG improvement (improvement of all body systems to BILAG C or better on consecutive visits, with no worsening) vs 22.2% in PBO. Epratuzumab was well tolerated; incidence of serious adverse events and infusion reactions was similar to PBO.

Table. Combined responder index, Week 12 (ITT population)

Dose regimen	PBO (n = 38)	Emab cd 200 mg 100 mg EOW (n = 39)	Emab cd 800 mg 400 mg EOW (n = 38)	Emab cd 2400 mg			Emab cd 3600 mg 1800 mg EOW (n = 38)
				600 mg weekly (n = 37[a])	1200 mg EOW (n = 37)	Combined group (n = 74)	
Responders n (%)	8 (21.1)	12 (30.8)	10 (26.3)	17 (45.9)	15 (40.5)	32 (43.2)	9 (23.7)
Odds ratio (95% CI) vs placebo		1.7 (0.6–4.7)	1.3 (0.5–3.9)	3.2 (1.1–8.8)	2.6 (0.9–7.1)	2.9 (1.2–7.1)	1.2 (0.4–3.4)
				p = 0.03[b]	p = 0.07[b]	p = 0.02[b]	

Emab = epraluzumab
[a] 2 patients randomized but never received drug.
[b] p values were not adjusted for multiple comparisons.

Conclusions: Epratuzumab was associated with meaningful and statistically significant improvements in disease activity in patients with moderate to severe active SLE at a cd of 2400 mg, with responder rates twice those of placebo. Results validate the combined index emphasizing BILAG and support Phase III trials of epratuzumab in SLE.

Disclosure: D. J. Wallace: Bristol-Myers Squibb, 5, Genentech and Biogen IDEC Inc, 5, Human Genome Sciences, Inc., 5, MedImmune, 5, Novo Nordisk, 5; **K. C. Kalunian:** Anthera, 2, 5, Bristol-Myers Squibb, 5, Cephalon, 2, 5, Cypress, 2, 5, Genentech and Biogen IDEC Inc, 2, 5, MedImmune, 2, 5, Novo Nordisk, 2, 5, Serono, 5, UCB, Inc., 2, 5, Zymogenetics, 2, 5; **M. A. Petri:** UCB, Inc., 2; **V. Strand:** Abbott Immunology Pharmaceuticals, 5, Alder, 5, Amgen Inc., 5, AstraZeneca, 5, Biogen Idec, 5, Canfite Pharma, 5, CBio, 5, Centocor, Inc., 5, Chelsea, 5, Crescendo, 5, Cypress Biosciences, Inc., 5, Euro-Diagnostica Inc., 5, Fibroge; **B. Kilgallen:** UCB, Inc., 3; **L. Kelley:** UCB, Inc., 3; **C. P. Gordon:** Aspreva, 2, 5, Bristol-Myers Squibb, 5, Genentech and Biogen IDEC Inc, 5, Merck Pharmaceuticals, 5, Roche, 5, UCB, Inc., 5.

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Aspreva Lupus Management Study (ALMS): Extra-Renal Activity Results from the Maintenance Phase. David A. Isenberg[4], Gerald B. Appel[1], Mary Anne Dooley[6], Ellen M. Ginzler[3], David Jayne[2], David Wofsy[5], Neil Solomons[7] and Laura Lisk[8]. [1]Columbia University, [2]Renal Unit, Addenbrooke's Hospital, [3]SUNY-Downstate Medical Center, Brooklyn, NY, [4]University College London, London, United Kingdom, [5]University of California, San Francisco, San Francisco, CA, [6]University of North Carolina at Chapel Hill, Chapel Hill, NC, [7]Vifor Pharma (formerly Aspreva Pharmaceuticals), Canada, [8]Vifor Pharma, UK

Background: The 36-month maintenance phase of the ALMS study (NCT00377637) compared the efficacy and safety of mycophenolate mofetil (MMF) with azathioprine (AZA) in patients with lupus nephritis (LN) classes III, IV and V achieving a clinical response in the induction phase with corticosteroids (CS) and either MMF or cyclophosphamide (IVC).

Methods: Patients were re-randomized 1:1 to a double-blind comparison of either placebo plus either oral MMF (2 g/day) or oral AZA (2 mg/kg/day). Patients were permitted to receive corticosteroids (maximum dose: 10 mg/day prednisone or equivalent). The primary efficacy outcome measure was time to treatment failure (death, end-stage renal disease, sustained doubling of serum creatinine, and/or renal flare [proteinuric or nephritic]). Patients who withdrew before reaching the primary endpoint were censored at the time of withdrawal. Although this was primarily an LN population, substantial extra-renal assessments were performed. Extra-renal secondary parameters included time to major extra-renal flare (British Isles Lupus Assessment Group [BILAG] score category A in one extra-renal system or three systems with concurrent category B scores) and the characterization of extra-renal activity. Immunology secondary parameters (levels of complement proteins C3 and C4, and titers of antibodies to double-stranded DNA [anti-dsDNA]) and adverse events (AEs) were also assessed.

Results: Of 227 patients randomized (intent-to-treat population), 127 completed the full 3 years (MMF, 73/116 [62.9%]; AZA, 54/111 [48.6%]): MMF was superior to AZA in the primary endpoint ($p=0.003$). Extra-renal disease characteristics and immunology parameters were similar across groups at baseline. There were very few occurrences of major extra-renal flare in either group during the study (8 [6.9%] for MMF, 7 [6.3%] for AZA), and time to major extra-renal flare did not differ between groups ($p=0.936$). However, there were differences in the characteristics of extra-renal activity. The most common manifestation of major extra-renal flare in the MMF group was mucocutaneous and in the AZA group was hematological. In the MMF group, 75 subjects (65.2%) experienced lupus-related AEs compared with 79 (71.2%) in the AZA group, with musculoskeletal events being the most common in both groups (MMF, 39/115 [33.9%]; AZA, 37/111 [33.3%]). At the end of the study, in patients who had completed 3 years, mean C3 and C4

levels were lower in the AZA group and mean anti-dsDNA titers were lower in the MMF group; differences were not statistically significant.

Conclusions: In this population of LN patients who had responded to induction therapy, there were low levels of extra-renal activity in the maintenance phase in both MMF and AZA groups.

Disclosure: D. A. Isenberg: Bristol-Myers Squibb, 5, Human Genome Sciences, Inc., 5, Merck Serono, 5, Teva Pharmaceuticals, 5; **G. B. Appel:** Centocor, Inc., 5, Genentech and Biogen IDEC Inc, 5, Roche, 5, Teva Pharmaceuticals, 5, Vifor Pharma (formerly Aspreva Pharmaceuticals), 2, 5, 9, Vifor Pharma, 2, 5, 9; **M. A. Dooley:** Amgen Inc., 2, Bristol-Myers Squibb, 2, Roche, 2, Teva Pharmaceuticals, 5, UCB, Inc., 9, Vifor Pharma, 2, 5, 9; **E. M. Ginzler:** Bristol-Myers Squibb, 9, Cephalon, 9, Genentech and Biogen IDEC Inc, 9, Gerson Lehrman Group, 9, Guidepoint Global, 9, Human Genome Sciences, Inc., 9, Medimmune, 9, Merck Serono, 9, Teva Pharmaceuticals, 9, Vifor Pharma, 9, Wye; **D. Jayne:** Hoffmann-La Roche, Inc., 9, Vifor Pharma, 9; **D. Wofsy:** Bristol-Myers Squibb, 5, Genentech and Biogen IDEC Inc, 5, Merck Serono, 5, Teva Pharmaceuticals, 5; **N. Solomons:** Vifor Pharma, 3; **L. Lisk:** Vifor Pharma, 3.

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Belimumab, a BLyS-Specific Inhibitor, Reduced Disease Activity and Severe Flares in Seropositive SLE Patients: BLISS-76 Study Results through Wk 76. R. Furie,[1] O. Zamani,[2] D. Wallace,[3] D. Tegzová,[4] M. Petri,[5] J.T. Merrill,[6] W. Chatham,[7] W. Stohl,[8] A. Schwarting,[9] S. Cooper,[10] Z.J. Zhong,[10] W. Freimuth,[10] D. Hough,[10] and R.F. van Vollenhoven,[11] for the BLISS-76 Study Group. [1]North Shore-LIJ Health System, Lake Success, NY; [2]Rheumazentrum Favoriten, Wien, Austria; [3]Cedars-Sinai/ UCLA, Los Angeles, CA; [4]Institute of Rheumatology and Rheumatological Clinic, Prague, Czech Republic; [5]Johns Hopkins University School of Medicine, Baltimore, MD; [6]Oklahoma Medical Research Foundation, Oklahoma City, OK; [7]UAB Arthritis Clinical Intervention Program, Birmingham, AL; [8]USC Keck School of Medicine, Los Angeles; [9]Universitätsmedizin der Johannes-Gutenberg-Universität Mainz, Sana Rheumazentrum Rheinland-Pfalz, Bad Kreuznach, Germany; [10]Human Genome Sciences, Rockville, MD; [11]The Karolinska Institute, Stockholm, Sweden.

Purpose: To assess the efficacy and safety of belimumab, a BLyS-specific inhibitor, in seropositive SLE patients.

Methods: In BLISS-76 (NCT00410384), a 76-wk, double-blind, international, phase 3 study, 819 seropositive SLE patients (ANA ≥1:80 and/or anti-dsDNA ≥30 IU/mL) with SELENA-SLEDAI (SS) score ≥6 on stable standard-of-care (SOC) therapy for ≥30 d were randomized to belimumab 1 or 10 mg/kg IV plus SOC vs placebo plus SOC on d 0, 14, and 28, and then q28d, for 72 wk. Efficacy analyses included SS, BILAG, and SS Flare Index (SFI). SLE Responder Index (SRI) response rate at 52 wk: SS improvement (≥4-point decrease), no new BILAG A or 2 new B flares, and no worsening (<0.3-point increase) in Physician's Global Assessment (PGA) vs baseline. SRI at wk 76 was a secondary endpoint.

Results: Belimumab 10 mg/kg plus SOC met the primary efficacy endpoint by achieving a significantly greater response rate vs placebo plus SOC at wk 52 (43% vs 34%; p=0.017); the rate with belimumab 1 mg/kg was 41% (p=0.09). Statistical significance with either belimumab dose was not achieved at wk 76 (32%, 39% [p=0.11], and 39% [p=0.13] for placebo, and belimumab 1 and 10 mg/kg, respectively). In post-hoc sensitivity analyses evaluating more rigorous response thresholds for the SS component of the SRI endpoint (ie, 5–7-point reductions), robust and consistent effects were achieved with belimumab 10 mg/kg at multiple time points, including statistically significant effects at wk 52 and 76. Between wk 24 and 76, belimumab reduced all flares (10 mg/kg; p<0.05) and severe flares (1 mg/kg; p<0.05). Fatigue improved in both belimumab treatment groups at wk 76 (1 mg/kg; p<0.05). Although not statistically significant, there were numeric trends favoring steroid sparing with belimumab. Belimumab was associated with reduction in SLE-specific and short-lived plasma cells, as well as other B-cell subsets including CD20+, activated, and plasmacytoid cells. Moreover, significant normalization of low complement was achieved with belimumab 10 mg/kg. Overall adverse events (AEs), laboratory abnormalities, and infections, as well as serious AEs including infections, malignancies, and deaths, were comparable across groups. Serious or severe infusion reactions occurred in 1.5% of patients with belimumab 10 mg/kg vs 0.7% with placebo.

Conclusion: In BLISS-76, belimumab significantly improved SRI response rate and reduced SLE disease activity in seropositive SLE patients at wk 52. Response rates at wk 76, while not statistically significant, were consistent with wk-52 results. Overall AEs, including serious AEs and infections, were comparable across groups.

Table. BLISS-76 Results Through Wk 76[a]

	SOC + Placebo (n=275)	SOC + Belimumab 1 mg/kg (n=271)	SOC + Belimumab 10 mg/kg (n=273)
Response (SRI, wk 76), n (%)	89 (32.4%)	106 (39.1%)	105 (38.5%)
SS ≥4-point reduction	93 (33.8%)	114 (42.1%)	113 (41.4%)
No worsening in PGA (<0.3 point increase)	160 (58.2%)	178 (65.7%)	172 (63.0%)
No new BILAG 1A/2B scores	162 (58.9%)	187 (69.0%)	173 (63.4%)
SRI wk 52	93 (33.5%)	110 (40.6%)	118 (43.2%)
SRI-5[b] wk 52	56 (20.4%)	84 (31.0%)**	89 (32.6%)***
wk 76	60 (31.8%)	77 (28.4%)	84 (30.8%)
SRI-6[b] wk 52	52 (18.9%)	78 (28.8%)	84 (30.8%)
wk 76	56 (20.4%)	73 (26.9%)	79 (28.9%)
SRI-7[b,c] wk 52	29 (13.4%)	42 (19.4%)	46 (21.3%)
wk 76	30 (13.9%)	47 (21.7%)	47 (21.8%)
Prednisone reduction from >7.5 mg/d by 25% from baseline to ≤7.5 mg/d during wk 64–76, n (%)	n=126 22 (17.5%)	n=130 35 (26.9%)	n=120 29 (24.2%)
Prednisone increase from ≤7.5 mg/d to >7.5 mg/d at wk 76 (last observation carried forward), n (%)	n=149 27 (18.1%)	n=141 19 (13.5%)	n=153 18 (11.8%)
SFI flare: wk 24–76	n=239	n=245	n=236
All flares, n (%)	194 (81.2%)	186 (75.9%)	173 (73.3%)*
(hazard ratio [HR])[d]		0.84	0.78
Severe SFI flare during wk 24–76, n (%) (HR)[d]	52 (21.8%)	31 (12.7%)** 0.55	37 (15.7%) 0.70
Change in FACIT-Fatigue score from baseline at wk 76, mean (SE)[e]	n=272 3.16 ±	n=271 5.23 ± 0.66*	n=269 5.00 ± 0.66
Anti-dsDNA at wk 76[f]			
Positive patients, median change (%)	0	−34.1#	−33.3#
Positive to negative, n (%)	11/112 (9.8%)	31/125 (24.8%)**	23/120 (19.2%)
Negative to positive, n (%)	7/74 (9.5%)	2/76 (2.6%)	2/69 (2.9%)
Normalization of low complement at wk 76[g]			
C3	n=70	n=70	n=78
Median change (%)	4.8	18.9	21.1**
Normalization, n (%)	13 (18.6)	19 (27.1)	40 (51.3)#
C4	n=93	n=98	n=102
Median change (%)	16.7	38.5***	51.9#
Normalization, n (%)	17 (18.3)	36 (36.7)**	52 (51.0)#
B cells, median change at wk 76 (%)			
CD20+	0	−55.7#	−54.8#
CD20+/69+ activated	−25.2	−43.2*	−49.1**
CD20+/27+ memory	2.6	22.0	15.0*
CD20+/27− naive	−3.4	−73.4#	−76.3#
CD20−/27^{BRIGHT} plasma	−7.7	−17.9	−42.9***
CD20−/138+ plasma	−22.2	−25.3	−52.7***
CD20+/138+ plasmacytoid	−35.1	−56.7**	−56.0***
$CD19+/27^{BRIGHT}/38^{BRIGHT}$	−11.8	−17.4	−38.8***
T cells, median change at wk 76 (%)			
CD3+/4+	5.0	8.3	17.9*
CD3+/8+	0	10.5*	16.7*
CD3+	0.3	8.0	17.5**
CD4/CD8R	3.8	5.7	2.4
AEs, n (%)			
All	253 (92.0%)	253 (93.4%)	253 (92.7%)
Serious	54 (19.6%)	63 (23.2%)	61 (22.3%)
Infections	190 (69.1%)	202 (74.5%)	202 (74.0%)
Serious infections	16 (5.8%)	19 (7.0%)	20 (7.3%)
All infusion/hypersensitivity reactions	27 (9.8%)	42 (15.5%)	37 (13.6%)
Hypersensitivity reactions	0	4 (1.5%)	0
Serious/severe infusion reactions	2 (0.7%)	2 (0.7%)	4 (1.5%)
Malignancies	1	4	2
Deaths	0	2	1
Discontinuations prior to week 76	89 (32.4%)	72 (26.6%)	82 (30.0%)
Discontinuations due to AEs	23 (8.4%)	18 (6.6%)	23 (8.4%)

[a]Patients who withdrew from study prior to wk-76 visit or used protocol-prohibited medications were considered treatment failures; [b]SRI-5 to SRI-7 refer to SS component of score, increasing from ≥5-point reduction to ≥7-point reduction; [c]among patients with SS score ≥7 at baseline. [d]p values obtained by Cox proportional hazard model for time to 1st flare; [e]positive change in FACIT-Fatigue indicates improvement; [f]anti-dsDNA: positive (≥30 IU/mL), negative (<30 IU/mL); [g]C3: normal/high (≥900 mg/L), low (<900 mg/L); C4: normal/high (≥16 mg/dL), low (<16 mg/dL).
*p<0.05, **p<0.01, ***p<0.001, #p<0.0001; otherwise not significant.

Disclosure: R. A. Furie: GlaxoSmithKline, 5, Human Genome Sciences, Inc., 2, 5, 9; **O. Zamani:** Human Genome Sciences, Inc., 9; **D. J. Wallace:** Human Genome Sciences, Inc., 9; **D. Tegzova:** Human Genome Sciences, Inc., 9; **M. Petri:** GlaxoSmithKline, 5, Human Genome Sciences, Inc., 2, 5, 6, 9; **J. T. Merrill:** Human Genome Sciences, Inc., 9; **W. W. Chatham:** Human Genome Sciences, Inc., 2, 9; **W. Stohl:** Human Genome Sciences, Inc., 2, 9; **A. Schwarting:** Human Genome Sciences, Inc., 9; **S. Cooper:** Human Genome Sciences, Inc., 1, 3; **Z. J. Zhong:** Human Genome Sciences, Inc., 1, 3; **W. Freimuth:** Human Genome Sciences, Inc., 1, 3; **D. R. Hough:** Human Genome Sciences, Inc., 1, 3; **R. van Vollenhoven:** GlaxoSmithKline, 5, 8, Human Genome Sciences, Inc., 5, 9; **for the BLISS-76 Study Group:** None.

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Efficacy and Safety of Ocrelizumab, a Humanized antiCD20 Antibody, in Patients with Active Proliferative Lupus Nephritis (LN): Results from the Randomized, Double-Blind Phase III BELONG Study. Eduardo F. Mysler[6], Alberto J. Spindler[9], Renato Guzman[2], Marc Bijl[8], David Jayne[1], Richard A. Furie[5], Romeo Maciuca[3], Saba Shahdad[7], David Close[4], Paul Brunetta[3] and Jorn Drappa[3]. [1]Addenbrookes Hospital, [2]Dept Rheumatology, [3]Genentech, [4]MedImmune Limited, [5]North Shore Long Island Jewish Health System, Lake Success, NY, [6]OMI, Buenos Aires, Argentina, [7]Roche, [8]Univ of Groningen, [9]Universidad Nacional Tucumán, Yerba Buena Tucuman, Argentina

Purpose: B cells are believed to contribute to LN pathogenesis. Ocrelizumab (OCR), a humanized monoclonal antibody that selectively targets $CD20^+$ B cells, was studied to determine the benefits and risks of OCR compared to placebo (PBO) in patients (pts) with active class III/IV LN also receiving corticosteroids plus standard of care (SOC) of mycophenolate mofetil (MMF) or Eurolupus (EL) cyclophosphamide (CYC) regimen.

Methods: Pts with active proliferative LN were randomized equally to PBO, OCR 400 mg, or OCR 1000 mg IV on days 1 and 15; single infusions were then given every 16 wks. Pts received either MMF (up to 3 g/d) or EL (IV CYC 500 mg q2 wks × 6 followed by azathioprine 2 mg/kg) and a protocol-defined steroid taper regimen. The primary endpoint was the Wk 48 overall renal response (ORR) consisting of complete (CRR) and partial (PRR) renal response. We report here interim safety results for all treated pts, and Wk 48 renal responses for pts enrolled ≥32 wks prior to stopping the study.Due to the smaller group sizes, inferential statistics (95% CI, p-value) are provided only for the pooled OCR group vs PBO.

Results: 381 pts were randomized through Sept 2009. 87 % were female, 80% class IV LN, 63% received MMF and 37% EL. Mean 24hr Upr/Cr ratio at entry was 3.9. An imbalance in serious infections (in pts receiving OCR, particularly with MMF, and in pts from Asia across all arms), and in opportunistic infections (7 OCR pts vs 1 in PBO; 6/8 received MMF) led to dosing being discontinued in Oct 2009, with pts continuing into safety follow-up. **Table** shows the Wk 48 renal responses for the 221 "32 Wks" pts: 51% in PBO vs. 63% in OCR had an ORR, a treatment difference of 11.9% (95% CI: −1.9%, 25.7%; p=0.075), with similar overall rates in the 400 and 1000 mg arms. There was no increase in ORR observed in pts receiving 400 mg OCR+MMF vs MMF alone whereas there was an increased ORR rate with both OCR doses in OCR+EL vs EL alone, with higher ORR, and CRR rates in the 400 mg EL group. **Table** shows interim safety results for all treated pts (N=378).

Table. Efficacy and Safety; Renal

	Renal Response at Week 48 All '32 Wks' Pts		
Number (%) Pts	**PBO N = 74**	**OCR 400 mg N = 74**	**OCR 1000 mg N = 73**
ORR (CRR + PRR)	38 (51)	46 (62)	47 (64)
CRR	24 (32)	30 (41)	23 (32)
PRR	14 (19)	16 (22)	24 (33)
UPr/Cr ≥50% reduction	43 (58)	50 (68)	49 (67)
UPr/Cr ≤0.5	27 (36)	32 (43)	26 (36)
MMF Pts	**PBO N = 46**	**OCR 400 mg N = 43**	**OCR 1000 mg N = 40**
ORR	26 (57)	25/43 (58)	30/40 (75)
CRR	17 (37)	17 (40)	15 (37.5)
PRR	9 (20)	8 (19)	15 (37.5)
EL Pts	**PBO N = 28**	**OCR 400 mg N = 31**	**OCR 1000 mg N = 33**
ORR	12 (43)	21 (68)	17 (52)
CRR	7 (25)	13 (42)	8 (24)
PRR	5 (18)	8 (26)	9 (27)
	Interim Safety Results (Safety Population)		
Number (%) Pts	**PBO N = 125**	**OCR 400 mg N = 126**	**OCR 1000 mg N = 127**
Adverse Events (AEs)	104 (83)	101 (80)	98 (77)
Serious AEs (SAEs)	36 (29)	45 (36)	30 (24)
Eurolupus	16/44 (36)	13/47 (28)	10/48 (21)
MMF	20/81 (25)	32/79 (41)	20/79 (25)
Infections	65 (52)	78 (62)	71 (56)
Serious infections (SIEs)*	18 (14)	31 (25)	21 (17)
Eurolupus	5/44 (11)	6/47 (13)	6/48 (13)
MMF	13/81 (16)	25/79 (32)	15/79 (19)
Infusion related reactions (IRRs)	6 (5)	14** (11)	15 (12)
Eurolupus	0	4/47 (9)	3/48 (6)
MMF	6/81 (7)	10/79 (13)	12/79 (15)
Deaths	5 (4)	3 (2)	5 (4)
Eurolupus	4/44 (9)	0	2/48 (4)
MMF	1/81 (1)	3/79 (4)	3/79 (4)

* Including infections treated with an IV antibiotic. **includes one serious event.

Conclusion: In this '32 wks' population, the ORR rate at 48 wks was overall 12% higher in the OCR group. The addition of OCR 400mg to MMF did not generate additional benefit, with an increased observed rate of serious infections (SIEs). The OCR+EL regimen had a higher ORR rate vs EL alone, in both dose groups, with a lower PBO+EL ORR rate compared to the PBO+MMF group. Incidence of SAEs, SIEs, and IRRs was lower in EL pts compared to MMF pts.

Disclosure: E. F. Mysler: Genentech and Biogen IDEC Inc, 6, Roche, 5, 6; **A. J. Spindler:** None; **R. Guzman:** None; **M. Bijl:** Roche, 2; **D. Jayne:** Roche, 2, 5; **R. A. Furie:** Genentech and Biogen IDEC Inc, 2, 5, Roche, 2, 5; **R. Maciuca:** Genentech and Biogen IDEC Inc, 3; **S. Shahdad:** Roche, 3; **D. Close:** None; **P. Brunetta:** Genentech and Biogen IDEC Inc, 3; **J. Drappa:** Genentech and Biogen IDEC Inc, 3.

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Belimumab, a BLyS-Specific Inhibitor, Reduced Disease Activity across Multiple Organ Domains: Combined Efficacy Results from the Phase 3 BLISS-52 and -76 Studies.

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Purpose: To assess the efficacy of belimumab in individual organ domains using BILAG and SELENA SLEDAI (SS) in SLE patients after 52 wk of treatment.

Methods: 1684 seropositive (ANA ≥1:80 and/or anti-dsDNA ≥30 IU/mL) SLE patients with SS ≥6 on stable standard-of-care therapy for ≥30 d were enrolled in the phase 3, randomized, double-blind, placebo-controlled, international studies of belimumab 1 or 10 mg/kg vs placebo, plus standard of care (NCT00424476; NCT00410384). Patients were dosed on d 0, 14, and 28, and then q28d, for 48 or 72 wk. Efficacy analyses included SS and BILAG measured every 4 wk. SLEDAI domain scores were determined using methods described by Bombardier et al (1992); traditional scoring methods were used for BILAG domains. Positive shifts in total SS domain scores between baseline and wk 52 defined worsening; negative shifts defined improvement. Improvement in BILAG domain scores was defined as a shift from A or B scores at baseline to a lower score; worsening was defined as a shift to a higher score from B, C, D, or E at baseline. Patients who withdrew and/or took protocol-prohibited/restricted medication were considered to have no improvement. In worsening analysis, missing data were analyzed with last-observation-carried-forward imputation methods, using the last available observation at or prior to withdrawal, or dropout due to use of a protocol-prohibited/restricted medication (whichever occurred earlier).

Results: SS and BILAG organ system involvement at baseline was generally similar in the belimumab and placebo groups, and between studies (table). The most common SS domains involved were dermal (82%), immunologic (80%), musculoskeletal (65%), and renal (16%). The most common BILAG domains involved were musculoskeletal (60%), mucocutaneous (59%), hematology (16%), renal (11%), and general (11%). For SS, there was significant improvement from baseline at wk 52 in the central nervous system (CNS), vascular, musculoskeletal, immunologic, and dermal domains with belimumab (≥1 dose) vs placebo. In patients without involvement at baseline in a specific organ system, there was significantly less worsening at wk 52 in the immunologic, renal, and hematologic domains with belimumab vs placebo. For BILAG, there was significant improvement from baseline at wk 52 in musculoskeletal and mucocutaneous domains, and a trend ($p<0.07$) in the vasculitis domain with belimumab (≥1 dose) vs placebo. There also was significantly less worsening from baseline at wk 52 in the hematology domain, and a favorable trend in the vasculitis and renal domains, with belimumab vs placebo.

Conclusion: Belimumab demonstrated beneficial effects, with reductions in disease activity and prevention of worsening across several SS and BILAG organ systems.

Table. Changes From Baseline at Wk 52: SS and BILAG Organ Domains

Parameter	SOC + Placebo, n (%)	SOC + Belimumab 1 mg/kg, n (%)	SOC + Belimumab 10 mg/kg, n (%)
SS[a]			
Dermal			
Improvement	211/469 (45.0%)	233/456 (51.1%)†	249/454 (54.8%)**
Worsening	12/93 (12.9%)	14/103 (13.6%)	14/109 (12.8%)
Immunologic			
Improvement	44/439 (10.0%)	90/445 (20.2%)#	124/455 (27.3%)#
Worsening	23/123 (18.7%)	17/114 (14.9%)	8/108 (7.4%)*
Musculoskeletal			
Improvement	183/372 (49.2%)	211/362 (58.3%)*	208/368 (56.5%)†
Worsening	13/190 (6.8%)	12/197 (6.1%)	8/195 (4.1%)
Renal			
Improvement	39/92 (42.4%)	43/90 (47.8%)	42/85 (49.4%)
Worsening	40/470 (8.5%)	22/469 (4.7%)	31/478 (6.5%)
Hematologic			
Improvement	18/40 (45.0%)	22/47 (46.8%)	12/42 (28.6%)
Worsening	34/522 (6.5%)	24/512 (4.7%)	17/521 (3.3%)*
Vascular			
Improvement	15/37 (40.5%)	19/36 (52.8%)	28/38 (73.7%)*
Worsening	2/525 (0.4%)	2/523 (0.4%)	3/525 (0.6%)
Serosal			
Improvement	18/32 (56.3%)	17/36 (47.2%)	20/37 (54.1%)
Worsening	10/530 (1.9%)	4/523 (0.8%)	4/526 (0.8%)
CNS			
Improvement	1/11 (9.1%)	9/15 (60.0%)*	12/19 (63.2%)*
Worsening	2/551 (0.4%)	3/544 (0.6%)	2/544 (0.4%)
Constitutional			
Improvement	7/10 (70.0%)	7/10 (70.0%)	6/12 (50.0%)
Worsening	4/552 (0.7%)	4/549 (0.7%)	6/551 (1.1%)
BILAG[b]			
Musculoskeletal			
Improvement	171/342 (50.0%)	200/327 (61.2%)**	204/339 (60.2%)*
Worsening	26/15 (5.0%)	20/515 (3.9%)	20/528 (3.8%)
Mucocutaneous			
Improvement	137/350 (39.1%)	156/326 (47.9%)*	150/315 (47.6%)*
Worsening	24/538 (4.5%)	23/531 (4.3%)	29/541 (5.4%)
Hematology			
Improvement	32/88 (36.4%)	35/96 (36.5%)	30/88 (34.1%)
Worsening	51/561 (9.1%)	31/557 (5.6%)*	37/559 (6.6%)
Renal			
Improvement	31/59 (52.5%)	33/62 (53.2%)	31/58 (53.4%)
Worsening	42/561 (7.5%)	27/553 (4.9%)†	34/560 (6.1%)
General			
Improvement	37/66 (56.1%)	33/53 (62.3%)	40/64 (62.5%)
Worsening	18/557 (3.2%)	16/558 (2.9%)	19/560 (3.4%)
Vasculitis			
Improvement	25/52 (48.1%)	32/48 (66.7%)†	36/51 (70.6%)†
Worsening	9/548 (1.6%)	2/543 (0.4%)†	3/544 (0.6%)†
CVS/Respiratory			
Improvement	13/21 (61.9%)	12/19 (63.2%)	14/21 (66.7%)
Worsening	5/558 (0.9%)	5/554 (0.9%)	6/561 (1.1%)
Neurology			
Improvement	5/6 (83.3%)	6/8 (75.0%)	3/7 (42.9%)
Worsening	4/562 (0.7%)	3/556 (0.5%)	6/562 (1.1%)

[a]The 9 SS organ system categories, as described by Bombardier et al (*Arthritis Rheum.* 1992;35: 630–40), included: *dermal*—rash, mucosal ulcers, alopecia; *immunologic*—increased DNA binding, low complement; *musculoskeletal*—arthritis, myositis; *renal*—urinary casts, hematuria, proteinuria, pyuria; hematologic—leukopenia, thrombocytopenia; *vascular*—vasculitis, cerebrovascular accident; *serosal*—pericarditis, pleuritis; *CNS*—seizures, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache; and *constitutional*—fever. Cerebrovascular accident was reassigned from the CNS to vascular domain. [b]BILAG class organ domains as described by Isenberg and Gordon (*Lupus.* 2000;9:651–4).
†p<0.10, *p<0.05, **p<0.01, ***p<0.001, #p<0.0001; otherwise, p = not significant.
CVS, cardiovascular system.

Disclosure: S. Manzi: Human Genome Sciences, Inc., 9; **J. Sanchez-Guerrero:** Human Genome Sciences, Inc., 9; **J. T. Merrill:** Human Genome Sciences, Inc., 9; **R. A. Furie:** GlaxoSmithKline, 5, Human Genome Sciences, Inc., 2, 5, 9; **D. Gladman:** Human Genome Sciences, Inc., 9; **S. Navarra:** Human Genome Sciences, Inc., 2, 5, 9; **E. M. Ginzler:** Human Genome Sciences, Inc., 2, 9; **D. D'Cruz:** GlaxoSmithKline, 5, Human Genome Sciences, Inc., 9; **A. Doria:** GlaxoSmithKline, 5, Human Genome Sciences, Inc., 9; **S. Cooper:** Human Genome Sciences, Inc., 1, 3; **Z. J. Zhong:** Human Genome Sciences, Inc., 1, 3; **D. Hough:** Human Genome Sciences, Inc., 1, 3; **W. Freimuth:** Human Genome Sciences, Inc., 1, 3; **M. Petri:** GlaxoSmithKline, 5, Human Genome Sciences, Inc., 2, 5, 9; **on Behalf of the BLISS-52 and -76 Study Groups:** None.

1457

Five-Year Experience with Belimumab, a BLyS-Specific Inhibitor, in Patients with Systemic Lupus Erythematosus (SLE). J. T. Merrill[6], D. J. Wallace[1], R. A. Furie[4], M. A. Petri[3], W. Stohl[10], W. W. Chatham[8], J. McCune[9], A. Weinstein[11], J. McKay[5], Z. J. Zhong[2], L. Pineda[2], J. Klein[2], W. Freimuth[2], E. M. Ginzler[7] and for the LBSL02/99 Study Group. [1]Cedars-Sinai/UCLA, Los Angeles, CA, [2]Human Genome Sciences, Inc, Rockville, Rockville, MD, [3]Johns Hopkins University School of Medicine, Timonium, MD, [4]North Shore LIJ Health System, Lake Success, NY, [5]Oklahoma Center for Arthritis Therapy & Research, Tulsa, OK, [6]Oklahoma Medical Research Foundation, Oklahoma City, OK, [7]SUNY Downstate Medical Center, Brooklyn, NY, [8]UAB Arthritis Clinical Intervention Program, Birmingham, AL, [9]University of Michigan Health System, Ann Arbor, MI, [10]USC Keck School of Medicine, Los Angeles, CA, [11]Washington Hospital Center, Washington, DC

Purpose: To examine 5-year safety of belimumab in an open-label extension study of SLE patients and evaluate long-term efficacy in a subgroup similar to those in recent phase 3 trials.

Methods: 449 SLE patients with SELENA-SLEDAI (SS) ≥4 enrolled in a phase 2, 52-wk, randomized, double-blind study of belimumab 1, 4, or 10 mg/kg q28d vs placebo, plus background SLE therapy (NCT00071487). At wk 56, placebo patients received belimumab 10 mg/kg; prior belimumab patients received the same dose or 10 mg/kg. At wk 80, 296 patients (66%) entered an uncontrolled continuation study (belimumab 10 mg/kg; NCT00583362). The 5-y dataset was divided into ten 6-mo intervals for reporting efficacy and adverse events (AEs). Analyses of disease activity included the SS Flare Index (SFI) and SLE Responder Index (SRI): improvement in SS (≥4 pt), no new BILAG A or <2 new B flares, and no Physician's Global Assessment worsening (<0.3 pt) vs baseline. All efficacy assessments were limited to the seropositive (ANA titer ≥1:80 and/or anti-dsDNA ≥30 IU/mL) patient subgroup (n=321), who were similar to those patients enrolled in the phase 3 trials. Safety assessments were performed in all patients.

Results: 19% of patients dropped out during the placebo-controlled portion of the study, 296 enrolled in the open-label extension at wk 80, and the discontinuation rate has been 3%–9%/y. Total belimumab exposure was 1415 patient-years (pty). Incidence rates (per 100 pty) of AEs remained stable or decreased over 5 y (table). In seropositive patients, SRI rate was 46% at wk 52 (vs 29% with placebo; p<0.05), increased to 55% by wk 76, and was maintained through wk 272 (59%). In this study, adjustments in background SLE therapy were permitted. The frequency of 1 new BILAG A or 2 new B flares decreased from 30% over the 1st 6 mo to 23% over the 2nd 6 mo (vs 33% and 25%, respectively, with placebo) and declined to 11% at the 4.5–5.0-y interval. The frequency of SFI flares decreased from 72% (severe 13%) over the 1st 6 mo to 62% (severe 8%) over the 2nd 6 mo (vs 76% [severe 9%] and 73% [severe 11%], respectively, with placebo) and further declined to 22% (severe 1%) at the 4.5–5.0-y interval. Autoantibody levels (anti-Sm, anti-dsDNA, anticardiolipin immunoglobulin-G) decreased over time with belimumab.

Table. AE Incidence (rate per 100 pty)[a]

	All Patients Treated With Belimumab									
Intervaly	1 (0.0-0.5 y)	2 (0.5-1.0 y)	3 (1.0-1.5 y)	4 (1.5-2.0 y)	5 (2.0-2.5 y)	6 (2.5-3.0 y)	7 (3.0-3.5 y)	8 (3.5-4.0 y)	9 (4.0-4.5 y)	10 (4.5-5.0 y)
No. patients (pty)	424 [206]	398 [183]	353 [166]	314 [147]	284 [136]	261 [128]	252 [122]	240 [116]	227 [111]	221 [100]
Overall AEs	409 (194)	337 (184)	304 (184)	271 (184)	244 (179)	226 (177)	210 (171)	207 (178)	183 (165)	154 (154)
Serious AEs	43 (20.8)	33 (18.0)	28 (16.9)	26 (17.7)	24 (17.6)	28 (21.9)	14 (11.4)	18 (15.5)	18 (16.2)	17 (17.0)
Overall infections	246 (119)	197 (108)	170 (103)	164 (112)	146 (107)	129 (101)	108 (88)	126 (108)	95 (86)	82 (82)
Serious infections	14 (6.8)	10 (5.5)	6 (3.6)	8 (5.4)	4 (2.9)	5 (3.9)	2 (1.6)	6 (5.2)	2 (1.8)	3 (3.0)
Malignancies	0 (0)	2 (1.1)	5 (3.0)	2 (1.4)	1 (0.7)	2 (1.6)	2 (1.6)	3 (2.6)	3 (2.7)	3 (3.0)

[a]Interval 1 includes initial placebo patients who initiated belimumab treatment at wk 56.

Conclusions: Belimumab added to standard-of-care therapy was well tolerated over 5 y. Seropositive patients treated with belimumab showed sustained improvement in disease activity, and a decline in BILAG and SFI flares over 5 y, without changing the background treatment rules.

Disclosure: J. T. Merrill: Human Genome Sciences, Inc., 9; **D. J. Wallace:** Human Genome Sciences, Inc., 9; **R. A. Furie:** GlaxoSmithKline, 5, Human Genome Sciences, Inc., 2, 5, 9; **M. A. Petri:** GlaxoSmithKline, 5, Human Genome Sciences, Inc., 2, 5, 6, 9; **W. Stohl:** Human Genome Sciences, Inc., 2, 9; **W. W. Chatham:** Human Genome Sciences, Inc., 2, 9; **J. McCune:** Human Genome Sciences, Inc., 2, 9; **A. Weinstein:** Human Genome Sciences, Inc., 2, 9; **J. McKay:** Human Genome Sciences, Inc., 9; **Z. J. Zhong:** Human Genome Sciences, Inc., 1, 3; **L. Pineda:** Human Genome Sciences, Inc., 1, 3; **J. Klein:** Human Genome Sciences, Inc., 1, 3; **W. Freimuth:** Human Genome Sciences, Inc., 1, 3; **E. M. Ginzler:** Human Genome Sciences, Inc., 2, 9; **for the LBSL02/99 Study Group:** None.

ACR REF Special Session
REF Marshall J. Schiff, MD, Memorial Lectureship: Everything a Rheumatologist Should Know About Spine Surgery but Was Afraid to Ask
Tuesday, November 9, 2010, 4:30 PM–6:00 PM

1458

Effectiveness of the Global Posture Reeducation Method (GPR) and Segmental Stretching in the Treatment of Chronic Back Pain: A Randomized Controlled Trial. Marilene M. dos Santos[3], Larissa S. Guimarães[5], Lorena O. Souza[5], Mariana M. Vasconcelos[5], Taís M. Camargo[1], Priscylla C. Develly[5], Bernardo L. F. Fernandes[4] and Virgínia F. M. Trevisani[2]. [1]Brazil, [2]Federal University of São Paulo-UNIFESP/EPM, São Paulo, SP, Brazil, [3]Federal University of São Paulo-UNIFESP/EPM, Poços de Caldas, MG, Brazil, [4]Pontifical Catholic University of Minas Gerais - PUC Minas, Poços de Caldas, MG, Brazil, [5]Pontifical Catholic University of Minas Gerais-PUC Minas, Brazil

Purpose: The purpose of this study was to evaluate the effectiveness of the Global Posture Reeducation method (GPR) and segmental stretching exercises in the treatment of chronic back pain.

Methods: A randomized controlled blinded assessor trial was conducted. One hundred and fifty patients of both sexes were selected, with a mean age of 40.15 ± 11.55 years-old, who had pain in some segment of the spine for at least three months. They were randomly distributed into three groups (n=50, each): G1 – submitted to GPR method; G2 – received the segmental stretching; and G3 – control. Patients in G1 and G2 received 16 individual treatment sessions, twice a week, for eight weeks. The outcomes measured were pain (visual analogue scale), function (Roland Morris questionnaire), quality of life by the Brazilian Portuguese version of Short Form-36 (SF-36), and pain medication consumption (all patients were instructed to register in a suitable form every time they consume any pain medication). Besides the evaluations before and after the end of the intervention, a follow up was conducted two months after the end of the treatment. Data were statistically analyzed at a significance level of $p<0.05$. An intragroup and intergroup comparison was performed.

Results: The baseline assessment demonstrates the homogeneity of the groups. The outcomes showed significant pain level reduction in the three groups, but in the intergroup's comparison, treated groups were better than control, and G1 (GPR) was still better than G2 (segmental stretching), presenting the largest pain intensity reduction. In quality of life in G1 and G2, there was significant improvement in all SF-36 domains (functional capacity, physical, emotional and social aspects, pain, general health status, vitality, and mental health). In G3 this improvement occurred in pain, social and emotional aspects, and functional capacity. In the intergroup's comparison, G1 and G2 were significantly superior to G3 in physical aspects, pain, and vitality components. The G1, treated with GPR, was still better than G3 when comparing social aspects and mental health. In Roland Morris questionnaire there were significant improvements in all groups, but in the comparison among them, G1 and G2 were significantly better. Regarding the consumption of pain medication, it was observed in the treated groups, G1 and G2, that the drug intake was significantly lower than in the control group (G3).

Conclusion: Based on the findings of our study, we conclude that both methods were effective and superior to control group in pain reduction, in the improvement of function and quality of life, and in the decrease of medication consumption, however, the GPR method proved to be superior to the segmental stretching for the treatment of chronic back pain.

Disclosure: M. M. dos Santos: None; **L. S. Guimarães:** None; **L. O. Souza:** None; **M. M. Vasconcelos:** None; **T. M. Camargo:** None; **P. C. Develly:** None; **B. L. F. Fernandes:** None; **V. F. M. Trevisani:** None.

1459

Epidemiology of Restricting Back Pain in Older Persons and Associations with Age, Sex, Obesity, and Depressive Symptoms. Una E. Makris[3], Liana Fraenkel[1], Ling Han[2] and Thomas M. Gill[3]. [1]Department of Veterans Affairs, West Haven, CT, [2]Program on Aging, New Haven, CT, [3]Yale University School of Medicine

Background: Despite the considerable morbidity and costs attributable to back pain, longitudinal data describing the clinical course and risk factors associated with this complaint in older persons are sparse.

Purpose: To describe the epidemiology of restricting back pain in community-living older persons and to evaluate the association of age, sex, obesity, and depressive symptoms with development of restricting back pain.

Methods: Participants, identified from the Yale Precipitating Events Project, included 550 nondisabled, community-living persons, aged 70 years or older, who did not report restricting back pain at baseline. Data were collected monthly for over 10 years. Restricting back pain was defined as staying in bed for at least half a day and/or cutting down on one's usual activities due to back pain. One or more consecutive monthly reports of restricting back pain defined an episode. We first determined the number and duration of restricting back pain episodes. We used Cox regression models to evaluate the association between age, sex, obesity, and depressive symptoms and the development of the first occurrence and recurrence of restricting back pain episodes. Interaction terms between sex and these baseline factors were tested using Cox models in first-event and recurrent events models.

Results: The mean age of our sample was 78.6 years, 63% were women, 92% were white, 19% were obese (BMI ≥30 kg/m2), and 15% reported depressive symptoms. During a median follow-up of 107 months, 126 (61.8%) of the men and 251 (72.5%) of the women participants developed restricting back pain. Among the 377 (68.5%) participants with restricting back pain, the median (interquartile range) number of episodes was 2.0 (1–4) for men and 3.0 (1–5) for women ($p = 0.01$). The median duration of restricting back pain episodes was one month. Of the 1528 total episodes of restricting back pain, only 6.4% were chronic (lasting three or more months). There were no differences in number or duration of restricting back pain episodes by age. The association between restricting back pain and age, sex, obesity, and depressive symptoms are listed in Table 1. Women with depressive symptoms had the highest risk of developing recurrent restricting back pain episodes (HR 2.89, 95% CI 2.03, 4.11) compared to men without depressive symptoms.

Table 1. Association between selected risk factors and restricting back pain (N = 550) estimated using Cox proportional hazard model

Effect*	Outcome	Model 1 (1st event)	Model 2 (Recurrent events)
Age ≥ 85	HR (95% CI)	1.28 (1.01–1.62)	1.03 (0.82–1.29)
	P value	<0.05	0.79
Female Sex	HR (95% CI)	1.27 (1.02–1.57)	1.41 (1.10–1.80)
	P value	0.03	0.01
BMI ≥ 30	HR (95% CI)	1.34 (1.05–1.72)	1.60 (1.21–2.12)
	P value	0.02	0.001
Depressive Symptoms	HR (95% CI)	1.73 (1.29–2.34)	2.04 (1.53–2.72)
	P value	<0.001	<0.001

* Both models simultaneously included these four variables.

Conclusion: Among community-living older persons, restricting back pain is common, short-lived, and frequently episodic. Women with depressive symptoms are most likely to develop restricting back pain. Additional research is warranted to further investigate the relationship between depressive symptoms and back pain, especially in older women.

Disclosure: U. E. Makris: None; **L. Fraenkel:** None; **L. Han:** None; **T. M. Gill:** None.

ARHP Concurrent Abstract Sessions
Don't Despair Over Health Disparities
Tuesday, November 9, 2010, 4:30 PM–6:00 PM

1460

Life Course Socioeconomic Position and Health Outcomes in People with Self-Reported Arthritis. Jack H. Shreffler[3], Britta Schoster[3], Kathryn Remmes Martin[2] and Leigh F. Callahan[1]. [1]Univ of North Carolina, Chapel Hill, NC, [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, [3]University of North Carolina, Chapel Hill

Purpose: Childhood and adult socioeconomic status (SES) positions have been demonstrated to be independently associated with health status outcomes in cardiovascular and other chronic diseases. The purpose of this study is to determine if current SES and childhood caregiver SES positions are independently associated with health outcomes, including measures of disability, physical health, and mental health status, in people with self-reported arthritis.

Methods: A practice-based research network of 22 family medicine practices in rural and urban areas of a southeastern state was established in 2001. Participants completed telephone surveys assessing health status, chronic conditions, community characteristics, health attitudes and beliefs, and socio-demographic variables in 2004 and again in 2006. The 2006 follow-up questionnaire obtained participants' current SES and the SES of their parent or caregiver during childhood. Regression models were conducted on 937 people with arthritis for health outcomes including adult/childhood pairs of single SES variables (education, occupation, or homeownership) as main explanatory variables with adjustment for age, BMI, and gender. Outcomes were SF12v2 Physical (PCS) and Mental (MCS) Component Summary scores, Health Assessment Questionnaire disability scale (HAQ), Center for Epidemiological Studies-Depression depressive symptoms scale (CES-D), and the CDC Health Related Quality of Life 5-item general health response (dichotomized to fair/poor versus good/very good/excellent).

Results: The average age of participants was 61 years (23–94) and 74% were female. 16% did not complete high school (NHS), non-homeownership (NHO) was 18%, and low occupational status (LOC) was 42%. The 3 SES measures for the participants were considerably higher than those reported for their primary caregiver during childhood. PCS score, 38(13) [mean (sd)], was significantly ($p<0.05$) reduced by −4.2, −2.7, and −2.7 for caregiver NHS, LOC, and NHO, respectively. General health self-reported as fair/poor (39%)

was more likely, OR=1.54 (95% CI=[1.17, 2.05]), for caregiver NHO, and nearly significantly, OR=1.6 (95% CI=[0.99, 2.70], p=0.056), for caregiver NHS. CES-D score, 11.9(12), was significantly increased by 2.6 and 2.5 for caregiver NHS and NHO, respectively. In addition, CES-D was nearly significant, β=1.6 [95% CI=−0.01, 3.25] (p=0.051) for LOC. Neither HAQ nor MCS was found to have independent, significant association with the three caregiver SES variables when the adult measures were included in the model. In the regression models producing the results above, SES measures for the adult participants were strongly associated with all outcomes, with the notable exceptions of PCS and MCS for homeownership.

Conclusions: SES measures at childhood show significant association with PCS, general health, and CES-D, independent of the participant's current adult SES levels. Healthcare providers should consider the potential influence of patients' SES as children when evaluating their current health status.

Disclosure: J. H. Shreffler: None; **B. Schoster:** None; **K. R. Martin:** None; **L. F. Callahan:** None.

1461

Perceived Helplessness as a Mediator between Household Income and Health Status in People with Self-Report Arthritis. Kathryn Remmes Martin[2], Britta Schoster[3] and Leigh F. Callahan[1]. [1]Univ of North Carolina, Chapel Hill, NC, [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, [3]University of North Carolina at Chapel Hill

Purpose: Lower income is associated with poorer health status among people with chronic disease. This study aimed to examine the role of perceived helplessness as a mediator in the relationship between household income and health status in people with self-report arthritis.

Methods: In 2004 and 2005, 439 people with self-reported physician-diagnosed arthritis were recruited from a southeastern Family Medicine Research Network and completed a telephone survey assessing health status, chronic conditions, neighborhood characteristics, health attitudes and socio-demographic variables. Six health status outcomes were: Health Assessment Questionnaire (HAQ), disability index; SF-12v2 Physical Component Summary (PCS), physical functioning; SF-12v2 Mental Component Summary (MCS), mental health; and 3 CDC Health Related Quality of Life Healthy Days measures: mental, physical and limited activity days. The proposed mediator, perceived helplessness, was assessed with the Rheumatology Attitudes Index (RAI). Path analyses were constructed with MPlus to examine the relationship between income, perceived helplessness, and each health status outcome, adjusting for age, race, gender, body mass index (BMI), education, occupation, homeownership, and block-group poverty-level.

Results: Participants were on average 56 years old, female (76.3%), non-Hispanic white (75.9%), had a mean BMI of 31.5, earned less than $45,000 (72.7%), had at or lower than a high school education (51.9%), had lower occupational status (54.7%), and were homeowners (74.3%). Income was directly and indirectly related to health status. Income was directly related to physically unhealthy days (β=−2.42, p=0.003), mentally unhealthy days (β=−2.17, p=0.002), lower MCS (β=1.96, p=0.0.03), limited activity days (β=−3.66, p<0.001), PCS (β=3.40, p<0.001), and disability (β=−0.27, p<0.001). Income was also indirectly related through helplessness. Individuals with lower income have greater perceived helplessness regarding their condition (β=−0.33, p<0.001). Those with greater helplessness reported greater number of physically unhealthy days (β=5.24, p<0.001), mentally unhealthy days (β=4.48, p<0.001), limited activity days (β=4.44, p<0.001), greater disability (β=0.33, p<0.001) and lower scores on MCS (β=−6.15, p<0.001) and PCS (β= −3.98, p<0.001). The Sobel test showed a significant indirect effect for physically unhealthy days (β=−1.74, p<0.001), mentally unhealthy days (β=−1.49, p<0.001), limited activity days (β=−1.48, p<0.001), MCS (β=2.04, p<0.001), PCS (β=1.32, p<0.001), and disability (β=−0.11, p<0.001).

Conclusions: Our findings indicate that lower levels of helplessness partially mediate the relationship between lower levels of income and poorer mental and physical health status outcomes in people with self-report arthritis. Enhancing perceived control in individuals with lower income levels may be a mechanism for reducing health disparities.

Disclosure: K. R. Martin: None; **B. Schoster:** None; **L. F. Callahan:** None.

1462

An Examination of How Coping with Prescription Medication Costs and Medication Underuse Influences Physical and Mental Health of Individuals with Arthritis. Kathryn Remmes Martin, Britta Schoster, Jack Shreffler and Leigh F. Callahan, University of North Carolina at Chapel Hill

Purpose: Our purpose is twofold: 1) to identify the overall frequency and characteristics of individuals who self-report prescription medication cost coping strategies, and 2) to examine the association between coping strategies and medication underuse and physical and mental health outcomes among a cohort of participants with arthritis from a southeastern state.

Methods: In 2006 and 2007, 729 people with self-reported physician-diagnosed arthritis completed a telephone survey assessing health status, chronic conditions, neighborhood characteristics, health attitudes and socio-demographic variables. Five health status outcomes used were: Health Assessment Questionnaire (HAQ), disability index; SF-12v2 Physical Component Summary (PCS), physical functioning; SF-12v2 Mental Component Summary (MCS), mental health; Center for Epidemiological Studies-Depression (CES-D) (<16; ≥16), depressive symptoms; self-rated health (excellent, very good, & good; fair & poor). Helplessness was also assessed with the Rheumatology Attitudes Index (RAI). Linear and logistic regression analyses using Stata v11 were conducted for each outcome to explore associations with the medication cost coping strategies while adjusting for age, race, gender, body mass index (BMI), co-morbid conditions, and participant education, income, occupation and homeownership.

Results: Participants were on average 61 years old, female (75.0%), non-Hispanic white (76.8%), had a mean BMI of 30.2, and a median income of below $45,000 (55.7%). Overall, participants reported spending less on food, heat, or basic needs (22.4%), borrowing money from a friend or relative outside of their household (16.1%), increased the amount of credit-card debt carried month-to month (11.7%) to pay for medications and taking fewer medications than prescribed due to medication costs (20.2%). Individuals who borrowed money had lower mental health (MCS) (β= −3.87, p=0.003) and greater disability (β=0.14, p=0.044). Individuals increasing credit card debt had worse physical functioning (β= −4.63, p=0.001), and self-rated health (OR =0.43, p=0.005), and reported greater helplessness associated with their condition (β= 0.47, p<0.001). Individuals who reported medication underuse had worse mental health (β= −4.24, p<0.001), greater disability (β=0.13, p=0.028), depressive symptoms (OR=2.03, p=0.004), and a trend for worse self-rated health (OR=0.62, p=0.066). Age, race, BMI, comorbid condition count, education, and income were statistically significant covariates in some of the models dependent on the outcome.

Conclusions: Our findings indicate that individuals with arthritis do use strategies to cope with mediation costs, one of which is medication underuse, and that these strategies have adverse mental and physical health outcomes. Health care practitioners should be alert to issues of medication cost to ensure optimal patient health and medication adherence.

Disclosure: K. R. Martin: None; **B. Schoster:** None; **J. Shreffler:** None; **L. F. Callahan:** None.

1463

Disability and Knee Osteoarthritis: Associations with Individual and Community Socioeconomic Status. Leigh F. Callahan, Joshua B. Knight, Jack H. Shreffler, Britta Schoster, Jordan B. Renner and Joanne M. Jordan. University of North Carolina, Chapel Hill

Purpose: Individual level socioeconomic status (SES) measures have been shown to be associated with disability and restricted function in osteoarthritis (OA), and limited studies have also demonstrated associations with community level SES measures independent of one's individual SES. To date this has not been evaluated in persons with knee OA. This study examined associations between educational attainment, occupation, and community poverty with disability in persons with knee radiographic OA (rOA) or symptomatic OA (sOA) in a population-based OA cohort in a southeastern state.

Methods: A cross-sectional analysis was conducted on individuals (64% Caucasian, 36% African American) with knee rOA (n=733) or knee sOA (n=487) who were assessed in the 2001–2003 time period. rOA was defined as Kellgren-Lawrence grade ≥ 2 in at least one knee. sOA was defined as K-L grade ≥ 2 and symptoms (pain, aching or stiffness) in the same knee. Educational attainment (<high school (HS) or ≥HS) and occupational status (managerial or non-managerial) were individual SES measures. Census block group poverty rate (<12%, 12–25%, >25%) was the community SES

measure. Disability was measured by the Health Assessment Questionnaire (HAQ). Covariates were age, gender, race, BMI, occupational activity score, and presence of hip symptoms. Race was not an effect modifier and was included as a covariate. Unadjusted and adjusted analyses were used to find associations of disability with each SES effect separately. Multivariable analyses were conducted using all SES variables, adjusting for covariates.

Results: In persons with knee rOA, education (β=0.21, C.I.= [0.11, 0.32]), occupation (β =0.15, C.I.=[0.05, 0.25]) and >25% poverty (β=0.22, C.I. = [0.07, 0.36]) were all significantly associated with disability in unadjusted models. All SES variables were also significantly associated with HAQ disability in persons with sOA: education (β=0.22, C.I.= [0.09, 0.35]), occupation (β =0.16, C.I.=[0.03, 0.29]) and >25% poverty (β=0.23, C.I. = [0.05, 0.41]). In adjusted models, occupation and community poverty were no longer significantly associated with rOA or sOA. In multivariable models, education was the only SES variable (in both rOA and sOA) significantly associated with disability (β=0.18, C.I.= [0.08, 0.29]) and (β=0.22, C.I.= [0.09, 0.36]), respectively. Covariates positively associated with disability were hip symptoms, female gender, obesity, and strenuous occupational activities.

Conclusions: In persons with knee rOA or knee sOA, education remained the important SES predictor of disability after adjusting for key risk factors. Occupation and community poverty were not independently significant when education was a main explanatory variable. These data underscore the importance of educational attainment with outcomes in knee OA.

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1464

Radiographic Knee Osteoarthritis and Knee Pain: Findings from 5 Racial/Ethnic Populations. Ke Wang[2], Noriko Yoshimura[7], Ling Xu[5], Jianhao Lin[6], Inje Kim[4], Michael Nevitt[8], Hiroshi Kawaguchi[7], David Felson[1], Xiaozheng Kang[6], Yuqing Zhang[1] and Hyun Ah Kim[3]. [1]BU. Sch. of Med., Boston, [2]BU. Sch. of Med., [3]Hallym Univ., Sacred Heart Hosp., Anyang, Korea, Republic of, [4]Hallym Univ., Sacred Heart Hosp., Korea, Republic of, [5]Peking Union Medical College, Beijing, China, [6]Peking University, Beijing, China, [7]The University of Tokyo, Tokyo, Japan, [8]Univ. of California at San Francisco, San Francisco, CA

Background: There is a consensus that the association between knee radiographic osteoarthritis (ROA) and knee pain is modest and only limited to knees with severe ROA. However, utilizing a novel approach comparing knees discordant for pain, recent results from both Framingham OA Study and Multicenter OA Study suggested that ROA was strongly associated with both frequent knee pain (FKP) and pain severity, even among knees with moderate ROA. To investigate whether such findings are consistent in other ethnic populations, we examined the relation of knee ROA to FKP and pain severity among 5 ethnic populations using data collected from 5 OA studies.

Methods: Subjects included were from 5 studies: urban Chinese (Beijing OA Study, BOA), rural Chinese (Wuchuan OA Study, Wuchuan), Japanese (Research on OA Against Disability, ROAD), Korean (Hallym Aging study, HAS), White (OA Initiative, OAI), and African American (OAI). Participants in each study were asked knee-specific questions regarding presence of FKP (i.e., pain lasting for ≥ a month in the past 12 months) and pain severity. We performed a within-person knee-matched case-control analysis among subjects whose FKP status or pain severity categories (no pain, mild/moderate pain, severe/extreme pain) were discordant between the two knees. We examined the relation of knee ROA to prevalence of FKP using a conditional logistic regression and to pain severity using a stratified proportional odds model by amalgamating conditional likelihood.

Results: Included were 252 urban Chinese (71% female, mean age 68, mean BMI 26), 221 rural Chinese (55% female, mean age 57, mean BMI 23), 297 Japanese (71% female, mean age 71, mean BMI 24), 98 Koreans (54% female, mean age 70, mean BMI 25), 556 Whites (46% female, mean age 62, mean BMI 29), and 141 African Americans (71% female, mean age 62, mean BMI 32). As shown in Table, knee ROA is strongly associated with presence of FKP across all 5 racial/ethnic populations (p for trend for all studies <0.01). The association is strong even for knees with moderate ROA: knees with K/L=2 had 6.8 (BOA), 3.8 (Wuchuan), 6.6 (HAS), 3.0 (ROAD), 7.2 (OAI White), and 17.6 (OAI African American) times higher prevalence of FKP than those with K/L=0. Knee ROA was also strongly associated with knee pain severity (p for trend for all studies <0.01).

Conclusion: Severity of knee ROA was strongly associated with FKP and pain severity in all ethnic groups.

Studies		BOA (Urban Chinese)	Wuchuan (Rural Chinese)	HAS (Korean)	ROAD (Japanese)	OAI (White)	OAI (AA)
Outcome: FKP				**OR**			
K/L grade	0	1.0	1.0	1.0	1.0	1.0	1.0
	1	1.9	2.1	2.3	1.1	4.2	1.0
	2	6.8	3.8	6.6	3.0	7.2	17.6
	3–4	16.8	9.4	10.0	24.2	36.9	55.5
	P for trend	<.0001	0.0046	0.0028	<.0001	<.0001	<.0001
Outcome: Pain Severity				**OR**			
K/L grade	0	1.0	1.0	1.0	1.0	1.0	1.0
	1	1.8	1.4	1.8	2.0	2.8	0.4
	2	6.3	5.6	9.7	3.0	6.5	4.7
	3–4	14.9	9.1	15.9	54.7	29.7	7.2
	P for trend	<.0001	0.0048	0.001	<.0001	<.0001	0.0004

Disclosure: K. Wang: None; **N. Yoshimura:** None; **L. Xu:** None; **J. Lin:** None; **I. Kim:** None; **M. Nevitt:** None; **H. Kawaguchi:** None; **D. Felson:** None; **X. Kang:** None; **Y. Zhang:** None; **H. A. Kim:** None.

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Impact of *Buenos Dias, Artritis*, a Spanish Health Communications Campaign Promoting Physical Activity among Spanish-Speaking People with Arthritis. Teresa J. Brady[2] and Jed Lam[1]. [1]Aeffect Inc., [2]Center for Disease Control, Atlanta, GA

Background: *Buenos Dias, Artritis* is a health communications campaign designed to promote physical activity among Spanish-speaking people with arthritis. The purpose of this study was to evaluate the effects of that campaign as implemented by 4 state health departments.

Methods: A quasi-experimental design was used. 4 state health departments conducted the campaign in one community in their state by placing radio ads and/or outdoor advertising, brochures in community locations and newspaper ads or other print materials. Data were collected from these Test communities (TC) and well as 2 Control communities (CC), selected to have similar proportions of Hispanic populations, at baseline (T1), immediately following campaign completion (T2) and 6 months after baseline (T3). Data were collected by random-digit dial telephone survey from purchased lists of randomly generated telephone numbers in geographic areas known to have higher rates of Hispanics with lower income and education levels. T1 respondents were ineligible for T2 survey.

Results: By design, T1 and T2 data were collected for approximately 1200 respondents (1213 and 1167 respectively), and 600 T3 respondents. Characteristics of T1 sample: 41% ages 55–64, (range 45–75), 68% from Mexico, 69% education less than high school graduate, and 75% female.

Changes in knowledge and confidence were seen. TC demonstrated significant increase in the percentage who believed that "moderate exercise can help you beat arthritis" at T3, (T1=84%, T3=89%)but control respondents also had a significant increase (T1=84%, T3=91%). However, the TC significant increase in beliefs that "moderate exercise can be helpful even if done 10 minutes at a time" (T1=84%, T3=91%), and that they could "reduce my arthritis pain by exercising regularly" (T1=76%, T3=82%) were not matched by increases in CC.

Exercise behavior increased significantly in TC but not CC at both T2 and T3. TC demonstrated significant increases in percentages "exercising at least 10 minutes per day" at T2 and T3 (T1=72%, T2=76%, T3=86%), and "exercising at least 3 days per week" at T2 and T3 (76%, 82%, 81% respectively). No comparable increase was seen in the CC.

Recognition of campaign tag line increased significantly in TC at T3, but recognition of 4 other taglines also increased significantly in TC. Unaided awareness of campaign sponsors increased in TC at T2 and most persisted at T3. There was no significant increase in CC. However, unaided recognition of the National Institutes of Health, which was not a sponsor, also increased in TC at T2.

Respondents in TC reported significant increases in 2 selected behavioral responses to the campaign's call to action at T3 (thought about exercising more, T1=66%, T3=78%; increased my exercise T1=42%, T3=53%). 2 other behavioral responses increased significantly in both TC and CC at T3.

Conclusion: B*uenos Dias, Artritis* health communications campaign produced significant increases in physical activity at T2 and T3, though few significant changes in knowledge or confidence were found. Unaided recognition of campaign sponsors increased at T2, but these increases did not persist at T3.

Disclosure: T. J. Brady: None; **J. Lam:** None.

1466

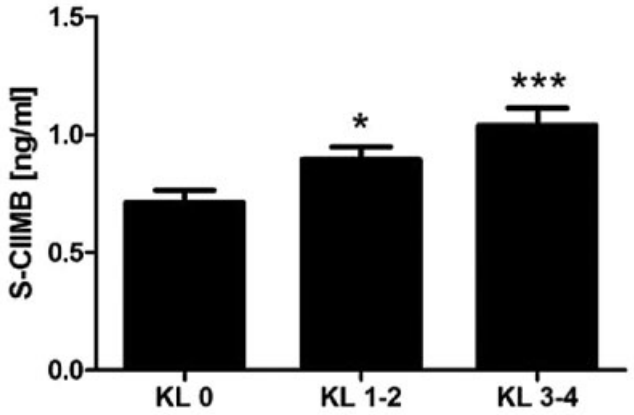
A Novel Serum Biomarker of Cartilage Destruction, Measured in OA and RA Patients, Is Significantly Associated with Kellgren-Lawrence Score. Anne C. Bay-Jensen[1], Erik B. Dam[3], Inger Byrjalsen[2], Tanja Schubert[4], Phillip Vergnaud[4], Per Qvist[1] and Morten A. Karsdal[1]. [1]Cartilage Biology and Biomarkers, Denmark, [2]CCBR-Synarc, Denmark, [3]Nordic Bioscience Imaging, Denmark, [4]Synarc-Lyon, France

Background: Type II collagen is the primary matrix protein in articular cartilage. In joint degenerative diseases, such as osteoarthritis (OA) and rheumatoid arthritis (RA), the collagens are degraded by matrix metalloproteinases (MMPs) and fragments of the protein are released into the circulation. We identified one such fragment of MMP-derived type II collagen (CIIM).

Methods: Type II collagen was cleaved with MMP *in vitro* and analyzed by mass spectrometry. A collagen type II specific neoepitope, CIIM, was identified (RDGAAG^{1053}). Monoclonal antibodies were raised against the neoepitope and used to develop an ELISA. CIIM assay was measured in the synovial fluid of 18 OA patients aged 62–81 and in serum of an adult population aged 21–80 (n=156). Knee OA was graded by standard Kellgren-Lawrence (KL) score. Serum levels was measured in serum samples from RA patients and age-matched controls (n=66).

Results: The CIIM ELISA showed good technical performance; a quantification range of 0.2–14.9ng/ml, inter- and intra assay variations below <15% and a dilution recovery of approximately 100%. CIIM was immunolocalized to classical arthritis features in OA cartilage. A high median level of CIIM [1.2ng/ml] was found in synovial fluid. Serum CIIM levels were significantly higher ($p<0.05$) in those individuals with OA detected by KL scores of 1–2 [0.9ng/ml] and 3–4 [1.0ng/ml] than in those with KL score of 0 [0.6ng/ml] (Fig. 1). The level of CIIM in RA serum [0.284ng/ml] was significantly higher ($p<0.01$) than age-matched controls [0.532ng/ml].

Conclusion: We developed and validated an ELISA for CIIM; a novel biomarker which we demonstrated is derived from MMP-degraded type II collagen. We found serum CIIM levels to be highest in those with the lowest KL score and with RA.



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A Small Molecule c-Fos/AP-1 Inhibitor T-5224 Inhibits Osteoclastogenesis and Bone Resorption. Hidetoshi Murao[3], Yukihiko Aikawa[4], Akira Hashiramoto[1], Tetsuya Yamamoto[4], Hisaaki Chaki[4], Hirokazu Narita[4], Shuichi Hirono[2] and Shunichi Shiozawa[1]. [1]Department of Biophysics, Kobe University of Graduate School of Health Sciences/The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan, [2]Department of Pharmaceutical Sciences, School of Pharmacy, Kitasato University, Tokyo, Japan, [3]Research Laboratories, Toyama Chemical Co., Ltd, Toyama, Japan, [4]Research Laboratories, Toyama Chemical Co., Ltd, Toyama, Japan

Purpose: c-Fos/activator protein-1 (AP-1) is an important transcription factor for cytokine production and joint destruction in rheumatoid arthritis (RA) and a potential target for the treatment of RA. We have previously reported a small molecule c-Fos/AP-1 inhibitor T-5224 prevented the development of arthritis and joint destruction in mouse collagen-induced arthritis (CIA). The purpose of this study was to investigate the effects of T-5224 on the osteoclastogenesis and bone resorption.

Methods: 1) *in vitro*: Macrophage-osteoclast precursor RAW264.7 cells were cultured with receptor activator for nuclear factor κB ligand (RANKL) (50 ng/mL) and/or T-5224 for 6 days. Osteoclastogenesis was examined by tartrate-resistant acid phosphatase (TRACP)-staining and pit formation assay. The expressions of cathepsin K, c-Fos, and NFATc1 were determined by Western blot analysis. 2) *in vivo*: CIA was induced in DBA/1J mice by the immunization with bovine type II collagen twice on day 0 and 21. T-5224 was orally administered once daily. The levels of serum TRACP 5b were measured using ELISA, and the mRNA expressions of RANKL and osteoprotegerin (OPG) in the hind paw were measured by RT-PCR. Bone mineral density (BMD) of the femur was assessed using micro-CT. The region of interest was positioned at a metaphyseal region at a point of 3% of the length of the femur from the growth plate.

Results: T-5224 suppressed the induction of TRACP-positive multinucleated cells under the RANKL-stimulation in RAW264.7 cells. The expressions of cathepsin K and NFATc1 were also inhibited by T-5224 in RANKL-stimulated cells. Meanwhile, the expression level of c-Fos was no difference with or without T-5224. Furthermore, T-5224 inhibited the formation of bone resorption pits *in vitro*. In mice with CIA, the marked elevation of serum TRACP 5b, a bone resorption marker, was observed on day 35, and this change was significantly suppressed by the administration of T-5224 from day 21. In addition, T-5224 dose-dependently inhibited the increase of RANKL mRNA and the decrease of OPG mRNA in the arthritic hind paws. The BMD of the femora of mice with CIA was lower than that of normal mice on day 50, and T-5224 inhibited the trabecular bone loss.

Conclusions: These findings suggest that T-5224 inhibits the osteoclastogenesis and bone resorption in arthritic lesions and is able to correct the imbalance of RANKL-OPG which leads to bone loss. Thus, c-Fos/AP-1 inhibitor appears to be a promising drug for rheumatoid bone destruction.

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Activation of Wnt and Bone Morphogenetic Protein Signalling Pathways in the Articular Cartilage in *Frzb*$^{-/-}$ Mice. Liesbet Lodewyckx[1], Jeroen Eyckmans[3], Frank P. Luyten[2] and Rik Lories[1]. [1]KU Leuven, Leuven, Belgium, [2]KU Leuven, Leuven, Belgium, [3]KU Leuven

Objective: Frizzled related protein (FRZB/sFRP3) is a secreted WNT antagonist isolated from articular cartilage and expressed in developing skeletal elements. Polymorphisms in the human *FRZB* gene are associated with susceptibility for osteoarthritis. Induction of experimental osteoarthritis in *Frzb*$^{-/-}$ mice results in enhanced cartilage degradation associated with increased Wnt signaling, *Mmp3* expression, Mmp activity and cortical bone thickness. In this study we used a whole mouse genome micro-array analysis and a bioinformatics approach to investigate differences between healthy cartilage in wild-type and *Frzb*$^{-/-}$ mice.

Methods: Articular cartilage from the tibia was isolated from 6 weeks old *Frzb*$^{-/-}$ mice and wild-type littermates. RNA was isolated using the Rneasy Fibrous tissue mini kit (Qiagen). RNA quality was assessed using an Agilent 2100 Bioanalyzer and RNA nanochips (Agilent technologies Inc). The transcriptional profiles were analysed using the whole genome Affymetrix GeneChip® Mouse Genome 430 2.0 Array. Articular cartilage from one tibia from 3 wild-type mice and 2 *Frzb*$^{-/-}$ mice was used (3 vs. 2 chips comparison). Gene expression analysis was based on the RMA expression values and the MAS 5.0 detection calls. PANTHER Classification System software, DAVID bioinformatics resources and FUNNET transcriptional analysis were used for pathway analysis.

Results: Using Benjamini-Hochberg corrected P-values ($p < 0{,}001$) in combination with a cut-off fold change $|\log2\text{-ratio}|>1$ the analysis showed that 696 transcripts were significantly upregulated in the *Frzb*$^{-/-}$ sample group. PANTHER pathway analysis identified overrepresentation of genes linked to the Integrin, Wnt and Cadherin signalling pathways (corrected p-values $3*10^{-9}$, $5*10^{-5}$ and $6*10^{-4}$ respectively). Not surprisingly, genes linked to skeletal development and extracellular matrix were enriched in the

analysis. DAVID analysis similarly identified the Wnt and Integrin pathways but also EGF signalling. FUNNET identified both Wnt and TGF/BMP signalling. With the Wnt signalling pathway both different Frizled receptor, Wnt9a ligand and distinct intracellular and extracellular antagonists were upregulated suggesting compensatory mechanisms in the absence of *Frzb*. In addition, upregulation of bone morphogenetic protein and other transforming growth factor beta superfamily members and receptors suggests compensatory upregulation of this pathway. The link with integrin upregulation further supports our earlier data that support of role for *Frzb* in mechanobiology.

Conclusions: In this study we demonstrated that loss of *Frzb* results in the upregulation of the WNT signalling pathway and a possible compensatory upregulation of BMP signalling. The upregulation of the integrin and cadherin signalling pathway suggest an important role for *Frzb* in the interactions of cells with surrounding cells and extracellular matrix.

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Adenosine A_1 Receptors Regulates RANKL-Induced Osteoclast Formation Via Regulation of c-fos and NFATc1 Expression. Wenjie He[2], Tuere Wilder[2] and Bruce N. Cronstein[1]. [1]New York Univ Med Ctr, New York, NY, [2]NYU School of Medicine

Purpose: Adenosine is a purine molecule necessary for normal cell metabolism and growth. Recent work from our laboratory using adenosine A_1 -deficient mice has demonstrated that adenosine A_1 receptors play a critical role in regulating bone turnover, raising the intriguing possibility of targeting A_1 receptors for therapeutic advancement in osteoporosis and other bone diseases. In the present study, we investigated the mechanism by which A_1 receptors regulate mouse osteoclast differentiation induced by macrophage-colony stimulating factor (M-CSF) and the receptor activator of NF-kappaB ligand (RANKL) from monocyte/macrophage cell lineage of bone marrow cells.

Methods: Osteoclast differentiation was studied in vitro as the M-CSF/RANKL stimulated formation of multinucleated (>3 nuclei), TRAP-positive cells from primary murine (C57Bl/6) bone marrow-derived precursors. Signaling events were studied by Western Blot for activated (phosphorylated) signaling molecules and changes in message were determined by RT-PCR.

Results: As we have previously demonstrated, the A_1 –receptor specific antagonist 8-Cyclopentyl-1,3-dipropylxanthine (DPCPX) dose-dependently inhibited RANKL-stimulated tartrate-resistant acid phosphatase (TRAP)-positive osteoclast formation from bone marrow cells and the bone-resorptive activity of mature osteoclasts ($p<0.001$, $n=3$, $IC_{50}=0.1\mu M$). This inhibition is accompanied by reduction of osteoclast-specific target genes including MMP9, Integrin αv, Integrin $\beta 3$, Cathepsin K and TRAP ($p<0.05$, $n=4$). Furthermore, DPCPX inhibited accumulation of the RANKL-stimulated c-fos mRNA at day 3 in bone marrow cells ($p<0.05$, $n=3$); c-fos is a key transcription factor for the differentiation of osteoclasts. DPCPX also dose-dependently suppressed RANKL-induced gene expression of nuclear factor of activated T-cells, cytoplasmic 1 (NFATc1) at day 4 in bone marrow cells ($p<0.05$, $n=3$). Among the RANK signaling MAPK pathways, DPCPX ($1\mu M$) inhibited phosphorylation of JNK ($p<0.001$, $n=4$), which is upregulated in response to RANKL in bone marrow macrophages.

Conclusion: Collectively, these data suggest that Adenosine A_1 receptor blockade inhibits RANKL-induced osteoclast formation by inhibiting activation of JNK/c-Jun pathway, thereby suppressing the gene expression of c-fos and NFATc1 in osteoclast precursors. These results are consistent with the hypothesis that endogenously released adenosine, acting at A_1 receptors, is critical for the expression and activation of critical signaling intermediates required for osteoclastogenesis. Moreover, these results further support the notion that blockade of adenosine A_1 receptors may be useful in the treatment and prevention of osteoporosis and premature bone loss.

Disclosure: W. He: None; **T. Wilder:** None; **B. N. Cronstein:** Amgen Inc., 5, Bristol-Myers Squibb, 5, Canfite Pharma, 1, 5, Combinatorx, 5, Cypress Biosciences, Inc., 5, Hoffmann-La Roche, Inc., 5, King Pharmaceuticals, 2, 5, NIH, 2, Prometheus Laboratories, 5, Regeneron Pharmaceuticals.

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Adenosine A_{2A} Receptor Agonists: Can They Prevent/Treat Joint Prosthesis Loosening? Aranzazu Mediero[1], Sally R. Frenkel[2], Tuere Wilder[1], Igor Immerman[3], Scott Hadley[3], R. Damani Howell[3], Maya Hawly[4], Elie Sellam[4] and Bruce N. Cronstein[5]. [1]Department of Medicine, NYU Langone Medical Center, New York, NY, [2]Department of Orthopaedic Surgery, NYU Hospital for Joint Diseases, New York, NY, [3]Department of Orthopaedic Surgery, NYU Hospital for Joint Diseases, [4]Institut Supérieur des Bio-Sciences de Paris, France, [5]New York Univ Med Ctr, New York, NY

Purpose: Survival of bone implants depends on biological fixation, and prosthesis loosening can be catastrophic leading to replacement of prostheses. Inflammation and osteoclast-mediated bone resorption in response to wear particles near prostheses contribute to loosening. Because we have demonstrated that adenosine A_{2A} receptor activation is anti-inflammatory and prevents osteoclast formation and function we hypothesized that adenosine A_{2A} receptor agonists might prevent osteoclast-mediated bone resorption at the site of prosthesis wear in a calvarial model of wear particle-induced bone resorption.

Methods: Eighteen C57Bl/6 mice age 6–8 weeks were anesthetized by intraperitoneal injection of ketamine and xylazine and a 1cm midline sagittal incision was made over the calvarium anterior to the line connecting both ears. Six animals received no particles (control), and 12 received 15 μl of polyethylene particle suspension. Of the 12 mice receiving particulate, 6 were injected subcutaneously at the surgical site with 20 μl of 10 μM CGS21680 (A_{2A} receptor agonist), and 6 mice were injected with saline 0.9%, beginning immediately after incision closure and continuing every other day until sacrifice. Animals were sacrificed after 14 days and the calvaria were removed, fixed, and prepared for microCT and histological staining with TRAP.

Results: Histologic examination of calvaria demonstrated lymphocytic infiltration in both particle-exposed groups. TRAP staining revealed a reduction in osteoclast differentiation after treatment with CGS21680. mCT showed pitting and increased porosity in both particle-exposed groups compared to controls, although in CGS21680-treated mice the reduction in cortical bone was significantly less than in the untreated particle-exposed mice ($p<0.01$). Control bone volume/trabecular volume was significantly greater ($p<0.005$) than in either particulate group, however, calvarial bone from CGS21680-treated mice had significantly greater mean bone volume than did the untreated group ($p<0.0005$). Trabecular thickness was significantly reduced in both CGS21680-treated and untreated particle-exposed groups as compared to control mice ($p<0.05$). Finally, digital morphometric analysis of microCTs reveals that CGS21680 significantly reduced the area of bone pitting compared to control particle-treated mice ($p<0.05$).

	Bone Volume/ Trabecular Volume	Bone Mineral Density	Trabecular Thickness	% Area of bone pitting
Control	0.7964 ± 0.0002	821.11 ± 138.79 mg/cc	0.1080 ± 0.00001 mm	4.6 ± 0.6%
Particulate	0.7436 ± 0.0005	810.28 ± 153.07 mg/cc	0.1041 ± 0.00003 mm	10.2 ± 1.1%
Particulate + CGS21680	0.7765 ± 0.0003	809.14 ± 161.64 mg/cc	0.1079 ± 0.00003 mm	7.8 ± 1.2%

Conclusions: Adenosine A_{2A} receptor activation reduces inflammation and bone destruction due to prosthetic wear particles. This observation suggests that delivery of an adenosine A_{2A} agonist in the cement may enhance orthopedic implant survival, delaying or eliminating the need for revision arthroplasty surgery.

Disclosure: A. Mediero: None; **S. R. Frenkel:** None; **T. Wilder:** None; **I. Immerman:** None; **S. Hadley:** None; **R. D. Howell:** None; **M. Hawly:** None; **E. Sellam:** None; **B. N. Cronstein:** Amgen Inc., 5, 9, Bristol-Myers Squibb, 5, Canfite Pharma, 1, 5, Combinatorx, 5, Cypress Biosciences, Inc., 5, Hoffmann-La Roche, Inc., 5, King Pharmaceuticals, 2, 5, Merck Pharmaceuticals, 9, NIH, 2, Pfizer Inc, 9, Prometheu.

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Adenosine A_{2A} Receptor Ligation Inhibits Osteoclast Formation. Aranzazu Mediero[1], Firas M. Kara[1], Maya Hawly[2], Elie Sellam[2] and Bruce N. Cronstein[3]. [1]Department of Medicine, NYU School of Medicine, New York, NY, [2]Institut Supérieur des Biosciences de Paris, Creteil, Ile de France, France, [3]New York Univ Med Ctr, New York, NY

Purpose: Adenosine is a nucleoside that is generated at sites of injury and hypoxia and which mediates its physiologic and pharmacologic effects via activation of one or more G protein coupled receptors (A_1, A_{2A}, A_{2B} and A_3). We have previously reported that adenosine A_1 receptor ligation is required for osteoclast formation and that blockade or deletion of adenosine A_1

receptors leads to increased bone density. Because all four adenosine receptors are expressed on osteoclasts and osteoclast precursors we determined whether adenosine A_{2A} receptors also regulate osteoclast formation *in vivo* and *in vitro*.

Methods: Osteoclast differentiation was studied *in vitro* as the GM-CSF/RANKL stimulated formation of multinucleated (≥3 nuclei), TRAP-positive cells from primary murine (C57Bl/6) bone marrow-derived precursors. Signaling events were studied by Western Blot for activated (phosphorylated) signaling molecules and changes in message were determined by RT-PCR. Histological examination of bones from A_{2A} knockout and wild type mice was carried out with TRAP and alcian blue stains. Murine bone was further analyzed by micro CT and electron microscopy.

Results: The highly selective A_{2A} receptor agonist CGS21680 inhibited osteoclast differentiation as much as 38±1% with an IC_{50} of approximately 50nM ($p<0.05$), reversed by the selective high affinity antagonist ZM241385. CGS21680 (1uM) stimulated phosphorylation of ERK1/2 (122±3 and 134±3% of control at day 3 and 7 of differentiation, $p<0.001$ for both) and JAK1 (107±1% of control phosphorylation at day 7 of differentiation, $p<0.01$), activation that was reversed by ZM241385 (not shown). Moreover, CGS21680 inhibited NFkB translocation to the nucleus (nuclear NFkB decreased by 44±5% at day 3, $p<0.001$). There was also a marked increase in cellular IkB levels (maximal IkB increased by 19±1% at day 7, $p<0.001$) whereas pretreatment with ZM241385 increased phosphorylation of IkB (maximal pIkB increased by 13±0.4% at day 6, $p<0.001$) and enhanced nuclear translocation of NFkB (by 14±2% at day 3, $p<0.01$). MicroCT analysis of femurs from A_{2A}KO mice showed significantly decreased bone volume/total volume ratio (17.49±0.95 for A_{2A}KO vs. 22.61±2.15 for wild type, $p<0.05$), trabecular number (4.4±0.2 for A_{2A}KO vs 5.8±0.07 for wild type, $p<0.001$) and increased trabecular space (0.19±0.006 for A_{2A}KO vs. 0.13±0.0004 for wild type, $p<0.001$). There were more osteoclasts in the TRAP-stained femurs of A_{2A}KO (50±13/lpf) than wild type mice (35±1/lpf, 6 fields each from femurs of 2 different mice each). Electron microscopy of osteoclasts in femurs from A_{2A}KO mice showed marked osteoclast membrane folding and increased osteoclast bone resorption.

Conclusions: These results indicate that adenosine A_{2A} receptors inhibit GM-CSF/RANKL-stimulated osteoclast differentiation and thereby regulate bone turnover. Because adenosine mediates the anti-inflammatory effects of methotrexate we further speculate that the capacity of methotrexate to inhibit bone erosion in patients with Rheumatoid Arthritis may be mediated by methotrexate-stimulated increases in adenosine concentration.

Disclosure: A. Mediero: None; **F. M. Kara:** None; **M. Hawly:** None; **E. Sellam:** None; **B. N. Cronstein:** Amgen Inc., 5, 9, Bristol-Myers Squibb, 5, Canfite Pharma, 1, 5, Combinatorx, 5, Cypress Biosciences, Inc., 5, Eli Lilly and Company, 9, Hoffmann-La Roche, Inc., 5, King Pharmaceuticals, 2, 5, Merck Pharmaceuticals, 9, NIH, 2.

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Alarmins S100A8 and S100A9 Skew Human Chondrocytes towards a Cartilage Breakdown Phenotype. Rik F. P. Schelbergen[4], Peter L. van Lent[5], Arjen B. Blom[5], Annet Sloetjes[5], Thomas Vogl[2], Johannes Roth[1] and Wim B. Van Den Berg[3]. [1]Children's Hospital Eastern Ontario, Ottawa, ON, Canada, [2]Institute of Immunology, Muenster, [3]Radboud Univ Nijmegen Med Cntr, Nijmegen, The Netherlands, [4]Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, [5]Radboud University Nijmegen Medical Centre

Background: Alarmins S100A8 and S100A9 are members of the S100 family of Ca2+-binding proteins that are associated with inflammation and cartilage and bone erosion during human rheumatoid arthritis (RA). Recently, we found that S100A8 and S100A9 are also associated with cartilage degradation in murine collagenase-induced osteoarthritis (OA). We also showed that S100A8 and S100A9 stimulate expression and activity of matrix metalloproteinases (MMPs) and pro-inflammatory cytokines in murine chondrocytes. We now investigated whether S100A8, S100A9 and/or the S100A8/S100A9 complex could also activate human chondrocytes from OA patients and skew them towards a cartilage breakdown phenotype.

Methods: Cartilage was collected from human OA patients undergoing joint replacement. Immunostaining was performed on paraffin sections of OA cartilage using antibodies against S100A8 and S100A9 and against VDIPEN and NITEGE, which are MMP- and A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)-induced cartilage breakdown neoepitopes. Chondrocytes were isolated from OA cartilage and stimulated with recombinant S100A8, S100A9, S100A8/A9 heterodimer and/or interleukin 1β (IL-1β). mRNA levels of MMPs, cytokines and cartilage matrix molecules were determined with RT-qPCR and protein levels of MMP and cytokine using Luminex.

Results: Immunostaining on OA cartilage showed that both S100A8 and S100A9 protein were expressed in and around chondrocytes. Furthermore, immunostaining of breakdown neoepitopes VDIPEN and NITEGE was found in the same areas as the S100 proteins.

Stimulation of OA chondrocytes with the monomers S100A8 and S100A9 for 24 hours strongly stimulated cartilage degrading molecules like MMPs and cytokines. mRNA expression of MMP1, -3, -9 and -13 was upregulated 6.0, 5.2, 4.3, and 2.8-fold respectively. Protein levels of MMP1, -3 and -13 were upregulated 3.4, 1.3 and 2.4-fold respectively. Moreover, particularly interleukin 6 (IL-6) levels were strongly upregulated on mRNA level (11-fold) and protein levels reached 10 ng/ml.

Apart from stimulating cartilage degradation, S100A8 and S100A9 monomers also inhibited new formation of cartilage matrix molecules. mRNA levels of aggrecan and collagen type II were significantly decreased 2- to 3-fold, suggesting that these proteins inhibit repair.

The S100A8/A9 heterodimer neither had effect on cartilage degradation nor on cartilage matrix production.

The effect of S100A8 and S100A9 was similar to IL-1β effects, but there was no additive effect of S100 with IL-1β, suggesting independent mechanisms.

Conclusions: S100A8 and S100A9 expression is found in areas with cartilage breakdown. Moreover these proteins inhibit new formation of matrix molecules and stimulate production of cartilage degrading molecules *in vitro* thereby skewing human chondrocytes towards a cartilage breakdown phenotype.

S100A8 and/or S100A9 may serve as therapeutic targets for the treatment of cartilage damage.

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Analysis of Secretome from Mesenchymal Stem Cells from Human Umbilical Cord Strome during the Chondrogenesis. María C. Arufe[1], Alexandre De la Fuente[2], Jesús Mateos[4], Patricia Fernández-Puente[4], Esther Rendal[4], Silvia Díaz[2], Isaac Fuentes[2], Francisco J. De Toro[2] and Francisco J. Blanco[3]. [1]INIBIC-Universidad de A Coruna, A Coruna, Osteoarticular and Aging Research Laboratory, Proteomics Unit-Associated Node to ProteoRed-Biomedical Research Center (INIBIC), Hospital Universitario A Coruna, La Coruna, Coruña, Spain, [2]INIBIC-Universidad de A Coruna, A Coruna, Spain, [3]INIBIC-Universidad de A Coruna, A Coruna, Spain. Osteoarticular and Aging Research Laboratory, Proteomics Unit-Associated Node to ProteoRed-Biomedical Research Center (INIBIC). Hospital Universitario A Coruna, La Coruna, Spain, [4]Osteoarticular and Aging Research Laboratory, Proteomics Unit-Associated Node to ProteoRed-Biomedical Research Center (INIBIC), Hospital Universitario A Coruña. La Coruña, Spain

Our goal is study the secreted proteins from Mesenchymal Stem Cells –MSCs- from umbilical cord stroma during their differentiation towards chondrocyte-like cells to discern the pathways which could be determinant in this chodrogenesis.

Material and Methods: Umbilical cord tissues were obtained from caesareans from normal women in the Maternity Facility at Complejo Hospitalario Universitario de A Coruña under the supervision of the hospital ethic committee. We isolated and growth MSCs from umbilical cord stromal tissue by enzymatic digestion and cultured the cells adhered to the plastic plate(1). The cells were characterized (2) using flow cytometry, immunohistochemistry and RT-PCR techniques. Chondrogenic process was performed using our previously published model (3). Briefly, we grow the cells during two days in medium suplemented with FCS 10%. After 2 days we washed the cells with PBS and added medium supplemented with KO serum and TGF-β3. Spheroids were formed by two days in culture and this three-dimensional structure help to produce the characteristic proteins which form part of the extracellular matrix of the cartilage. The spheroid were situated in a well with the chondrogenic factors plus RPMI during 12 h to recover the protein secreted to the medium by the spheroids at 4, 7, 14, 28 and 46 days of differentiation avoiding the serum contamination.

SDS-PAGE was done using pre-cast NuPAGE® NOVEX gels (Invitrogen) to ensure reproducibility in the separation of the proteins. Gels were stained with Silver Nitrate and the entire lane was divided in 16 sections. Each section was excised and subjected to in-gel digestion with trypsin. The peptide mixture was cleaned and desalted with home-made Poros R2

columns, injected and separated in a nanoLC system, mixed with α-cyano and deposited in a MALDI plate using an automatic MALDI spotter. The MS run for each fraction was analyzed in an ABI 4800 MALDI-TOF/TOF instrument and fragmentation was done using a CID system.

Results: 87 identified proteins were related with the chondrogenic differentiation process from a total of 209 proteins. Some of the proteins related with chondrogenesis obtained with this method were:

Name	SwissProt Accession #	Type	Day
Collagen alpha-1	P02452	Collagen	4, 7
Collagen alpha-2	P08123	Collagen	4, 7
Decorin	PO7585	Proteoglycan	4, 7
Calreticulin	P27797	Chaperone	4, 7
Collagen alpha-3	P12111	Collagen	14, 28
Lumican	P51884	Proteoglycan	7, 14, 28
Fibulin	P23142	Glycoprotein	14, 28
Biglycan	P21810	Proteoglycan	46
Nidogen	P14543	Glycoprotein	46

Conclusions: 1. This technique is suitable to analyze medium complexity samples as secretome.

2. The chondrogenesis differentiation designed through spheroid formation have revealed be an excelent method to obtain chondrocytes-like cells from mesenchymal stem cells of human umbilical cord stromal tissue.

3. Pathways related with differentiation process are been activated during the chondrogenesis process.

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Biochemical Markers of Bone Balance (CTX-I/Osteocalcin) Improve with Tocilizumab Treatment in a Population of RA Patients with an Inadequate Response to Anti-TNF Therapy. Morten Karsdal[2], Thasia G. Woodworth[3], Andy Kenwright[4], Inger Byrjalsesn[1], Adam Platt[4] and Georg Schett[5]. [1]CCBR Synarc, Ballerup, Denmark, [2]Nordic Bioscience, Herlev, Herlev, Denmark, [3]Roche Products Ltd., Welwyn, Welwyn Garden City, United Kingdom, [4]Roche, Welwyn, United Kingdom, [5]University of Erlangen-Nuremberg, Erlangen, Germany

Background: Bone resorption and bone formation are maintained in a dynamic equilibrium required for optimum bone and joint maintenance and integrity. In active RA, inflammation is associated with bone resorption, which characteristically dominates bone formation, resulting in osteopenia, bone fragility, and fracture. Biochemical markers of bone and cartilage turnover can provide an assessment of the effect of therapeutic intervention on the restoration of the balance between bone resorption and formation; indeed, previous analyses of tocilizumab (TCZ)-treated MTX inadequate response populations from OPTION and LITHE studies demonstrated dose-dependent improvement in markers of bone formation (osteocalcin [OC], PINP) and bone balance (CTX/OC ratio).

Objectives: To evaluate changes in biochemical markers of bone metabolism in an anti-TNF refractory RA patient population utilizing the 24-week RADIATE study, in which TCZ 8 mg/kg and 4 mg/kg every 4 weeks showed efficacy superior to that of weekly MTX/pbo in patients refractory to one or more anti-TNF agents. In addition, MMP-3 and ICTP, a biochemical marker of MMP activity, were measured.

Methods: Assays for OC, PINP, ICTP, CTX-I, and MMP-3 were conducted on serum acquired from 299 consenting patients (out of 499 in RADIATE) at BL and week 16. Approximately 50% were receiving low-dose corticosteroids (<10 mg qd).

Results: Patients were refractory to at least one anti-TNF with highly active RA (mean DAS28 ~6.8) and had mean disease duration of 12 years. Both TCZ doses decreased CRP and significantly inhibited cathepsin K–mediated bone resorption, as measured by decrease in CTX-I. OC levels remained stable, resulting in an overall improvement in bone balance with TCZ added to MTX, as measured by CTX-1/OC ratio. Further, MMP-3 and ICTP levels decreased, consistent with lower type I collagen turnover in joint tissue.

Conclusions: In these anti-TNF refractory patients, TCZ and MTX significantly reduced the levels of biochemical markers of cathepsin K bone resorption and MMP-mediated tissue destruction. This observation suggests that this treatment regimen has a positive effect on bone balance, the equilibrium between formation and resorption, which will ultimately lead to improved joint health. TCZ dose-related decrease in CRP provides further evidence that TCZ treatment may limit joint damage in these patients.

Table 1. Baseline Characteristics (ITT population)

	Placebo + MTX		TCZ 4 mg/kg + MTX		TCZ 8 mg/kg + MTX	
N	97		101		101	
Female, n (%)	76 (78)		82 (81)		87 (86)	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age, y	52.4	13.0	51.4	12.3	54.1	11.1
TJC/SJC	31/19	16/11	32/19	15/10	31/18	15/9
DAS28	6.8	1.1	6.9	0.9	6.8	0.9
CRP, mg/dL	3.9	4.5	3.3	3.8	3.0	3.7

Table 2. Percentage Change (geometric mean) in Biochemical Markers and CRP: Baseline to Week 16 (ITT population)

	Placebo + MTX		TCZ 4 mg/kg + MTX		TCZ 8 mg/kg + MTX	
N	76		81		83	
	G mean	**±1 SEM Range**	**G mean**	**±1 SEM Range**	**G mean**	**±1 SEM Range**
CTX-1	−3.3	−8.4, 1.8	−25.5†	−29.1, −22	−19.5*	−24, −15.1
Osteocalcin	0.7	−4.7, 6.1	−2.3	−7.2, 2.6	6.9	1.1, 12.7
CTX-1/OC	−4	−9.1, 1.2	−23.8*	−28.3, −19.2	−25.3*	−29.1, −21.4
PINP	1.5	−2.8, 5.7	1.8	−2.4, 5.9	2.8	−1.6, 7.3
MMP-3	3.6	−3.9, 11.1	−30†	−35.1, −24.9	−42.6†	−47.3, −38.9
ICTP	7	3.3, 10.8	−18.2†	−22.1, −14.2	−18.4†	−21.9, −15
N	85		90		90	
CRP	22.1	9, 35.1	−37.9*	−46.1, −29.7	−94.2†	−95, −93.3

*$p < 0.01$ vs placebo; †$p < 0.001$ vs placebo.

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Chondrogenic Differentiation of Bone Marrow Mesenchymal Stem Cells Grown on Type I Collagen and Heparan Sulfate Scaffolds. Silvia Díaz-Prado[4], Emma Muiños[3], C. G. Trejo-Iriarte[1], D. Lozano[2], N. García-Honduvilla[1], Isaac Fuentes[3], Francisco J. De Toro[3], P. Esbrit[2], Julia Buján[1] and Francisco J. Blanco[3]. [1]Department of Medical Specialties. University of Alcalá de Henares, Madrid, Spain, [2]Laboratory of Bone and Mineral Metabolism. Fundación Jiménez Díaz (Capio Group). Madrid, Spain, [3]Osteoarticular and Aging Res. Lab. CIBER-BBN, Rheumatology Div, INIBIC-Complejo Hosp, Univ. A Coruña, A Coruña, Spain, [4]Osteoarticular and Aging Res. Lab. CIBER-BBN. Rheumatology Div. INIBIC-Complejo Hosp. Univ. A Coruña, Coruña, Spain

Background: Articular cartilage lesions are not able to repair. To avoid the need for prosthetic replacement different cell treatments were developed with the aim of generating a repaired tissue. The transplantation of mesenchymal stem cells (MSCs) has been suggested as an alternative therapeutic approach for treatment of cartilage defects.

Aim: Evaluate the chondrogenic potential of bone marrow mesenchymal stem cells (BM-MSCs) grown on type I collagen and different concentrations of heparan sulfate (HS) scaffolds.

Materials and Methods: BM-MSCs and chondrocytes were cultured on type I collagen and different concentrations of HS scaffolds for 16 and 30 days. BM-MSCs were cultured in chondrogenic medium or DMEM with 20% FBS plus 100 nM PTHrP. Chondrocytes were grown in DMEM with 10% FBS plus 100 nM PTHrP. Chondrogenic differentiation was confirmed by histochemical and immunohistochemical analysis.

Results: BM-MSCs and chondrocytes were able to proliferate on type I collagen and various concentrations of HS scaffolds, since cells showed high percentages of positivity for PCNA proliferation marker. Increased cell proliferation has been associated with a high rate of scaffold degradation, although the thicker collagen fibers take longer to be degraded. The results indicated that BM-MSCs proliferated better in chondrogenic medium than in the usual growth medium (DMEM 20%). The study groups with BM-MSCs

grown in chondrogenic medium +100 nM PTHrP, regardless the HS concentration, showed high percentage of cells regarding the scaffold area (more than 80% after 16 days in culture and more than 90% after 30 days in culture). Moreover, they also showed high percentages of positivity for safranin O (Saf O), aggrecan Agg) and type II collagen (Col II) (Table 1 and Figure 1). Masson′s trichrome (Mt) staining showed that cells formed aggregates and produced extracellular matrix. Von Kossa (VKos) stainings, performed in BM-MSCs grown for 30 days in chondrogenic medium, exhibited the presence of calcifications.

	16 DAYS				30 DAYS			
	Col I	Col I +1%HS	Col I +2%HS	Col I +3%HS	Col I	Col I +1%HS	Col I +2%HS	Col I +3%HS
Mt	-/+	++	++	++	+++	+++	+++	+++
Saf O	++	+++	+++	+++	+++	+++	+++	+++
VKos	-/+	++	++	+	-/+	+	+	+
Col I	+	+++	+	+	+	-/+	-/+	++
Col II	++	++	++	++	+++	++	++	+++
COL X	+	+++	+++	+++	+++	+	+	++
Runx2	-/+	+	+	++	-	-	-/+	-
Agg	+	++	++	++	++	+	+	+
Pcna	++	+++	+++	++	+++	-/+	-/+	+++

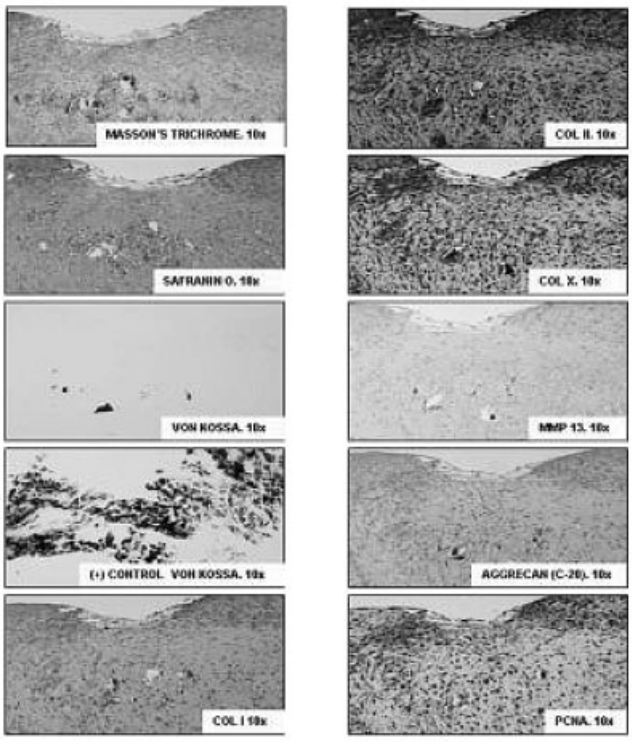

Figure 1. Histochemical and immunohistochemistry analysis of BM-MSCs cultured over type 1 collagen and 3% HS scaffolds on chondrogenic medium after 30 days in culture.

Conclusions: Our data demonstrated that type I collagen and heparan sulfate scaffolds were optimal for BM-MSCs and chondrocyte growth and that BM-MSCs cultured over these scaffolds on chondrogenic medium were able to differentiate to chondrocyte-like cells.

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CXCR1/2 Signalling Is Required but Is Not Sufficient To Maintain the Phenotypic Stability of Human Articular Chondrocytes. Joanna C. Sherwood[1], Pramod Achan[2], Giovanna Nalesso[2], Costantino Pitzalis[2] and Francesco Dell'Accio[2]. [1]Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom, [2]Barts and The London School of Medicine and Dentistry, Queen Mary University of London

Background: The production of ELR+ CXC chemokines is widely studied in arthritis and has been postulated to contribute to the inflammatory phenomena that eventually lead to cartilage breakdown. Articular chondrocytes however, also express their own chemokine receptors. The function of CXC chemokine receptors in these cells is puzzling because chondrocytes are encased in a dense extracellular matrix and are not known to migrate in vitro. In this study we have hypothesized that ELR+ CXC chemokine signalling via the receptors CXCR1 and CXCR2 in chondrocytes is required for the phenotypic stability of human articular chondrocytes, but is not sufficient to maintain the stable phenotype of these chondrocytes during in vitro expansion.

Methods: Adult human articular chondrocytes (AHAC) were enzymatically released and expanded in monolayer culture under standard conditions for blockade experiments and in the presence of CXCL6 or CXCL8 for phenotype preservation experiments. The expression of CXCR1 and CXCR2 was confirmed using PCR, Western blot and immunocytochemistry, and functionality was tested using an in vitro calcium influx assay. CXCR1/2 signalling was blocked at a downstream level using pertussis toxin and at specific receptor level using blocking antibodies. The expression of molecular markers associated with the cartilage phenotype was assessed using real time PCR. The content of highly sulphated proteoglycans in chondrocyte micromasses was analysed using Alcian blue staining at pH0.2 followed by guanidine extraction and quantification.

Results: Early passage articular chondrocytes expressed CXCL1, CXCL8 and CXCL6 as well as their receptors CXCR1 and CXCR2. Receptor expression was confirmed at protein level by Western blotting. Confocal microscopy confirmed the localization of both receptors in both in vitro cultured cells and in human cartilage explants at the cell membrane as well as within the cytoplasm, as expected for the well known internalization and recycling of these receptors and for the autocrine/paracrine production of their ligands. The blockade of CXCR1/2 signalling at both G protein and at receptor level in early passage AHAC resulted in a downregulation of some but not all molecular markers associated with the cartilage forming capacity of AHAC, including type II collagen, aggrecan and the cartilage specific transcription factor SOX9. Both methods resulted in the decrease of sulphated proteoglycan levels of cells cultured in micromass. However, the addition of CXCR1 and CXCR2 ligands during cell expansion did not allow for the maintenance of phenotypic molecular markers at gene expression level.

Conclusions:

- CXCR1 and CXCR2 are expressed and are functional in adult human articular chondrocytes.
- CXCR1 and CXCR2 blockade results in the downregulation of some but not all molecular markers associated with the capacity of AHAC to form stable cartilage in vivo.
- CXCR signalling is required for the phenotypic stability of articular chondrocytes in vitro and therefore may play a role in cartilage homeostasis in vivo.
- CXCR1 and CXCR2 signalling are not sufficient to maintain the phenotypic stability of articular chondrocytes during in vitro expansion.

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Effects of NSAIDs and the Cyclooxygenase-Inhibiting Nitric Oxide Donator (CINOD) NCX 429 on Human Chondrocytes and Cartilage from OA Patients. Manlio Bolla[1], Serena Viappiani[2], Mandar Dave[4], Jyoti Patel[4], Steven B. Abramson[3] and Mukundan Attur[3]. [1]NicOx Research, Sophia Antipolis, France, [2]NicOx Research, [3]NYU Hospital for Joint Diseases, New York, NY, [4]NYU Hospital for Joint Diseases

Background: The role of nitric oxide (NO) in osteoarthritis (OA) is controversial. NO, particularly when metabolized to peroxynitrite, is a recognized mediator of inflammation, which induces catabolic effects and promotes chondrocyte apoptosis. Conversely, NO delivered at low concen-

trations by NO donors exerts anti-inflammatory effects. Cyclooxygenase-Inhibiting Nitric Oxide Donators (CINODs) are anti-inflammatory compounds designed to inhibit both COX-1 and COX-2 while releasing nitric oxide, an important modulator of vascular tone. We studied the effect of naproxen and the CINOD NCX 429 in human chondrocytes and cartilage tissues from OA patients, to understand whether NO donation from CINODs may modulate the inflammatory/metabolic response.

Methods: The experiments were performed with human cartilage and chondrocytes isolated from OA cartilage. Isolated chondrocytes stimulated with IL-1β to induce inflammation, followed by measurement of inflammatory and matrix parameters, such as iNOS, COX-2, MMP1 and 13, PGE2, NO, matrix metalloproteinases, collagen degradation and NF-κB nuclear translocation. Reference NSAIDs naproxen and celecoxib were used in comparison to NCX 429 (10 and 50 μM), and incubated 16 h before IL-1β challenge. Cartilage explants culture supernatants (untreated and treated with modulators) were harvested at 24 and 72 hours post-treatment. RNA was extracted from chondrocytes and estimated by qPCR. NF-κB binding was assessed using Marligen Bioscience kit and both cytoplasm and nuclear p65 subunit of NF-κB was also assessed by Western blot.

Results: The reference NSAIDs and the CINOD similarly upregulated MMP1 but inhibited MMP13, showing comparable net effect on collagen degradation as assayed by CTX-II ELISA. They similarly inhibited ADAMTS4, but only 50 μM NCX 429 downregulated COX-2 expression. In isolated OA chondrocytes, NCX 429 (10 and 50 μM) significantly and completely inhibited IL-1β-induced PGE2 production, and both the constitutive and IL-1β-stimulated induction of NF-κB activity. Western blot analysis of p65 subunit isolated from nuclear fraction showed that the cells treated with CINOD (both in unstimulated and IL-1β stimulated cells) had increased p65 accumulation although decreased NF-κB binding and also inhibited NF-κB promoter mediated luciferase reporter assay.

Conclusions: Reference NSAIDs and the CINOD NCX 429 appear to similarly modulate human OA chondrocytes, both in unstimulated and stimulated conditions. NO has been considered detrimental for chondrocytes; however, donation of low concentrations of NO is recognized to be beneficial in a variety of conditions. Here, the CINOD NCX 429 does not differ from reference NSAIDs, indicating that CINODs do not adversely affect chondrocytes via NO donation. In addition, NCX 429 showed inhibition of the NF-κB signalling, therefore presenting interesting anti-inflammatory features to be further explored.

Disclosure: M. Bolla: NicOx, 1, 3; **S. Viappiani:** NicOx, 1, 3; **M. Dave:** NicOx, 2; **J. Patel:** NicOx, 2; **S. B. Abramson:** NicOx, 2, 5; **M. Attur:** NicOx, 2.

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Endogeneous TIMP3 Induce Death Receptor Ligand-Independent Apoptosis in Mesenchymal Cells. Christina Wunrau[2], Doreen Wendholt[3], Noreen Pundt[3], Thomas Pap[1] and Berno Dankbar[3]. [1]IEMM, University Hospital Muenster, Münster, Germany, [2]Institute of Experimental Musculoskeletal Medicine-IEMM, University Hospital Muenster, Münster, Germany, [3]Institute of Experimental Musculoskeletal Medicine-IEMM, University Hospital Muenster, Muenster, Germany

Background: The tissue inhibitors of metalloproteinases (TIMP) 1–4 are a family of natural inhibitors that control the activity of matrix metalloproteinases (MMP) in the extracellular matrix. Among all TIMP, TIMP3 plays a special role and has been shown to induce apoptotic cell death. As little is known about the underlying mechanisms, we set out to investigate the pro-apoptotic effect of recombinant and lentiviral overexpressed TIMP3 in the human mesenchymal cell line Cal78.

Methods: Mesenchymal Cal78 cells were transduced with pLenti6/V5-D-TOPO-TIMP3 or the control vector pLenti6/V5-GW/lacZ. The induction of apoptosis was evaluated using the Caspase 3/7 assay after transduction with or without administration of 100 ng/ml Fas ligand, TNFα and TRAIL for 16 hours. Furthermore, the cell proliferation was assessed by BrdU incorporation. To identify underlying mechanisms we performed Western blot analysis to find out the MAPK activation using specific anti phospho-antibodies.

Results: To determine the induction of apoptosis we measured Caspase activity and these data show a strong apoptosis induction reflected by a five-fold increase in lentiviral infected cells overexpressing TIMP3 compared to control (pLenti6/V5-GW/lacZ) or uninfected cells. The induction of apoptosis was further increased by TNFα, FasL and TRAIL. Interestingly, exogenous TIMP3 (recombinant hTIMP3, 2μg/ml) did not induce caspase 3 and 7 activity. Proliferatiion analyses revealed a four-fold higher proliferation after lentiviral infection with TIMP3. In addition, the withdrawal of serum leads to an enhanced TIMP3-induced apoptosis. Moreover, lentiviral overexpression of TIMP3 resulted in a decreased phosphorylation of cRaf, Erk1/2, p90RSK and Akt.

Conclusion: Taken together, these findings demonstrate that TIMP3 directly induce apoptosis in mesenchymal cells, which is independent of death receptor ligands. The fact that the withdrawal of serum leads to an enhanced TIMP3-induced indicates the importance of serum-derived survival factors. TIMP3-mediated induction of apoptosis involves the inhibition of MAPK/Erk1/2 as well as the Akt signaling pathway.

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Endogenous Joint Repair after Damage in the Red-Spotted Newt. Matthias Geyer[1], Thilo Borchardt[2], Carina Schreiyaeck[1], Ulf Müller-Ladner[1] and Robert Dinser[1]. [1]Department of Rheumatology, Justus Liebig University Giessen, Kerckhoff-Klinik, Bad Nauheim, [2]Max Planck Institute for Heart and Lung Research, Bad Nauheim

Background: Mammalian joint structures fail to repair after severe trauma or in osteoarthritis. Adult newts are able to regenerate lost extremities. We have previously shown that they are also able to rebuild a damaged knee joint after induction of joint instability through intraarticular injection of collagenase. We wanted to extend this observation on other modes of damage and start studying molecular mechanisms.

Methods: To induce apoptotic cell death in chondrocytes, monoiodoacetate was injected into the knee joints of red spotted newts. Alternatively, the femoral cartilage was removed surgically. The time course of clinical and histological damage was analysed. In parallel, RNA was extracted from whole joints 10, 20, and 40 days after damage with collagenase or surgery and hybridized to a cDNA array derived from regenerating newt hearts.

Results: Monoiodoacetate induced chondrocytic cell death predominantly in the deep zone of the articular cartilage in newts, associated with a loss of proteoglycans, in the absence of clinical disease. Histology returned to normal after 20 days. Surgery induced severe joint damage associated with complete loss of function of the joint, reflected in severe histological changes. Within 40 days, clinical function normalised. Histologically, cartilage reformed, leading to intact joint structures within 90 days. A number of genes was found to be deregulated. No gene was downregulated in both damage models, but several genes were found upregulated. These include matrix proteins like fibronectin, decorin, and collagens I, II, and III. Several complement factors and clusterin were found in addition to factors like periostin and olfactomedin that have not been previously associated with joint formation. Several enzymes of vitamin A metabolism that have been implicated in chondrogenesis were also upregulated.

Conclusion: Newts are able to regenerate joint structures irrespective of the exact mode of damage (apoptosis, instability, surgical loss of tissue). A cDNA analysis reveals several genes that may be key factors determining the enhanced repair potential of newts compared to mammals.

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Experimental Osteoarthritis in Rats Is Attenuated by Treatment with a Selective Inhibitor of Sphingosine Kinase 2. Leo R. Fitzpatrick[3], Cecelia Green[1], Lynn W. Maines[1] and Charles D. Smith[2]. [1]Apogee Biotechnology Corporation, [2]Apogee Biotechnology Corporation and Medical University of South Carolina, [3]Penn State College of Medicine, Hummelstown, PA

Osteoarthritis (OA) is a progressive degenerative disease characterized by cartilage degradation and chondrocyte apoptosis, which may involve aberrant sphingolipid metabolism. Sphingosine kinases (SK1 and SK2) catalyze the formation of sphingosine-1-phosphate (S1P) from sphingosine, and are potential drug targets for a variety of hyperproliferative and inflammatory diseases. ABC294640 (ABC) is a novel orally bioavailable compound that selectively inhibits SK2, and has therapeutic activity in models of rheumatoid arthritis.

Aims: The goals of the present study were to utilize the Monosodium Iodoacetate (MIA) model of OA to assess the effects of ABC294640 on: 1) cartilage and bone destruction in the knee joints of MIA-treated rats; and 2) the resultant pain to the animals.

Methods: Differential hind-limb weight-bearing (measured with an incapacitance meter and calculated as the % right (R)\R+ left (L) leg measure-

ments) was used as an indicator of knee pain throughout the study, and baseline data were collected on Day 0. To induce OA, anesthetized male Wistar rats (n = 22) were injected with 3 mg of MIA into the R knee joint and saline into the L knee. A control group of rats (n = 4) received saline injections in both knees. On Day 0, MIA-treated rats were randomized to receive either sham oral dosing (n = 13), ABC (50 mg/kg bid, n = 9) or Tramadol (100 mg/kg, one hr before incapacitance readings only, n=4). Oral ABC dosing continued until study Day 27. Incapacitance readings were obtained weekly during this period. On Day 28, the R knee joints were harvested for histological evaluations. Safranin-O was used to evaluate cartilage proteoglycan staining in the knee joints. Cartilage thickness measurements were done from images of the joint histology sections.

Results: Weight bearing (%) in sham/MIA rats significantly ($p < 0.01$) decreased from 48.8 ± 0.8 (Day 0) to 41.9 ± 2.9 (Day 28). In contrast, these values in ABC treated rats were virtually the same on Day 0 (49.0 ± 0.5%) and Day 28 (48.8 ± 2.6%). The ABC results were similar to data with Tramadol treatment. Knee joint histology scores (48 point scale) were reduced from 30.9 ± 3.3 (sham treatment) to 24.1 ± 4.0 (ABC treatment) demonstrating that ABC-treated rats had less evidence of cartilage and bone destruction. There was a significant ($p=0.0036$) inverse correlation between histological damage and weight-bearing in rats. Of note, proteoglycan staining in the tibia (figure 1) and femur were less disrupted in ABC/MIA animals than in sham/MIA rats.

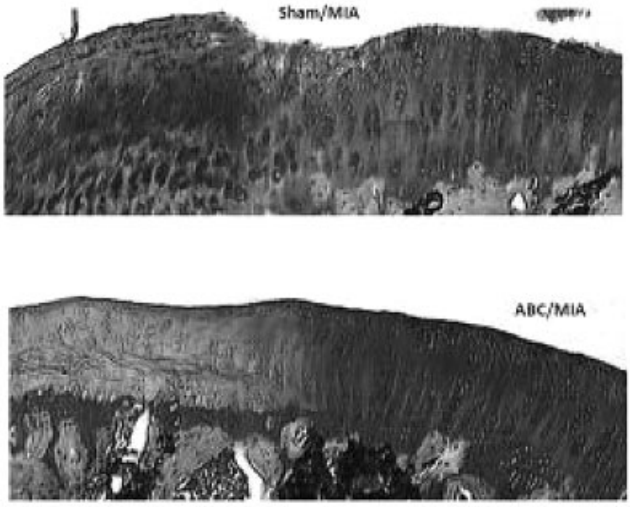

Figure 1. Cartilage proteoglycan staining: rat tibia.

Similarly, cartilage thickness in the knee joints of ABC/MIA-treated rats (0.30 ± 0.05 mm) was not different from control rats (sham/saline, 0.36 ± 0.03 mm); whereas that of sham/MIA rats was substantially decreased (0.21 ± 0.03 mm).

Conclusion: The selective SK2 inhibitor ABC294640 attenuated histological damage and joint pain in the MIA-induced OA model in rats. Therefore, clinical studies of this agent may be warranted.

Disclosure: L. R. Fitzpatrick: Apogee Biotechnology Corporation, 9; **C. Green:** Apogee Biotechnology Corporation, 3; **L. W. Maines:** Apogee Biotechnology Corporation, 3; **C. D. Smith:** Apogee Biotechnology Corporation, 4.

1481

Expression of MMP-13 and ADAMTS-5 Is Mediated Via Nuclear Orphan Receptor NR4A3 Signalling in Human Chondrocytes. Martin H. Stradner[2], Hannes Angerer[3], Daniela Krusch[1], Florentine C. Fürst[3], Marie-Luise Kremser[3], Daniela Setznagl[3] and Winfried B. Graninger[3]. [1]Karl-Franzens University Graz, [2]Medical University Graz, Graz, Austria, [3]Medical University Graz

Purpose: Nuclear orphan receptors act as ligand-independent transcriptionally activated regulator proteins. In a global analysis of nuclear receptor expression in OA cartilage by Collins-Racie et.al. the nuclear orphan receptor NR4A3 was found to be highly deregulated. As its function in chondrocytes is still unknown, we evaluated the influence of NR4A3 on chondrocyte gene expression.

Methods: Human cartilage specimens were obtained from patients undergoing total knee joint replacement. Chondrocytes were isolated using collagenase B. Primary human chondrocytes and the human chondrocyte cell-line C28I2 were grown in monolayer and cultured in Ham′s F-12/DMEM (1:1) and 10% FCS. Expression of NR4A3 was evaluated by reverse-transcriptase PCR. For siRNA knock-down of NR4A3 C28I2 cells were transfected with specific anti-sense oligonucleotides using lipofectamine. After 24h gene expression of ADAMTS-4 and -5, MMP-13, iNOS, aggrecan and pro-collagen II, was investigated using real-time PCR.

Results: NR4A3 mRNA was found to be expressed in OA chondrocytes and the C28I2 cell-line. siRNA knock-down achieved 60% (± 4%) reduction of NR4A3 mRNA expression. The decrease in NR4A3 expression led to a decline of MMP-13 expression by 52% (± 9%). Furthermore ADAMTS-5 mRNA expression was reduced by 50% (± 3%). Gene expression of ADAMTS-4, iNOS, aggrecan and pro-collagen II remained unaltered in the presence of diminished NR4A3 expression.

Conclusions: We confirmed the expression of the nuclear orphan receptor NR4A3 in OA chondrocytes and C28I2 cells. Furthermore its presence is required for maintenance of MMP-13 and ADAMTS-5 expression. Therefore NR4A3 could be a novel promising therapeutic target in OA chondrocytes.

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1482

Histamine Contributes to Inflammatory Joint Disease by Regulating the Expression of RANKL and OPG through Altered NR4A Activity in Human Chondrocyte Cells. Viviana Marzaioli[2], Jason P. McMorrow[2], Alice McEvoy[1] and Evelyn P. Murphy[2]. [1]Dublin Institute of Technology, Kevin Street, Dublin, Ireland, [2]UCD Veterinary Sciences Centre and Conway Insitute for Biomolecular and Biomedical Research, University College Dublin, Ireland

Background: Mast cells, a major source of histamine *in vivo*, are found in increased numbers in rheumatoid arthritis synovial tissue. In the K/BxN arthritis model, mast cells are required to promote autoantigen-induced inflammatory arthritis. It has recently been shown that IL-33 enhances autoantibody-mediated articular inflammation via IgG mast cell degranulation and pro-inflammatory mediator release. Furthermore, histamine stimulates chondrocyte production of matrix metalloproteinases and osteoclast differentiation directly, and indirectly, through altered RANKL and OPG expression in osteoblasts. The aim of this study was to elucidate the receptor mediated signalling pathways and transcriptional events regulated by histamine in human chondrocytes.

Methods: Histamine receptors (HR1,-2, 3,-4), nuclear transcription factors (NR4A1,-2,-3), RANKL and OPG mRNA levels were measured in human chondrocytes using real-time PCR (qPCR). HR subtype involvement was monitored using selective HR antagonists. NR4A protein levels and transactivity were evaluated by western blot, immunocytochemistry and luciferase reporter assays. ShRNA for control and NR4A1, 2, 3 were generated using lentivirus transduction.

Results: Differential expression of histamine receptor subtypes (HR1–4) was detected. HR1 and HR2 receptors are highly expressed in chondrocyte cells with minimal expression of HR3 and HR4. Histamine robustly modulates RANKL and OPG levels, in a time-and concentration-dependent fashion, leading to significantly increased RANKL/OPG expression ratio ($p<0.005$). Histamine rapidly and differentially modulates expression of all three NR4A transcription factors. Within 2-hours, histamine maximally modulates NR4A3 (300-fold), NR4A2 (100-fold) and NR4A1 (10-fold) transcript levels. The study of HR receptor antagonists reveals that histamine selectively signals through HR1 and HR2 in chondrocyte cells to modulate RANKL, OPG and NR4A1–3 expression. Our data further demonstrates histamine-dependent activation of NF-kB and CREB signalling pathways through HR1 and HR2 receptors, respectively. Consistent with mRNA analysis, histamine promotes NR4A nuclear localization and significantly enhances the capacity of NR4A proteins to mediate target gene expression. Specific knockdown of NR4A-1,-2,-3 mRNA and protein levels (>50%) results in significantly reduced endogenous production of OPG (>60%) by chondrocytes. Finally, in NR4A-depleted cells, histamine regulation of RANKL and OPG expression is completely lost.

Conclusion: These data reveal that histamine, through HR1 and HR2, contributes to the development of inflammatory joint disease by regulating the expression of RANKL and OPG through altered NR4A activity in human chondrocyte cells.

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1483

Human Amniotic Membrane as Scaffold for Human Articular Cartilage Repair. Emma Muiños-López[4], Silvia M. Díaz-Prado[3], Tamara Hermida-Gómez[2], Esther Rendal-Vázquez[1], Isaac Fuentes-Boquete[3], María C. Arufe-Gonda[3], Francisco J. De Toro[3] and Francisco J. Blanco[2]. [1]Cryobiology Unit. Complejo Hosp. Univ. A Coruña, A Coruña, Spain, [2]Osteoarticular and Aging Res. Lab. CIBER-BBN, Rheumatology Div, INIBIC-Complejo Hosp, Univ. A Coruña, A Coruña, Spain, [3]Osteoarticular and Aging Res. Lab. CIBER-BBN, Rheumatology Div. INIBIC-Complejo Hosp, Univ. A Coruña, A Coruña, Spain. INIBIC-University of A Coruña, A Coruña, Spain, [4]Osteoarticular and Aging Res. Lab. CIBER-BBN. Rheumatology Div. INIBIC-Complejo Hosp. Univ. A Coruña, Coruña, Spain

Introduction: Human amniotic membrane (HAM) is a highly abundant and easily accessible tissue that may potentially be an important chondrocyte carrier for cartilage regeneration *in vivo*.

Objective: Develop an *in vitro* repair model of focal injuries of human articular cartilage, based on the usefulness of cryopreserved HAM as support for chondrocyte proliferation.

Materials and Methods: Four *in vitro* repair models of focal injuries of human articular cartilage were developed. For this purpose chondrocytes, isolated from cartilage slices obtained from femoral heads, were grown on the basement layer of HAM for 3–4 weeks. Then a chondrocyte pellet was implanted into 2 mm focal defects of human articular cartilage and the HAM providing chondrocytes was placed in direct contact with the cartilage surface to be repaired. These implants were cultured in DMEM supplemented with 10% FBS for 8 weeks. The repair tissues were analyzed by histochemistry (hematoxylin-eosin, Masson′s trichromic, toluidine blue and safranin O) and immunohistochemistry for type I and II collagen and aggrecan.

Results: Human chondrocytes cultured on HAM and transplanted onto focal injuries of human articular cartilage penetrated into the nearby surface of the chondral defect producing a more regular area and contributed on the closing of the chondral defect. The chondrocyte pellet implanted in the lesion filled the chondral defect and showed good integration between the repair tissue and native cartilage. Stainings were done to detect specific major components of the extracellular matrix to obtain more detailed information about the structure and composition of the repair tissue. Type II collagen, safranin O, toluidine blue and Masson′s trichromic stainings of repair tissue were positive, whereas aggrecan and type I collagen stainings were weak (Table 1 and Figure 1). The morphology of the newly-formed tissue exhibited a fibrocartilaginous appearance and high cellularity.

Table 1. Semi-quantitative histochemical and immunohistochemistry analysis of the in vitro human articular cartilage repair model.

TYPE STAIN	Native Cartilage		Focal Injure	
	Matrix	Cells	Matrix	Cells
Modified Masson's trichromic	+++	−	−	−
Safranine O	+++	−	++	−
Toluidine Blue	+++	−	++	−
Type I Collagen	+	++	+	++
Type II Collagen	+++	+++	+	+++
Aggrecan	+	−	−	+

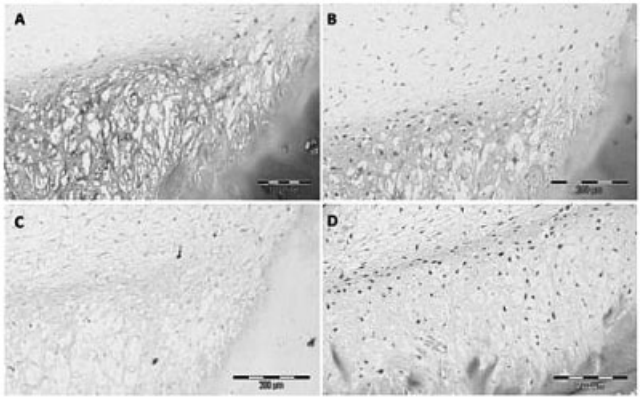

Figure 1. Histochemical and immunohistochemistry analysis of the in vitro human articular cartilage repair model. **A.** Toluidine blue. **B.** Safranin O. **C.** Col I. **D.** Col II.

Conclusions: These results indicated that cryopreserved amniotic membrane could be used as support for chondrocytes proliferation in cell therapy to repair focal injuries of human articular cartilage.

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1484

Increased Expression of Arthritic Marker Genes in the Cartilage of SirT1 Null Mice. Odile H. Gabay[2], Eun Jin Lee[2], Richard Booth[2], Viktoria Gagarina[2], Mona Dvir-Ginzberg[1] and David J. Hall[2]. [1]Hebrew University, Jerusalem, Israel, [2]NIH, Bethesda, MD

Background: Osteoarthritis (OA), the most frequent age related disease present in the west, is a multi-factorial imbalance between cartilage anabolism and catabolism. To understand the mechanisms underlying OA, we focused on the protein deacetylase SirT1, a factor known to prolong organism lifespan. SirT1 has been previously shown to regulate apoptosis and cartilage-specific gene expression in human chondrocytes. Recent data also indicates that SirT1 is a potent inhibitor of the matrix metalloproteinases (MMPs). MMPs are the most well known of arthritis marker genes that play a central role in cartilage degeneration. In order to evaluate the role of SirT1 in cartilage homeostasis, we assessed MMP and ADAMTS expression in the cartilage of SirT1 null mice.

Method: We used SirT1 Wild-type (WT) and SirT1 Null mice in the analysis. The SirT1 Null mice do not express SirT1. Articular cartilage was harvested from hind paws in 1 to 3 week and 4 months old mice. The cartilage was processed for both immunohistochemistry and subculture of chondrocytes.

Results: Articular cartilage tissue sections from SirT1 Null mice exhibited low levels of type 2 collagen, aggrecan and glycosaminoglycans (GAG) compared to SirT1 WT mice at 1 week or 3 weeks. Protein levels of aggrecan and type 2 collagen were also decreased in the chondrocytes derived from SirT1 Null mice. In contrast, protein levels of MMP-3, MMP-8, MMP-9 and MMP-13 were elevated in the SirT1 Null mice compared to WT. Finally, DBC1 (deleted in breast carcinoma 1), a known Sirt1 associated protein that represses SirT1 enzymatic activity, was found to be elevated in the SirT1 Null mice compared to WT.

Conclusion: The data from this animal model indicate that SirT1 is a negative regulator of the genes responsible for cartilage degradation in arthritis; namely the MMPs and DBC1. The role of SirT1 as a putative anti-arthritic gene is consistent with its general function as an anti-aging/anti-inflammatory protein.

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1485

Increasing Osteoclastic Bone Loss Inspite of Fewer Osteoclast Precursors during Chronic Autoimmune SKG-Arthrtitis Evaluated by 3D Stereological Estimators. Kresten K. Keller[3], Kristian Stengaard-Pedersen[2], Frederik Dagnæs-Hansen[5], Jens R. Nyengaard[6], Shimon Sakaguchi[1] and Ellen-Margrethe Hauge[4]. [1]Department of Experimental Pathology, Institute for Frontier Medical Science, Kyoto University, [2]Dept. of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, [3]Dept. of Rheumatology, Aarhus University Hospital, Århus, Denmark, [4]Dept. of Rheumatology, Aarhus University Hospital, Denmark, [5]Institut of Medical Microbiology and Immunology, Aarhus University, Denmark, [6]Stereology and Electron Microscopy Research Laboratory, Aarhus University, Denmark

Background: Bone destruction in rheumatoid arthritis (RA) is the result of osteoclastic bone resorption and is mediated through the receptor activator of NFκB ligand (RANKL) system. Experimental models and designs that allow detailed studies of osteoclast number and activity are therefore important. The aim of this study was to quantify arthritic changes in a new mouse model of rheumatoid arthritis focusing on osteoclast number using new 3D design-based stereological methods.

Methods: Arthritis was induced in 7-week-old female SKG-mice with intraperitoneal injection of 2 mg Zymosan A. Quantitative histology was

made on 4 control mice and 4 arthritic mice euthanized after 6 and 12 weeks. The right hind paw was embedded undecalcified in methylmethacrylate and cut exhaustively generating 7-μm-thick vertical uniform random sections from approximately 10 section levels spaced by 350–800 μm depending on the random rotation of the sectioning plane. Sections were stained with Masson-Goldner Trichrome and enzymatic TRAP staining. A computer controlled microscope and stereological software (NewCAST) was used for histological quantification. Total volumes were estimated according to the Cavalieri principle, total surfaces were estimated using the vertical sections design, and the number of TRAP-positive cells was counted in a physical disector. TRAP-positive cells on the bone surface were defined as active osteoclasts and TRAP-positive cells in inflammatory tissue were defined as osteoclast precursors. All analyses were performed blinded by a single observer. Spearman's rank correlation or the Kruskal-Wallis test followed by the Mann-Whitney U-test were used. Data are given as the correlation coefficient (r) or median(range).

Results: The arthritis score increased during the 12-week period and was paralleled by an increase in the volume of inflammatory tissue ($r=0.90$, $p<0.001$). The number of osteoclasts on bone ($r=0.77$, $p<0.05$) and osteoclast-covered bone surface ($r=0.62$, $p<0.05$) increased significantly leading to a decrease in the volume of bone ($r=-0.65$, $p<0.05$). However, the number of osteoclast precursors declined between week 6 (14072 (10869–19040)), and 12 (7610 (3126–7893)) ($p<0.05$). Furthermore, the total cartilage surface ($r=-0.74$, $p<0.05$) and cartilage volume ($r=-0.65$, $p<0.05$) decreased during the 12 weeks of arthritis.

Conclusions: We showed that the SKG-model of autoimmune polyarthritis in mice developed osteoclastic bone erosion leading to loss of bone. The loss of bone and the bone surface attacked by actively resorbing osteoclasts continued in the chronic stage although fewer osteoclast precursors were present in the inflamed synovium. Thus bone erosion may progress although osteoclastogenensis is slowing. Bone loss was prominent, but loss of cartilage also occurred. Furthermore, for the first time 3D quantitative histology has been applied in a mouse model of RA. The methods proved valuable, and are expected to be important for studying the *in vivo* effect of anti-inflammatory and anti-resorptive interventions in experimental arthritis.

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1486

Influence of NPP1 on Osteoarthritis (OA)-Associated Cartilage Calcification. Jessica Bertrand[3], Martin Fürst[5], Wolfgang Rüther[1], Frank Rutsch[2], Yvonne Nitschke[2] and Thomas Pap[4]. [1]Centre for Orthopaedics and Trauma Surgery, [2]Department of Pedriatrics, [3]Insitute for Experimental Musculoskeletal Medicine, Münster, Germany, [4]Insitute for Experimental Musculoskeletal Medicine, [5]MedBaltic

Background: Calcification of cartilage is a common finding during osteoarthritis and is directly linked to the severity of cartilage degradation. The pyrophosphate pathway functions to keep a sensitive balance of pyrophosphate (PPi) and phosphate (Pi), thereby preventing the generation of calcium crystals. Based on previous data that have linked the expression of the nucleotide pyrophosphatase phosphodiesterase (NPP1) to pathological matrix calcification and have demonstrated a regulation of NPP1 by inflammatory mediators, we sought to study the expression of NPP1 in OA cartilage and its association with cartilage calcification.

Methods: In a cohort of 120 consecuitve OA patients, we analysed the calcification of cartilage using digital contact radiography (DCR). We used cartilage samples of these patients to isolate RNA and assessed the NPP1, ANK and TNAP expression by quantitative real time PCR. The tip-toe walking (ttw/ttw) mouse that carries a mutation in the enpp1 gene encoding for NPP1 was used as an animal model. The calcification of cartilage was analysed using advanced imaging technology, including fluorid PET-scanning and μCT. Using van Kossa in combination with safranin orange stainings of knee sections we assessed the calcification of articular cartilage and meniscus histologically. We analysed the expression of NPP1 in an ACL model of induced OA using immunhistochemical stainings.

Results: In our cohort of OA patients, we found a correlation of NPP1 expression with cartilage calcification ($p<0.05$), whereas we found no correlation for ANK. These data could be confirmed in the ttw/ttw mice, in which we could show an enhanced calcification activity in the joint regions as well as in cartilage of non weight bearing areas such as in ear cartilage. Using both histological analysis and in vivo imaging, we found typical OA like changes in the knees of these mice, such as formation of osteophytes and roughening of the cartilage surface. In addition we could show that NPP1 expression was also increased in the animal model of OA in comparison to uninduced controls.

Conclusion: We conclude from our data, that NPP1 is an important player in OA associated cartilage calcification and might constitute a promising target for the development of novel therapeutics for the disease.

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1487

Inhibitory κBα Is a Direct Bone Morphogenetic Protein Target Gene and an Essential Mediator of Anti-Catabolic Effects of BMPs. Olexandr Korchynskyi[3], Paul-Peter Tak[3], Alisa E. Koch[2], Peter ten Dijke[1] and Dhavalkumar D. Patel[4]. [1]Department of Molecular Cell Biology, Leiden University Medical Cente, Leiden, The Netherlands, [2]Department of Veteran's Affairs and the University of Michigan, Ann Arbor, MI, [3]Division of Clinical Immunology & Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [4]Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Loss of articular cartilage in the joints and structural changes to the intervertebral discs, are common problems in patients with degenerative spine and joint disease, but also in those with chronic inflammation-driven arthritis. Increasing evidence supports a role for BMP7 in preventing joint and intervertebral disk damage and in disk regeneration in part by rescuing the catabolic effects of TNF-α and IL-1β. The precise molecular mechanism mediating the preventive and regenerative effects of BMP7 is unknown. NF-κB signaling is a major pathway triggered by proinflammatory cytokines. Our transcriptional profiling studies revealed that the activation of BMP signaling leads to increased expression of Inhibitory κBα (IκBα), that is a key negative regulator of the NF-κB pathway. We therefore explored whether anti-catabolic effects of BMPs on cartilage and bone are mediated by BMP-induced IκBα expression.

Methods: cDNA microarrays-based gene expression profiling was used to identify novel BMP target genes. Positive hits were confirmed using Northern and Western blotting and Real-Time PCR. Luciferase reporter assays and ChIP assays were used to characterize the BMP-responsive region in the IκBα promoter. Anti-catabolic effects of BMPs were validated in vitro using preosteoblastic cell lines and primary human bone marrow-derived mesenchymal stem cell (hMSC) osteoblast differentiation, EMSA and lentiviral shRNA approaches.

Results: Real-Time PCR showed that activation of IκBα mRNA by BMPs does not require de novo protein synthesis, thus suggesting IκBα is a direct BMP target gene. Using ChIP assays we demonstrated that intracellular mediators of BMP signals Smad1/5 and Smad4 bound to the highly conserved proximal region of the IκBα promoter. A proximal fragment of the IκBα promoter was found to be activated by BMP2 and BMP7. EMSA assay showed that BMP7-induced IκBα expression blocked formation of the TNF-α-induced NF-κB transcriptional complex. Furthermore, BMP treatment was found to inhibit the TNF-α and LPS-induced NF-κB transcriptional response in mouse preosteoblasts and hMSC and rescued the differentiation of MSC from inhibition by proinflammatory stimuli. shRNA-mediated knockdown of IκBα expression confirmed an essential role of IκBα in mediating the anti-catabolic effects of BMPs. Anti-catabolic effects of BMPs in vivo and their mechanism were further validated using transgenic TNF-α mice model.

Conclusion: BMP-induced IκBα expression is a key mechanism mediating preventive and regenerative effects of BMP7 on cartilage and bone. These results may lead to the development of novel strategies for cartilage and bone regeneration, using the combination of BMP7 with pharmacological agents.

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1488

Interleukin-10 Regulates Bone Metabolism by Suppressing Osteoclastogenesis In Vivo. Seungwoo Han[4], Younkwan Jung[3], Eunsoo Kim[2] and Gunwoo Kim[1]. [1]CIHR Group in Skeletal Development and Remodeling, Department of Physiology and Pharmacology, University of Western Ontario, London, ON, Canada, [2]Dongsan Medical Center, Keimyung University, Daegu, Korea, Republic of, [3]Laboratory for Arthritis and Bone Biology, Fatima Research Institute, Korea, Republic of, [4]Laboratory for Arthritis and Bone Biology, Fatima Research Institute, Department of Internal Medicine, Daegu Fatima Hospital, Daegu, Korea, Republic of

Background: Interkeukin (IL)-10 is a potent anti-inflammatory cytokine which is produced primarily from T cells and activated macrophages and acts on the macrophage lineage. IL-10 also has potent inhibitory effects on osteoclastogenesis, but the molecular basis of its action is poorly understood. Recent studies showed IL-10 may down-regulate osteoclastogenesis through inhibition of the expression of NFATc1, c-Fos and c-Jun (1) and inhibition of calcium signaling downstream of RANK by inhibiting transcription of TREM-2 (2). However, there has been no study about the role of IL-10 in osteoclastogenesis in vivo and under inflammatory condition such as TNF-α induced osteoclastogenesis.

Objective: To elucidate the role of IL-10 in osteoclast formation under physiological and pathological condition.

Methods: 3-month old male IL-10 KO and WT littermates were used (n = 7 mice/group). We compared the bone phenotype by microcomputed tomographic analysis, histologic analysis and TRAP staining. And we conducted in vitro induction of osteoclast formation by bone marrow monocytes from IL-10 KO and WT mice.

Results: We analyzed the IL-$10^{-/-}$ mice for abnormal bone phenotypes. Microcomputed tomographic analyses showed that these mice had severe osteoporosis accompanied by markedly lower trabecular bone volume, number, and thickness, as well as a smaller number of bone nodules compared to wild-type mice. Histomorphometric analysis also revealed reduced bone mass in the IL-$10^{-/-}$ mice. Notably, TRAP stain showed higher osteoclast numbers and larger osteoclast surface areas in these mice. Moreover, we observed a higher rate of bone formation accompanying the accelerated bone resorption rate in the IL-$10^{-/-}$ mice, suggesting that their osteoporosis was caused by enhanced bone turnover and remodeling. Together, these observations indicate that IL-10 has a suppressive role in osteoclastogenesis during in vivo bone remodeling.

We then attempted to investigate the roles of IL-10 in the processes underlying pathological bone destruction. We examined the effect of TNF-α on osteoclastogenesis using IL-$10^{-/-}$ precursors, because TNF-α is a major mediator of inflammation induced by TLRs and has been suggested to be able to induce osteoclastogenesis. Consistent with previous reports, TNF-α induced the development of a small number of osteoclasts in cultures of wild-type precursor cells. Notably, osteoclastogenesis was enhanced in cultures of IL-$10^{-/-}$ precursor cells treated with TNF-α. The mRNA expression levels of Nfatc1 and Acp5 in the IL-$10^{-/-}$ osteoclast precursors were also augmented by TNF-α, indicating that IL-10 also has a suppressive role in TNF-α–induced osteoclastogenesis.

Conclusion: Our results show that IL-10 inhibits osteoclast formation under physiological and pathological conditions and suggest a model where downregulation of IL-10 contributes to RANKL-mediated osteoclastogenesis.

Disclosure: S. Han: None; **Y. Jung:** None; **E. Kim:** None; **G. Kim:** None.

1489

Interleukin-1-Induced Cyclooxygenase-2 and Inducible Nitric Oxide Synthase Expression in Human OA Chondrocytes Is Associated with Histone H3K4 Methylation. Fatima Ezzahra El-Mansouri[3], Nadir Chabane[3], Nadia Zayed[3], Johanne Martel-Pelletier[2], Jean-Pierre Pelletier[1] and Hassan Fahmi[3]. [1]CHUM-Notre-Dame Hospital, Montreal, QC, Canada, [2]CR-CHUM, Notre-Dame Hospital, Montreal, QC, Canada, [3]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC, Canada

Objective: Increased expression of inducible NO synthase (iNOS) and cyclooxygenase (COX)-2 plays a key role in the pathogenesis of osteoarthritis (OA). Methylation of lysine 4 on histone H3 (H3K4) was shown to be of fundamental importance in the regulation of gene expression. In the present study, we investigated the role of H3K4 methylation in interleukin-1b (IL-1)-induced COX-2 and iNOS expression in human OA chondrocytes

Methods: Chondrocytes were stimulated with IL-1 for various time periods and the expression of iNOS and COX-2 mRNAs and proteins were evaluated using real-time reverse transcriptase-polymerase chain reaction (RT-PCR) and Western blotting, respectively. H3K4 methylation at the iNOS and COX-2 promoters was evaluated using chromatin immunoprecipitation (ChIP) assays. The role of histone methylation was further evaluated using the methyltransferase inhibitor, 5′-deoxy-5′(methylthio) adenosine (MTA).

Results: IL-1 induced iNOS and COX-2 mRNA and protein in a dose- and time-dependent manner. The induction of iNOS and COX-2 expression by IL-1 was associated with H3K4 di- and trimethylation at the iNOS and COX-2 promoters, whereas the levels of H3K4 monomethylation remained unchanged. Treatment with MTA inhibited IL-1-induced H3K4 methylation as well as IL-1-induced iNOS and COX-2 expression.

Conclusion: These results indicate that H3K4 methylation contributes to IL-1-induced iNOS and COX-2 expression and suggest that this pathway could be a potential target for pharmacological intervention in the treatment of OA.

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miR-7 and miR-130b Are Differentially Regulated during Mesenchymal Stem Cell Commitment. Glyn Palmer[4], Laura S. Danielson[2], Mukundan Attur[3], Steven B. Abramson[1] and Eva Hernando[2]. [1]Hospital for Joint Dis/NYU, New York, NY, [2]NYU-Department of Pathology, [3]NYU-Hospital for Joint Diseases, [4]NYU-Hospital for Joint Diseases, New York, NY

Purpose: Stem cell-based therapies aimed at introducing progenitor cells into cartilage lesions hold great promise for the restoration of damaged articular surfaces following joint injury or osteoarthritis. Key to the generation of a functional repair tissue is the controlled differentiation into the desired phenotype. To this end microRNAs (miRNAs) may be important molecules that regulate this process. By acting as transcriptional repressors, their modulation during differentiation may enable commitment to a specific lineage by suppressing the expression of other lineage markers. In this study we profiled MSCs for miRNA expression following induction into the chondrocyte (C), osteoblast (O) and smooth muscle (SM) lineages.

Results: Human bone marrow-derived Mesenchymal Stem Cells (MSCs) were obtained from NIH, or from the discarded hips of patients undergoing joint replacement surgery. SM differentiation was induced by treating monolayer cultures with 1 mM thromboxane-A2 [DP1] in the presence of 0.25% serum. C differentiation was induced by seeding MSCs in aggregate cultures in the presence of dexamethasone and TGF-b1 (10 ng/ml). O differentiation was induced by treatment of monolayer cultures with dexamethasone, ascorbate and beta-glycerolphosphate. Profiling of miRNAs by microarray (Agilent) or QPCR (SA Biosciences) revealed differential regulation of miR-7 and miR-130b, among 376 probes. Following SM and C differentiation, miR-7 expression was down-regulated up to 6.9-fold and 3-fold respectively. Conversely, during O differentiation, its expression was induced approximately 7-fold. Analysis of theoretical mRNA targets using TargetScan online software (www.targetscan.org) identified conserved sites in several genes associated with chondrocyte and myoblast lineages. Putative chondrogenic targets were found to include COL2A1, IGFR1, and GDF5, while potential smooth muscle modulators included EGFR1, PIK3CD, IRS1/IRS2, KLF4, CNN3 and IGF1R. Following a similar trend to miR-7, miR-130b was down-regulated up to 3.2-fold and 3.1-fold in C and SM differentiation respectively, while O differentiation induced its expression 2-fold. TargetScan analysis identified putative chondrogenic targets, TGF-BRII, Sox5, BMP-2 and IGF1; Potential smooth muscle regulators included ESR1, TGF-BRII, MBLN1, TGFBR1 and IGF2BP1. Together these observations suggest that miR-7 and miR-130b act to negatively regulate myogenic and chondrogenic cell fates via regulation of lineage specific genes.

Conclusion: Our findings suggest that miR-7 and miR-130b, via the targeting of lineage specific molecules, regulate cell fate in adult human MSCs by inhibiting smooth muscle and chondrocyte differentiation, thereby promoting ‘default’ differentiation into the osteoblast lineage.

[DP1]0.25% FBS 24 hours prior to addition of 1.0mM of the TxA2 chemical analog U46619

Disclosure: G. Palmer: None; **L. S. Danielson:** None; **M. Attur:** None; **S. B. Abramson:** None; **E. Hernando:** None.

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MMP-3 and DKK-1 Levels in Juvenile Idiopathic Arthritis. Matthew L. Stoll[2], Michelle L. Christadoss[2], Marilynn G. Punaro[2] and Nancy J. Olsen[1]. [1]Penn State Hershey Medical Center, Hershey, PA, [2]UT Southwestern Med Ctr, Dallas, TX

Purpose: MMP-3 and DKK-1 are markers of cartilage and bone breakdown, respectively. Prior studies in children and adults with arthritis have shown that MMP-3 levels are elevated and correlate with markers of disease activity(1,2). In RA, DKK-1 has been shown to be a marker of radiographic progression(3). There are no published studies of DKK-1 levels in children, healthy or otherwise.

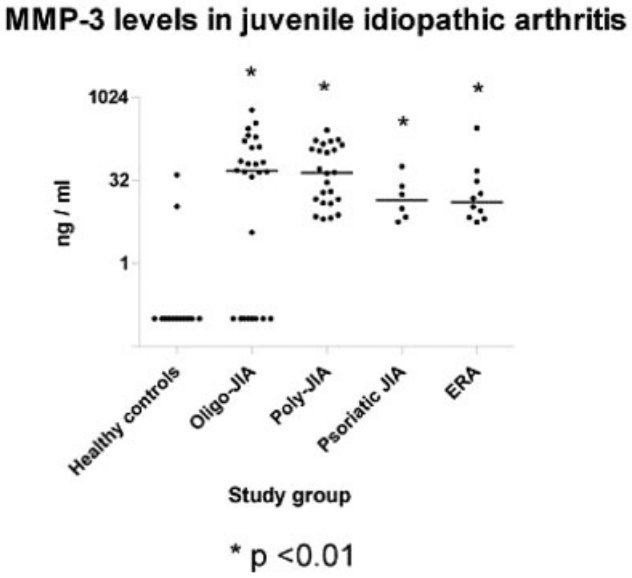
Methods: For DKK-1 measurements, serum was obtained from 29 children with oligoarticular JIA and 11 healthy control subjects. For MMP-3

measurements, serum was obtained from 67 children with JIA and 12 healthy control subjects. MMP-3 and DKK-1 values were measured through ELISA assays using kits provided by the manufacturer (Alpco).

Results: MMP-3 levels were significantly elevated in each JIA subtype as compared to the healthy controls (Figure 1), and among JIA patients showed a modest but statistically significant correlation with joint count ($r = 0.294$, $p = 0.007$) and ESR ($r = 0.344$, $p = 0.005$) at the time of the study. Differences between the arthritis sub-groups were not statistically significant. 8/27 oligoarticular JIA children, but none of the other arthritis patients, had undetectable MMP-3 levels ($p = 0.004$); this difference remained significant when the three subjects in long-term remission, all of whom had undetectable levels, were excluded ($p = 0.032$). One subject thought to be a healthy control based upon her physical exam had an elevated MMP-3 level, and subsequently had an MRI and physical exam that were consistent with inflammatory arthritis. Another subject thought to have oligoarticular JIA had negative MMP-3 levels; MRI revealed a synovial cyst.

DKK-1 levels were only measured in oligoarticular JIA patients and healthy controls. Values were comparable, with median levels of 25.3 (IQR 22.8–36.6) and 27.9 ng/ml (IQR 22.5–30.4) in patients and controls, respectively ($p = 0.942$). These levels were an order of magnitude higher than those reported in most prior studies in adults(4,5). There was no association with DKK-1 levels and the age of the child.

Conclusions: Measurement of serum MMP-3 may be a useful biomarker in children with an unclear presentation of joint pain and may help assess severity of the condition. However, perhaps because growing children have considerable bone turnover at baseline, DKK-1 may be a less useful biomarker in this population as compared to adults.



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Modeling Osteoclast Precursor Master Fusogens and Mononuclear OCP Donors with Raw Cell Line Clones. Yawen Ju, Masahiko Takahata, Kofi Mensah, Grace Chiu, Christopher T. Ritchlin, Lianping Xing and Edward M. Schwarz. University of Rochester

Purpose: Osteoclasts (OC) are multinucleated bone-resorbing cells derived from mononuclear osteoclast precursors (OCP) following stimulation with RANKL and M-CSF. Raw264.7 cells are a heterogeneous murine monocyte/macrophage cell line, of which some can form OCs and others cannot. DC-STAMP is a receptor on OCP, and is required for cell fusion to form multinucleated OC. Recently we demonstrated that the surface expression of DC-STAMP by RANK+ OCPs defines OCP fusion potential. RANKL induces DC-STAMP^{lo} OCPs to function as master fusogens, and DC-STAMP^{hi} OCPs to serve as mononuclear donors that cannot fuse on their own to form mature OCs. In order to investigate the molecular mechanisms by which DC-STAMP contributes to OCP fusion and OC formation, we aimed to isolate and characterize Raw cell clones with OCP master fusogen vs. mononuclear donor phenotypes based on their DC-STAMP expression before and after RANKL stimulation.

Methods: Raw 264.7 cells were cloned by limiting dilution: diluted 50 cells in 10ml alpha-MEM media, seeded 100ul/well in 96 well-plate and selected single cell clones. The clones were treated with 100ng/ml RANKL, and their osteoclastogenic potential was assess by TRAP staining. The surface expression of DC-STAMP was determined by flow cytometry following 7AAD staining to gate the live cells, and FITC-conjugated 1A2 monoclonal anti-DC-STAMP antibody.

Results: Seven Raw cell clones were obtained and their OC formation and DC-STAMP surface expression were examined. Clone 5 formed large multinucleated TRAP+ OCs three days after RANKL treatment, while it took five days for the parental raw cell line to form OCs under a same culture condition. Clone 5 also expressed a low basal level of surface DC-STAMP (MFI= 32.0), which was similar to DC-STAMP^{lo} (MFI=16.5) identified in the parental cells following three days of RANKL treatment. In contrast, the Clone 1 could not form OCs after five days of RANKL treatment. Clone 1 also had a high basal level of surface DC-STAMP expression (MFI= 60.8), which was similar to RANKL-induced DC-STAMP^{hi} (MFI=55.4) of the parental cells.

Conclusions: Two Raw 246.7 cell sub-clones were isolated to investigate DC-STAMP-mediated OCP fusion in response to RANKL treatment. Clone 5 forms OCs faster and has low basal DS-STAMP expression, while Clone 1 forms OCs much slower, and expresses high basal DC-STAMP. These clones mimic the heterogeneous DC-STAMP expression levels and OC forming potential of the parental Raw cells, and can be used as cell models of master fusogens (Clone 5) or mononuclear OCP donors (Clone 1). Our ongoing studies to clone DC-STAMP ligand using these clones via differential microarray analysis will be discussed.

Disclosure: Y. Ju: None; **M. Takahata:** None; **K. Mensah:** None; **G. Chiu:** None; **C. T. Ritchlin:** None; **L. Xing:** None; **E. M. Schwarz:** None.

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Multi-Targeted Kinase Inhibitor PKC412 Diminishes Osteoclastogenesis and Counteracts Osteoclast Mediated Bone Resorption *In Vitro*. Despoina Sykoutri[1], Silvia Hayer[3], Josef S. Smolen[4] and Kurt Redlich[2]. [1]Division of Rheumatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria, [2]Division of Rheumatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria, [3]Division of Rheumatology, Department of Internal Medicine III, Medical University of Vienna, [4]Krankenhaus Lainz, Vienna, Austria

Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by osteoclast mediated bone erosions. Small molecule multi-kinase inhibitors are being explored as potential therapeutic targets in RA. PKC412 is a small molecule multi-kinase inhibitor targeting class III tyrosine-protein-kinases such as FMS-like tyrosine kinase 3 (FLT-3) and multiple isoforms of serine/threonine protein kinase C. PKC412 has been shown to inhibit macrophage function *in vitro*. However, the role of PKC412 in modulating the commitment of the monocyte/macrophage lineage to osteoclast precursors, their differentiation into pre-osteoclasts and their differentiation into mature osteoclasts has not been fully elucidated. We aimed to investigate the effect of PKC412 on osteoclast differentiation and function.

Methods: We differentiated mouse bone marrow derived cells in the presence of macrophage-colony stimulating factor (M-CSF) and receptor activator of nuclear factor kappaB ligand (RANKL) into tartrate-resistant acid phosphatase positive (TRAP+) mononuclear osteoclasts (pre-osteoclasts) and TRAP+ multinucleated mature osteoclasts, and added PKC412 in increasing concentrations (10nM to 10μM) to the culture. We also assessed the role of PKC412 in the bone resorbing capacity of osteoclasts by culturing osteoclasts on dentine slices. To further characterize the effect of PKC412 on cell proliferation we performed MTT assays. We used quantitative PCR to evaluate expression levels of mRNA encoding for osteoclast specific markers such as nuclear factor of activated T-cells cytoplasmic 1 (NFATc1), matrix metalloproteinase 9 (MMP-9), Cathepsin K and TRAP. Flow cytometry analysis for Annexin V and 7-AAD was performed to determine potential apoptotic effects of PKC412 on pre-osteoclasts and osteoclasts.

Results: We found that increasing concentrations of PKC412 (IC50:

250nM) dose-dependently reduced osteoclast numbers. Furthermore, numbers of pre-osteoclasts were also significantly decreased after addition of PKC412, indicating an effect of PKC412 on early stages of osteoclastogenesis. In line with this finding, we could show a dose-dependent reduction of pre-osteoclast proliferation using MTT proliferation assays. Moreover, we detected a significant time- and dose-dependent increase in the ratio of apoptotic cells in the PKC412-treated cells by Annexin V and 7-AAD staining. Additionally, in the presence of PKC412 we obtained a significant reduction in osteoclast size and nuclei number, as well as in the size of resorption pits on dentin slices. This indicates that the bone resorbing capacity of osteoclasts is altered by PKC412. Consistently, we were able to demonstrate a dose dependent downregulation of mRNA coding for osteoclast markers, such as NFATc1, MMP-9, Cathepsin K and TRAP in the presence of PKC412.

Conclusion: These results suggest a regulatory role of PKC412 in pre-osteoclast differentiation und osteoclastogenesis through apoptosis induction.

Disclosure: D. Sykoutri: None; **S. Hayer:** None; **J. S. Smolen:** None; **K. Redlich:** None.

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Potential Role of the LKB1-AMPK and CaMKKb-AMPK Pathways in Controlling the Progression of OA. Robert Terkeltaub[3], Bing Yang[4], Martin K. Lotz[1] and Ru L. Bryan[2]. [1]Scripps Rsch Inst, La Jolla, CA, [2]UCSD/VAMC, San Diego, CA, [3]VA Medical Ctr, San Diego, CA, [4]VA Medical Ctr

Purpose: LKB1, a tumor suppressor, and CaMKKb (Ca^{2+}/calmodulin-dependent protein kinase kinase beta) are serine/threonine protein kinases that act upstream of AMPK (AMP-activated protein kinase), a super-regulator of energy homeostasis. AMPK exists as a heterotrimer composed of an alpha catalytic subunit and two regulatory beta and gamma subunits. Phosphorylation of AMPK (Thr-172) within the catalytic domain of the a subunit by upstream kinases is essential for AMPK activation. We have previously observed that articular chondrocytes express functional AMPK, and activation of AMPK attenuates pro-catabolic responses of chondrocytes to inflammatory cytokines. In addition, phosphorylation of AMPKa is significantly decreased in human OA knee articular chondrocytes. Here, we investigated the role of two AMPK upstream kinases LKB1 and CaMKKb in regulation of chondrocyte matrix catabolism.

Methods: Expression and activation status (Ser428 phosphorylation) of LKB1 were examined in cultured human knee articular chondrocytes (first passage) and in human knee articular cartilage sections from different normal and OA (grade I to IV) donors. Knockdown of LKB1 and CaMKKb in human chondrocytes was achieved via transfection with LKB1 and CaMKKb siRNA. Activation of AMPK (AMPKa Thr172 phosphorylation) and pro-catabolic responses including nitric oxide (NO) generation and expression of MMP-13 in response to IL-1b and TNFa in normal human chondrocytes were assessed and compared. Expression of the chondrocyte hypertrophy marker type × collagen was also examined.

Results: Expression and constitutive phosphorylation of LKB1 were observed in normal and low grade OA human knee articular chondrocytes. However, both expression and phosphorylation of LKB1 were markedly decreased in OA chondrocytes beyond grade III, which correlated with decreased expression and phosphorylation of AMPKa. Treatment of articular chondrocytes with IL-1b and TNFa induced de-phosphorylation of LKB1 and AMPKa. Importantly, knockdown of LKB1 and CaMKKb in articular chondrocytes attenuated phosphorylation of AMPKa, and resulted in significant enhancement of MMP-3 release and nitric oxide (NO) generation induced by IL-1b and TNFa. In addition, type × collagen protein expression induced by TNFa was markedly enhanced in chondrocytes with knockdown of LKB1 or CaMKKb.

Conclusions: Human knee OA articular chondrocytes with grade III and beyond exhibit markedly decreased LKB1 phosphorylation that correlates with decreased AMPK phosphorylation. Knockdown of LKB1, as well as CaMKKb, by RNAi enhanced chondrocyte hypertrophy and pro-catabolic responses of articular chondrocytes to inflammatory cytokines, and was closely linked with decreased AMPK activation defined to regulate the pro-catabolic responses. These findings identify therapeutic potential of activation of the LKB1-AMPK and CaMKKb-AMPK pathways in order to inhibit the progression of OA.

Disclosure: R. Terkeltaub: None; **B. Yang:** None; **M. K. Lotz:** None; **R. L. Bryan:** None.

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S100A8 Enhances Osteoclastic Bone Resorption in Experimental Antigen-Induced Arthritis. Lilyanne C. Grevers[3], Teun J. de Vries[1], Vincent Everts[1], Annet W. Sloetjes[3], Thomas Vogl[2], Johannes Roth[2], Wim B. van den Berg[3] and Peter L. van Lent[3]. [1]Department of Oral Cell Biology, ACTA, UVA and VU University Amsterdam, Amsterdam, The Netherlands, [2]Institute of Experimental Dermatology, University of Münster, Muenster, Germany, [3]Radboud University Nijmegen, Medical Centre, Nijmegen, The Netherlands

Background: Rheumatoid Arthritis (RA) is characterized by bone destruction in the joints caused by enhanced formation and activity of osteoclasts. In RA, local inflammatory mediators produce many factors that stimulate osteoclastogenesis. The "alarmins" S100A8 and S100A9 are the most up-regulated proteins present in RA synovial fluid and significantly correlate with joint destruction. The aim of the present study was to investigate the role of S100A8 on osteoclastic bone resorption in murine antigen-induced arthritis (AIA).

Methods: Bone destruction was analyzed 7 and 21 days after AIA induction in knee joints of S100A9−/− mice, which also lack S100A8 expression, and wild type controls. Bone marrow precursors from S100A9−/− and wild type mice were differentiated into osteoclasts in-vitro. Additionally, osteoclast precursors were stimulated with recombinant S100A8 (rS100A8) during osteoclastogenesis. Receptor involvement was investigated using an anti-RAGE blocking antibody or TLR4−/− osteoclast precursors. In-vitro experiments were analyzed for the formation of TRACP-positive multinucleated cells ($TRACP^+$ MNCs), actin ring formation by immunolocalization, mRNA expression levels of osteoclast markers, and resorption pit formation on bone.

Results: Bone erosions were significantly suppressed in S100A9−/−mice 7 and 21 days after AIA induction. In-vitro, bone marrow-derived precursors from S100A9−/− mice developed normally into functional osteoclasts. Stimulation of osteoclast differentiation with rS100A8 resulted in increased numbers of predominantly smaller sized $TRACP^+$ MNCs (3–5 nuclei per cell), as compared to unstimulated controls. mRNA expression of DC-STAMP, an important cell-cell fusion factor was moderately down-regulated (ddCt = −1.39), which might explain the smaller size of the osteoclasts. The expression of TRACP, cathepsin K and calcitonin receptor was not changed. Furthermore, actin ring formation, essential for the bone resorptive capacity of osteoclasts, was enhanced and bone resorption levels were significantly increased in S100A8 stimulated osteoclasts (50% versus 35% in unstimulated controls, $P<0.03$) The stimulatory effects of S100A8 on osteoclast maturation and function could not be inhibited by RAGE blockade, whereas the increased osteoclast numbers, actin ring formation and resorption pit formation were completely abrogated using TLR4−/− osteoclasts.

Conclusion: This study demonstrates that S100A8 stimulates osteoclast formation and activity and indicates that both S100A8 and TLR4 are important factors in mediating osteoclastic bone destruction in experimental arthritis.

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Serum Biomarkers Predict Progressive Structural Damage in the BeSt Study. Yijing Shen[1], Linda Dirven[4], Guy Cavet[1], Michael Centola[5], B. A. C. Dijkmans[2], Lyndal K. Hesterberg[1], Thomas Huizinga[4], Willem F. Lems[6] and Cornelia F. Allaart[3]. [1]Crescendo Bioscience, Inc., [2]JBI, Amsterdam, The Netherlands, [3]Leiden Univ Med Ctr, Leiden, The Netherlands, [4]Leiden University Medical Center, [5]Oklahoma Med Research Foundation, Oklahoma City, OK, [6]VU University Medical Center

Background: The ability to predict progressive structural damage has the potential to improve disease management and outcomes in rheumatoid arthritis (RA) patients. Blood-based biomarkers measuring the current rate of joint destructive damage could identify patients at risk for accelerated bone and cartilage damage. We aim to identify serum biomarkers for progressive structural damage, to build and evaluate predictive models to estimate the current rate of structural damage, and to compare the performance of serum biomarkers to that of conventional measures, including DAS, CCP, CRP, and RF status.

Methods: We examined 90 individual candidate biomarkers in longitu-

dinal serum samples (baseline and year 1) with imaging results and clinical data from 160 patients followed in the BeSt trial, a 5-year blinded study comparing four different treatment arms (sequential monotherapy, step-up combination, combination therapy with prednisone, and combination therapy with infliximab) in aggressive early RA. The concentrations of individual biomarkers were assessed for their association with change in total Van der Heijde-modified Sharp Scores (mSS) at 2 years. Statistical models using combinations of serum biomarkers were built to predict the rate of change of total mSS. Good disease control may influence the computation of mSS rate of change; hence additional analyses incorporating therapy change information into the biomarker model were also performed. Various models built by conventional measures were compared to the serum biomarker model. Performance of the models was evaluated by the Pearson correlation coefficient between actual and predicted rates of change and by the area under the ROC curve (AUC) in cross-validated test sets. Mean mSS rate of change in the test sets was used to dichotomize patients into high and low groups for AUC calculation.

Results: Candidate serum biomarkers predicted damage better at Year 1 than at baseline, probably because baseline samples were collected before therapy took effect. We identified serum biomarker combinations (cor = 0.60, AUC = 0.75) that predicted change in mSS from Year 1 to Year 2 and were superior to DAS28ESR (cor = 0.33, AUC = 0.61), CRP (0.38, AUC=0.67), DAS28ESR with CCP (cor = 0.22, AUC = 0.61), or DAS28ESR with RF (cor = 0.37, AUC = 0.62) in predicting radiographic progression. In total, 35 individual biomarkers were associated with joint damage progression with false discovery rate (FDR) <0.1, 18 at FDR<0.05. Incorporating therapy information into the biomarker model didn't change model performance.

Conclusion: The best performing models included markers of bone and cartilage destruction, pro-inflammatory cytokines and acute phase proteins. Combinations of biomarkers were able to predict radiographic outcomes despite therapy changes and good control of disease activity. Serum biomarker-based indices have the potential to improve prediction of structural damage progression over standard clinical measures of disease activity in RA patients.

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Strontium Ranelate Inhibits Key Factors Affecting Bone Remodelling in Human Osteoarthritic Subchondral Bone Osteoblasts. Johanne Martel-Pelletier[2], Steeve Kwan Tat[3], Anne-Christine Goulet[3], Judith Caron[1], Daniel Lajeunesse[4] and Jean-Pierre Pelletier[4]. [1]ArthroLab Inc., Montreal, [2]CR-CHUM, Notre-Dame Hospital, Montreal, QC, Canada, [3]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, [4]University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC, Canada

Background: In osteoarthritis (OA) the progression of cartilage degeneration has been associated with the remodelling of the subchondral bone. Human OA subchondral bone osteoblasts were shown to have an abnormal phenotype and altered metabolism leading to an abnormal resorptive process. Bone resorption is suggested to occur, at least in part, through the increased levels of two proteolytic enzymes, MMP-2 and MMP-9, and RANKL, which are mainly produced by osteoblasts. In this study, we investigated in human OA subchondral bone osteoblasts the modulatory effect of strontium ranelate (SrRan) on key factors that affect the bone remodelling process.

Methods: Osteoblasts were cultured in a medium containing 0.1, 1 and 2 mM of SrRan during 18h for mRNA determination and 72h for protein determination. The effect of SrRan was evaluated on the expression (PCR) of MMP-2, MMP-9, OPG, RANKL (total), RANKL-1, and RANKL-3, on the production of OPG (ELISA) and membranous RANKL (flow cytometry). After incubation of osteoblasts with pre-osteoclasts (differentiated human peripheral blood mononuclear cells), the resorbed surface was measured using a sub-micron synthetic calcium phosphate thin film.

Results: The expression (mRNA) levels of MMP-2 and MMP-9 were significantly decreased by SrRan at 1 mM ($p\leq0.005$, $p\leq0.024$, respectively) and 2 mM ($p\leq0.003$, $p\leq0.007$) for MMP-2 and also at 0.1 mM ($p\leq0.05$) for MMP-9. Both the expression ($p\leq0.003$) and synthesis ($p\leq0.002$) of OPG were significantly increased with SrRan at 1 and 2 mM. RANKL (total) as well as the isoforms RANKL-1 and RANKL-3 were increased by SrRan at the higher concentrations tested. Of note, it is known that the different RANKL isoforms differentially regulate RANKL membranous localization: RANKL-3, in contrast to RANKL-1, prevents it. This is reflected by the significant ($p\leq0.02$) reduction in the level of membranous RANKL by SrRan at 2 mM. In addition, osteoblasts treated with SrRan induced a significantly ($p\leq0.002$) decreased resorbed surface compared to the control cells.

Conclusion: This study provides new and interesting data on the mode of action of SrRan on the metabolism of human OA subchondral bone osteoblasts. The data suggest that this drug may exert a positive effect on OA pathophysiology by inhibiting, in subchondral bone osteoblasts, the synthesis of key factors leading to bone resorption, a feature often associated with OA and recognized as a marker of this disease progression.

Disclosure: J. Martel-Pelletier: I.R.I.S., 2, 5; **S. Kwan Tat:** None; **A.-C. Goulet:** ArthroLab Inc., 3; **J. Caron:** ArthroLab Inc., 3; **D. Lajeunesse:** None; **J.-P. Pelletier:** I.R.I.S., 2, 5.

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Study of Chondrogenic Potential of Subpopulations of Cells Expressing Mesenchymal Stem Cell Markers Derived from Human Synovial Membranes. María C. Arufe[4], Alexandre De la Fuente[3], Silvia Diaz[2], Isaac Fuentes[2], Francisco J. de Toro[1] and Francisco J. Blanco[5]. [1]Dpto. Medicine, Area of Anatomy and Human Embryology, Campus Oza s/n. Fac. of Health Science, University of A Coruna, CIBER-BBN, Instituto de Salud Carlos III, Spain, [2]Osteoarticular and Aging Research Lab. Cellular Therapy Unit, INIBIC-CHUAC, A Coruña, Dpto. Medicine, Area of Anatomy and Human Embryology, Campus Oza s/n. Fac. of Health Science, University of A Coruna, CIBER-BBN, Instituto de Salud C, [3]Osteoarticular and Aging Research Lab. Cellular Therapy Unit, INIBIC-CHUAC, A Coruña, Spain, CIBER-BBN, Instituto de Salud Carlos III, Spain, [4]Osteoarticular and Aging Research Lab. Cellular Therapy Unit. INIBIC-CHUAC, A Coruna, Dpto. Medicine, Area of Anatomy and Human Embryology, Campus Oza s/n. Fac. of Health Science, University of A Coruna, CIBER-BBN, Instituto de Salud Carlos, [5]Osteoarticular and Aging Research Lab. Cellular Therapy Unit, INIBIC-CHUAC, A Coruña.Cathedra BIOIBERICA of Cell Therapy University of A Coruna, A Coruña, Spain, CIBER-BBN, Instituto de Salud Carlos III, Spain

Introduction: Synovial membrane mesenchymal stem cells (MSCs) have been demonstrated to be a good source of cells for the study of cartilage tissue engineering. Multiple stem cells markers have been found by flow cytometry and immunofluorescence in MSCs from human synovial membrane pools. In this study we analyzed the chondrogenic potential of subpopulations of MSCs derived from human synovial membranes enriched for CD73, CD106 and CD271 markers.

Material and Methods: Subpopulations of human synovial membrane MSCs enriched for CD73, CD106 and CD271 markers were isolated using a cytometry sorter and characterized by flow cytometry for MSC markers. The expression of Sox9, Nanog and Runx2 genes by these cells was measured by reverse transcriptase-polymerase chain reaction. The chondrogenesis of each subpopulation was assessed by culturing the cells in a defined medium to produce spontaneous spheroid formation and differentiation towards chondrocyte-like cells. The examination of the spheroids by histological and immunohistochemical analyses for collagen type II (COL2), aggrecan, collagen type I (COL1), metalloprotease 13 (MMP13) and collagen type $\times$ (COLX) levels were performed to assess their chondrogenesis capacity. The adipogenesis and osteogenesis potential of each subpopulation was determined using commercial media; the resulting cells were stained with oil red O or red alizarin to test the degree of differentiation.

Results: The subpopulations had different profiles of cells positive for the MSC markers CD44, CD69, CD73, CD90 and CD105 and showed different expression levels of the genes Sox9, Nanog, Runx2 involved in chondrogenesis, undifferentiation and osteoblastogenesis, respectively. Immunohistochemical analysis demonstrated that COL1, COL2, COLX, MMP13 and aggrecan were expressed in the spheroids as soon as 14 days of culture. The $CD271^+$ subpopulation expressed the highest levels of COL2 staining compared to the other subpopulations. CD105 and Runx2 were shown by immunohistochemistry and genetic analysis to have significantly higher expression CD271+ subpopulation than the other subpopulations.

Conclusions: Spheroids formed from CD271-enriched and CD73-enriched MSCs from normal human synovial membranes mimic the native cartilage extracellular matrix more closely than $CD106^+$ MSCs and are

possible candidates for use in cartilage tissue engineering. Both cell types have potential for promoting the differentiation of MSCs into chondrocytes, presenting new possibilities for achieving intrinsic cartilage repair.

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TGF-β-Induced CD4+CD25+Foxp3+ Regulatory T Cells Suppress Bone Erosion in Collagen-Induced Arthritis through Restraining the Osteoclastogenesis. NIng Kong[3], Ziyan Yang[2], Julie Wang[3], Ryan Park[3], Grant Dagliyan[3], Peter S. Conti[3], Hejian Zou[1] and Song Guo Zheng[3]. [1]Fudan University Medical School, [2]UCLA Department of Biomed, [3]USC Keck School of Medicine

Background: It is well-known that osteoclasts are responsible for the bone destruction in rheumatoid arthritis (RA) and collagen induced arthritis (CIA). Previous study has demonstrated that activated natural CD4+CD25+ regulatory T cells (nTregs) can inhibit osteoclastogenesis and CIA in a factor receptor activator of NF-kB ligand (RANKL) dependent pathway by blocking osteoclast differentiation from osteoclast precursors (OCP). Since we and other groups have identified that TGF-β-induced CD4+CD25+Foxp3+ regulatory T cells (iTregs) have the similar phenotypic and functional characteristics as nTregs, here we try to learn if iTregs also have the suppressive capacity on osteoclastogenesis and CIA.

Methods: In vitro, osteoclasts were induced from bone-marrow cells with RANKL and macrophage colony-stimulating factor (M-CSF). Naive CD4+ cells were isolated from splenocytes of normal DBA1/J mice and stimulated with anti-CD3/CD28 coated beads with IL-2 (Tcon) or IL-2+TGF-β (iTregs) for five days. On day 0, Tcon and iTregs were added to cultures for the induction of osteoclasts formation at different ratios in the presence of anti-CD3 monoclonal antibody. Osteoclast formation was determined by staining with tartrate-resistant acid phosphatase (TRAP), identified and counted by microscopes. In vivo, 3×106 iTregs were adaptively transferred to DBA1/J mice on d14 after immunization with CFA and bovine CII. The prevalence and severity of CIA mice were monitored every other day. After four-week transfer, mice accepted CT scanner on joints. The histological analysis of joints was performed and joints were stained for the identification of osteoclasts.

Results: Addition of 10% of iTregs almost completely suppressed osteoclast formation in cultures compared with addition of similar doses of Tcon cells. Addition of anti-TGF-β or anti-IL-10 antibody to cultures cannot abolish the suppressive activities and cell-contact was required for the suppressive effect. In addition, CIA mice received iTregs have a significant lower prevalence and clinic scores than mice received Tcon cells or no cells. Of note, CT scanner showed that the joints of CIA mice received iTregs had much less bone erosion than other two groups. Accordingly, histological analysis revealed that the joints in CIA mice received iTregs had much less osteoclasts than that in mice received Tcon cells or CIA models.

Conclusions: iTregs can inhibit osteoclastogenesis in vitro and in vivo, and eventually suppress bone erosion in CIA diseases. This study implicates that manipulation of iTregs may have a therapeutic effect on rheumatoid arthritis and other autoimmune diseases.

Disclosure: N. Kong: None; **Z. Yang:** None; **J. Wang:** None; **R. Park:** None; **G. Dagliyan:** None; **P. S. Conti:** None; **H. Zou:** None; **S. G. Zheng:** None.

1500

The Calcitonin Receptor Is Localized to Specific Phenotypes of Cartilage Chondrocytes *In Situ*. Pingping Chen-An, Yadong Li, Bodil C. Sondergaard, Toni Silvestra-Segovia, Per Qvist, Morten A. Karsdal and Anne C. Bay-Jensen. Cartilage Biology and Biomarkers, Denmark

Background: Arthritis is associated with excessive cartilage loss. Salmon calcitonin is reported to have chondro-protective effect on degenerative joint disease. We have recently shown that the calcitonin receptor (CTR) was expressed by primary chondrocytes; however it was also evident that not all chondrocytes expresses the CTR. Articular cartilage can be divided into different zonal layer, which encumbers different chondrocyte phenotypes; the superficial layer–discoid chondrocytes, the upper zone–spherical chondrocytes, mid zone–resting chondrocytes, deep zone–hypertrophic chondrocytes, calcified cartilage and subchondral bone. We therefore investigated, which of these chondrocytes express the CTR *in situ*.

Methods: Full-depth articular cartilage tissue was isolated from the tibia plateau of 20 different patients undergoing total knee replacement. The tissue was fixed, decalcified and embedded in paraffin. Sections of 5 μm were cut, blocked for unspecific binding and stained for the calcitonin receptor using the monoclonal antibody MAb 31/01-1H10 (Welcome receptor, Australia). Dako envision+ system was used for visualization of the antibody binding. Adjacent sections were stained with proteoglycans using safranin O and fast green staining. Sections were evaluated by Mankin score and specific arthritic features were identified in the cartilage. Anotations on positive staining were made of these features. Statistics were performed by Fishers' exact test.

Results: All sections had some degree of pathological features ranging from Mankin score 4 to 10. No or limited immune-reactivity was observed in the discoid chondrocytes of the superficial zone and spherical chondrocytes of the upper zone. In contrast when the superficial zone was lost a fraction of the spherical chondrocytes, namely those with clonal activity, displayed the receptor. At no time did we observe the CTR in the mid zone. Furthermore, we found the receptor to be present in a portion of hypertrophic chondrocytes of the deep zone. These observed distributions were significant ($p<0.05$). Furthermore, strong proteoglycan staining (intense red staining) was seen in the CTR positive anotations. Since we only observed immune-reactivity in cells with high metabolic activity, assessed by proteoglycan staining and general morphology, and did not observe any staining in the mid zone chondrocytes, it might indicated that the expression of the CTR is related to chondrocytes with high metabolic activity.

Conclusions: We here report that human articular cartilage chondrocytes do express the CTR *in situ*, and that this expression is associated with chondrocytes with high metabolic activity. The presence of the CTR suggests that chondrocytes are target for treatment with salmon calcitonin. These data support previous data that identifies the expression of CTR in primary osteoarthritic chondrocytes.

Disclosure: P. Chen-An: None; **Y. Li:** None; **B. C. Sondergaard:** None; **T. Silvestra-Segovia:** None; **P. Qvist:** None; **M. A. Karsdal:** None; **A. C. Bay-Jensen:** None.

1501

The Enhanced Expression of Suppressor of Cytokine Signaling (SOCS)-3 in Human Pathological Chondrocytes Impairs the TLR4 and IGF-1 Signaling in These Cells. Fons A. J. van de Loo, Miranda B. Bennink, Onno J. Arntz, Henk M. van Beuningen, Peter M. van der Kraan, Sharon S. Veenbergen and Wim B. van den Berg. Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Introduction: Osteoarthritis (OA), a degenerative joint disease, and Rheumatoid arthritis (RA), an inflammatory joint disease, are both characterized by progressive loss of the articular cartilage matrix due to an imbalance between matrix synthesis and degradation. Loss in the chondrocytes ability to respond to growth factor stimulation may be a key factor contributing to the development of OA and RA. We recently found that enforced expression of SOCS3 caused IGF-1 resistance in chondrocytes, thereby preventing upregulation of matrix proteoglycan synthesis. This study is designed to determine the expression of SOCS3 in human pathological chondrocytes and unravel the biological/functional consequences.

Methods: Chondrocytes were isolated from cartilage of patients undergoing surgical joint replacement. The mRNA and protein levels of SOCS1 and SOCS3 were measured by qPCR and westernblotting. Levels of SOCS3 were compared to a human immortalized chondrocyte cell-line (G6), mesenchymal-stem cells differentiated chondrocytes, and primary chondrocytes isolated from healthy bovine cartilage or from a SLE patient. The regulation of SOCS1 and 3 expression was studied in OA chondrocytes by incubation with different cytokines and TLR agonists. To determine the functional consequences the cytokine and TLR ligand induced nitric-oxide production and IGF-1-stimulated proteoglycan (PG) synthesis was studied.

Results: The SOCS3 mRNA expression in articular chondrocytes and cartilage was markedly upregulated (32-fold) in 21/24 OA, 5/5 RA patients, 3/3 trauma patients tested, as compared to the G6 cell-line, stem cell-differentiated chondrocytes, and chondrocytes derived from a SLE-patient. Exposure of the mesenchymal stem cell-derived chondrocytes with conditioned media of OA synovial explants upregulated SOCS3 to the same extent as seen in the OA chondrocytes. Exposure of OA chondrocytes to different cytokines (IL-1β, IL-17, IL-18) and TLR ligands (LPS, Pam2Cys, Poly(I:C), FK156, MDP could not further upregulate SOCS3 expression. In contrast, SOCS1 expression was markedly lower (20-fold) in comparison to SOCS3 in OA chondrocytes and could be upregulated to the level of SOCS3 using

IL-1β, IFNg, IL-17, Pam2Cys, Poly(I:C), and especially with the combination of IFNg and Poly(I:C). SOCS3 expression in OA chondrocytes was confirmed at the protein level. This means that the SOCS3 and SOCS1 genes are independently regulated and that SOCS3 has reached the maximal expression level. In the OA chondrocytes, the TLR4 ligand LPS was unable to induce NO production and IGF-1 failed to stimulate PG synthesis. Forced expression of SOCS3 in bovine cartilage-derived chondrocytes blocked the LPS (NO) and IGF-1 (PG-synthesis) response in these cells.

Conclusion: We found increased SOCS3 but not SOCS1 expression in human pathological chondrocytes. SOCS3 could block TLR4 and IGF-1 activation in chondrocytes. This suggests that SOCS3 modifies normal chondrocyte function and this could play a major role in the development of cartilage pathology seen in osteoarthritis and rheumatoid arthritis patients.

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1502

The HCO_3^-/Cl^- Anion Exchanger SLC4A2 Regulates pH and Actin Organization within Osteoclasts. Fabienne Coury[1], Andrew K. Stewart[3], Sebastien Stephens[2], Lynn Neff[2], William C. Horne[2], Seth L. Alper[3], Roland Baron[2] and Antonios O. Aliprantis[1]. [1]Department of Immunology and Infectious Diseases, Harvard School of Public Health, and Department of Medicine, Harvard Medical School, Boston, MA, [2]Department of Oral Medicine Infection and Immunity, Harvard Dental School, [3]Division of Nephrology, Beth Israel Deaconess Medical Center

Overactivation of bone resorption by osteoclasts occurs in numerous rheumatic diseases such as osteoporosis and rheumatoid arthritis. To resorb bone, osteoclasts secrete acid into a resorption lacuna between their apical ruffled membrane and the bone surface. This process is facilitated by reorganization of their actin cytoskeleton to form a sealing zone, which, like a gasket, seals off the resorption lacuna to prevent acid leakage. To prevent cytoplasmic alkalinization during lacunar acid secretion, electroneutral exchange of bicarbonate for chloride occurs through an anion exchanger, Solute carrier family 4, anion exchanger, member 2 (SLC4A2, AE2). We recently showed that in the absence of Slc4a2, mice develop osteopetrosis due to impaired osteoclast function. Accordingly, SLC4A2-deficient osteoclasts are unable to secrete acid and resorb bone. Here, we show that SLC4A2 may serve an additional and previously unrecognized function in the osteoclast: the regulation of actin dynamics and podosome organization. In vitro, SLC4A2 deficient osteoclasts display a delay in actin belt formation. The actin belts ultimately formed by SLC4A2-null osteoclasts are thicker and made up almost completely of punctuate, large podosomes lacking the diffuse actin cloud characteristic of wild-type belts. Furthermore, the average podosome life span is significantly longer in the actin belts of null osteoclasts, while actin polymerization is increased. Interestingly, while SLC4A2 was not required for microtubule assembly, we show it is required to recruit c-Src to the actin belt. c-Src is a major intracellular mediator of osteoclast activation, coordinates organization of the actin belt and is required for osteoclast function in vivo. We also show that SLC4A2 is exclusively expressed at the basolateral membrane of mouse osteoclasts. In addition, in its absence, osteoclasts are unable to exchange Cl^- for HCO_3^- and display intracellular alkalinization. Taken together, our results indicate that SLC4A2 regulates two cell biological processes required for mature osteoclasts to efficiently resorb bone: reorganization of the actin cytoskeleton and acid secretion. Whether the effect of SLC4A2 deficiency on the osteoclast cytoskeleton represents a direct function for this molecule in actin organization or an indirect effect of intracellular alkalinization is currently under investigation. Inhibitors designed to block SLC4A2 as a treatment for diseases characterized by excessive bone remodeling may need to take into account the binary function of this molecule in the osteoclast.

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1503

WNT3A Signals Simultaneously through Multiple Pathways in Human Articular Chondrocytes, Resulting in Distinct Outcomes. Giovanna Nalesso[2], Costantino Pitzalis[1] and Francesco Dell'Accio[2]. [1]William Harvey Research Institute, Barts and the London Queen Mary School of Medicine and Dentistry, Bromley Kent, United Kingdom, [2]William Harvey Research Institute, Barts and the London Queen Mary School of Medicine and Dentistry

Background: Disruption of Wnt signalling leads to osteoarthritis. Wnts signal through β Catenin/TCF or through non canonical pathways involving Ca++/CamKII, PKC, PKA, and the planar cell polarity pathway. Individual Wnt ligands are known to signal through different pathways depending of the cellular context. Canonical and non canonical signalling are active in cartilage and may play distinct roles in osteoarthritis. The purpose of the study was to systematically dissect WNT3A signalling in chondrocytes and understand the mechanisms through which disruption of this signalling leads to cartilage breakdown.

Methods: Articular chondrocytes were isolated from preserved cartilage of patients undergoing knee arthroplasty for osteoarthritis. Mouse cartilage explants were obtained from the femoral head of adult mice. The activation of the canonical and calcium dependent pathways upon Wnt3a stimulation was evaluated by the SUPER8TOPFlash, CREB, and NF-AT reporter assays, calcium mobilization assay, Western blotting for β catenin or p-CAMK2, and Axin-2 mRNA expression.

Results: Wnt3a induced the simultaneous activation of the canonical and CaMKII-dependent pathways. More importantly, using a systematic strategy of stimulation of Wnt3a and blockade of individual pathways, we have been able to demonstrate reciprocal inhibition of the two pathways and to separate specific downstream effects. We have built a model that, through such reciprocal inhibition, explains why excessive Wnt3A stimulation or blockade leads to cartilage destruction through different mechanisms.

Conclusions:

- Wnt3A signals simultaneously through the canonical and CamKII dependent pathways in cartilage
- The β catenin and the CamKII-dependent pathways are reciprocally inhibitory and have distinct outcomes.

Disclosure: G. Nalesso: None; **C. Pitzalis:** None; **F. Dell'Accio:** None.

ACR Poster Session C

Cell-Cell Adhesion, Cell Trafficking and Angiogenesis

Wednesday, November 10, 2010, 9:00 AM–6:00 PM

1504

A Novel Role for Inducible Fucosyltransferase2 as a Regulator of Angiogenesis. Mohammad A. Amin[1], Jeffrey H. Ruth[2], Pei-suen Tsou[2], Phillip L. Campbell[2], Hubert Marotte[2], SolHee Lee[2], Sivakumar Nallasivam[2], Steven E. Domino[2] and Alisa E. Koch[3]. [1]University of Michigan, Ann Arbor, MI, [2]University of Michigan, [3]Unversity of Michigan, Ann Arbor, MI

Purpose: Fucosyltransferases (Futs) are involved in the synthesis of fucosylated glycans and blood group antigens. A number of studies have shown the role of some Futs in angiogenesis and inflammation. The importance of angiogenesis is well established in diseases such as rheumatoid arthritis (RA). This is a novel study which demonstrates that Fut2, heretofore not known to regulate angiogenesis, is cytokine inducible in human dermal microvascular endothelial cells (HMVECs) and plays an essential role in inflammatory angiogenesis.

Methods: We performed reverse transcriptase polymerase chain reaction (RT-PCR) and quantitative PCR to determine Fut2 mRNA expression in HMVECs after stimulation with interleukin-1β (IL-1β). To determine the role of signaling molecules in Fut2 mRNA expression, we stimulated HMVECs with IL-1β in the presence or absence of chemical signaling inhibitors and collected RNA to examine the role of signaling molecules in Fut2 expression. We harvested endothelial cells (ECs) from Fut2 null and wild type (wt) mice and performed Matrigel tube formation assays *in vitro*. We also used Matrigel plug and the inflammatory sponge granuloma angiogenesis assays *in vivo* to elucidate the significance of Fut2 in angiogenesis by employing Fut2 null and wt mice. To evaluate the mechanism by which Fut2 contributes to angiogenesis, we stimulated Fut2 null and wt mouse ECs with IL-1β, and performed enzyme linked immunosorbent (ELISA) assays to determine if Fut2 deficient ECs produced lower amounts of angiogenic factors than their wt counterparts.

Results: IL-1β enhanced Fut2 mRNA expression in HMVECs compared to nonstimulated cells with a maximum increase at 60 minutes. Phosphatidylinositol 3 kinase and p38 were critical in HMVEC IL-1β stimulated Fut2 mRNA expression. Fut2 null ECs exhibited a significant 2 fold decrease in tube formation compared to wt ECs, indicating that Fut2 may be an important factor in angiogenesis *in vitro*. To determine whether Fut2 contributed to angiogenesis *in vivo*, we performed mouse Matrigel plug and inflammatory sponge granuloma angiogenesis assays using Fut2 null and wt mice. Fut2 null

mice were deficient in angiogenesis in both the Matrigel plug and the sponge granuloma compared to wt mice ($p<0.05$). To determine the mechanism of impaired angiogenesis in the absence of Fut2, ECs harvested from Fut2 null and wt mice were stimulated with IL-1β. Vascular endothelial growth factor (VEGF) was less in Fut2 null ECs at both the mRNA and protein levels, suggesting a novel role for Fut2 as regulator of angiogenesis.

Conclusions: These data suggest an intriguing role for Fut2 as regulator of angiogenesis. Fut2 may be a potential therapeutic target controlling production of angiogenic factors such as VEGF in angiogenesis-dependent diseases such as RA.

Disclosure: M. A. Amin: None; **J. H. Ruth:** None; **P.-s. Tsou:** None; **P. L. Campbell:** None; **H. Marotte:** None; **S. Lee:** None; **S. Nallasivam:** None; **S. E. Domino:** None; **A. E. Koch:** None.

1505

CD86 Is Involved in the Intercellular Contacts between IL15 Activated Natural Killer Cells and THP-1 Cells That Result in TNF Production. Amalia Lamana, Belen Diaz-Sanchez, gips. Ortiz, Santos Castañeda, Rosario Garcia-Vicuña and Isidoro Gonzalez-Alvaro. Rheumatology Department. HU La Princesa. IIS Princesa, Madrid, Spain

Background: We have previously described that the interaction between NK cells activated with interleukin 15 (IL15) and macrophages leads to persistent TNF production and may be relevant in the perpetuation of rheumatoid arthritis in a subset of patients (1). Abatacept, an effective drug for controlling this disorder, inhibits the costimulatory signal induced by the interaction of CD28 expressed on T cells with CD80 and CD86 expressed on macrophages.

Aim: To study the pattern of CD28 expression on NK cells and its potential implication in the interactions that result in TNF secretion in cultures of NK and THP-1 cells.

Methods: We studied by flow cytometry the expression of CD16, CD28 and CD56 on different NK lineage tumor cell lines (NKL, NK3.3 and YT Indy obtained from ATCC) and on NK cells from peripheral blood (PB) of 33 healthy donors (HD). In addition, PB lymphocytes (PBL) were stimulated or not with IL15 (50 ng/ml) for 16 h. Resting and activated cells were washed twice with medium and co-cultured with THP-1 cells (10 PBL by each THP-1 cell) in the presence or absence of CTLA4-Ig, anti CD86 and anti CD80 (as a control since THP-1 cells do not express this molecule) blocking monoclonal antibodies (mAb). After 24 hours, supernatants were harvested and TNF production was measured by ELISA. In some conditions, cells were separated by a permeable support (transwell) that allowed the passage of soluble mediators but not cells. Furthermore, we performed experiments with PBL depleted in CD28 or CD16 positive cells.

Results: NKL and YT Indy tumoral cell lines expressed CD28. NK cells from HD could be classified according on their pattern of CD16 and CD56 expression as: group 1 (GR1) is CD56dim CD16high; group 2 (GR2) is CD56dim CD16negative; and group 3 (GR3) is CD56 high CD16low/negative. The most abundant population was GR1 (median 60% of NK; interquartile range [IQR] 48–75%) where cells lack CD28. The median percentage of NK subpopulation with GR2 profile was 17% (IQR 12–34%). A subset of GR2 NK cells, ranging from 5 to 50%, expressed CD28. The GR3 subpopulation represented about 5% of PB NK cells and did not express CD28. Supernatants from PBL and THP-1 cells showed TNF production that increased ($80+/-15\%$; $p<0.001$) when PBL were pre-treated with IL15 and was abrogated when the two cellular types were separated by transwells. Interestingly, the presence of anti-CD86 mAb in the culture medium decreased TNF production ($-50+/-30\%$; $p=0.02$) mainly when PBL were pre-activated with IL15. CTLA4-Ig decreased TNF production only in a subpopulation of HD. On the other hand, IL15 did not increase the CD28 expression on NK cells and the depletion of CD28 positive cells did not impair TNF production, whereas depletion of CD16 positive cells abrogated its production.

Conclusions: In this study we have described that blockade of CD86 decreases the production of TNF in a model that is mediated by IL15-activated NK cells. Although we have detected a subpopulation of NK cells expressing CD28, this subset do not seem to be involved in the model. More studies are needed to determine the CD86 ligand on CD16+ NK cells since in a subset of donors CTLA4-Ig was also able to decrease TNF production.

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Disclosure: A. Lamana: Spanish Foundation of Rheumatology, 3; **B. Diaz-Sanchez:** RIER. RETIC program. ISCIII., 3; **A. M. Ortiz:** Bristol-Myers Squibb, 2; **S. Castañeda:** None; **R. Garcia-Vicuña:** Bristol-Myers Squibb, 2, 5, Roche, 2, 5, Schering-Plough, 5; **I. Gonzalez-Alvaro:** Abbott Laboratories, 5, Bristol-Myers Squibb, 2, Roche, 2, 5.

1506

Characterization of CCR7 and Its Ligands CCL19 and CCL21 in Rheumatoid Arthritis. Sarah R. Pickens[5], Michael V. Volin[1], Richard M. Pope[4], Arthur M. Mandelin[2] and Shiva Shahrara[3]. [1]Midwestern University, [2]Northwestern University, Chicago, IL, [3]Northwestern Univ Feinberg, Chicago, IL, [4]Northwestern Univ Med School, Chicago, IL, [5]Northwestern University, Chicago, IL

Introduction: The aims of this study were to characterize the expression of CCR7 and its ligands CCL19 and CCL21 in rheumatoid arthritis (RA) synovial tissue (ST) and synovial fluid (SF) and to demonstrate the role of CCL19 and CCL21 in RA pathogenesis.

Methods: Immunohistochemistry was employed to determine expression patterns of CCR7, CCL19 and CCL21 in RA and NL STs. CCL19 and CCL21 expression levels were also determined in normal (NL), osteoarthritis (OA) and RA ST, as well as in SF from OA, juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA) and RA patients using ELISA. CCL19 and CCL21 mRNA levels were quantified in NL and RA peripheral blood (PB) monocytes and macrophages, as well as in RA SF macrophages by real-time RT-PCR. Next, we identified proinflammatory factors that modulate expression of CCL19 and CCL21 in PB differentiated macrophages using real-time RT-PCR. Finally, production of proinflammatory factors was examined in CCL19 and CCL21 activated macrophages and RA ST fibroblasts employing ELISA.

Results: We found that ST lining and endothelial cells positively stained for CCR7 and that the immunostaining was 2 fold higher in RA compared to NL STs. Consistently, CCL19 and CCL21 expression was significantly increased in RA ST lining (1.3 and 3 fold respectively) and endothelial cells (1.5 and 2 fold respectively) compared to NL ST. Levels of CCL21 were generally higher in RA and OA STs compared to CCL19. However, NL ST had similar levels of CCL19 and CCL21. Further, CCL19 and CCL21 levels were elevated in RA (2.5 and 1.5 fold respectively) and PsA SFs (2 and 1.6 fold respectively) compared to OA SFs. Interestingly, CCL19 levels were significantly increased in RA SF macrophages compared to RA and NL PB macrophages, while CCL21 expression was upregulated in RA SF and PB macrophages compared to the same cells in NL PB. Next, we showed that CCL19 expression levels were greatly induced by LPS (70 fold) and IL-1β (6.5 fold) activation of macrophages compared to untreated cells. However, only RA SF stimulation (2.5 fold) upregulated levels of CCL21 in macrophages compared to untreated cells. Additionally we found that CCL19 and CCL21 were capable of inducing the production of VEGF and Ang-1 from RA ST fibroblasts and secretion of IL-8 and Ang-1 from macrophages.

Conclusion: Our results suggest that CCR7 and its ligands CCL19 and CCL21 are elevated in RA ST lining and endothelium, and ligation of CCR7 may play an important role in mediating angiogenesis in RA synovium.

Disclosure: S. R. Pickens: None; **M. V. Volin:** None; **R. M. Pope:** None; **A. M. Mandelin:** None; **S. Shahrara:** None.

1507

Chemerin Levels Are Increased in Rheumatoid Arthritis Patients Who Smoke, Correlate with Disease Activity, and Decrease after Adalimumab Treatment. Marieke Herenius[2], Cristina Lebre[3], Ana Oliveira[3], Carla Wijbrandts[3], Daniëlle Gerlag[3] and Paul P. Tak[1]. [1]Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, [2]Division of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, Utrecht, The Netherlands, [3]Division of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Background: Chemerin is a recently discovered chemokine that modulates chemotaxis and activation of dendritic cells and macrophages. The expression of chemerin in rheumatoid synovial tissue strongly suggests involvement of chemerin in the migration/accumulation of dendritic cells and macrophages in the inflamed joint. Furthermore, we have recently shown in synovial biopsy explant cultures that chemerin levels are upgulated by TNF-a and that chemerin can induce TNF-a. Elevated chemerin levels have also been related to dyslipidemia and hypertension in obesity, thereby linking it to the metabolic syndrome.

Objective: To explore the role of chemerin in rheumatoid arthritis (RA) in relationship to known cardiovascular risk factors and to evaluate the effects of anti-TNF treatment on serum levels of chemerin.

Methods: 49 patients with active RA (disease activity score evaluated in 28 joints (DAS28)) ≥ 3.2) were started on adalimumab therapy (40 mg subcutaneously every other week). Blood was drawn from patients while fasting at baseline and 16 weeks after the initiation of therapy. Chemerin

levels were measured by ELISA. Known risk factors for cardiovascular disease were determined at baseline.

Results: Baseline chemerin levels correlated with DAS28 and ESR ($r=0.38$, $p=0.007$ and $r=0.40$, $p=0.005$, respectively). Of interest, we found chemerin levels to be significantly higher in current smokers (n=9, median 162ng/ ml, IQR 159–168 ng/ml) than non-smokers (n=33, median 143 ng/ml, IQR 130–169 ng/ml, $p=0.03$). Baseline chemerin levels were not related to sex, age, BMI, serum lipid levels (TC, HDL, LDL, TG, Apo A-I, Apo B, Lp(a))or cardiovascular events in the medical history. After 16 weeks of adalimumab treatment there was a significant reduction of DAS28, ESR, CRP ($p<0.001$, $p<0.001$, and $p<0.001$, respectively) associated with a reduction of serum levels of chemerin from 152 ng/ml (±34 ng/ml) to 141 ng/ml (±29 ng/ml) ($p=0.025$).

Conclusions: Levels of chemerin are related to disease activity and reduce after adalimumab treatment. Interestingly, smoking might increase levels of chemerin, a potent chemoattractant for dendritic cells and macrophages, promoting clinical signs and symptoms of RA and perhaps also the metabolic syndrome.

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1508

Contribution of NR4A2 Gene Expression in Modulation of Thrombospondin-1 in Human Joint Disease. Jason P. McMorrow[3], Ursula Fearon[3], Douglas J. Veale[1], Oliver M. FitzGerald[2] and Evelyn P. Murphy[3]. [1]St Vincents Univ Hospital, Dublin, Ireland, [2]University College Dublin, Ranelagh Dublin, Ireland, [3]University College Dublin, Dublin, Ireland

Background: During joint inflammation perpetuation of angiogenesis leads the reorganisation and increase in blood vessel number. During early stages of disease an angiogenic switch occurs which shuts off angiogenic inhibitors such as Thrombospondin-1 (TSP-1) and leads to increased production of pro-angiogenic mediators. The NR4A subfamily of orphan nuclear receptors have recently emerged as novel transcriptional regulators of angiogenic growth factor and cytokine action in inflammatory diseases. The aim of this study was to examine the levels of the TSP-1 in human serum, expression of TSP-1 in synovial tissue and to monitor the effects of anti-TNFα therapy on both systemic and local TSP-1 levels.

Methods: TSP-1, VEGF, NR4A, and IL-8 mRNA levels were determined in using real-time PCR. TSP-1 protein levels were quantified in synovial tissue (ST) by immunohistochemistry (IHC) in a cohort of patients (n=10) pre and post anti-TNF therapy. TSP-1 serum levels were measured by ELISA in healthy volunteers (n=5) and 2 cohorts of patients (n=12; n=15) receiving anti-TNFα treatment. TSP-1 promoter activity was monitored by luciferase reporter assays.

Results: TSP-1 protein levels were measured in patient serum at baseline (n=12) and compared to levels in healthy volunteers (n=5). A significant decrease in TSP-1 expression was observed in patients with active disease ($p<0.007$). Following anti-TNFα treatment, TSP-1 serum levels were restored (n=15; $p<0.047$). TSP-1 and NR4A2 expression and localisation was measured in the ST of patients (n=10) receiving anti-TNFα therapy. Our findings demonstrate that low expression levels of TSP-1 in inflamed tissue in the lining layer and subling endothelial cells. TSP-1 expression was highly cell associated. High levels of NR4A2 were quantified in all patient tissue. Post-treatment, NR4A2 levels are significantly reduced, while TSP-1 protein levels are enhanced demonstrating a significant diffuse pattern of expression.

Using primary synoviocyte cells (n=9), analysis revealed negligible levels of TSP-1 mRNA, high levels of NR4A1–3 and IL-8 transcripts in low passage cells. In high passage cells, reciprocal levels of TSP-1, NR4A and IL-8 expression were observed. Stable NR4A2 expression in normal synoviocyte cells resulted in decreased TSP-1 mRNA and protein levels. To determine whether NR4A effects on TSP-1 expression occurred at the transcriptional level, we evaluated transactivation of the hTSP-1 (2872 bp) promoter using a series of promoter deletions cotransfected with NR4A2. NR4A2 reduced TSP-1 promoter activity by approx. 50%. Within the promoter deletions we identified a repressor region. Deletion of this promoter region resulted in NR4A2 activity transformed from a repressor to transcriptional activator of TSP-1 expression.

Conclusion: These data reveal that moderate expression of TSP-1 in human inflammatory joint disease can be significantly enhanced during anti-TNF treatment and identifies a novel role for NR4A2 as a transcriptional repressor of TSP-1 expression in human synovial tissue.

Disclosure: J. P. McMorrow: None; **U. Fearon:** None; **D. J. Veale:** None; **O. M. FitzGerald:** None; **E. P. Murphy:** None.

1509

Role of the Metalloproteinase ADAM-8 in the Regulation of the Inflammatory Response. PSGL-1 Shedding by ADAM-8 in Human Neutrophils. Maria Jesus Dominguez-Luis[4], Ana Urzainqui-Mayayo[1], Ada Maria Herrera-Garcia[4], Ana Diaz-Martin[5], Maria Teresa Arce-Franco[5], Faustino Mollinedo[2], Francisco Sanchez-Madrid[1] and Federico Diaz-Gonzalez[3]. [1]Immunology Service, Hospital de La Princesa, Madrid, Spain, [2]Instituto Superior del Cancer, Salamanca, Spain, [3]Rheumatology Service, Hospital Universitario de Canarias, La Laguna, Tenerife, Spain, [4]Rheumatology Service, Hospital Universitario de Canarias, La Laguna, Spain, [5]Rheumatology Service, Hospital Universitario de Canarias, Spain

ADAM (A disintegrin and metalloproteinase domain) proteins are a family of transmembrane proteases with heterogeneous functions and expression profile. One of its members, ADAM-8 is constitutively present at both cell surface and intracellular granules levels in human neutrophil, and it has been implicated in the L-selectin shedding. However, the potential role of this metalloproteinase in the regulation of other "sheddable" proteins involved in the initial phase of the inflammatory response such as PSGL (P-selectin glycoprotein ligand)-1, had not been investigated.

Objective: To study the capability of ADAM-8 to process the ectodomain of PSGL-1 in human neutrophils.

Methods: In this study have been used human peripheral blood neutrophils from healthy donors, HL-60 cells (human promyelocytic leucemia cells) and CEM (T-lymphoblastic leucemia cell line). The association PSGL-1/ ADAM-8 was studied by co-immunoprecipitation assays in HL60 cells. The membrane and intracellular expression of these two proteins in neutrophils was assessed by flow cytometry and confocal immunofluorescence microscopy. Supernatant concentration of PSGL-1 was determined by ELISA. Native and catalytically inactive ADAM-8 was expressed in CEM line (not possess endogenous ADAM-8) by nucleofection. PSGL-1 function was evaluated in a flow chamber by the dynamic behavior of CEM cells preincubated with termolisyn-activated recombinant ADAM-8 over a P-selectin-coated surface.

Results: Both confocal microscopy studies and co-immunoprecipitation assays showed the association ADAM-8/PSGL-1 in human neutrophils and HL60, respectively. Pull-down assays established that the binding capacity of ADAM-8 to PSGL-1 was lost if cytoplasmic tail of PSGL-1 was truncated before amino acid 18. Incubation of human neutrophils with thermolysin-activated recombinant soluble ADAM-8 resulted in PSGL-1 shedding assessed by ELISA respect to cells incubated with inactive soluble ADAM-8 (t-student, $p<0.05$). In addition, CEM cells transfected with native ADAM-8 showed a reduction in PSGL-1 surface expression (by flow cytometry) and a decrease in the number of cells that roll on recombinant P-selectin (in flow chamber) respect to cells transfected with a catalytic-inactive ADAM-8 (t-student, $p<0.05$).

Conclusions: Both the membrane and soluble form of ADAM-8 are able to regulate the PSGL-1 and L-selectin surface expression in human neutrophils. All these data support a potential relevant role for ADAM-8 in the recruintment of neutrophils into tissues during the inflammatory response.

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ACR Poster Session C
Cytokines, Mediators, Gene Regulation II
Wednesday, November 10, 2010, 9:00 AM–6:00 PM

1510

***In Vitro* Hypoxia-Induced Mitochondrial Genome Mutagenesis and Dysfunction.** Monika Biniecka[2], Edward Fox[1], Chin T. Ng[2], Wei Gao[2], Ursula Fearon[2], Douglas Veale[2] and Jacintha O'Sullivan[2]. [1]Department of Pathology, University of Washington, Seattle, WA, [2]Translation Research Group, Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Co. Dublin, Ireland

Background: Hypoxia is characterized by an inadequate supply of molecular oxygen and has been associated with increases in reactive oxygen species (ROS) production. O_2 sensing and ROS source in response to hypoxia is though to be mediated by Electron Transport Chain, hence mitochondrial genome is highly susceptible to attack by oxygen radicals. Oxidative stress is postulated as a primary source of mitochondrial DNA mutations (mtDNA)

and clonally expanded mitochondrial mutagenesis has been detected in patients with rheumatoid arthritis. In this study we examine whether *in vitro* hypoxia induces mitochondrial dysfunction resulting in mitochondrial genome mutagenesis and we examine the role of HIF-1α and NF-kB in mediating these events.

Method: K4 cells (immortalised human synoviocyte cells) were exposed to normoxia (21%) or hypoxia (1%). Levels of mtDNA point mutations were quantitatively evaluated using Random Mutation Capture assay. Intracellular ROS production and mitochondrial membrane potential (MMP) were measured using fluorescent molecular probes. Markers of oxidative DNA damage (8-oxo-dG) and lipid peroxidation (4-HNE) were determined in cell culture supernatants by ELISA. Protein expression of HIF-1α and NF-kB were assessed by Western blots. The effect of antioxidant treatment on mitochondrial mutagenesis and dysfunction were examined by culturing cells under normoxic (21%) and hypoxic (1%) conditions in the presence or absence of manganese superoxide dismutase (MnSOD) or N-Acetyl Cysteine (NAC) or a hydroxylase inhibitor dimethyloxalylglycine (DMOG).

Results: Hypoxia significantly increases the level of mitochondrial DNA point mutations ($p<0.05$), ROS production ($p<0.05$) and MMP ($p<0.01$) in comparison to normoxia. Treatment with of MnSOD, NAC and DMOG significantly reduced hypoxia-induced mtDNA mutagenesis, intracellular ROS production and attenuated MMP hyperpolarization (all $p<0.05$). Levels of 8-oxo-dG and 4-HNE were significantly higher in K4 supernatants exposed to hypoxia ($p<0.0002$ and $p<0.005$ respectively) than to normoxia and cell stimulation with MnSOD, NAC and DMOG suppressed hypoxic secretion of these oxidative stress markers (all $p<0.002$). MnSOD, NAC and DMOG stabilized HIF-1α protein accumulation under hypoxia. There was no difference in the levels of NF-kB protein expression between all oxygen and antioxidant treatment groups.

Conclusion: Hypoxia drives mitochondrial dysfunction manifested by ROS overexpression and altered MMP. Hypoxia-induced mtDNA mutations are a consequence of elevated oxidative damage indicating ROS as a primary source of mitochondrial mutagenesis. Early detected oxidative stress and mitochondrial genome instability are transient and can be rescue after treatment with MnSOD, NAC and DMOG. Hypoxic HIF-1α activation after antioxidants and hydroxylase inhibitor treatment may contribute to gene expression that prevents mtDNA damage following oxidative stress thus HIF-1α antagonizes hypoxia-induced mitochondrial mutagenesis.

Disclosure: M. Biniecka: None; **E. Fox:** None; **C. T. Ng:** None; **W. Gao:** None; **U. Fearon:** None; **D. Veale:** Abbott Immunology Pharmaceuticals, 2, 5, 8, Centocor, Inc., 5, 8, GlaxoSmithKline, 2, 5, 8, Mundipharma, 2, 8, Opsona, 2, 8, Pfizer Inc, 5, 8, Schering-Plough, 5, 8, Wyeth Pharmaceuticals, 2, 5, 8; **J. O'Sullivan:** None.

1511

Allograft Inflammatory Factor-1 Facilitates the Migration of Fibroblasts and Has a Correlation with the Pathogensis of Skin Fibrosis in a Murine Model of a Murine Model of Sclerodermatous GVHD. Aihiro Yamamoto[1], Eishi Ashihara[2], Yoko Nakagawa[2], Hiroshi Obayashi[3], Takahiro Seno[1], Masatoshi Kadoya[1], Masahide Hamaguchi[1], Hidetaka Ishino[1], Masataka Kohno[1], Taira Maekawa[2] and Yutaka Kawahito[1]. [1]Department of Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, [2]Department of Transfusion Medicine and Cell Therapy, Kyoto University Hospital, [3]Institute of Bio-Response Informatics

Allograft inflammatory factor (AIF)-1 is an IFN-γ-inducible, Ca^{2+}-binding EF-hand protein that is encoded within the HLA class III genomic region in the direct vicinity of TNF-α. AIF-1 has been identified in chronic rejection of rat cardiac allografts and is thought to be involved in the immune response. We previously showed that AIF-1 was strongly expressed in synovial tissues in rheumatoid arthritis and that rAIF-1 increased the IL-6 production of synoviocytes and peripheral blood mononuclear cells. Recently, the expression of AIF-1 has been reported in systemic sclerosis (SSc) tissues, whose clinical features and histopathology are similar to those of chronic graft-vs-host disease (GVHD). To clarify the pathomechanism of fibrosis, we underwent bone marrow transplantation and made sclerodermatous (Scl) GVHD mice. We examined the expression and function of AIF in Scl GVHD mice on day 21 after BMT. We demonstrated that immunoreactive AIF-1 and IL-6 were significantly expressed in infiltrating mononuclear cells and fibroblasts in thickened skin of Scl GVHD mice compared with control. The immunohistochemical findings were confirmed by Western blot analysis. Wound healing assay also revealed that rAIF-1 increased the migration of normal human dermal fibroblasts (NHDF) directly, but cell growth assay didn't showed that rAIF-1 increased the proliferation of them. These findings suggest that AIF-1, which can induce the migration of fibroblasts and the production of IL-6 in affected skin tissues, is an important molecule promoting fibrosis in GVHD. Although the biological function of AIF-1 has not been completely elucidated, AIF-1 can induce IL-6 secretion on mononuclear cells and fibroblast chemotaxis. AIF-1 may accordingly provide an attractive new target for antifibrotic therapy in SSc as well as Scl GVHD.

Disclosure: A. Yamamoto: None; **E. Ashihara:** None; **Y. Nakagawa:** None; **H. Obayashi:** None; **T. Seno:** None; **M. Kadoya:** None; **M. Hamaguchi:** None; **H. Ishino:** None; **M. Kohno:** None; **T. Maekawa:** None; **Y. Kawahito:** None.

1512

Bach1 Regulates Heme Oxygenase-1 Expression of Human Monocytes in Response to LPS: Implication in Behcet's Disease. Mitsuhiro Takeno, Takuya Miyazaki, Yohei Kirino, Sei Samukawa, Maasa Hama and Yoshiaki Ishigatsubo. Yokohama City University Graduate School of Medicine

Background: Heme oxygenase (HO)-1 is an inducible anti-inflammatory protein which regulates innate immune functions and involved in pathogenesis of various rheumatic diseases. We have found that increased TLR4 expression is associated with defective HO-1 expression in leukocytes from Behcet's disease patients, leading to an augmentation of inflammatory responses. However, effects of lipopolysaccharide (LPS), a TLR4 ligand, on HO-1 expression have been controversial in monocytic cells: both enhancing and reducing effects have been reported. We here investigated the regulatory roles of the transcriptional repressor Bach1 and the activator Nrf2 in HO-1 expression of human monocytes in response to LPS.

Methods: Peripheral blood mononuclear cells (PBMC) were isolated from healthy donors. Expressions of HO-1, Bach1, and Nrf2 were semiquantitiatively analyzed by immunoblotting at the protein level nd real-time PCR techniques at the mRNA level, respectively. Transcriptional activity of HO-1 gene was determined by luciferase assay. The binding of Bach1, and Nrf2 to Maf-recognition elements (MARE) was determined by chromatin immunoprecipitation assays.

Results: Immunoblotting studies showed that freshly isolated peripheral monocytes expressed substantial amounts of HO-1, along with nuclear Nrf2 and cytoplasmic Bach1. In contrast, HO-1, Nrf2 and Bach1 proteins were little expressed in unstimulated human myelogenous leukemic cell lines such as U937. In response to LPS, HO-1 was reduced in primary monocytes, but upregulated in U937 cells. The differences were associated with distinct kinetics of Nrf2 and Bach1. Immunoblottting studies in cytoplasmic and nuclear fractions, and chromatin immunoprecipitation assays revealed that, in peripheral monocytes, Nrf2 predominantly bound to MARE, the upstream enhancer lesions of HO-1 gene, while LPS promoted nuclear translocation of Bach1 and preferential bindings of Bach1 to MARE. On the other hand, Bach1 was highly bound to MARE in U937 cells under a resting condition, whereas treatment with LPS reversed the biding proportions of the two proteins. Thus, HO-1 expression level is regulated by the binding proportion of Nrf2 and Bach1 to MARE. Furthermore, the LPS-mediated HO-1 reduction was abrogated by Bach1 siRNA.

Conclusions: The present study demonstrates that LPS suppresses HO-1 expression through nuclear translocation of Bach1 in human peripheral monocytes and suggests that Bach1 is a possible therapeutic target in inflammatory diseases including Behcet's disease.

Disclosure: M. Takeno: None; **T. Miyazaki:** None; **Y. Kirino:** None; **S. Samukawa:** None; **M. Hama:** None; **Y. Ishigatsubo:** None.

1513

BMS-582949 Is a Dual Action p38 Kinase Inhibitor Well Suited To Avoid Resistance Mechanisms That Increase p38 Activation in Cells. Gary Schieven[1], Rosemary Zhang[2], Sidney Pitt[2], Ding-Ren Shen[2], Jian Cao[2], John Sack[2], Arthur Doweyko[2] and Petra Ross-MacDonald[2]. [1]Bristol-Myers Squibb, Princeton, NJ, [2]Bristol-Myers Squibb

Purpose: Multiple p38 kinase inhibitors (p38i) have been reported to show tachyphylaxis (only transient benefit) in clinical studies of RA, suggesting the induction of resistance mechanisms. By contrast, BMS-582949 has demonstrated clinical efficacy in a PhIIa RA study without tachyphylaxis. Potential kinase resistance pathways in cells and the effect of BMS-582949 on such pathways were investigated to better understand the mechanism by which BMS-582949 avoids tachyphylaxis.

Methods: The phosphorylation of p38 in the cells was measured with phosphospecific antibodies to measure effects on p38 activation. Cells were

treated with p38i alone or in combination with LPS to provide an inflammatory stimulus, and changes in gene expression were measured utilizing microarrays.

Results: BMS-582949 was found to inhibit p38 activation in cells, as measured by phosphorylation of p38. Furthermore, BMS-582949 treatment of cells in which p38 had been activated by LPS rapidly reversed p38 activation as shown by loss of phosphorylation of p38. BMS-582949 is therefore a dual action p38 kinase inhibitor, inhibiting both p38 kinase activity and p38 activation in cells. By contrast, SCIO-469, a p38i that was reported to show tachyphylaxis, did not inhibit p38 activation in cells. In gene expression analysis of cells treated with p38i, all changes observed for p38 pathway components were consistent with cellular feedback to drive p38 activation more strongly. Treatment of either hepatocytes or monocytes with p38i alone resulted in up to 80% increased MKK6 expression, and treatment of monocytes with p38i plus LPS (compared to LPS alone) resulted in increased expression of several upstream activating kinases and p38a itself, while decreasing expression of MKP-1 which dephosphorylates and deactivates p38. X-ray crystallography revealed that BMS-582949 binding to p38a results in a conformational change of the activation loop which is phosphorylated by upstream kinases, whereas SCIO-469 had little effect. BMS-582949 may therefore inhibit phosphorylation of p38 by upstream MKK by inducing a less accessible conformation of the activation loop.

Conclusions: BMS-582949 acts as a dual action kinase inhibitor in cells, inhibiting both p38 kinase activity and activation of p38. Treatment of cells with a variety of p38 inhibitors resulted in changes expected to drive cellular p38 activation more strongly. Increasing activation of p38 may be a resistance pathway by which cells can overwhelm effects of p38 inhibitors that only inhibit p38 kinase after it is activated. By blocking activation of p38 kinase, BMS-582949 appears to be well suited to resist such cellular responses that would drive p38 activation more strongly.

Disclosure: G. Schieven: Bristol-Myers Squibb, 3; **R. Zhang:** Bristol-Myers Squibb, 3; **S. Pitt:** Bristol-Myers Squibb, 3; **D.-R. Shen:** Bristol-Myers Squibb, 3; **J. Cao:** Bristol-Myers Squibb, 3; **J. Sack:** Bristol-Myers Squibb, 3; **A. Doweyko:** Bristol-Myers Squibb, 3; **P. Ross-MacDonald:** Bristol-Myers Squibb, 3.

1514

Both Insulin Receptor and Nampt Activity Are Implicated in Visfatin/ Nampt Induced PGE2 Synthesis in Articular Chondrocytes. Marjolaine Gosset[4], Francis Berenbaum[2], Colette Salvat[4], Alain Sautet[1], Martin Holzenberger[3] and Claire Jacques[4]. [1]Faculty of Medicine P&M Curie, Paris, France, [2]Faculty of Medicine P&M Curie, UR4 Paris Universitas, Paris, France, [3]Inserm U893, Paris, France, [4]UR4 Paris Universitas, Paris, France

Purpose: We recently reported on visfatin expression in articular chondrocytes and its role in prostaglandin (PG)E2 release in cartilage. However, the signaling pathways of visfatin remain unclear. Visfatin was first reported as a protein that binds to the insulin receptor (IR). More recently, a nicotinamide phosphoribosyltransferase (NAMPT) enzymatic activity involved in nicotinamide mononucleotide (NMN) production, a precursor of the cofactor NAD+, has been demonstrated. The aim of this study was to decipher the signaling pathways implicated in visfatin induced PGE2 release in chondrocytes.

Methods: IR expression from OA human chondrocytes and immature murine articular chondrocytes (iMACs) were assessed using real-time RT-PCR, immunoblotting and immunocytofluorescence. A highly specific monoclonal antibody raised against IR was used. Phosphorylation of IR and AKT was analyzed using Western Blot. IR tyrosine kinase activity was inhibited by using HNMPA-(AM)3 and a siRNA strategy was used to investigate the role of IR in visfatin induced PGE2 release. The role of IGF-1 Receptor (IGF-1R) in visfatin signaling was assessed using primary chondrocytes from IGF-1R knockout mice (IGF-1R−/−) and iMACs treated with an IGF-1R blocking antibody. NAMPT activity was inhibted using APO 866. PGE2 was measured by EIA.

Results: (1) Visfatin is known to bind to, and to activate IR in various cell types. However, IR is not considered to be usually present on chondrocytes. We therefore tested the implication of IGF-1R, a close homologue to IR, in visfatin signaling. When stimulated with 5μg/ml visfatin, IGF-1R−/− chondrocytes unexpectedly exhibited higher PGE2 release than IGF1R+/+ controls (228±4 compared to 86±29 pg/ml, $p<0.05$), ruling out a direct role of IGF-1R in the visfatin effect. Moreover, visfatin (5μg/ml – 24h) induced PGE2 release in iMACs treated with 2 and 5μg/ml IGF-1R blocking antibody compared to control cells (respectively a 1.3 and a 1.9 fold, $p<0.05$ – visfatin treated cells released 110±16 pg/ml PGE2, n= 3). (2) IR was expressed in cultured human chondrocytes from healthy (n=3) and OA patients (n=7) and in iMACs (n=3). (3) Insulin (100nM - 24h) did not trigger PGE2 release in iMACs (control: 118±68 pg/ml and insulin-stimulated cells: 130±79 pg/ml, n=3, NS). (4) Dose-responses of insulin from 0 to 1μM was performed in term of phosphorylation of IR and Akt. Moreover, insulin (100nM) from 0 to 60min triggered IR and Akt phosphorylation. (5) Blocking IR activity using HNMPA-(AM)3 (100nM-24h pre-treatment) inhibited visfatin (5μg/ml-24 h) induced PGE2 release (54% decrease, n=3, $p<0.05$). Moreover, blocking IR expression by siRNA inhibited visfatin-induced PGE2 release (5μg/ml visfatin: 3576±265 pg/ml versus visfatin + IR siRNA1: 1864±515 pg/ml and visfatin + IR siRNA2: 930±216 pg/ml corresponding to a 48% and 74% decrease respectively, n=2, $p<0.05$). (6) Inhibition of the NAMPT activity of visfatin using APO866 from 0 to 1μM gradually induced a decrease in PGE2 release up to 32% (visfatin treated cells released 95±30 pg/ml PGE2, n=3, $p<0.05$).

Conclusions: In chondrocytes, visfatin exerts pro-inflammatory events by both activation of its cognate receptor and Nampt activity.

Disclosure: M. Gosset: None; **F. Berenbaum:** None; **C. Salvat:** None; **A. Sautet:** None; **M. Holzenberger:** None; **C. Jacques:** None.

1515

Comparison of IL-17F and IL-17A Effects and Signaling in Human Rheumatoid Arthritis Synoviocytes. Arnaud Hot, Saloua Zrioual, Anne Tournadre, Vanina Lenief and Pierre Miossec. Immunogenomics and Inflammation Research Unit and Department of Immunology and Rheumatology, Hospital Edouard Herriot, Lyon, France

Objective: IL-17A is implicated in rheumatoid arthritis (RA) pathogenesis; however the contribution of IL-17F remains to be clarified. Using microarrays and gene specific expression assays, we compared the effects IL-17A versus IL-17F on gene expression and signaling in human RA synoviocytes.

Methods: IL-17A and IL-17F expression was studied in OA and RA synovium by immuno-histochemistry. The comparison between IL-17A and IL-17F stimulatory effect on RA synoviocytes was assessed at the protein level by ELISA and at the mRNA level by microarrays (Affimetrix U133 +2) and real-time RT-PCR. IL-17RA and IL-17RC inhibition was achieved by small interfering RNA (siRNA). Western blotting, qRT-PCR, and DNA binding assay were used to evaluate mitogen-activated protein kinase (MAPK), activator protein 1 (AP-1) and nuclear factor kappa B (NF-κB) expression and activation. TNFRII expression was studied by real-time RT-PCR and immunofluorescence, and neutralizing antibody was used to analyse its contribution to CCL20 secretion.

Results: IL-17A and IL-17F were detected in plasma cell like cells in RA but not OA synovium. In microarrays, IL-17A and IL-17F alone had very similar but not identical regulatory effects, IL-17F being less active. Indeed, IL-17A was more potent to induce IL-6 or IL-8 secretion than IL-17F, which was inactive alone. Both cytokines induced a rather similar expression pattern in the presence of TNF-α. Based on a cooperation index, 130 and 203 genes were synergistically induced by IL-17A or IL-17F plus TNF-α, respectively. Among these, the new target genes CXCR4, LPL and IL-32 were validated by real-time RT-PCR. Virtually all IL17A and IL-17F inducible genes were dependent on NF-κB activation, whereas a minor number was modulated by p38. IL-17A induced activation of all three MAPK (ERK, p38 and JNK) and downstream transcription factors AP-1 and p65 NF-κB. IL-17F was less potent but induced activation of p50 NF-κB. IL-17A and less IL-17F induced TRAF 6 but not MyD88. Inhibition of either IL-17RA or IL-17RC expression via siRNA led to near complete abrogation of IL-6 expression mediated by IL-17A and the combination of IL-17F and TNF-α. IL-17A and IL-17F upregulated TNFRII expression, but had no effects on TNFRI, IL17RA or IL17RC. TNFRII blockade inhibited the synergistic induction of CCL20 by IL-17A or IL-17F and TNFα.

Conclusion: IL-17A and IL-17F are both expressed in RA synovium. In the presence of TNFα, they induced very similar but not identical pattern expression pattern in RA synoviocytes. The enhanced expression of TNFRII contributes to the synergistic effect of IL-17A and F with TNF-α. Targeting IL-17F could be a promising treatment of RA.

Disclosure: A. Hot: None; **S. Zrioual:** None; **A. Tournadre:** None; **V. Lenief:** None; **P. Miossec:** None.

1516

Down-Regulation of Pyrin Promotes Up-Regulation of the Anti-Apoptotic Gene, *BCL2*, Via the Signal Transducer, gp130, and Leads to the Activation of the PI3K/Akt Pathway. Geryl M. Wood[4], James Balow, Jr[3], Hong-Wei Sun[2], Ivona Aksentijevich[3], Jae Jin-Chae[3], Nitza Shoham[1] and Daniel L. Kastner[3]. [1]Allergy Immunology Laboratory, Meir Hospital, Kfar-Saba, Israel, [2]Biodata Mining and Discovery, Office of Science and Technology, National Institutes of Health, NIAMS, [3]Laboratory of Clinical Investigation, National Institutes of Health, NIAMS, [4]Laboratory of Clinical Investigation, National Institutes of Health, NIAMS, Bethesda, MD

Purpose: Familial Mediterranean fever (FMF) is a periodic fever syndrome characterized by episodes of self-limited fever and localized inflammation. The gene causing FMF, *MEFV*, encodes a protein, pyrin, which is expressed in myeloid cells and in the myeloid leukemia cell line, THP.1. Identification of several pyrin-interacting proteins has led to the conclusion that pyrin participates in at least three cellular pathways that are connected to inflammation: cell death, cytokine secretion and cytoskeletal signaling.

Methods: RNA interference (RNAi) technique was employed to compare gene expression profiles between the human myeloid leukemia cell line, THP.1, expressing endogenous pyrin (scrambled control, SC) and cells in which the gene had been knocked down (si*MEFV*). Affymetrix cDNA microarray analysis was used to identify potential novel pyrin-dependent pathways. Western blot and qRT-PCR analysis was used for validation. Flow cytometry and kinase inhibition assays were used to study functionality and mechanism.

Results: Among our differentially expressed genes, we identified two up regulated genes involved in cell survival, *BCL2* and *gp130*. Consistent with these findings, pyrin truncated mice show impaired macrophage apoptosis after IL4/LPS stimulation, independent of IL1b. Western blot and qRT-PCR analyses using independent samples, confirmed the THP.1 microarray data. Western blots comparing BCL2 expression in PBMCs from healthy controls and FMF patients revealed a significantly higher level of BCL2 in FMF patients than controls. These data were in agreement with the Bcl2 expression found in CD11b+ cells from knock-in mice expressing human mutations. The influence of pyrin knockdown on apoptosis was explored. Inducing apoptosis after staurosporine stimulation showed 1.8-fold less apoptosis in si*MEFV* cells compared to SC. To examine the involvement of *gp130* in siMEFV up-regulation of BCL2, we co-transfected siRNA for *gp130* and *MEFV*. We demonstrate reduction in BCL2 after the addition of siRNA for *gp130* compared to si*MEFV* alone. Since the PI3K/Akt survival pathway is activated thru gp130 signaling, we investigated this pathway as a possible mechanism of action. Western blot detection showed no difference in expression of PI3K phosphorylation between SC and siMEFV, in contrast to Akt, which revealed increased levels of phosphorylation in siMEFV treated cells compared to SC. Also, the PI3k/Akt inhibitor LY294002 was able to reduce BCL2 up-regulation by siMEFV with further reduction evident when Akt IV, a specific Akt inhibitor was employed.

Conclusion: These data support the hypothesis that knocking down pyrin in myeloid cells inhibits apoptosis in part via the gp130 receptor, which activates the PI3k/Akt pathway and leads to an increase in *BCL2* expression. It suggests that in some cases, the human mutations may function like the knockdown system.

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1517

Effect of the PEG Component of Certolizumab Pegol on Calcium Flux in Cellular Systems. Gianluca Fossati[2] and Andrew Nesbitt[1]. [1]New Medicines, UCB, Slough, Berkshire, United Kingdom, [2]New Medicines, UCB, Slough, UK

Background: Certolizumab pegol (the only PEGylated Fab′ anti-TNF [CZP]) has a very low incidence of injection site pain (ISP) in all clinical studies. It has been hypothesized that this could be due to inhibition of mast cell degranulation by the PEG component of CZP.[1] Mast cells (from human peripheral blood monocytes) could be involved in mediating ISP as they are present at high numbers in the skin and can rapidly secrete many inflammatory mediators in preformed granules. Changes in Ca^{2+} flux from intracellular stores or by influx from outside the cell are primary indicators of cell activation and when mast cells degranulate, this is preceded by a calcium flux into the cell. PEG has been shown to bind metal ions (in particular calcium ions)[2] and, therefore, the aim of this study was to determine if PEG could inhibit calcium flux in a cellular system.

Methods: Peripheral blood monocytes, positively isolated using MACS beads, were incubated for 30 min with the fluorophore Fluo-4 which changes its fluorescence emission when it chelates calcium. Calcium flux was measured using flow cytometry by detecting the Fluo-4 emission at 515–535 nm. Ionomycin was added at 2 μg/mL and the emission measured over a 4-min period relative to background, which was assessed for 1 min prior to ionomycin addition. The effect of a range of concentrations of the 40 kDa PEG component of CZP on calcium flux induced by ionomycin was assessed. In addition, the effect of PEG on an ionomycin-induced calcium flux in cultured mast cells was determined by a similar method except that the flux was measured using a fluorimeter.

Results: Ionomycin caused a dramatic flux of calcium in the monocytes. PEG caused a dose-dependent inhibition of calcium flux in these cells over a range of concentrations from a minimum of 40 mg/mL. This is a physiological concentration of PEG as the equivalent local concentration of PEG which is injected into patients is 88.9 mg/mL. The IC_{50} for inhibition of the calcium flux caused by PEG was around 10 mg/mL. The maximum inhibition observed was 84.2% obtained at 40 mg/mL, with the effect titrating out around 1 mg/mL. In mast cells the IC_{50} was around 11 mg/mL.

Conclusion: The PEG component of CZP inhibits calcium flux in monocytes and mast cells at a concentration relevant at the site of injection. This inhibition of calcium flux could, therefore, explain the low levels of ISP observed with CZP in the clinic. This effect would only be observed at the site of injection as systemic concentrations of the drug are below the levels where an effect is seen.

References:

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Disclosure: G. Fossati: UCB, Inc., 3; **A. Nesbitt:** UCB, Inc., 1, 3.

1518

Expression of the Wnt Inhibitor sFRP-1 in Synovial Fibroblasts Is Regulated by the Histone Methyltransferase EZH2. Michelle Trenkmann[1], Matthias Brock[3], Renate E. Gay[2], Christoph Kolling[5], Rudolf Speich[4], Beat A. Michel[2], Steffen Gay[2] and Lars C. Huber[3]. [1]Center of Experimental Rheumatology, University Hospital Zurich/Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland, [2]Center of Experimental Rheumatology, University Hospital Zurich/Zurich Center of Integrative Human Physiology (ZIHP), Switzerland, [3]Center of Experimental Rheumatology, University Hospital Zurich/Zurich Center of Integrative Human Physiology (ZIHP), Switzerland/Department of Internal Medicine, University Hospital, Zurich, Switzerland, [4]Department of Internal Medicine, University Hospital Zurich, Switzerland, [5]Schulthess Clinic, Zurich, Switzerland

Background: Methylation of histone 3 lysine 27 (H3K27) by the histone methyltransferase EZH2 is associated with silencing of affected gene promoters. We have previously reported that EZH2 expression is increased in rheumatoid arthritis synovial fibroblasts (RASF) compared to osteoarthritis (OA) SF and further induced by TNF-α. Here we identified secreted frizzled-related protein (sFRP)-1, an inhibitor of the Wnt signalling pathway, as a specific target gene of EZH2 in SF.

Methods: RASF (n=5) were transfected with a vector containing the EZH2 coding sequence or an siRNA targeting EZH2. After 72h and 96h, cells were analyzed for SFRP1 expression at mRNA (by quantitative real-time PCR) and protein levels (by ELISA). Constitutive and TNF-α stimulated expression of SFRP1 was measured in OASF and RASF for both mRNA and protein. To investigate the level of histone methylation within the *SFRP1* gene promoter in RASF (n=10) and OASF (n=7), chromatin immunoprecipitation (ChIP) was performed by using antibodies specific for H3, H3K4me3 and H3K27me3.

Results: Overexpression of EZH2 in RASF resulted in a reduction of SFRP1 mRNA (15±17%, p=0.086 after 72h; 18±9%, p<0.05 after 96h, respectively). Secretion of sFRP-1 protein decreased from 689±216 pg/ml to 507±56 pg/ml (p=0.11) after 72h and from 1095±101 pg/ml to 836±150 pg/ml (p<0.05) after 96h. Conversely, silencing of EZH2 in RASF led to an increase of SFRP1 mRNA level by 15±12% (p<0.05) after 72h and of 15±35% (p=0.38) after 96h.

The constitutive expression of SFRP1 mRNA was strongly reduced in RASF by 86% as compared to OASF (delta Ct RASF: 7.1±2 (n=15), OASF: 4.5±1.7 (n=12), p<0.005). These findings could be confirmed on the protein

level by ELISA (566±354 pg/ml for RASF, 1285±845 pg/ml for OASF, $p<0.01$) and Western blot (n=10 and 7). Stimulation with TNF-α significantly reduced SFRP1 mRNA after 24h and 48h in RASF (by 56±13% and 85±6%, $p\leq0.0001$, n=6) and OASF (by 48±14% and 82±7%, $p\leq0.0001$, n=7). ChIP analysis revealed that the promoter of SFRP1 is trimethylated at H3K27 in SF (H3K27me3/H3 ratio RASF: 0.45±0.36, OASF: 0.22±0.08, p=0.12). Conversely, the H3K4me3/H3 ratio, which is a mark of active gene transcription, was reduced in RASF (0.31±0.27) compared to OASF (0.66±0.32, $p<0.05$). The mRNA expression of SFRP1 correlated positively with occupation of the activating H3K4me3 ($R^2=0.71$, $p<0.0001$) and negatively with occupation of the repressing H3K27me3 mark ($R^2=0.4$, $p<0.01$) in its promoter.

Conclusion: Our data strongly indicate that EZH2 regulates the expression of the Wnt inhibitor sFRP-1 in SF. We show that the levels of sFRP-1 are constitutively decreased in RASF and further reduced by stimulation with TNF-α. Wnt signalling has been shown to be activated in RASF and to contribute to the invasive and aggressive behaviour of these cells. We provide here the first evidence that this aberrant Wnt activation appears to be, at least in part, due to an epigenetic dysregulation of its inhibitor sFRP-1.

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1519

Fms-Like Tyrosine Kinase 3 Ligand (Flt3L) Levels Are Elevated in Arthritis: Role of Flt3L in Regulating Monocyte Migratory Pattern in RA. Inês Ramos[2], Ana Oliveira[3], Geurt Schilders[3], Saïda Aarrass[3], Cristina Lebre[3] and Paul P. Tak[1]. [1]Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, [2]Division of Clinical Immunology and Rheumatology, Academic Medical Center/University of Amsterdam, Amsterdam, The Netherlands, [3]Division of Clinical Immunology and Rheumatology, Academic Medical Center/University of Amsterdam, Amsterdam, The Netherlands

Background: Fms-like tyrosine kinase 3 ligand (Flt3L) is a potent endogenous growth factor for myeloid (m)DC and plasmacytoid (p)DC. Its administration to mice and humans leads to dramatic increases of various DC subsets while Flt3L−/− mice show reduced DC numbers. Flt3L and its receptor have been poorly studied in the setting of autoimmune diseases in general and in experimental arthritis in particular. Since in rheumatoid arthritis (RA), circulating blood DC subsets numbers are reduced and enriched in synovial fluid (SF) and synovial tissue (ST), we investigated whether Flt3L can contribute to local accumulation of DC in these compartments by inducing migration of cells from the peripheral blood (PB).

Methods: Patients with active RA, psoriatic arthritis (PsA), other forms of spondyloarthritis (SpA), osteoarthritis (OA), gout and healthy donors (HD) were included in this study. Soluble (s)Flt3L levels in SF and serum were determined using a commercially available ELISA. Expression of membrane-bound (m)Flt3L, Flt3L receptor (CD135) and chemokine receptors in PB mononuclear cells (PBMC) and SFMC were assessed by FACS. Immunohistochemical analysis was performed to detect Flt3L and CD135 RA synovial tissue. Monocytes from HD were isolated and cultured for 24h with recombinant Flt3L and chemokine receptor expression was assessed by FACS.

Results: The levels of Flt3L in RA, PsA, and SpA, OA and gout SF were significantly higher compared to paired serum. In addition, Flt3L levels were significantly higher in RA, PsA and SpA SFs compared to gout SF. In PB monocytes, B cells and mDC the expression of mFlt3L in RA was higher compared to HD. Flt3L receptor expression was confined to monocytes and mDC and higher in RA SF compared to PB. Immunohistochemistry and immunofluorescence data showed the presence of Flt3L and Flt3L receptor in RA ST. Interestingly, Flt3L increased the expression of the chemokine receptors CCR1, CCR2 and CCR5 by monocytes in vitro.

Conclusion: The increased levels of Flt3L in RA SF could contribute to the specific accumulation of DC in the synovial compartment compared to PB in inflammatory joint disease. Flt3L-induced expression of CCR1, CCR2 and CCR5 by monocytes might be important for the increased recruitment of DCs as well as monocytes and lymphocytes into the inflamed compartment. Achieving a detailed understanding of Flt3L function(s) in RA may lead to the development of novel immunotherapies for immune-mediated inflammatory diseases.

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1520

Functional Expression of CD13/Aminopeptidase N by RA Synovial Cells In Vitro and In Vivo. Rachel Morgan, Judith Endres and David A. Fox. University of Michigan

Purpose: Aminopeptidase N (CD13, EC 3.4.11.2) is a metalloproteinase expressed on and secreted by myeloid cells and fibroblasts. Previously published data has documented increased CD13-related enzymatic activity in RA synovium compared to OA, and has proposed a role for CD13 as a T cell chemoattractant. The mechanisms whereby T cells become localized to the synovial lining and contribute to synovial inflammation and joint destruction remain incompletely understood. While CD13 has been identified on synovial fibroblasts (FLS), ELISA assay of CD13 in synovial fluid, serum or culture supernantants has not yet been reported. The purpose of this study was to critically examine CD13 expression and function in RA synovium.

Method: Novel monoclonal antibodies (mAb) were developed from splenocytes of mice immunized with an RA FLS line that had been treated with IL-17. Hybridoma supernatants were screened by flow cytometry to detect cell surface structures upregulated by IL-17 but not TNF. This approach yielded one mAb, termed 591.1D7.34, which was used to immunoaffinity purify a protein that was identified as CD13 by amino acid sequencing. 1D7 and another anti-CD13 mAb, WM15, were then used to create a sandwich ELISA for CD13. CD13 enzymatic activity was measured in parallel by cleavage of L-Leucine 7-amido-4-methyl coumarin hydrochloride (L-leu-AMC) to release the fluorescent molecule AMC.

Results: We detected substantial amounts of CD13 in synovial fluids and synovial fibroblast cell lysates, sera and culture supernatants by ELISA, with a significant ($p<0.0001$) increase in CD13 in RA synovial fluids (1191±121.6 ng/ml) when compared to OA (646.1±45.64 ng/ml). Similar to previously published data we also found a significant difference in CD13-type enzymatic activity between RA and OA synovial fluids (3402±239.6 nmoles of substrate cleaved per hour per ml of synovial fluid versus 2250±93.18 nM/hr, $p<0.0001$). This activity was depleted by 1D7 immunoprecipitation. Recombinant CD13 was chemotactic for T cells.

Conclusion: CD13 is released by synovial fibroblasts into the synovial fluid and its expression is upregulated on FLS by IL-17. These findings suggest a mechanism by which IL-17 may enhance synovial inflammation in RA independent of TNFα. We have shown that the CD13 protein is present in significant amounts and accounts for most of the L-leu-AMC cleavage activity in synovial fluids. These data support the concept of CD13 as a multifunctional pro-inflammatory mediator that can serve as a T cell chemoattractant in the RA joint.

Disclosure: R. Morgan: None; **J. Endres:** None; **D. A. Fox:** None.

1521

Gottron's Papules Exhibit Accumulation of CD44 Variant 7 (CD44v7) and Its Binding Partner Osteopontin: A Unique Molecular Signature. Jessica Kim[1] and Victoria P. Werth[2]. [1]New York University School of Medicine, [2]University of Pennsylvania, Philadelphia, PA

We previously reported an abundance of chondroitin sulfate (CS) in dermis from dermatomyositis (DM) lesions (SID 2008). Because the CD44v7 variant has CS side-chains (Invest Ophthmol Vis Sci 48:1164, 2007) and can mediate autoimmunity in the gut (J Immunol 161:1069, 1998), we examined its distribution in CS-rich regions of DM skin. Surprisingly, CD44v7 was abundant in Gottron's papules, a hallmark lesion of DM overlying interphalangeal (IP) joints, but not in lesional or non-lesional dermis in other regions. Staining density of CD44v7 in Gottron's dermis was double that of healthy IP dermis ($p<0.0001$). Moreover, healthy IP dermis showed far more CD44v7 than did healthy non-IP dermis from the same volunteer, indicating location-specific induction, independent of DM. We hypothesized a role for mechanical stretching, because it induces CD44v7/v8 in non-dermal cells (Invest Ophthmol Vis Sci 48:1164, 2007). We found that confluent dermal fibroblasts cultured on membranes and stretched constantly for 6 hours showed a 62%±3% increase in CD44v7 mRNA levels relative to unstretched cells ($p<0.0001$). Interaction of CD44v7 with the cytokine-like molecule osteopontin has been implicated in chronic inflammation (JCI 107:1055, 2001). Here, we found 2.8-fold increased density of osteopontin staining in the dermal matrix of all DM skin compared to healthy controls ($p<0.05$), with no significant difference between Gottron's vs. non-Gottron's skin. IFN-γ stimulates osteopontin expression by monocytoid cells, and IFN-γ polymorphisms associate with myositis. Treatment of dermal fibroblasts with IFN-γ for 6 hours provoked a ~10-fold increase in OPN mRNA ($p<0.0001$).

Lastly, adhesion studies show that stretching of dermal fibroblast monolayers overnight in the presence of exogenous recombinant osteopontin results in a 2.3-fold increase in the binding of THP-1 human monocytes ($p<0.0001$). Overall, we propose that stretch-induced expression of CD44v7 over joints, in concert with IFNγ-induction of osteopontin, provides a unique molecular signature of Gottron's papules in DM and may contribute to their pathogenesis.

Disclosure: J. Kim: None; **V. P. Werth:** None.

1522

Identification of the NR4A Family of Orphan Nuclear Receptors as Mediators of Adenosine A2A Receptor Activation. Jason P. McMorrow[2], Evelyn P. Murphy[2] and Bruce N. Cronstein[1]. [1]New York Univ Med Ctr, New York, NY, [2]University College Dublin, Dublin, Ireland

Background: The effects of adenosine signalling on the regulation of inflammation suggest that targeting adenosine receptor activation/inactivation could have important therapeutic implications in wound healing and inflammatory disease. In recent studies we report that adenosine, acting at A2A receptors, plays an important role in bleomycin-induced dermal fibrosis, a model for scleroderma. Activation of A2A receptors on cultured human dermal fibroblasts directly stimulates collagen production. What remains to be elucidated are the cell-specific signal transduction events and the transcriptional mediators that act to promote adenosine receptor-mediated responses during these processes.

Aim: To establish cell-specific effects of a selective A2A receptor agonist, CGS-21680, on the expression of the NR4A family of transcription factors in the presence of signaling inhibitors and inflammatory stimuli.

Methods: THP-1 monocyte cells were differentiated to macrphages by stimulation with PMA (10 ng/mL) for 48 h. Normal human dermal fibroblasts (NHDF) and macrophage cells were treated for 1 hour with medium or the selective adenosine A2A receptor agonist, CGS-21680 (10-8-10-6 M), in the presence or absence of the A2A receptor antagonist, ZM241385 (10-6 M). In some experiments NHDF were pre-treated with the MEK inhibitor, U-0126 or the p38 inhibitor, SB202190 for 1 hour before treatment with CGS-21680. Protein and total RNA was harvested and NR4A levels measured by western analysis and real-time PCR.

Results: Treatment of human macrophage-derived THP-1 cells and dermal fibroblast NHDF cells with increasing concentrations of CGS-21680 robustly induces the expression of all three NR4A family members (NR4A1, 2 and 3) in a time dependent manner. The temporal effects of CGS-21680 on NR4A transcription are abolished in cells pre-treated with the A2A antagonist ZM-241385 (1 μM) and blocked by protein inhibitors directed against PKA and MEK1/2. In THP-1 cells, co-treatment with CGS-21680 and LPS or IL-4 resulted in significantly ($p<0.005$) enhanced NR4A1, 2 and 3 transcription. In contrast, minimal effects on NR4A expression are measured in cells co-treated with TNF-α or IL-1. Furthermore, in LPS- and IFN-γ-treated NHDF cells, CGS-21680 effects on NR4A1, 2 and 3 expression is significantly reduced while, in cells co-treated with TGF-β, levels remain unchanged.

Conclusion: This study identifies the NR4A family as novel transcriptional mediators downstream to adenosine A2A receptor activation. In addition, these data reveal that cytokine-specific effects on A2A receptor mediating signaling are cell-type dependent.

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1523

Increased Expression of Acid Sensing Ion Channel (ASIC) Mediated by ERK/MAPK Pathway in Mouse Anti-Type II Collagen Antibody-Induced Arthritis. Juyoun Kim[2], Keon Uk Park[2], Jinyeong Chae[3], Hyun-OK Kim[1] and Sang-Hyon Kim[2]. [1]Department of Rheumatology, College of Medicine and Institute of Health Science, Jinju, Korea, Republic of, [2]Keimyung University Dongsan Medical Center, Daegu, Kungsang Province, Korea, Republic of, [3]Keimyung University Dongsan Medical Center, Daegu, Kungsang, Korea, Republic of

Introduction: The collagen-induced knee joint inflammation (CIA) model produces sensitization of nociceptors innervating the knee joint, a substrate for primary hyperalgia; and sensitization of neurons in the dorsal horn, a substrate for secondary hyperalgia. Different acid-sensing ion channel (ASIC) isoforms have been identified and critical for development of secondary hyperalgesia in peripheral sensory neurons innervating skin and muscle. This study was aimed to investigate the ASIC expression in mouse anti-type II collagen antibody-induced arthritis (CIA) and its association with ERK expression.

Methods: Mice were divided into 2 groups; control, CIA. Histological and X-ray assessment of arthritis were done. Measurement of type II collagen specific antibodies, TNFα, IL-17, and IL-6 were done. Both mRNA and protein levels of ASIC1, ASIC2, and ASIC3 were evaluated. We examined ERK/MAPK expression and its activation in the knee joint with or without CIA.

Results: Histological and X-ray assessment revealed increased infiltration of inflammatory cells, synovial hyperplasia, and the destruction of the articular cartilage and bone in CIA group. ASIC1, ASIC2, and ASIC3 were markedly increased compared with those in control. The concentrations of anti-type II collagen antibody in CIA were significantly higher than those in control ($P<0.05$). Serum concentrations of TNF-α ($P<0.005$) and IL-6 ($P<0.05$) in CIA group were also increased. ERK pathway activation was noted by increased p-ERK expression.

Conclusion: Taken together, these results implicate that increased ASIC involved in the joint pain in mice anti-type II collagen antibody-induced arthritis. Activation of ERK pathway could be related to ASIC expression in arthritis.

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1524

Increased Levels of Soluble Programmed Death 1 (sPD-1) and Its Soluble Ligand (sPD-L1) in Early Rheumatoid Arthritis Are Associated with Disease Activity and Progression. Stinne R. Greisen[4], Tue K. Rasmussen[5], Kristian Stengaard-Pedersen[1], Merete L. Hetland[2], Kim Hørslev-Petersen[6], Malene Hvid[4] and Bent Deleuran[3]. [1]Arhus University Hospital, Aarhus, Denmark, [2]Copenhagen Univ Hosp Hvidovre, Hvidovre, Denmark, [3]Institute of Medical Microbiology and Immunology, University of Aarhus and 2Department of Rheumatology Aarhus University Hospital, 8000 Aarhus C, Denmark, [4]Institute of Medical Microbiology and Immunology, University of Aarhus, 8000 Aarhus C, Denmark, [5]Institute of Medical Microbiology and Immunology, University of Aarhus, 8000 Aarhus C, Denmark and Department of Dermato-Venerology, Aarhus University Hospital, 8000 Aarhus C, Denmark, [6]King Christian X Hospital for Rheumatic Disease, University of Southern Denmark, Graasten, Denmark

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease. Disturbance of the balance between immune modulatory and inflammatory factors results in joint inflammation progressing to destruction. The regulatory molecules Programmed Death 1 (PD-1) mainly expressed on activated T cells and its ligand (PD-L1), expressed by antigen presenting cells, are believed to negatively regulate T cell induced activation. They are both recently reported present in a soluble form, sPD-1 and sPD-L1.

Objective: To investigate the presence of sPD-1 and sPD-L1 in early RA patients and their correlation with core parameters for disease activity, radiographic progression as well as to the follicular CD4 T cells (TFH) cytokine IL-21 and dendritic cell associated cytokine IL-23.

Methods: In a longitudinal sample set of early RA patients ($n=40$, <6 months' disease) we measured plasma levels of sPD-L1 and sPD-1 by ELISA (R&D systems), at baseline (0 month) and after 9 months of treatment with methotrexate, and investigated for correlations with disease activity in 28 joints (DAS28), C-reactive protein (CRP), and total Sharp score (TSS). To remove heterophillic antibodies, heat aggregated goat IgG (25ug/ml) was added to buffers. Statistical correlations were assessed by Spearman's rho, and data are expressed as median with IQR in parenthesis. In a transverse sample set ($n=30$) of chronic RA patients (>8 years of disease) we measured sPD-1 and sPD-L1 in plasma.

Results: In patients with early RA, plasma levels of sPD-L1 and sPD-1 were both significantly higher at 0 months than after 9 months of treatment. Treatment reduced sPD-L1 from 29.9 ng/ml (10.5–85.3) to 16.8 ng/ml (4.8–35.2), $p<0.001$and sPD-1 from 421 pg/ml (40.0–2560.0) to 40.0 pg/ml (40.0–840.0), $p<0.05$. In chronic RA patients levels of sPD-1, but not sPD-L1 tended to be lower than in early RA patients. In early RA, the change in sPD-1 was associated with DAS28 at 9 months ($r2=0.401$, $p=0.021$), and TSS at 2 years ($r2=-0.468$, $p=0.02$). No association to CRP was observed. Plasma levels of sPD-1 as well as sPD-L1 at 0 months strongly correlated

with IgM-RF (PD-1: (r2=0.737, p<0.0001) and PD-L1: (r2=0.417, p=0.016)). PD-1 at 0 months additionally correlated with anti-CCP antibodies (r2=0.515, p=0.002). Interestingly, plasma levels of both IL-21 and IL-23 at 0 months correlated with plasma levels of sPD-1 and sPD-L1 at 0 months in early RA (all p<0.05).

Conclusion: The significantly elevated plasma levels of both sPD-1 and sPD-L1 in early RA patients, point to strong activation of antigen presenting cells and T cells in the initial phases of the disease. The fact that we observed association to core disease parameters as well as IgM-RF, anti-CCP antibodies and IL-21 and IL-23, further supports PD-1 pathways involvement in this central mechanism in RA. We believe that decrease in sPD-1 together with the unchanged presence of sPD-L1 in chronic patients compared with early RA supports a shift from T cells to antigen presenting cells as the predominant cell types, involved in perpetuating the inflammation in RA.

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1525

Lack of IL-17RA Signaling Prevents Autoimmune Inflammation of the Joint and Give Rise to a Th2-Like Phenotype in Collagen-Induced Arthritis. Anne-Marie Mus, Odilia Corneth, Patrick Asmawidjaja and Erik Lubberts, Erasmus MC. University Medical Center

Introduction: IL-17A plays an important role in collagen-induced arthritis (CIA). On the other hand, CIA developed normally in IL-17F deficient mice. This could be due to IL-17A that is still expressed in these mice. It has been shown that around 20% of the IL-17A deficient mice still develop marked collagen-induced arthritis with a somewhat lower severity that the control littermates. Spontaneous arthritis development in the IL-1Ra deficient mice could not be completely prevented in double IL-17A/IL-17F deficient mice. However, it is still not fully clear how important the role of the IL-17A and IL-17F signaling is in the development of autoimmune collagen-induced arthritis.

Objective: To examine the role of the IL-17RA signaling in the development of CIA.

Methods: Since the IL-17RA deficient (IL-17RA−/−) mice can not signal for IL-17A and IL-17F these mice were used in this study and were compared to control mice and the CIA resistant IL-23p19 deficient (IL-23p19−/−) mice. All mice were immunized intra-dermally with chicken type II collagen (CII) in CFA at days 0 and 21. The arthritis incidence and severity were scored macroscopically. In a set of experiments, mice were given a third CII/CFA injection at day 50. At days 20, 34, and 69 sera was collected for CII-specific IgG's measurements by ELISA. In addititon, at days 10 and 69, splenic $CD4^+$ T cells were isolated and intracellular flow cytometry of different cytokines was performed.

Results: CII-immunized control mice developed CIA from day 24 onwards with an incidence between 40–60%. As expected, the IL-23p19−/− mice did not develop CIA. Interestingly, the IL-17RA−/− mice were completely protected and did not develop CIA even after a third CII/CFA injection. In contrast to the low percentage of IL-17^+ $CD4^+$ T cells in the IL-23p19−/− mice, there was a significant increase in the percentage of these cells in the IL-17RA−/− group compared to the control group at day 69. No significant difference was found in the percentage of IFN-gamma$^+$ $CD4^+$ T cells between all three groups. Interestingly and in contrast to the IL-23p19 knockout mice, the IL-17RA deficient showed a Th2-like phenotype in splenic $CD4^+$ T cells at day 69. No difference was noted for FoxP3 expression in the splenic $CD4^+$ T cells between the three different mouse groups. Moreover, the CII-specific IgG2a levels in the sera of IL-17RA−/− was significantly lower compared to the control group at day 20 and lower although not statistically significant at day 69. At this latter time point, CII-specific IgG1 levels in the sera of IL-17RA−/− was increased although not statistically significant compared to the control.

Discussion: These data revealed a critical role for the IL-17RA signaling in the development of autoimmune inflammation of the joint. Moreover, these data show a Th2-like phenotype in IL-17RA−/− mice immunized with CII, suggesting that IL-17 receptor signaling is involved in the suppression of Th2 cytokines in autoimmune collagen arthritis.

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1526

Lower Expression of Fli-1 Leads to Decreased Inflammatory Cell Infiltration in the Kidneys from NZM2410 Mice. Sarah Williams[4], Emmanuel Reyes-Cortes[2], Eva Karam[3], Eiji Suzuki[3], Gary S. Gilkeson[1] and John Zhang[5]. [1]Med Univ of South Carolina, Charleston, SC, [2]Medical University of South Carolina, Charleston, SC, [3]Medical University of South Carolina, [4]Ralph H. Johnson VA Medical Center, Charleston, SC, [5]Ralph H. Johnson VA Medical Center and Medical University of South Carolina, Charleston, SC

Background and Purpose: Fli-1 expression levels, a member of the Ets family of transcription factors, are a mitigating factor in the development of nephritis in murine models of systemic lupus erythematosus (SLE). Lupus nephritis is a major cause of death in both models and human patients, and is characterized by immune complex formation and inflammatory cell infiltration. Overexpression of the Fli-1 protein in transgenic mice resulted in the development of a lupus-like disease with nephritis. Expression of Fli-1 in SLE patients and animal models of lupus is higher compared to normal controls. In this study, we examined the effects of reduced Fli-1 expression on inflammatory cell infiltration in conjunction with nephritis development in NZM2410 mice, an animal model of SLE.

Methods: We generated Fli-1 heterozygous knockout NZM2410 mice ($Fli1^{+/-}$; **Fli-1** homozygous knockout is embryonic lethal) and wild-type (WT) littermate ($Fli1^{+/+}$) mice for use as controls. The expression levels of monocyte chemotactic protein-1 (MCP-1) and Chemokine (C-C motif) ligand 5 (CCL5, also known as RANTES) in the kidneys from 18-week-old mice were analyzed by real-time PCR. Pathological scores of the kidneys from 34-week-old mice were assessed and the number of macrophages, neutrophils, T cells and B cells in the kidneys were stained with specific antibodies and counted in 10 random high power fields (HPF). These numbers were averaged and directly compared between WT and $Fli-1^{+/-}$ NZM2410 mice. The MCP-1 in serum was measured by ELISA.

Results: Since expression of CCL5 and MCP-1 were demonstrated to initiate inflammatory cell infiltration in the kidneys of lupus mice, we first examined the expression of MCP-1 and CCL5 in the kidneys from both $Fli-1^{+/-}$ and WT controls. Expression of MCP-1 and CCL5 in the kidneys from 18-week old $Fli-1^{+/-}$ NZM2410 mice was significantly decreased compared to that from WT littermates. $Fli-1^{+/-}$ NZM2410 mice also had significantly reduced renal pathology scores compared to those from WT littermates (WT mice: 6.846 ± 0.9635; $Fli-1^{+/-}$ mice: 3.882 ± 1.043, $p<0.05$). The number of macrophages, neutrophil granulocytes, T cells and B cells in the kidneys from $Fli-1^{+/-}$ NZM2410 mice decreased by 44 – 75% compared to WT littermate controls. The serum MCP-1 levels in Fli-1+/− NZM2410 mice were significantly lower at the age of 34 weeks compared with WT littermates (WT mice: 118.9 ± 17.7 pg/ml; $Fli-1^{+/-}$ mice: 67.7 ± 7.1 pg/ml, $p< 0.01$).

Conclusion: Our data indicate that lower expression of Fli-1 results in decreased expression of CCL5 and MCP-1 in the kidneys with significantly reduced infiltration of inflammatory cells, which leads to lower overall kidney pathological scores in NZM2410 mice. Therefore, Fli-1 plays an important role in the development of nephritis in NZM2410 mice.

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1527

Mechanisms and Clinical Relevance of TRAIL-Triggered Responses in Synovial Fibroblasts of Rheumatoid Arthritis Patients. Rachel Audo[4], Flavia Calmon Hamaty[5], Dominique Baeten[1], Bernard G. Combe[2], Michael Hahne[4] and Jacques Morel[3]. [1]Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, [2]Department of Rheumatology. Teaching Hospital of Lapeyronie, Montpellier, France, [3]Department of Rheumatology. Teaching Hospital of Lapeyronie, Montpellier, France, [4]IGMM, UMR5535, CNRS, Montpellier, Montpellier, France, [5]IGMM, UMR5535, CNRS, Montpellier

Background: Studies in mice suggest a protective role for the TNF-related apoptosis-inducing ligand (TRAIL) in arthritis. We investigated the role of TRAIL in rheumatoid arthritis (RA) patients. We have shown that exposure to TRAIL induces apoptosis only in a portion of RA Fibroblast-Like Synoviocytes (FLS) and that in the surviving cells, TRAIL induced proliferation. In the present study, we compared FLS resistant and RAFLS-sensible to TRAIL-induced apoptosis including levels of the TRAIL receptors

(TRAIL-R) and clinical features of respective patient. Furthermore, we evaluated TRAIL levels in RA patients.

Method: FLS were extracted from synovial tissue of RA patients (n=30) and analyzed by FACS for expression of TRAIL-receptors. We obtained DAS28 within the 3 months of surgery for 13 patients. TRAIL-responses of FLS were analyzed by FACS for apoptosis and thymidine-incorporation for proliferation. TRAIL receptor activity was assessed by RNA silencing. HIC were performed to evaluate TRAIL level in synovial tissues from RA (n=7) and OA patients (n=4). ELISA was used to determine TRAIL-levels in synovial fluid of osteoarthritis (OA; n=20), spondylarthritis (SpA; n=20) and establish RA patients (n=30). Serum levels of TRAIL and its soluble decoy-receptor osteoprotegerin (OPG) were measured by ELISA in 72 patients fulfilling the ACR criteria (1987) with recent (<2 years) and active (>3 swollen joints) RA that were not treated or had a stable background treatment for at least 1 month (M0). 48 of the RA patients were followed up at 6 months (M6).

Results: Depending on the patient, we observed variability in RAFLS sensitivity to TRAIL-induced apoptosis. We therefore classified the cultures depending on their sensitivity (<10%; RAFLS-R, n=10 and >at 30%, RAFLS-S, n=11). Disease activity of RA patients inversely correlated with susceptibility of FLS to TRAIL-induced apoptosis (r=-0.688, p=0.0092, n=13). TRAIL-S cells expressed significantly lower levels of TRAIL-R1 (p=0.014) and silencing of TRAIL-R1 increased TRAIL-induced apoptosis in RA FLS (p<0.05; n=7). TRAIL levels were elevated in the arthritic joints of patients with established RA and synovial fluids displayed elevated TRAIL levels compare to those of OA and SpA patients (p<0.0001 and p=0,002 respectively). In early RA, patients in remission at M6 (DAS28<2.6) (n=14) had a lower ratio OPG/ TRAIL at baseline than patients without remission (n=34) (0.54 ± 0.25 and 0.94 ± 0.71 respectively, p=0.028), but high serum levels of TRAIL at M6 were associated with joint damages (p=0.0063).

Conclusion: Surprisingly, TRAIL-R1 seems to be a survival factor protecting RAFLS against TRAIL-induced apoptosis. Furthermore, we found a negative correlation between TRAIL sensitivity RAFLS in vitro and RA activity, suggesting that RAFLS develop resistance to TRAIL-induced apoptosis to escape TRAIL protective role. Indeed, in early RA patient, a low OPG/TRAIL ratio at baseline was associated with remission at 6 months but persistent TRAIL serum levels are associated with joint damage. These findings suggest a dual role for TRAIL in RA and resistance of RA FLS to TRAIL-induced apoptosis is associated with a disease promoting activity of TRAIL in RA.

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1528

Pro-Inflammatory Activity of SIRT1 in Monocytes. Fabienne Niederer[1], Caroline Ospelt[1], Fabia Brentano[1], Beat A. Michel[2], Christoph Kolling[4], Michael O. Hottiger[3], Renate E. Gay[2], Steffen Gay[2] and Diego Kyburz[2]. [1]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland, [2]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Switzerland, [3]Institute of Veterinary Biochemistry and Molecular Biology, University Zurich, Switzerland, [4]Schulthess Clinic, Zurich, Switzerland

Purpose: Sirtuins are a conserved family of NAD+ dependent histone deacetylases (HDAC) and mono-ADP-ribosyltransferases. The human sirtuins are critical regulators of many cellular processes, including cell survival and inflammation. Here we focused on the expression of SIRT1 in monocytes and tissues from patients with rheumatoid arthritis (RA) and osteoarthritis (OA) and assessed the function of SIRT1 in monocytes.

Methods: To study the expression of SIRT1 in RA and OA tissues, Western blot and immunohistochemistry were performed. Monocytes from peripheral blood were negatively isolated from healthy donors or RA patients using magnetic MicroBeads (MACS separation). Levels of SIRT1 mRNA were measured with SYBR green Real-time PCR. Healthy monocytes were stimulated (n=9) with the Toll-like receptor 4 (TLR4) ligand LPS (10 ng/ml) for 8 hours in the presence or absence of a SIRT1 inhibitor, EX-527 (9 uM). Moreover, freshly isolated monocytes (n=5) were transfected to overexpress a wild type or an enzymatically inactive mutant form of SIRT1 for 18 hours, following LPS-stimulation (10 ng/ml) for 8 hours. The levels of TNF-α protein were measured in the supernatants of stimulated monocytes by ELISA (BD Bioscience).

Results: Performing Western blot analysis of SIRT1 in RA and OA tissues, we found an upregulation of SIRT1 in whole RA tissues. Immunohistochemistry in synovial tissues showed the expression of SIRT1 in monocytes/macrophages. Consistently, levels of SIRT1 mRNA in monocytes from RA patients were expressed at dCt = 7.55 ± 0.31 and in healthy controls at dCt = 8.69 ± 0.72, p=0.12. Treatment of LPS-stimulated monocytes with the SIRT1 inhibitor EX-527 significantly reduced TNF-α production by 37 ± 17% (p<0.01). Monocytes transfected with a vector encoding an enzymatically inactive form of SIRT1 showed a prominent downregulation of TNF-α by 81 ± 21% (p=0.04) compared to wild type SIRT1 transfected cells.

Conclusion: SIRT1 is overexpressed in RA tissues and monocytes. The inhibition of SIRT1 activity significantly reduced the production of TNF-α in monocytes. Thus, SIRT1 appears to contribute to the characteristic inflammatory phenotype of synovial cells in rheumatoid arthritis.

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1529

Ras GTPase Homologues Make Redundant Contributions to RA FLS Activation and Broad Silencing of Ras Proteins Decreases Inflammation and Joint Destruction in Experimental Arthritis. Daphne de Launay[1], Jeroen Vreijling[1], Joana Abreu[1], Aleksander Grabiec[1], Marjolein van Maanen[2], Marjolein Sanders[2], Margriet Vervoordeldonk[2], Henrik Oerum[3], Kees Fluiter[1], Paul Peter Tak[1] and Kris Reedquist[1]. [1]Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [2]Academic Medical Center, University of Amsterdam, The Netherlands, [3]Santaris Pharma A/S, Horsholm, Denmark

Changes in expression and activation of Ras proteins are thought to contribute to the pathologic phenotype of stromal fibroblast-like synoviocytes (FLS) in rheumatoid arthritis (RA). Here we examined the expression of each Ras protein in the synovial tissue of RA patients and disease controls, and the contributions of H-, K-, and N-Ras homologues to FLS activation in vitro and experimental arthritis in vivo.

Methods: Synovial Ras homolog expression was determined by immunohistochemistry and digital image analysis in patients with RA (n = 10), inflammatory osteoarthritis (n = 4) and reactive arthritis (n = 7). In a second cohort consisting of patients with RA (n = 20) and psoriatic arthritis (PsA) (n = 19), Ras homolog expression was monitored by immunohistochemistry and mRNA expression. Ras protein and mRNA expression was examined in RA and PsA FLS. The activation status of Ras homolgues in RA FLS following stimulation with TNF and IL-1 was determined by affinity precipitation and immunoblotting. RA FLS were transfected with active mutants of H-, K-, and N-Ras, and Ras protein expression was specifically or broadly silenced using locked nucleic acids (LNA), and effects on basal and IL-1-dependent cytokine and MMP-3 production assessed. The potential therapeutic effects of broad, pan-Ras silencing in murine collagen-induced arthritis (CIA) were examined using pan-Ras and control LNA (1 mg/kg, 3 times weekly ip, 8 mice per group).

Results: Similar levels of each Ras homolog were expressed in RA and disease control synovial tissue, although H-Ras protein and mRNA expression was significantly elevated in RA synovial tissue and FLS compared to PsA. Each Ras protein was also expressed in RA FLS and activated by TNF and IL-1. H-Ras, but not other Ras homolgues, was sufficient and required for spontaneous FLS MMP-3 production ($P < 0.05$), while multiple Ras proteins induced IL-6 and IL-8 induction, and each silencing of each Ras homolog suppressed IL-1-induced IL-6 production ($P < 0.05$). The three Ras homologues also redundantly activated overlapping sets of MAP kinase, NF-kappaB and PI3-kinase intracellular signalling pathway in FLS. In vivo, pan-Ras LNA, which significantly suppressed synovial expression of H- and N-Ras, decreased clinical severity of CIA in mice compared to control LNA ($p< 0.005$), as well as cartilage destruction ($P < 0.05$), bone erosion ($P < 0.05$), and the ratio of anti-collagen IgG2a/IgG1 auto-antibodies ($P < 0.01$).

Conclusions: Overlapping contributions of Ras homologues to global inflammatory parameters of RA FLS activation and pathology in CIA, suggesting a therapeutic potential in broadly, rather than specifically, targeting closely related Ras proteins may be effective in treating RA.

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1530

Resveratrol Inhibits TNF-α-Induced MMP-9 Expression through a mTOR Independent Pathway. Xiaoxia Zhu[2], Jianhua Qiu[1] and Hejian Zou[2]. [1]Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [2]Department of Rheumatology, Huashan Hospital, Fudan University, Shanghai, China

Autoimmune diseases are characterized by progressive inflammation manifested with overexpression of matrix metalloproteinases (MMPs) and pro-inflammatory cytokines such as TNFα, IL-1β. Blockade of TNFα or IL-1β signaling has been successfully applied to clinical therapy of some autoimmune diseases such as rheumatoid arthritis. Resveratrol, a natural phytoalexin, has been shown to have anti-inflammation properties. However, the mechanism is not fully understood. Here, we investigated whether resveratrol attenuates TNFα-induced inflammation and potential mechanism in NIH/3T3 fibroblasts. Upregulation of MMP-9, MMP-13 and IL-1β were observed 6 hours or 24 hours after TNF-α treatment in NIH/3T3 fibroblasts examined by gel zymography and/or quantitative real-time PCR. Increase of phosphorylated Akt, mammalian target of rapamycin (mTOR) and S6 ribosomal protein (S6RP) were also detected in the cells. Nevertheless, Resveratrol suppressed TNFa induced upregulation of MMP-9, MMP-13, IL-1β. Resveratrol also inhibited phosphorylation of Akt, mTOR, S6RP induced by TNFa. However, Rapamycin, a special mTOR inhibitor, failed to attenuate overexpression of MMP-9 induced by TNFa. Our results indicate that resveratrol inhibits TNFα-induced inflammation via a mTOR-indepenent fashion. Resveratrol may be a potential therapeutic candidate for treatment of autoimmune diseases, although its mechanism remains to be further elucidated.

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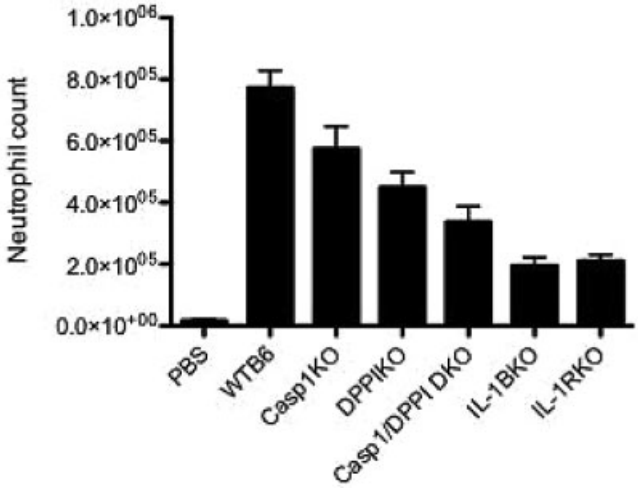
1531

Role of Dipeptidyl Peptidase I (Cathepsin C) in the Maturation of IL-1β In Vivo. Hajime Kono[1], Zubin Patel[2], Tamiko Yanagida[1], Maki Takayama[1] and Kennth Rock[2]. [1]Teikyo University School of Medicine, [2]University of Massachusetts Medical School

Background: IL-1β plays a pivotal role in rheumatic diseases including crystal-induced arthritis, autoinflammatory diseases and rheumatoid arthritis. IL-1β is transcribed as a nonfunctional pro-protein that requires specific cleavage to be converted to a functionally active form. Caspase-1 was identified as an enzyme that plays a dominant role in the maturation of IL-1β. Recent advances revealed that the activity of Caspase-1 is controlled by the formation of supramolecular complex, the inflammasome. In Vitro studies using macrophages or monocytes showed that the maturation of IL-1β in response to monosodium urate, silica or cholesterol crystals totally depends on inflammasome activation. Although we and others showed that the acute neutrophilic inflammatinon to crystals almost entirely depends on IL-1β In Vivo, mice deficient in inflammasome components showed only a modest reduction in these responses. The results thus prompted us to explore the contribution of other enzymes that might generate IL-1β In Vivo. Neutrophil-derived serine proteases (cathepsin G, neutrophil elastase, and proteinase 3) are expressed specifically in mature neutrophils and are thought to play an important role in inflammation and reported to have activity to generate active IL-1β In Vitro. These serine proteases are transcribed as inactive zyomgens and require processing by lysozomal cysteine protease dipeptidyl peptidase I (DPPI, Cathepsin C) to become active. To investigate the role of neutrophil serine proteases in IL-1b dependent acute inflammation In Vivo, we generated the DPPI/Caspase-1 double deficient mice and analyzed the neutrophilic responses to crystals or dead cells.

Materials and Methods: DPPI/Caspase-1 double deficient mice were generated by mating the single deficient mice. Silica crystals (0.125 or 0.5mg) were injected intraperitoneally into these various mice as well as wild type control, IL-1β deficient and IL-1 receptor deficient mice. The neutrophil and monocyte numbers in the peritoneal lavage were quantified by flow cytometry after 4 or 14 hours of injection. One way ANOVA with Dunnett's multiple comparison test was used to compare the groups.

Results: Fourteen hours after injection of silica crystal, the mean total number of neutrophil in the peritoneal cavity were 1.9×10^{-6} (WT), 2.1×10^{-6} (Caspase-1 KO), 1.3×10^{-6} (DPPI KO), 1.0×10^{-6} (DPPI/Caspase-1 DKO), 0.4×10^{-6} (IL-1β KO), 0.3×10^{-6} (IL-1R KO) and 0.0×10^{-6} (PBS injected WT control). The 4 hour result of neutrophil recruitment in response to silica injection was shown in Figure 1.



Conclusion: The data indicate that DPPI plays a role in the crystal induced acute inflammatory responses in addition to Caspase-1. The residual response in DPPI+caspase I-double deficient mice indicates that that there must be additional proteases that contribute to IL-1β maturation In Vivo.

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1532

The Expression of the Anti-Apoptotic Transcription Factor NFkappaB-P65 Is Markedly Diminished in Chondrocytes of Murine Osteoarthritic Cartilage and in a Subset of Human Osteoarthritic Cartilage Samples. Fons A. J. van de Loo, Onno J. Arntz, Miranda B. Bennink, Esmeralda Blaney-Davidson, Peter M. van der Kraan and Wim B. van den Berg. Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Introduction: Chondrocytes play a central role in cartilage pathology as seen in rheumatoid arthritis (RA) and osteoarthritis (OA) patients by a deranged synthesis of extracellular matrix (ECM) components and the enhanced release of ECM destructive metalloproteinases (MMPs). Nuclear factor-kappaB (NF-kappaB) is an important transcription factor in the regulation of MMPs, but is also regarded as a survival factor in cells. We studied the regulation of NF-kappaB-P65 in chondrocytes in rheumatoid arthritis, osteoarthritis, mouse models of arthritis and osteoarthritis and the functional consequences of decreased level of NFkappaB-P65.

Methods: NF-kappaB-P65 was measured in primary chondrocytes of arthritic cartilage obtained from joint replacement surgery, and in cartilage of a spontaneous osteoarthritis mouse model (STR/ORT), streptococcal cell wall-, antigen-induced arthritis, and of young (14 weeks) and old (>12 months) mice by Western blotting, immunohistochemistry or RT-qPCR. To study the functional consequences of decreased level of NF-kappaB-P65 in chondrocytes the murine H4 chondrocyte-cell line was stably transduced with a lentivirus expressing a short-hairpin RNA against NF-kappaB-P65. To study the biological consequences, conditioned medium of OA synovium was added to the murine H4 chondrocyte cell line with the lowest NF-kappaB-P65 level.

Results: High NF-kappaB-P65 levels were detected by immunohistochemistry and Western blot in chondrocytes of RA patients, whereas in a subset of OA cartilage samples the levels were unexpected low (6 out of 12). In mouse models the level of NF-kappaB-P65 showed the same regulation. NF-kappaB-P65 levels in cartilage from murine arthritis models was increased up to 250% at day 2 after induction of streptococcal cell wall- or antigen-induced arthritis and at day 7 returned to the basal level of naive knee joints, whereas in STR/ORT mice levels were diminished more than 75% when joints became affected, as determined by immunohistochemistry. Levels of NF-kappaB-P65 in young and old mice were equal, but the older groups showed more variation, detected by immunohistochemistry. *In vitro*, we selected chondrocyte cell-lines with different levels of NF-kappaB-P65. By adding TNFalpha, cell death was only induced in the cells with low levels of NF-kappaB-P65, as detected by 7-AAD staining. A clear negative correlation between TNFalpha induced cell death and the levels of NF-kappaB-P65 in chondrocyte cell-lines was found. Adding conditioned me-

dium of synovial explants from different OA patients to the murine chondrocyte cell-line with the lowest NF-kappaB-P65 level, resulted in more than 60% chondrocyte death in 3 of the 5 conditioned medium samples tested which could be prevented by preincubation of these media with soluble-TNFR1 (Enbrel). TNFalpha was detected using a Luminex assay in the same samples that caused cell death.

Conclusions: This study clearly demonstrated that lower levels of NF-kappaB-P65 makes chondrocytes more vulnerable for TNFalpha, a cytokine which can be produced during OA, and that this anti-apoptotic transcription factor is downregulated in chondrocytes in murine OA and in 50% of OA patients.

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TLR2 Mediates Acute Serum Amyloid A Induced Pro-Inflammatory Effects in Rheumatoid Arthritis. Mary Connolly[3], Ashwini Maratha[1], Sinead Nic an Ultaigh[3], Sinead Miggin[2], Ursula Fearon[3] and Douglas J. Veale[3]. [1]Institute of Immunology, National University of Ireland Maynooth, Maynooth, Ireland, [2]Institute of Immunology, National University of Ireland Maynooth, [3]Translational Research Group, Dublin Academic Medical Centre, St. Vincents University Hospital., Ireland

Introduction: Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by progressive joint destruction. Serum amyloid A (A-SAA) is an acute phase protein with cytokine-like properties. Previously we have shown that A-SAA correlates with RA disease activity, is produced at high levels locally in the joint and promotes synovial tissue angiogenesis, migration and MMP production. Recently, A-SAA was identified as a ligand for Toll Like Receptor 2 (TLR2), however no study has examined a role for TLR2 in mediating A-SAA-induced inflammation in RA.

Objective: To examine A-SAA-induced inflammation *via* TLR2 in rheumatoid arthritis

Methods: A-SAA and TLR2 expression in synovial tissue (ST) was examined by immunohistochemistry. Human embryonic kidney (HEK) 293 cells overexpressing TLR2/TLR4 were transfected with the NF-κB luciferase reporter gene plasmid. After 24 hr, cells were stimulated with A-SAA (10 and 50μg/ml), the TLR2 ligand Pam_2CSK_4 or the TLR4 ligand LPS. After 8 hr, ligand-induced reporter gene activity was assessed. Primary fibroblasts (RASFCs) isolated from synovial biopsies obtained at arthroscopy and human microvascular endothelial cells (HMECs) were stimulated with A-SAA (10μg/ml) $\pm$ anti-TLR2 (OPN 301, 1μg/ml). IL-8 was measured by ELISA. Proliferation, invasion and ICAM expression were quantified by crystal violet assay, transwell invasion assays and flow cytometry. Migration and angiogenesis were examined using wound repair and tubule formation assays respectively.

Results: A-SAA and TLR2 expression were observed in the lining layer and perivascular regions of RA synovium. A-SAA induced a 12-fold increase in NF-kB reporter gene activity in HEK293-TLR2 cells ($p<0.05$), an effect greater than that observed with Pam_2CSK/Pam_3CSK. In contrast, A-SAA failed to induce NF-kB reporter gene activity in HEK-TLR4, confirming specificity for TLR2. A-SAA induced IL-8 expression in RASFCs from 2.58$\pm$1.51pg/ml to 3453.19$\pm$1715.33pg/ml, an effect inhibited in the presence of anti-TLR2, where IL-8 levels fell to 1461.15$\pm$819.04pg/ml. A-SAA induced HMEC proliferation by 60.9% ($p<0.001$) which was significantly reduced by 38.2% in the presence of anti-TLR2 ($p<0.05$), similar to RASFCs. A-SAA increased ICAM expression on HDECs and RASFCs by 65.4% and 64.3% respectively, which was dramatically inhibited by 59.8% and 38.8% in the presence of anti-TLR2 ($p<0.05$). Furthermore, A-SAA-induced invasion and wound repair were inhibited by anti-TLR2, with no effect on TNFα-induced events. Finally, A-SAA induced angiogenic tube formation by 31.7%, an effect that was inhibited in the presence of anti-TLR2 by 24.5%.

Conclusion: A-SAA mediates pro-inflammatory events in RA including chemokine induction, adhesion, migration and angiogenesis, *via* TLR2. TLR2 blockade may represent a therapeutic strategy for the treatment of arthritis.

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TNF-a and Chemerin Cross-Talk in Rheumatoid Arthritis. M. C. Lebre[2], M. I. Ramos[2], C. Hofstra[3], H. van Eenennaam[3], S. Aarrass[2] and Paul P. Tak[1]. [1]Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, [2]Division of Clinical Immunology & Rheumatology, Academic Medical Center/University of Amsterdam, Amsterdam, The Netherlands, [3]Merck Research Laboratories, Oss, The Netherlands

Background: Rheumatoid arthritis (RA) synovium is characterized by a dense infiltrate, consisting of macrophages, T and B cells, plasma cells and dendritic cells (DC). Inflammatory chemokines present in RA synovium may contribute to the accumulation of these immune cells. We have recently shown that plasmacytoid DC (pDC) are enriched in RA synovial tissue (ST) compared to $CD1c^+$ myeloid DC. In line with these observations, we have shown that chemerin (and its receptor chemR23) expression is upregulated in RA ST compared to non-RA arthritis patients. Moreover, in RA ST ChemR23 was specifically expressed by $CD68^+$ macrophages and pDC, while chemerin expression was confined to endothelial cells (CD31 and vWF positive).

Objective: To investigate the regulation of chemerin expression in an ex-vivo model of human RA.

Methods: Arthroscopic synovial tissue biopsies were obtained from patients with active RA and cultured in medium or in the presence of recombinant (r)-TNF-a or r-chemerin. After 6 days, cell-free supernatants were harvested and the levels of TNF-a or chemerin were analyzed by Luminex or ELISA, respectively. When indicated, anti-chemerin or anti-ChemR23 neutralizing antibodies were added to TNF-a-stimulated cultures.

Summary of the Results: RA synovial biopsies released chemerin spontaneously. Interestingly, TNF-a stimulation induced significantly higher levels of chemerin compared to medium control. In addition, RA synovial biopsies released TNF-a spontaneously and addition of chemerin to the cultures strongly induced TNF-a release, suggesting a vicious cycle. Of importance, spontaneous and TNF-a-induced chemerin could be blocked by the addition of neutralizing antibodies against chemerin or against ChemR23. Moreover, spontaneous TNF-a could also be blocked by the addition of neutralizing antibodies against chemerin.

Conclusion: These findings suggest that elevated levels of chemerin in RA synovial tissue might regulate local TNF-a release and vice-versa in a positive feedback loop. The reciprocal interplay between chemerin and TNF-a is novel and might represent an attractive candidate for future drug development by blocking the chemerin/ChemR23 system to disrupt disease perpetuation.

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1535

Toll-Like Receptor 4 Signalling Is Specifically TAK1-Independent in Synovial Fibroblasts. Fons A. J. van de Loo[1], Ben T. van den Brand[1], Shahla Abdollahi-Roodsaz[1], Onno J. Arntz[1], Michael Kracht[2], Jeroen Geurts[1] and Wim B. van den Berg[1]. [1]Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, [2]Rudolf-Buchheim-Institute of Pharmacology, University of Giessen, Hannover, Germany

Introduction: Activated synovial fibroblasts are key players in the pathogenesis of rheumatoid arthritis (RA) by driving inflammation and joint destruction. Numerous molecules including cytokines and toll-like receptor (TLR) ligands induce pro-inflammatory signalling and gene expression through a hierarchical network of kinases. Upstream mitogen-activated protein kinase kinase kinases (MAP3Ks) represent an attractive target for RA treatment. In this study we sought to determine the role of the MAP3K transforming growth factor-β activated kinase1 (TAK1) in cytokine and TLR-mediated signalling.

Methods: TAK1 activity was inhibited using either a small molecule inhibitor or lentivirallyoverexpressed kinase-inactive TAK1-K63W mutant in murine embryonic and human dermal and synovial fibroblasts. Fibroblasts were stimulated with IL-1, TNF, TLR2 or TLR4 agonists and responses were evaluated using transcriptional reporters and analysis of gene expression of collagenases (MMP3,13), cytokines (IL-1β,-6) and chemokines (IL-8, MCP-1).

Results: TAK1 inhibition abrogated cytokine- and TLR-induced activation of NF-κB and *Saa3*-promoter reporters in murine and human dermal fibroblasts. In synovial fibroblasts, TAK1 crucially regulated IL-1 and

TNF-mediated NF-κB, but not *Saa3*-promoter activation.Furthermore, TAK1 was required for inducible mRNA expression of IL-1β, IL-6, IL-8, MMP3 and MMP13, but not MCP-1, in response to IL-1, TNF and TLR2 agonist. Unexpectedly, TLR4-induced NF-κB activation and gene expression was fully TAK1-independent.

Conclusion: In general, TAK1 plays a prominent role in regulation of IL-1- and TNF mediated signalling in fibroblasts. Interestingly, TLR4 signalling is specifically TAK1-independent in synovial fibroblasts. Consequently, therapeutic TAK1 inhibition in arthropaties may not dampen the damage-associated molecular pattern-mediated TLR4 activation of synovial fibroblasts.

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Tyrosine Kinase Inhibitors Reduce NMDA Receptor NR1 Expression, Nuclear Translocation and Thermal Hyperalgesia/CentralSensitization in a Rat Arthritis Model. Terry A. McNearney[5], Ying Lu[5], Zaiming Ye[2], Liping Zhang[3], Giulio Taglialatela[5], Todd Pappas[1], Wen-Ru Zhang[5] and Karin N. Westlund[4]. [1]Asuragen, Inc, Austin, TX, [2]MD Anderson Medical Center, Houston, TX, [3]University of Kentucky, Lexington, TX, [4]University of Kentucky, Lexington, KY, [5]University of Texas Medical Branch, Galveston, TX

Objective: This study was designed determine if the central changes of the spinal cord in response to a peripheral inflammatory knee joint arthritis in rats are mediated by non-receptor tyrosine kinase.

Methods: *S*pinal microdialysis administration of non-receptor tyrosine kinase inhibitors was used to measure their impact on secondary thermal hyperalgesia upon application of noxious radiant heat to the ipsilateral footpad in a kaolin and carrageenan (k/c)-induced knee arthritis model. NMDA NR1 cellular expression and nuclear localization by immunocytochemistry and Western blot analysis of the lumbar spinal cord were also measured. Statistics: Student's t-tests and one-way ANOVA Newman Keuls Multiple Comparison tests. A p value <0.05 was considered significant.

Results: Tyrosine kinase inhibitors genistein and lavendustin A, (but not lavendustin B or diadzein) effectively reduced 1) the development of secondary hyperalgesia, 2) the increases in glutamate NMDA receptor subunit NR1 expression in spinal cord that normally ensue 4 hours after intra-articular k/c-induced knee joint inflammation and 3) nuclear translocation of NR1. Genistein or staurosporin also inhibited the upregulation and shift of NMDA NR1 protein staining to the nuclear membrane and nucleus that is notable within 4 hours after treatment of neuroblastoma (SH-SY5Y) cell cultures with glutamate. Nuclear translocation of the NMDA NR1 subunit was also evident with activation of human primary and clonal synoviocytes. Nucleotide sequencing from clonal synoviocyte cDNA confirmed a putative nuclear localization sequence, similar to sequences derived from neuronal cells.

Conclusion: Tyrosine phosphorylation is necessary for spinal cord responses to peripheral inflammation including centrally mediated nociceptive sensitization producing secondary hyperalgesia. Tyrosine phosphorylation is required for NMDA receptor mediated NR1 subunit nuclear translocation, upregulation and perhaps other long term plastic changes. These studies implicate NR1 in direct interactions with the nucleus suggesting a role for NR1 as a fast intracellular mediator.

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ACR Poster Session C
Epidemiology and Health Services Research: OP/OA
Wednesday, November 10, 2010, 9:00 AM–6:00 PM

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An Evaluation of Prescription Insurance Coverage Inconsistencies—Prior Authorization Does Not Mean Approval. Dawn C. Crate[2] and Daniel A. Albert[1]. [1]Dartmouth-Hitchcock Med Ctr, Lebanon, NH, [2]Dartmouth-Hitchcock Medical Center

Purpose: To evaluate the medication prior authorization process for rheumatology prescriptions.

Method: Cases were acquired through the prescription insurance coverage prior authorization process in the Rheumatology Section between March 1, 2010 and June 18, 2010. Each case was charted in a table to reflect the length of time it took to receive the outcomes including:

specific medication prior authorization
patient diagnosis
diagnosis as on or off label (using FDA standards)
whether the insurance company requested a peer to peer or step therapy (alternate medication)
number of times insurance company was contacted before outcome was given
outcome and reason for outcome

Results: The Dartmouth-Hitchcock Rheumatology Clinic referred 65 patients for insurance carrier prior authorization between March 1, 2010 and June 18, 2010. This population represents 16% of the total number of patients seen in clinic during that timeframe. The prescription prior authorization process averaged to two hours per patient from initial referral to completion. Time spent per request ranged from twenty minutes to three hours, 100% of the cases needed more than one phone call to determine the outcome,62.5% of the total cases required a peer to peer (medical provider required to contact an insurance company physician), 75% of the cases were approved. Out of the 75% approved, 12.5% were found to not need a prior authorization, 50% of the cases that were approved were denied once the claim was submitted through billing. These cases are now in an appeal process. 37% of the cases were for off label use and out of those 50% were approved then denied when the claim was submitted. Categories of problems include:

1) FDA approved medications not covered
2) Insurance company representative conveyed incorrect information about coverage
3) Approval given then subsequently withdrawn (denied)
4) Medication denied then approved without appeal
5) Insurance company confused about their own appeal process
6) Pharmacy told patient prior approval needed when it wasn't and vice versa.

Conclusion: There is no consistent prescription prior authorization process within the insurance company industry. The lack of standardization creates problems such as an approval is initially granted and then upon review the approved medication coverage is denied. Insurance carriers also may initially approve a medication but then require reauthorization at the time of renewal. Patients are frequently required by the insurance company to trial one or more medications before approval will be given for the prescribed treatment plan.

The current lack of process amongst the insurance company industry for prescription medication prior authorization is time consuming, inefficient and costly for physicians, clinic staff, patients and insurance carriers.

Disclosure: D. C. Crate: None; **D. A. Albert:** None.

1538

Arthritis Prevalence and Access to Care in Indigenous People: Results of a Population-Based Study. Allen J. Lehman[1], Matthew H. Liang[3], Linda Li[2], John M. Esdaile[2], Catherine L. Backman[5], Phyllis Jorgensen[4], Kim Roberts[4], Linda Lavender[4] and Diane Lacaille[2]. [1]Arthritis Research Centre of Canada, Vancouver, BC, Canada, [2]Arthritis Research Centre of Canada; University of British Columbia, [3]Harvard, Boston, MA, [4]Kwakiutl District Council Health Centre, [5]University of British Columbia, Vancouver, BC, Canada

Purpose: North American Indigenous people are believed to have a high prevalence of arthritis yet limited research has examined the burden of arthritis and access to care. Our objectives were to: 1) identify the prevalence of chronic pain in peripheral joints, neck or back with functional limitations; 2) identify the prevalence of reported diagnoses of arthritis; and, 3) evaluate access to care for arthritis, in three on-reserve Indigenous populations.

Methods: A household survey of all adults living in three on-reserve communities was performed using a community case-finding strategy. Band Council support was provided and public forums were held to obtain community feedback prior to survey. Surveys were administered face-to-face by three trained interviewers residing in the community. The interview administered to each community member asked about chronic pain in the joint, neck, and back, and related functional limitations. Those indicating functional limitations secondary to arthritis/joint problems were then asked

about their access to health care services and barriers to care. Descriptive analyses were conducted.

Results: Of 536 residents of these communities, 402 (75%) completed the initial interview. Participants' mean age was 46 yrs (range=19–93), 52% were female, 61% were married and 23% were never married. Thirty-percent (n=119/402) reported a physician or health professional diagnosis of arthritis (excluding fibromyalgia), with 79 identifying specific type(s), including rheumatoid arthritis (n = 27), hip osteoarthritis (OA; n = 24), knee OA (n = 33), hand OA (n = 25), neck/back arthritis (n = 15), or other (n = 12). In comparison, non-age adjusted prevalence estimates reported in national surveys using the same question was 19% for off-reserve Indigenous People and 16% for non-Indigenous people. Chronic joint, neck, or back pain and functional limitations were reported by 41% (166/402). Of these 166 individuals, 140 reported at least one health care professional visit for their problem: family doctor = 75%; physical therapist = 28%; occupational therapist = 20%; rheumatologist = 16%; traditional healer = 15%; dietician = 13%; counsellor or psychologist = 7%. Assistive devices were used by 39%, and 70% used medications in the past 12 mos. Difficulties obtaining care in the past 12 mos were reported by 28% (n=47/166), such as long wait lists (n = 20), difficult access to rheumatologists (n = 19), poor transportation availability and/or high costs (n =16), lack of awareness of health care professional to see (n = 12), high treatment costs (n = 11), and perceived inadequate or culturally inappropriate health care (n = 10).

Conclusions: The burden of arthritis was high in the three Indigenous communities evaluated. The prevalence of reporting a diagnosis of arthritis exceeded that reported in national surveys for off-reserve Indigenous People and non-Indigenous people; and a large proportion (41%) reported chronic joint, neck or back pain with functional limitations. Along with suboptimal access to care, these findings suggest the need for further research to determine the specific types of arthritis and to identify solutions for improving health equity and access to care.

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1539

Aspirin vs. Low Molecular Weight Heparin for Prophylaxis Against Venous Thromboembolism after Total Knee or Hip Replacement in Lower Risk Individuals: A Cost-Utility Analysis. John T. Schousboe[1] and Gregory A. Brown[2]. [1]Park Nicollet Institute, Minneapolis, St Louis Park, MN, [2]Park Nicollet Institute, Minneapolis, MN

Introduction: Venous thromboembolism (VTE) is common following total joint replacement (TJA) surgery, but there is substantial disagreement as to the best way to prevent VTE events. The American Academy of Orthopedic Surgeons guideline recommends aspirin after TJA for patients at average or lower risk of VTE or at high risk of bleeding. The American College of Chest Physicians guideline recommends stronger anticoagulants (adjusted dose warfarin, low molecular weight heparin, or fondiparinux) for VTE prophylaxis after TJA, and specifically recommends against aspirin. Our objective was to estimate the lifetime incremental costs per quality adjusted life year gained for 10 days of low molecular weight heparin (LMWH) vs. aspirin 160 mg daily following joint replacement surgery.

Methods: A Markov cohort model allowing 6 transient events following TJA (deep vein thrombosis, pulmonary embolism, operative site hemorrhage, non-operative site major hemorrhage, intracranial hemorrhage, and thrombocytopenia), and 5 chronic health states (healthy post TJA, post TJA VTE without post-phlebitic syndrome, post TJA VTE with post-phlebitic syndrome, post intracranial hemorrhage, prosthetic joint infection). Costs and loss of quality of life associated with each event and chronic health state were derived from the medical literature. The absolute risks of VTE and bleeding events on LWMH following TJA were derived from a pooled analysis of clinical trials, and the relative risks of VTE and major bleeding on aspirin vs. LMWH were derived from literature estimates of each drug vs placebo. LMWH and aspirin were compared for four sets of individuals; those without any additional risks for VTE (non-obese, no personal or family history of VTE), obese individuals but without additional risk factors, and those with a family history of VTE.

Results: The costs (2008 U.S. $) per QALY gained for LMWH compared to aspirin prophylaxis post TJA for those age 55 to 85 are as follows:

	Scenario		
Age	No Added VTE Risks	Obese (BMI >30 mg/kg^2)	Family History of VTE
55	Aspirin Dominant	$35,762	$1,850
65	$635,488	$31,644	LMWH Dominant
75	$326,842	$31,819	LMWH Dominant
85	$246,044	$27,310	LMWH Dominant

Results were highly sensitive to the relative risks of VTE and major bleeding events on aspirin vs LMWH, modestly sensitive to the risks of and quality of life loss associated with post-phlebitic syndrome.

Conclusion: Aspirin may be a cost-effective reasonable choice for VTE prophylaxis following TJA for those individuals with no additional risk factors for VTE events, based on currently available data. For those with one or more additional VTE risk factor, LMWH is preferred over aspirin. A randomized controlled trial of aspirin vs LMWH post TJA might clarify the relative risks and benefits of these two strategies.

Disclosure: J. T. Schousboe: Park Nicollet Foundation, 2; **G. A. Brown:** AAOS Guideline & Technology Oversight Committee, 2, 4, 9, Karemetrix, 2, 4, 9, Orthopedic Solutions, 2, 4, 9, Park Nicollet Foundation, 2, 4, 9, Smith & Nephew, Inc., 2.

1540

Assessment of the Incremental Cost of Osteoporosis-Related Fractures among Women in a Large U.S. Managed Care Population. Hema Viswanathan[1], Jeffrey White[6], Sally W. Wade[5], Jingbo Yu[3], Jeffrey R. Curtis[4], Bradley Stolshek[2], Claire Merinar[2], Joel Kallich[2], Akhila Balasubramanian[2] and John Adams[2]. [1]Amgen Inc., Thousand Oaks, CA, [2]Amgen Inc., [3]HealthCore, Inc., [4]University of Alabama - Brimingham, Birmingham, AL, [5]Wade Outcomes Research and Consulting, [6]WellPoint, Inc.

Purpose: While incremental or attributable costs of osteoporosis (OP)-related fractures have been reported, data on the economic impact of OP-related fractures in commercial health plan populations are limited. The objective of this study was to quantify the incremental cost of OP-related fractures among women in a large U.S. managed care plan between 2004 and 2008.

Methods: Female patients were identified from a large, commercially-insured population with integrated pharmacy and medical claims. Patients were included if they were age 45 to 64 years, had an OP medication claim between 1/1/2005 and 4/30/2008 (first claim defines index date), and had continuous coverage for 12 months pre-index. Patients were excluded if they had: pre-index Paget's disease or malignant neoplasm, were in a skilled nursing facility, on combination therapy at index, or had a fracture ≤ 6 months post-index. Clinically-diagnosed and coded fractures were identified using published claims criteria; total direct costs were assessed in the 6 months pre- and post-fracture event date. Event dates were assigned to patients with no fracture; propensity score weighting was used to increase comparability of fracture and non-fracture patients. A generalized linear model was used to compare differences in 6 months pre-/post-event cost for patients with fracture and those without fracture. Covariates included demographics, prior fractures, comorbidities, and other potential confounders. Generalized estimating equations methods were used to account for repeated measures.

Results: The study population included 47,650 women (N = 2,461 with fracture) with a mean (± SD) age of 56.4 ± 4.7 years. Mean unadjusted total costs showed minor variation in the 6 months pre-event vs post-event for non-fracture patients. Mean pre-/post-event cost differences were substantially larger for patients with vertebral, hip, or other fractures (Table).

Table. Unadjusted Mean Total Direct Costs Per Patient

	Mean Total Direct Costs Per Patient (95% Confidence Interval) for Patients With:			
	Vertebral Fracture	Hip Fracture	Other Fracture	No Fracture
Number of Patients	214	138	2,109	45,189
6 Months Pre-Event	$12,888 ($8,381, $17,395)	$7,766 ($5,542, $9,989)	$5,195 ($4,751, $5,640)	$3,207 ($3,136, $3,278)
6 Months Post-Event	$27,303 ($21,088, $33,517)	$23,935 ($19,133, $28,737)	$12,218 ($11,185, $13,250)	$3,226 ($3,159, $3,292)
Post-Event Minus Pre-Event (Difference)	$14,415 ($7,559 $21,271)	$16,169 ($11,484, $20,855)	$7,023 ($6,011, $8,034)	$19 ($56, $94)

After adjusting for covariates, OP-related fractures were associated with an estimated $9,512 (95% CI: $8,364, $10,660, $p < 0.0001$) per patient in

additional direct health care costs across all fracture types during the 6 months immediately after the fracture.

Conclusion: On average, women with an OP-related fracture incurred nearly $10,000 in additional health care costs in the 6 months post-fracture compared with patients with no fracture. Efforts to reduce fracture risk may ultimately lower associated direct health care costs.

Disclosure: H. Viswanathan: Amgen Inc., 1, 3; **J. White:** None; **S. W. Wade:** Amgen Inc., 5; **J. Yu:** Amgen Inc., 2; **J. R. Curtis:** Novartis, Eli Lilly, 2, 5, 8, Novartis, Merck, Procter & Gamble, Eli Lilly, 2, 5, 8, Procter & Gamble, Merck, 2, 5, 8; **B. Stolshek:** Amgen Inc., 1, 3; **C. Merinar:** Amgen Inc., 1, 3; **J. Kallich:** Amgen Inc., 1, 3; **A. Balasubramanian:** Amgen Inc., 1, 3; **J. Adams:** Amgen Inc., 5.

1541

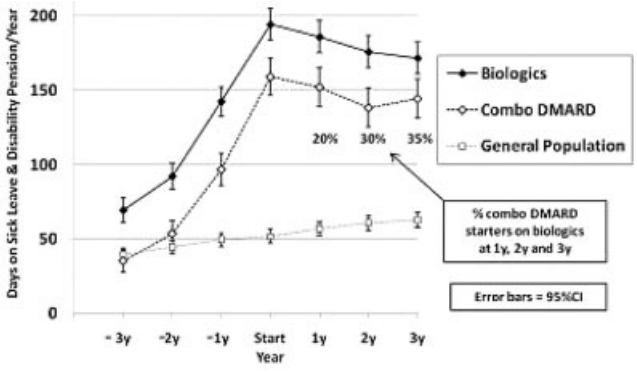
Bending the Cost Curve in Early RA: Sick Leave and Disability Pension before and after Initiation of Biologics or DMARD Combination Therapy. Martin Neovius[1], Julia F. Simard[1], Johan Askling[2] and ARTIS Study Group[3]. [1]Karolinska Institute, Stockholm, Sweden, [2]Karolinska Institute, [3]Sweden

Background: Biologic treatment is effective but expensive. Increased work force participation arguably holds the greatest potential for offsetting some of the treatment cost. It has been speculated that treatment may improve productivity in patients with RA, and early RA in particular, but long-term work ability development in this patient segment in relation to intensified anti-rheumatic treatment is not well-described.

Objective: To estimate the sick leave and disability pension trajectory over seven years in patients with early RA before and after treatment initiation with biologics or combo-DMARDs.

Methods: Patients aged 16–59 years old and a disease duration of less than five years when initiating treatment with biologics or combo-DMARDs (n=860/547; mean age 45y/46y; 76%/73% women; median RA duration 2.2y/1.2y) in 2000–2004 were identified in the Swedish Rheumatology Quality Register. For each RA case, five age-, sex-, education-, and county-matched general population comparators were sampled. Sick leave and disability pension data from 1997 to 2007 were retrieved from national registers.

Results: During the year of treatment initiation, patients selected for biologic therapy had a mean 194 (136+59) days of sick leave and disability pension registered, compared to 159 (133+26) days in patients starting combo-DMARDs, and 52 (20+32) days in matched general population comparators. A rapid increase in annual days of sick leave and disability pension was observed before start of intensive anti-rheumatic therapy, but thereafter the number of days/year decreased for patients who had either initiated biologics or combo-DMARDs. However, the gap compared to the general population remained wide and three years after treatment start patients in the treatment groups had a mean of near or above 150 days of sick leave and disability pension registered annually.



Conclusion: Using seven years of real world data in patients with less than five years RA duration, rapidly increasing productivity losses were observed before initiation of intensive drug treatment. Treatment initiation was associated with a breakpoint in and small reversal of this development, but a large unmet need remained in these patients compared to general population comparators.

Disclosure: M. Neovius: None; **J. F. Simard:** None; **J. Askling:** Bristol-Myers Squibb, 9; **ARTIS Study Group:** Schering-Plough, 9.

1542

Differences in Clinical and Economic Profiles of Rheumatoid Arthritis Patients Using Frequently Dosed Subcutaneous or Less Frequently Dosed Intravenous Biologic Therapy. Chureen T. Carter[1], O. Tunceli[3], Susan C. Bolge[2], Leigh Denny[2], C. Fang[3] and Joseph Singer[3]. [1]Centocor Ortho Biotech Services, LLC, Horsham, PA, [2]Centocor Ortho Biotech Services, LLC, [3]HealthCore, Inc.

Background: Adalimumab (ADA) and etanercept (ETA) are subcutaneously (SC) administered biologics with frequent recommended dosing of every other week or weekly in rheumatoid arthritis (RA), respectively. Abatacept (ABA) and infliximab (IFX) are intravenously (IV) administered biologics with less frequent recommended dosing during the maintenance period of every 4 or 8 weeks, respectively. Due to differences in dosing and routes of administration among therapies, the selection of appropriate treatment becomes multi-factorial. Patient characteristics may influence treatment selection. The purpose of this analysis was to describe the baseline clinical and economic profiles associated with frequently dosed SC and less frequently dosed IV biologic therapies (BIO) initiated in RA patients.

Methods: Commercially-insured patients aged ≥ 18 years at index, with ≥ 2 pre-index ICD-9 diagnosis codes for RA (714.xx), and who had initiated SC (ADA, ETA) or IV (ABA, IFX) BIO between 1/1/2004-10/31/2009 were identified from the HealthCore Integrated Research database. Patients had continuous enrollment 6 months pre-index and 12 months post-index, and did not receive any biologics pre-index. Patients were required to have 1 prescription of SC or IV BIO at index and on or after the 365th follow-up day. Patients with selected inflammatory conditions were excluded. Baseline demographic and clinical characteristics, as well as, pre-index healthcare costs were evaluated by index BIO administration route.

Results: A total of 2,931 RA patients receiving BIO were identified [1,902 initiated SC (ADA n=621, ETA n=1,281) and 1,029 patients initiated IV (ABA n=91, IFX n=938)]. Patients were mostly female in both groups (SC=76%, IV=74%). Patients initiating IV BIO were significantly older than SC patients (59 ± 14 years vs. 50 ± 12 years, $p<0.0001$, respectively). Chronic conditions such as ischemic heart disease, myocardial infarction, hypertension, and chronic obstructive pulmonary disease were significantly more common among IV users ($p<0.0001$ for all comparisons). Patients initiating IV BIO had higher mean pre-index all cause ($1,749 vs. $1,409; $p<0.0001$) and mean pre-index RA-related costs ($1,361 vs. $968; $p<0.0001$) compared to patients initiating SC BIO.

Conclusions: Patient profiles were different for frequently dosed SC and less frequently dosed IV biologic users. Patients receiving IV therapies were generally older, had more selected chronic conditions, and had higher RA-related baseline costs compared to patients receiving SC therapies. Future research of clinical and economic outcomes during treatment with SC or IV biologics in RA should adjust for the different patient types at baseline.

Disclosure: C. T. Carter: Centocor Ortho Biotech Services, LLC, 3; **O. Tunceli:** Centocor Ortho Biotech Services, LLC, 5; **S. C. Bolge:** Centocor Ortho Biotech Services, LLC, 3; **L. Denny:** Centocor Ortho Biotech Services, LLC, 3; **C. Fang:** Centocor Ortho Biotech Services, LLC, 5; **J. Singer:** Centocor Ortho Biotech Services, LLC, 5.

1543

DXA Screening and Use of Osteoporosis Medications in Two Large Regional Healthcare Systems. Amy Warriner[5], Ryan C. Outman[4], Jeffrey R. Curtis[5], Adrian Feldstein[1], Harry Glauber[3], Junling Ren[2], Douglas Roblin[2], Ana Rosales[1], Robert Unitan[3] and Kenneth G. Saag[7]. [1]Kaiser Permanente Center for Health Research, Portland, OR, [2]Kaiser Permanente Center for Health Research, Atlanta, GA, [3]Kaiser Permanente Northwest, [4]Univ of Alabama at Birmingham, Birmingham, AL, [5]Univ of Alabama at Birmingham, Birmingham, AL

Statement of Purpose: To compare the effect of a patient panel-support tool (PST) vs. standard of care on dual energy x-ray absorptiometry (DXA) screening in two large healthcare systems. Despite U.S. guideline recommendations for all women 65 years and older to have a screening bone density scan with central DXA, less than one-third of eligible U.S. women have undergone DXA testing.

Methods: We evaluated DXA receipt and use of prescription osteoporosis medications among women aged 65–90 in two large healthcare systems. Women were eligible for inclusion in the analysis if they had at least 24 months of enrollment at Kaiser Permanente Georgia (KPGA) or Northwest (KPNW). Primary outcomes included a DXA scan in the past 5 years and use of osteoporosis medications in the past year. The analysis included data

obtained in 6 month intervals from January 2005 through July 2009. From this data, we examined the effect of a PST (KPNW) vs. standard of care (KPGA). The PST uses EMR data to graphically display "care gaps" for each patient, based on current evidence. Through this mechanism, primary care physicians within the KPNW system are alerted to order a DXA in patients without a DXA in the previous 5 years (start date February 26, 2007).

Summary of Results: The number of women undergoing screening DXA increased significantly in the KPNW group with the proportion increasing from 25.3% in January 2005 to 58.7% in July 2009 (Risk Difference {RD} 33.3%, 95% CI 32.5 – 34.1%). This differs from KPGA, in which minimal change in DXA scan use occurred between January 2005 and July 2009, 43.1% and 45.3%, respectively (RD 2.2%, 95% CI 0.6–3.9%). The majority of the increased DXA use was seen following the implementation of the PST, Figure 1.

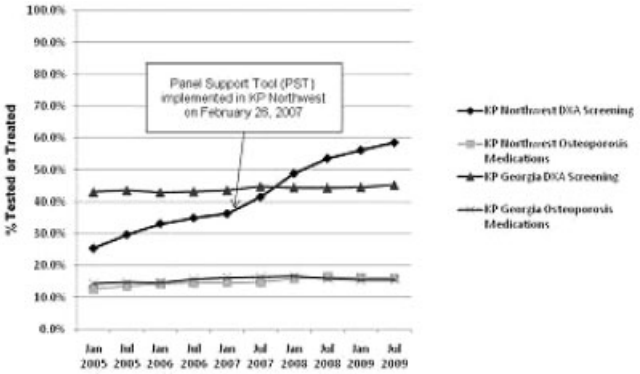


Figure 1. Percentage of women aged 65–90 receiving DXA screening or prescription of osteoporosis medications in 2005–2009 in KP Northwest and KP Georgia.

However, the number of women taking an osteoporosis medication did not increase significantly over the 5 year period in either region, +3.4% in KPNW and +1.3% in KPGA.

Conclusions: Among older women, DXA testing increased incrementally over the past 3 years in the KPNW healthcare system, following the implementation of a PST. However, despite the increased screening, the use of osteoporosis-specific medications for fracture risk reduction did not increase significantly. In a similar healthplan that did not implement such a program, the rates of DXA testing remained relatively flat. Further randomized studies are needed to confirm effectiveness of methods to improve appropriate DXA utilization.

Disclosure: A. Warriner: None; **R. C. Outman:** None; **J. R. Curtis:** Eli Lilly and Company, 2, 8, Merck Pharmaceuticals, 2, 5, Novartis Pharmaceuticals Corporation, 2, 8, Proctor and Gamble, 2, 5; **A. Feldstein:** Amgen Inc., 2, Merck Pharmaceuticals, 2, sanofi-aventis, 2; **H. Glauber:** None; **J. Ren:** None; **D. Roblin:** None; **A. Rosales:** None; **R. Unitan:** None; **K. G. Saag:** Amgen Inc., 2, 5, 8, Aventis Pharmaceuticals, 5, Eli Lilly and Company, 2, 5, GlaxoSmithKline, 2, Merck Pharmaceuticals, 2, 5, Novartis Pharmaceuticals Corporation, 2, 5, 8, Proctor and Gamble, 5, Roche, 2, 5.

1544

Erectile Dysfunction Is Associated with Gout in the Campaign Against Cancer and Heart Disease (CLUE II). Janet W. Maynard, Mara A. McAdams, Alan N. Baer, Judith Hoffman-Bolton, Allan C. Gelber and Josef Coresh. Johns Hopkins

Purpose: Erectile dysfunction (ED) is related to a variety of chronic medical conditions, including hypertension, obesity, and cardiovascular disease. We sought to identify whether gout was associated with ED independent of risk factors for cardiovascular disease in a community-based setting.

Methods: The CLUE II cohort consists of individuals, aged 13 to 87 years, who resided within or surrounding Washington County, Maryland. All participants received follow-up questionnaires (1996, 1998, 2000, 2003, and 2007). At baseline in 1989, participants were asked to self-report gender, race, age, and height. On the 2007 follow-up questionnaire, participants self-reported weight and a physician or health professional diagnosis of gout, ED, diabetes, and hypertension. This study was restricted to CLUE II participants who responded to the 2007 questionnaire (7,142) and were male. We assessed whether having gout was associated with ED. The distributions of variables among the men with gout versus those who did not have gout were compared using chi-squared or t-tests, as appropriate. We assessed the relationship between gout and ED with odds ratios from logistic regression.

Results: Of the 2,605 male participants responding to the 2007 questionnaire, 256 (9.8%) had gout and 779 (29.9%) had ED. A significantly greater proportion of participants with gout had ED (102, 39.8%) compared to participants without gout (677, 28.8%), $p<0.001$. The mean age of participants with gout was significantly greater than those without gout (68.7±11.3 years vs. 65.0 ±12.3 years, $p<0.001$). A significantly greater proportion of participants with gout were obese (BMI ≥ 30 kg/m^2) (47.9%) compared to those without gout (32.1%), $p<0.001$. Similarly, a significantly greater portion of participants with gout were hypertensive (72.0%) compared to those without gout (47.8%), $p<0.001$. A greater proportion of gout participants were diabetic (15.2%) than participants without gout (8.6%), $p<0.001$. There was a statistically significant association between gout and ED, even after adjustment for age (Table). However, this association was not observed after adjustment for hypertension, obesity, and diabetes.

Table. Association between Gout and Erectile Dysfunction.

	ED and Gout OR (95% CI)
Model 1: Unadjusted	**1.64 (1.25, 2.13)**
Model 2: Age	**1.38 (1.05, 1.83)**
Model 3: Model 2 + hypertension	1.24 (0.94, 1.64)
Model 4: Model 3 + obesity	1.19 (0.90, 1.59)
Model 5: Model 4 + diabetes	1.15 (0.85, 1.53)

Significant values ($p<0.05$) are **bold**.
Abbreviations: OR (odds ratio), CI (confidence interval)

Conclusion: In a community-based cohort we found that men with gout are more likely to have ED than men without gout, even after adjustment for age. However, this relationship may be mediated by obesity, diabetes, and hypertension, which are known risk factors for ED. Potential causal mechanisms need to be investigated, but even in their absence, the association suggests that physicians should explore this common treatable condition with their gout patients.

Disclosure: J. W. Maynard: None; **M. A. McAdams:** None; **A. N. Baer:** None; **J. Hoffman-Bolton:** None; **A. C. Gelber:** None; **J. Coresh:** None.

1545

Floor and Ceiling Effects and Choice of Physical Function Instruments. Eswar Krishnan[3], Bharathi Lingala[4], Bonnie Bruce[1] and James F. Fries[2]. [1]Stanford Dept of Medicine, Palo Alto, CA, [2]Stanford Univ Medical Ctr, Palo Alto, CA, [3]Stanford University, Palo Alto, CA, [4]Stanford University

Background: The spectrum of physical function ranges from high-level nursing home to long-distance runner, and improvement anywhere along this continuum represents an improvement in health. Yet, our measurement tools, from the SF-36 and the HAQ to the IRT-based new PROMIS tools, do not contain floor items sufficiently basic to assess low levels of function nor sufficiently difficult ceiling items to test function above the average. In many populations more than half may be beneath the floor or above the ceiling. As a result, instrument performance might suffer at population extremes, leading to much larger sample size requirements. We sought to estimate the size of this effect and to suggest remedies

Methods: We initially performed a simulation study that estimated the sample size requirements of an IRT-calibrated 8 item questionnaire at 3 separate settings: general population, and populations where physical function was 1 standard deviation worse and 1 standard deviation better than general population. Based on the results we performed a prospective observational study of 451 patients with RA (rheumatid arthritis). Mean 12-month score changes (Δ) in Physical function short form (PF10), PF-10 improved using IRT techniques, and PROMIS PF short form were measured and used to compute sample size needed for a 2.5% change with 80% power at a p value of 0.05.

Results: Whereas 50 patients were needed for detecting a change at 80% among those with physical function worse than general population (typical of patient populations) the corresponding sample size needs in the general population setting was 140. In samples of individuals with physical function 1 standard deviation superior to general population,(positive health), the sample size need was 325. In the empirical study the median sample size needs for those with no measurable disability at baseline (HAQ-DI =0), and those at progressively higher baseline disability categories (0.01<HAQ-DI≤1.50; and HAQ-DI ≥1.6) the median estimated sample sizes were 146, 228 and 284 respectively.

Conclusion: Our data document the profound deterioration in instrument performance when the function of the study population does not match the coverage range of the items used. We did not have sufficient items addressing the floors of physical function to enable precise estimation of change, even in the PROMIS PF 154 item bank. Traditional power calculations in such instances will over-estimate power, and power should be separated estimated in upper, middle, and higher ranges of severity as well as overall. The immediate need is extension of item bank content toward the extremes and validation of new items against populations with matching levels of impairment. This can lead to development of new short-forms appropriate to the population studied. The extended item banks become large in size, and this in turn argues for early transition to a Computerized Adaptive Testing (CAT) environment to reduce questionnaire burden while extending sensitive measurement across the range.

Disclosure: E. Krishnan: None; **B. Lingala:** None; **B. Bruce:** None; **J. F. Fries:** None.

1546

Fragility Fractures in Brazilian Community-Dwelling Elderly: Prevalence and Risk Factors. Jaqueline B. Lopes, Camille P. Figueiredo, Liliam Takayama, Valeria F. Caparbo and Rosa M. R. Pereira. Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo

Purpose: Estimate the prevalence of fragility fractures and investigate factors associated with this condition in Brazilian community-dwelling elderly.

Methods: 1075 elderly subjects (659 women/416 men) from São Paulo, Brazil were evaluated using specific questionnaire including risk factors for osteoporotic fractures. Fragility fractures were defined as those resulting of a fall from standing height or less after 50 years of age at sites characteristic of bone fragility. Traumatic fractures and those occurring at the face, skull, ankle, elbow and finger were not considered. Anthropometric data was obtained by physical examination and body mass index (BMI) was calculated. Bone mineral density (BMD) was measured by DXA in hip and lumbar spine. Laboratory tests were also determined.

Results: The prevalence of fragility fractures was of 11.9% (127) and the main fracture sites were forearm (50.4%), humerus (19.7%), femur (11.2%) and ribs (8.7%). Women had higher prevalence (15.3%; 95%CI 12.6–18.1) than men (6.5%; 95%CI 4.1–8.9) (P<0.001). In women, the main factors associated with fractures were Caucasian race (OR=1.7; 95%CI 1.1–2.8; P=0.027), BMI (OR=0.9; 95%CI 0.89–0.98; P=0.002) and femoral neck T-score (OR=0.7; 95%CI 0.5–0.9; P<0.001). After adjustment for these significant variables, the logistic-regression analyses revealed that Caucasian race (OR=1.7, 95%CI 1.03–2.7 P=0.038) and femoral neck T-score (OR=0.7, 95%CI 0.51–0.86; P=0.002) remains a significant factor for fragility fractures in women. In men, the main factors associated with fragility fractures were current smoking (OR=3.2; 95% CI 1.4–7.6; P=0.007), diabetes mellitus (OR=3.1; 95%CI 1.3–7.1; P=0.008), chronic faller (OR=2.9; 95%CI 1.1–7.6; P=0.033) and femoral neck T-score (OR=0.4, 95%CI 0.2–0.6; P<0.001). The logistic-regression analyses revealed that current smoking (OR=2.5, 95% CI 1.2–6.2; P=0.048), diabetes mellitus (OR=4.5; 95%CI 1.8–11.1; P=0.001) and femoral neck T-score (OR=0.4, 95%CI 0.2–0.6; P<0.001) were independent factors in predicting fragility fractures in men.

Conclusions: Our results suggest that fragility fractures are common in Brazilian community-dwelling elderly, and a low hip BMD was an important risk factor for this condition in both genders. In men, diabetes and smoking are also related to this complication. The identification of these factors may improve the prediction of fracture risk and enhance the evaluation of patients with osteoporosis.

Disclosure: J. B. Lopes: CAPES, 2; **C. P. Figueiredo:** CAPES, 2; **L. Takayama:** None; **V. F. Caparbo:** None; **R. M. R. Pereira:** CNPQ 300559/2009-7, 2, FAPESP 2003/09313-0, 2.

1547

Higher Serum Urate Levels Correlate with Increased Prevalence of Comorbidities in the US General Population: NHANES 1999–2008. Yanyan Zhu[1], Bhavik Pandya[2] and Hyon Choi[1]. [1]Boston University of School of Medicine, Boston, MA, [2]Takeda Pharmaceuticals International, Inc, Deerfield, IL

Objective: To estimate the prevalence of major comorbidities according to individuals' serum urate (sUA) levels based on a recent, nationally representative sample of US men and women regardless of whether or not they had gout.

Methods: Using the National Health and Nutrition Examination Survey (NHANES) 1999–2008 data from 24,693 participants (11,816 men and 12,877 women) aged 20 years and older, we determined the prevalence of major comorbidities according to individuals' sUA levels, including hypertension, diabetes, myocardial infarction, heart failure, stroke, renal impairment, and obesity, regardless of whether or not they had gout. Obesity was defined as body mass index ≥30 kg/m^2. Comorbidities were defined based on an affirmative answer to a question asking if a physician or other health professional had diagnosed the corresponding condition.

Results: The prevalence of major comorbidities correlated with an increase in sUA levels. Among individuals with sUA levels ≥10 mg/dL, 66% had hypertension, 32% diabetes, 23% history of myocardial infarction, 33% history of heart failure, 12% history of stroke, 18% renal impairment, and 65% obesity (Table).

Table. Prevalence of Comorbidities According to sUA Level Categories in NHANES 1999–2008

	Prevalence, % (95% Confidence Interval) Serum Urate Levels (mg/dL)						
Cormorbidities	**<4.0**	**4.0–5.9**	**6.0–6.9**	**7.0–7.9**	**8.0–8.9**	**9.0–9.9**	**≥10.0**
Hypertension	16.9 (14.9–18.8)	26.6 (25.4–27.7)	34.4 (32.2–36.5)	41.4 (38.6–44.1)	50.0 (44.2–55.7)	67.2 (59.3–75.2)	66.0 (52.6–79.4)
Renal Impairment	1.3 (0.8–1.8)	1.8 (1.5–2.0)	2.4 (1.8–2.9)	2.3 (1.6–2.9)	5.1 (3.8–6.5)	9.2 (3.0–15.5)	17.7 (8.9–26.6)
Diabetes	6.1 (5.1–7.2)	7.2 (6.6–7.8)	8.1 (7.1–9.0)	8.4 (6.8–10.1)	11.6 (8.4–14.9)	23.4 (14.8–31.9)	32.4 (19.4–45.4)
Myocardial Infarction	1.7 (1–2.4	2.8 (2.5–3.2)	3.8 (2.9–4.7)	5.9 (4.6–7.1)	7.8 (5.9–9.7)	16.1 (9.6–22.5)	23.1 (14.3–31.9)
Heart Failure	1.0 (0.6–1.4)	1.7 (1.4–2.0)	2.5 (2.0–3.1)	4.4 (3.3–5.5)	6.4 (4.5–8.2)	13.4 (7.8–18.9)	32.9 (20.2–45.6)
Stroke	1.8 (1.2–2.4)	2.5 (2.1–2.9)	2.4 (2.0–2.9)	4.4 (3.2–5.6)	4.6 (2.8–6.4)	11.8 (7.3–16.4)	11.7 (5.0–18.4)
Obesity	16.9 (15.2–18.6)	29.2 (27.9–30.5)	41.2 (38.9–43.5)	46.3 (43.3–49.4)	52.9 (48.7–57.0)	56.6 (48.1–65.2)	65.3 (53.6–77)

Conclusions: These findings from the latest nationally representative sample of US adults indicate that the prevalence of comorbidities proportionally increases with increasing levels of serum urate.

Disclosure: Y. Zhu: None; **B. Pandya:** Takeda Pharmaceuticals International, Inc, 3; **H. Choi:** Takeda Pharmaceuticals International, Inc, 5.

1548

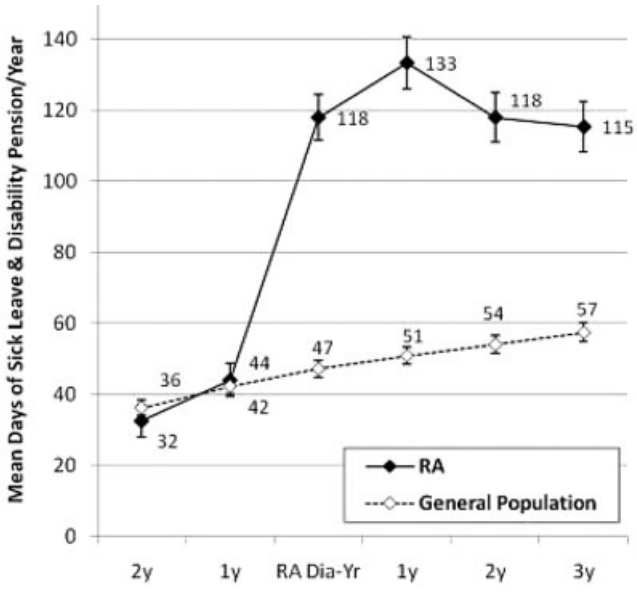
How Large Are the Productivity Losses in Contemporary Patients with RA, and How Soon in Relation to Diagnosis Do They Develop? A Six-Year Nationwide Cohort Study. Martin Neovius[1], Julia F. Simard[1], Johan Askling[2] and ARTIS Study Group[3]. [1]Karolinska Institute, Stockholm, Sweden, [2]Karolinska Institute, [3]Sweden

Background: Marked changes in the therapeutic approaches to early RA have taken place the last decade. Whether the increasing treatment intensity and number of treatment options have led to improvements in work ability is unclear. Furthermore, nationwide assessments of the societal burden due to reduced work ability in contemporary patients with RA are lacking.

Objective: To estimate the sick leave and disability pension trajectory in patients diagnosed with early RA 1999–2007, and productivity losses in prevalent patients with RA in 2007.

Methods: Patients of working age diagnosed with early RA in 1999–2007 were identified in the Swedish Rheumatology Quality Register (early RA cohort: n=3,084; mean age 46y; 73% women). Additionally, prevalent patients on Jan 1, 2008, were identified in the National Patient Register and the Swedish Rheumatology Quality Register (prevalent RA cohort: n=25,934; mean age 52y; 73% women). For each patient with RA, five age-, sex-, education-, county-, and time period-matched general population comparators were sampled. Sick leave and disability pension days were retrieved from national registers for 1997 to 2007.

Results: In the early RA cohort, sick leave and disability pension increased from a mean 44 to 118 days/year (mean difference 74, 95%CI 69–79) from the year before to the year of RA diagnosis. A further increase to 133 days/year (mean difference 15, 95%CI 11–20) was observed the following year, followed by a rebound to 118 and 115 days/year the subsequent two years. During the three years following RA diagnosis, sick leave halved from a mean 103 to 51 days/year while disability pension doubled from 30 to 64 days/year.



In the prevalent RA cohort, patients had a mean 158 (31+126) days of sick leave and disability pension compared to 71 (15+56) in comparators in 2007 (mean difference 87, 95%CI 84–90). Large variations existed across age, sex and education level, but RA cases had consistently greater productivity losses. The annual costs associated with sick leave and disability pension were $24,000 per patient with $13,000 attributable to RA.

Conclusion: Despite better drugs and improved treatment strategies, data from contemporary patients with early and established RA indicate large unmet needs.

Disclosure: M. Neovius: None; **J. F. Simard:** None; **J. Askling:** Bristol-Myers Squibb, 9; **ARTIS Study Group:** Abbott Laboratories, 9, Bristol-Myers Squibb, 9, Roche, 9, Schering-Plough, 9, Wyeth Pharmaceuticals, 9.

1549

Incidental Capture of Chikungunya Associated Chronic Rheumatism along with Other Rheumatic Musculoskeletal Disorders in a Rural Community in South India: A BJD India WHO COPCORD (Community Oriented Program for Control of Rheumatic Diseases) Project.

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Background: Chikungunya (CHIKV) is a predominantly self limiting, severely painful, febrile, arboviral, musculoskeletal illness. Although post CHIKV chronic rheumatism is reported in <10% cases, prospective community data is sparse. In 2007, Kerala (a south Indian state) witnessed an unprecedented CHIKV epidemic. We present the burden of chronic rheumatic musculoskeletal disorders (RMSD) following the epidemic, captured inadvertently during a rural community survey (25 miles from Trivandrum, the state capital) in 2008.

Method: An updated COPCORD Bhigwan (India) model (Chopra. J Rheumatol 2009; 36:614-22) questionnaires were used in a house-house survey to identify painful RMSD (last seven days) in a randomized population of 5133 adults. Respondents recorded pain sites on a human mannequin. Rheumatology physicians evaluated all cases. Diagnosis was clinical but often guided by the ACR criteria. We relied on typical narration, records and serology to classify CHIKV. A validated modified Indian Health Assessment Questionnaire (HAQ) - (Chopra. J Rheumatol 2000; 27:1365-72) was used to evaluate functional disability. Moderate and severe grades were considered significant.

Results: Painful RMSD, the predominant self-reported ailment, was present in 30% of the community (Mean age of 53.24±15.3 years, 72% women). Common pain sites were knees (83.5%), elbows (36%), low back (31.1%) and shoulders (29.5%). Cases were broadly classified as ill-defined aches (28%), soft tissue rheumatism (21%), degenerative joint disease (20%), post-infectious arthropathy (19%), inflammatory arthritis (4%) and miscellaneous (8%). The crude point prevalence rates of RMSD are shown below.

Table 1. Crude prevalence rates of RMSD in each group

Diagnoses	Prevalence (%)	95% CI (%)
Soft tissue rheumatism	**10.13**	**9.3–10.96**
• Periarthritis shoulder	2.16	1.83–2.49
• Plantar fasciitis	1.56	1.28–1.84
• Fibromyalgia	1.29	1.03–1.55
Degenerative arthropathy	**9.72**	**8.91–10.53**
• Knee OA	5.77	5.23–6.31
• Nodular OA	1.85	1.54–2.16
Infection related arthropathy	**9.16**	**8.37–9.95**
• Post CHIK polyarthralgias	5.73	5.2–6.26
• Post CHIK reactive arthritis	2.45	2.1–2.8
• Post CHIK tenosynovitis	0.95	0.73–1.17
Inflammatory arthritis	**1.79**	**1.43–2.15**
• Rheumatoid arthritis	0.51	0.35–0.67
• SSA	0.58	0.41–0.75

CHIKV related RMSD was classified in 14% cases, of which 283 (Mean age: 45.64±11.37 years, 76% women) were naive for RMSD prior to the epidemic. Polyarticular onset (OR −4.35; 95% CI 2.77–6.83), wrist pain at onset (OR −4.23; 95% CI 2.62–6.45) and female sex (OR −2.747; 95% CI 1.76–4.28) were predictors of chronic rheumatism in this group. Similar to Bhigwan COPCORD the prevalence of RA and SSA was conspicuous. Significant HAQDI was scored by 17% respondents. Difficulty in the HAQ items of walking, squatting and sitting cross-legged corresponded with the dominant pain sites in knees and lower back. In the age group 25–54 years, 9% had ceased work due to RMSD.

Conclusion: Though ill defined rheumatism remained the dominant category in this rural community, a wide spectrum of RMSD was observed. Such has been the conclusion of several COPCORD surveys. In the current study, CHIKV enhanced the community burden of RMSD. A long term follow up is warranted to study the future impact.

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Disclosure: A. J. Mathew: Bone and Joint Decade – India, 2; **V. Goyal:** None; **E. George:** None; **D. Varughese:** None; **J. Antony:** None; **A. Chopra:** Bone and Joint Decade–India, 6.

1550

Mortality Outcomes amongst Patients with Rheumatiod Arthritis with and without Joint Surgery: A Comparative Study.

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Objective: To examine the association between joint surgery and mortality in patients with rheumatoid arthritis (RA).

Methods: A retrospective medical record review was performed of all cases of adult onset RA incident from a defined geographic population base who fulfilled criteria for RA in 1980–2007. The arthritis related surgeries included in the study were primary total joint arthroplasty (TJA), joint reconstructive procedures (JRP), soft tissue procedures (STP) and revision arthroplasty. Cox models with time-dependent covariates for surgery occurring during follow-up were used to examine the influence of surgery on mortality.

Results: The study included 814 RA patients (mean age: 56 years; 68% female) with mean follow-up of 9.6 years, during which 204 died. A total of 190 patients underwent ≥1 surgical procedures involving joints during follow-up. The presence of any joint surgery was significantly associated with mortality (hazard ratio [HR]: 1.4; 95 % confidence interval [CI]:1.01, 1.96; $p = 0.04$) compared to patients not requiring joint surgery. This association was more pronounced among patients with JRP (HR: 2.77; 95% CI: 1.85, 4.14; $p < 0.001$). Following additional adjustment for risk factors known to be associated with mortality in RA patients (age, sex, calendar year, body mass index, smoking, rheumatoid factor positivity, severe extra-articular manifestations, comorbidities [cardiovascular disease, renal disease, liver disease, dementia, cancer, alcohol abuse] and use of glucocorticoids), the mortality risk associated with any joint surgery was somewhat attenuated

(HR: 1.37; 95% CI: 0.96, 1.97; p=0.08), but the association with JRP persisted (HR: 2.86; 95% CI: 1.89; 4.33; p<0.001).

Conclusion: Overall, there were significant differences in survivorship in patients with RA undergoing joint surgeries compared to patients who did not require joint surgery, especially among patients with JRP. This association persisted following adjustment for known risk factors for mortality possibly indicating a higher disease burden in these patients.

Disclosure: C. A. Shourt: None; **C. S. Crowson:** None; **S. E. Gabriel:** None; **E. L. Matteson:** None.

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Oral Tobacco Use Is Significantly Associated with Rheumatic Musculoskeletal (RMSK) Pain: Result of a WHO ILAR COPCORD (Community Oriented Program for Control of Rheumatic Diseases) Rural Population Study in India. Arvind Chopra[1], Sarika Chaturvedi[4], Manjit Saluja[2], Vaijayanti Lagoo Joshi[2] and Sanjiv Sarmukadam[3]. [1]Center for Rheumatic Diseases, Pune, India, [2]Center for Rheumatic Diseases, [3]Center for Rheumatic Diseses, [4]FRCH, Pune, India

Tobacco is a risk factor for RA and osteoporosis but its role in RMSK pain is not reported. Oral tobacco is a popular custom in India with alleged benefits of enabling work (or? bearing pain) in a socioeconomically challenged scenario.

We reported significant oral tobacco use in patients with RMSK pain from 4000 village Bhigwan (South Pune) COPCORD survey (Chopral.J Rheumatol 2002; 29: 614). In 2004, we completed 8000 urban population COPCORD survey in Pune (West India) and though there were urban rural differences (Joshi, Chopra. J Rheumatol 2009; 36: 614), oral tobacco use remained significant (OR 1.78, 95% CI 1.30, 2.4: not published). In 2008, we completed another 4775 non-random population ((90% response, 95% Hindu Maharashtarian ethnic) survey in village Ralegan Sidhi (East Pune) using Bhigwan model. Surveys were cross sectional and populatons matched well with Indian census 2001.Phase I Ralegan data analysis results are presented.

Methods: The methodology of COPCORD Bhigwan has been published (see above ref). The screening question was "Have you suffered from pain/swelling/stiffness in the joints or musculoskeletal soft tissues within the last seven days (considered current) or sometime in the past (last 3 months)?" Respondents marked pain sites on a human mannequin. All evaluations were carried out free of cost. Data was entered in MS Excel format and analyzed using statistical package(SPSS). 11 of the 19 variables from phase 1 database were selected in a step wise procedure for logistic regression analysis; RMSK (past or current) was the dependent variable. Variables discarded in the final run were *marital status, *literacy (read and write), alcohol use, *combined farm and house work, *vehicle accident, *sprain, *fracture and *sprain/fracture; *found significant in univariate analysis.

Results: 1513 population (32%) reported RMSK pain; women preponderant(2:1). In 85% cases, pain lasted > 4 weeks at multiple sites (>3). 37% men and 32% women used oral tobacco (rubbed tobacco powder on teeth and gums at least twice daily) and recalled several years of prior use. 49.8% cases recorded tobacco use (p<0.05). Table shows OR.

Risk factor	Odds ratio	95% Confidence Interval	
		Lower limit	Upper limit
Age	Coefficient = 0.0351, Coeff/SE = 14.8		
Sex (female)	1.54	1.27	1.87
Diet (Non-vegetarian)	0.741	0.643	0.855
Religion (Hindu)	1.70	1.20	2.41
Attended school	0.704	0.601	0.825
Oral Tobacco Use (past/current)	1.28	1.09	1.49
Farming	1.20	1.01	1.41
Household work	2.01	1.66	2.43
Intense Labour	1.40	1.20	1.64
Accident, any type	4.55	3.60	5.75
Agriculture related trauma	1.59	0.947	2.67

Increasing age, female gender, oral tobacco use, working in farms, house hold work, intense labor (as perceived by the subject) and accident of any type were significantly associated with RMSK pain. Non- vegetarian diet and school education (irrespective of years) seems to provide protection. Additional work in the fields besides house hold chores did not increase the risk.

Conclusion: In this rural COPCORD, oral tobacco use was a significant risk factor for RMSK pain. This validates our earlier conclusion from previous urban and rural COPCORD in the Pune region. Not surprisingly, history of accident trauma was a significant risk factor in the current report. Tobacco and trauma have important preventive bearing in public health, more so in developing economies.

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Osteoporosis Medication Adherence and Fracture Risk among Women in a Large U.S. Health Plan. Hema Viswanathan[1], Sally W. Wade[5], Jeffrey R. Curtis[4], Jingbo Yu[3], Jeffrey White[6], Bradley Stolshek[2], Claire Merinar[2], Akhila Balasubramanian[2], Joel Kallich[2] and John Adams[2]. [1]Amgen Inc., Thousand Oaks, CA, [2]Amgen Inc., [3]HealthCore, Inc., [4]University of Alabama at Birmingham, [5]Wade Outcomes Research and Consulting, [6]WellPoint, Inc.

Purpose: Osteoporosis (OP) poses a significant economic and clinical burden. Low adherence may mitigate treatment efficacy, including fracture risk reduction. This study examined the association between OP medication adherence during the first year on therapy and subsequent fracture risk using recent data from a commercially insured population.

Methods: Female patients were identified from a large, commercially insured U.S. population with integrated pharmacy and medical claims. Patients were included if they were ≥ age 45, new to OP therapy (no OP medication claims in prior year) with first (index) OP medication claim between 1/1/2005 and 4/30/2008, and had continuous coverage for ≥ 12 months pre- and post-index. Patients were excluded if they had: pre-index Paget's disease or malignant neoplasm, or were in a skilled nursing facility, or on multiple OP medications at index. Clinically-diagnosed and coded fractures were identified using published claims criteria. Patients who had a fracture in the first year on therapy were excluded. This ensured that the time periods for assessing exposure (medication) and outcome (fracture) did not overlap. Logistic regression was used to assess the association between the medication possession ratio (MPR: < 0.5, 0.5 to 0.8, > 0.8) during the 12 months post-index and fracture risk thereafter in bisphosphonate users. Covariates included baseline demographic and clinical characteristics including comorbidities and prior fracture.

Results: The analysis included 35,958 patients who were new to OP therapy, had a mean age (± SD) of 59.4 ± 9.2 years (range: 45 to 102 years), and had a mean post-index follow up of 834.3 days. At index, 99.6% of patients used a bisphosphonate. Over 12 months post-index, the mean MPR was 0.57 (95% CI: 0.57, 0.58). Mean 12-month MPR was lower among patients with fracture (N = 1,006) compared with those without fracture (N = 34,952; 0.54 vs 0.57, respectively; $p < 0.001$). Patients were clustered at the upper and lower ends of the MPR range. In multivariate modeling, bisphosphonate users with a MPR > 0.8 (N = 12,318) over 12 months had a 18% lower risk of subsequent fracture compared with those with a MPR < 0.5 (N = 13,878), even after controlling for demographic characteristics, insurance type, prior fracture, select comorbidities, and other potential confounders ($p = 0.007$; Table).

Table. Adjusted Fracture Risk by Level of Adherence Among Female Bisphosphonate Users*

Medication Possession Ratio (MPR)	Number of Patients	Odds Ratio for Fracture	95% Confidence Interval	*p*-value
<0.5	13,878	Reference	NA	NA
0.5 to 0.8	5,233	0.805	0.668, 0.971	0.023
>0.8	12,318	0.822	0.713, 0.947	0.007

* Adjusted for demographic characteristics, insurance type, prior fracture, select comorbidities, and other potential confounders

Conclusion: In this study, female patients in a large, commercial health plan had a mean 12-month MPR of 0.57 for OP medications. Women with low adherence (MPR < 0.5) experienced an increased fracture risk even after controlling for a large number of fracture-related covariates.

Disclosure: H. Viswanathan: Amgen Inc., 1, 3; **S. W. Wade:** Amgen Inc., 5; **J. R. Curtis:** Novartis, Eli Lilly, 2, 5, 8, Novartis, Merck, Procter & Gamble, Eli Lilly, 2, 5, 8, Procter & Gamble, Merck, 2, 5, 8; **J. Yu:** Amgen Inc., 2; **J. White:** None; **B. Stolshek:** Amgen Inc., 1, 3; **C. Merinar:** Amgen Inc., 1, 3; **A. Balasubramanian:** Amgen Inc., 1, 3; **J. Kallich:** Amgen Inc., 1, 3; **J. Adams:** Amgen Inc., 5.

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Patient Age, Ethnicity and Wait Times Determine the Likelihood of Non-Attendance at a First Specialist Rheumatology Assessment. Valerie Milne[2], Robin Kearns[1] and Andrew A. Harrison[2]. [1]University of Auckland, New Zealand, New Zealand, [2]University of Otago, Wellington, New Zealand, New Zealand

Purpose: Failure to attend first specialist assessment in rheumatology clinics not only results in lost opportunities for early diagnosis and treatment with DMARDs but also wastes health resources. Long wait times and deprivation have been linked with non-attendance at outpatient appointments [1,2]. This study aims to identify factors that predict non-attendance at rheumatology FSA with a view to optimising use of resources and patient outcomes.

Method: Administrative data for 1,953 new referrals over a 2-year period were collected from a public rheumatology unit that provides rheumatology services for three New Zealand health boards. Bivariate odds ratios were generated to test the association between attendance and geographic, demographic and clinic referral variables. Variables that were significant at the 0.05 level were included in linear regression models that tested their association with wait times.

Results: Referral appointments were completed for 87 percent of patients. Of the uncompleted referrals, 6 percent cancelled in advance and 7 percent failed to attend without prior warning. Patient age ($p<0.001$) and ethnicity ($p=0.002$) predicted failure to attend. New Zealand Maori (OR 0.74, CI –0.97) and Pacific Island (OR 0.72, CI 0.54–0.95) patients were less likely to attend their FSA than New Zealand Europeans, and patients in the 20–29 age group were less likely to attend than 40–49 year olds (OR 0.55 CI 0.41–0.74). Gender was not a significant factor in attendance.

Likelihood of failing to attend was also associated with longer wait times ($p=<0.002$). However, although age and ethnicity affected attendance, wait times were independent of these factors, with referral location and clinic location being significant predictors of long wait times ($p<=0.001$). Patients referred from locations near to the hub of the rheumatology service had shorter mean wait times than those living further away. Patients referred from the health board providing the service were significantly more likely to have a shorter wait to the FSA than patients from within the other two health boards (OR 0.56 CI 95% O.51–0.61 and OR 0.40 CI 0.34–0.47).

Conclusion: In this study age, ethnicity, wait times and location of services were important predictors of non-attendance at FSA. Attendance rates could potentially be improved by focussing clerical resources on at-risk demographic groups and by restructuring the clinical service to reduce wait times and geographic barriers. This could result in more efficient use of clinic resources and more timely intervention in inflammatory arthritis.

1. Leung, G. M. et al. (2003) *Medical Care* 41(11), 1293–1300.
2. Garcia Popa-lisseanu, M. G. et al (2005) *J Rheumatol* 32, 913–919.

Disclosure: V. Milne: None; **R. Kearns:** None; **A. A. Harrison:** None.

1554

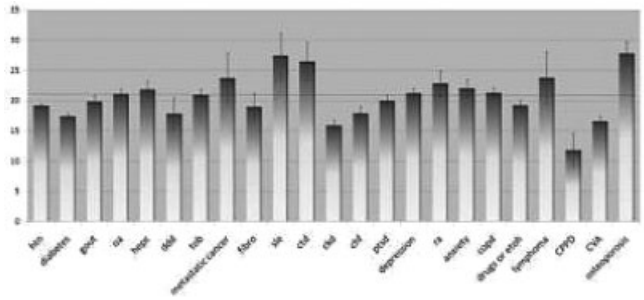
Predictors of Vitamin D Deficiency among Veterans. Joshua Baker[3], Alexis Ogdie[3], Li yun Zhang[2], Jan Dinella[4], H. Ralph Schumacher[5] and Sally W. Pullman-Mooar[1]. [1]Philadelphia, PA, [2]Second Hospital of Shanxi Medical University, China, [3]University of Pennsylvania, Philadelphia, PA, [4]University of Pennsylvania, [5]VA Medical Center - 151K, Philadelphia, PA

Introduction: Due to a number of factors, vitamin D deficiency is increasingly recognized as highly prevalent in many populations and of increasing concern among rheumatologists due to its noted effects on bone, immunity, and cardiovascular health. It remains unclear which patients are highest risk for vitamin D deficiency.

Methods: 4076 patients with vitamin D levels performed at our VA Medical Center were extracted within a 24-month period, between 2007 and 2008, from the electronic medical record. Diagnosis codes and other demographic data were also extracted. A predictive model was created using multivariable logistic regression analysis with vitamin D deficiency (<20 ng/mL) as the outcome.

Results: Patients with vitamin D deficiency were more likely to be younger, black, female, had higher pain scores on VAS scales, and had a greater number of diagnoses including diabetes, obesity, stroke, and renal disease. The lowest levels of vitamin D were founds in patients with CKD, diabetes, degenerative disc disease, and stroke. The 7 patients with calcium pyrophosphate deposition disease (CPPD) had the lowest levels of vitamin D of all diagnoses evaluated. In multivariable logistic regression, the strongest independent predictors of deficiency were younger age, black race, winter month, elevated systolic blood pressure, obesity, and a history of stroke, renal disease, and diabetes. Interestingly, patients with osteoporosis, RA, and SLE had significantly increased levels of vitamin D compared to other groups, possibly secondary to supplementation practices within those groups. These findings were similar when a cutoff of <30 ng/mL was used (not shown).

Conclusions: Our results suggest that, among veterans, increased attention should be paid to the risk of vitamin D deficiency in patients who are black, obese, and have multiple co-morbidities, including a history of hypertension, renal disease, stroke, and diabetes. Further study in patients with CPPD disease is indicated. Our limitations include indication bias and lack of data on supplementation.



Variable	Odds Ratio	P value	95% CI
Age (per year)	0.99	<0.001	0.983–0.992
Black Race*	2.82	<0.001	2.24–3.54
Male	0.90	0.2	0.76–1.06
VAS Pain 1–5†	0.94	0.4	0.78–1.11
VAS Pain 5–10†	1.11	0.2	0.94–1.31
# Diagnoses 6–12‡	1.11	0.5	0.84–1.47
# Diagnoses >12‡	1.41	0.02	1.05–1.90
No Recorded Diagnosis‡	1.00	1	0.80–1.24
Diabetes	1.40	0.007	1.10–1.77
CKD	1.87	0.005	1.21–2.89
COPD	0.67	0.009	0.50–0.91
CVA	1.91	0.001	1.30–2.82
Depression	0.71	0.01	0.54–0.93
Obesity§	1.44	<0.001	1.26–1.64
Osteoporosis	0.36	<0.001	0.20–0.64
Winter (Nov-Apr)	1.41	<0.001	1.23–1.60
HTN (SBP >140)	1.31	0.001	1.12–1.53

* Compared to White, † Compared to VAS Pain of 0, ‡ Compared to 1–5 Diagnoses, § BMI>30

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1555

Projecting the Effects of a 5-Point Reduction in Body Mass Index on Knee or Hip Osteoarthritis and Health-Related Quality of Life in a Closed Population to 2031: A Microsimulation Study. Eric C. Sayre[1], Jacek A. Kopec[4], Behnam Sharif[4], William M. Flanagan[3], Philippe Fines[3], Mushfiqur Rahman[5], Michal Abrahamowicz[2], David Buckeridge[2], Sam Harper[2], John Lynch[7], Douglas Manuel[6], Jillian Oderkirk[3] and Michael Wolfson[6]. [1]Arthritis Research Centre of Canada, Vancouver, BC, Canada, [2]McGill University, Canada, [3]Statistics Canada, Canada, [4]University of British Columbia, Canada, [5]University of British Columbia, Canada [6]University of Ottawa, Canada, [7]University of South Australia, Canada

Purpose: Body mass index (BMI) is a risk factor for knee or hip osteoarthritis (OA). Obesity (BMI>=30) increased from 10 to 15% in Canada between 1990 and 2000. BMI reduction is expected to reduce OA and improve health-related quality of life (HRQoL). The purpose of this study is to project in a national cohort the effect of a risk-targeted 5-point reduction in BMI on OA and HRQoL between 2001 and 2031.

Method: We used the Population Health Model (POHEM) platform to develop a stochastic continuous-time microsimulation model of physician-diagnosed OA. Incidence rates were calibrated to agree with administrative data for British Columbia, Canada. Projected upward trends in BMI under the base case (no intervention), the effect of obesity on OA incidence and the impact of OA on HRQoL were modeled using Canadian national surveys and

hospital data. The effect of BMI on OA was fit categorically: underweight (<18.5), normal (<25.0), overweight (<30.0) and obese (>=30.0). A closed population weighted for 2001 Canada that reflected projected mortality was followed in POHEM to 2031, aged 20+. BMI was reduced by 0 or 5 points in 2001 in persons with BMI>=25. Outcomes included OA prevalence and incidence (per 1000 person years), average Health Utilities Index Mark 3 (HUI), and health-adjusted life years (HALE). Monte Carlo error was estimated via subsamples. HRQoL models included BMI only indirectly through rates of OA.

Results: There were 22,483,400 in-scope subjects in the simulated population in 2001, 14,317,129 in 2031. Average age in 2001 is 45.89 (95% Monte Carlo CI=45.79, 45.99), in 2031 is 67.43 (67.37, 67.50). In 2001, average BMI is 25.55 (25.53, 25.58), OA incidence 7.42 (7.35, 7.49), OA prevalence 12.23% (12.00, 12.46), average HUI 0.874 (0.872, 0.875), proportion obese 14.99% (14.77, 15.20) and proportion overweight 33.66% (33.38, 33.94).

Under the base case, in 2031, average BMI is 27.79 (27.75, 27.82), OA incidence 21.03 (20.89, 21.16), OA prevalence 33.11% (32.98, 33.25), average HUI 0.752 (0.750, 0.753), proportion obese 26.82% (26.6, 27.04) and proportion overweight 37.15% (36.97, 37.33), with the rest normal or underweight. HALE for 20 year-olds is 27.06 (26.92, 27.21), for 40 year-olds 24.71 (24.61, 24.80) and for 60 year-olds 16.94 (16.81, 17.07).

With a 5-point targeted reduction in BMI, in 2031, average BMI is 25.56 (25.53, 25.58), OA incidence 19.29 (19.16, 19.42), OA prevalence 30.69% (30.55, 30.82), average HUI 0.756 (0.754, 0.758), proportion obese 11.57% (11.4, 11.74) and proportion overweight 38.19% (38.01, 38.36). HALE for 20 year-olds is 27.14 (26.99, 27.28), for 40 year-olds 24.81 (24.72, 24.91) and for 60 year-olds 17.00 (16.87, 17.12).

Conclusion: Reducing at-risk BMI by 5 points in 2001 would lead to a moderate reduction in OA (1.74 incidence and 2.42% prevalence) by 2031, but only very small improvements in HRQoL attributable to rates of OA. (Lowering BMI will have additional direct benefits on HRQoL.) Monte Carlo error was small, but future studies should incorporate additional error such as around parameter estimates. Future studies should vary BMI reduction and the target group, and simulate open populations including births and immigration.

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1556

Racial Differences in Gout Risk and Uric Acid Levels in Both Men and Women in the Atherosclerosis Risk in Communities (ARIC) Study. Janet W. Maynard, Mara A. McAdams, Alan N. Baer, Allan C. Gelber and Josef Coresh. Johns Hopkins

Purpose: Gout is a common form of inflammatory arthritis; yet, few studies have evaluated the relationship between race and gout in both women and men. We evaluated the association of race with gout and uric acid levels in the Atherosclerosis Risk in Communities (ARIC) Study, a large population-based and racially-diverse cohort.

Methods: ARIC is a population-based cohort study of 15,792 individuals (55% women) recruited in 1987–1989. Our study population consisted of African-American and Caucasian men and women with and without gout. A participant was considered to have gout if 1 or more of the following criteria were met: a) gout was self-reported, b) surveillance of hospital discharge summaries revealed an ICD-9 code for gout (274.0, 274.1, 274.8, or 274.9), or c) the participant reported use of a medication taken primarily to treat gout (allopurinol, colchicine, or probenecid) at any study visit. The distributions of baseline variables among the men with gout versus those without gout were compared using chi-squared or t-tests, as appropriate. We stratified by gender and used multivariate logistic regression to model the association of race and prevalent gout. The multivariate models included baseline age, BMI, protein, organ meat, shellfish, and alcohol intake, hypertension, antihypertensive medication use, income, education, tobacco use, diabetes, and renal function. Lastly, we generated a multivariate model with the previously mentioned confounders and uric acid.

Results: 399 women (4.6%) and 702 men (9.9%) had gout in the ARIC cohort. In both men and women, a significantly higher proportion of African-Americans had gout ($p<0.001$). After stratifying by gender, the mean serum uric acid level was higher in African-Americans compared to Caucasians ($p<0.001$ in women and men). The mean difference in uric acid levels for African-Americans versus Caucasians was 0.57 mg/dL (0.50, 0.64) in women and 0.31 mg/dL (0.22, 0.40) in men. African-American race was associated with an increased risk of gout even after adjusting for known confounders in both men and women (Table). However, after further adjustment for uric acid levels at baseline, the effect was not statistically significant.

Table. Association of Race with Gout in the Atherosclerosis Risk in Communities (ARIC) Study.

	Caucasians	African-Americans
Women		
Gout cases, n (%)	203 (3.4)	196 (7.4)
Uric acid level (mg/dL) (mean ± SD)	5.3 ± 1.4	5.9 ± 1.5
Age-adjusted OR (95% CI)	1.00 (Ref)	2.42 (1.97, 2.96)
Multivariate OR (95% CI)	1.00 (Ref)	1.57 (1.17, 2.10)
Multivariate Model including uric acid OR (95% CI)	1.00 (Ref)	1.34 (0.99, 1.80)
Men		
Gout cases, n (%)	490 (9.0)	212 (13.0)
Uric acid level (mg/dL) (mean ± SD)	6.7 ± 1.3	7.0 ± 1.6
Age-adjusted OR (95% CI)	1.00 (Ref)	1.55 (1.31, 1.85)
Multivariate OR (95% CI)	1.00 (Ref)	1.42 (1.12, 1.79)
Multivariate Model including uric acid OR (95% CI)	1.00 (Ref)	0.99 (0.77, 1.27)

Key: OR=odds ratio; CI=confidence interval

Conclusions: African-American race is associated with a greater than 50% increase risk of gout in both men and women, even after adjustment for known confounders. This suggests that above and beyond differential prevalence of medical comorbidities, including hypertension, race increases gout risk. This increased gout risk may be mediated by higher uric acid levels in African-Americans compared to Caucasians.

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Racial/Ethnic and Sex Differences in Somatosensory Abnormalities in Subjects with or at High Risk of Knee Osteoarthritis: Preliminary Analysis of the Multicenter Osteoarthritis (MOST) Study. Jasvinder Singh[2], Niu Jingbo[5], Laura Freylaw[9], Joachim Scholz[6], Lars Arendt-Nielsen[1], Cora E. Lewis[8], Clifford Woolf[6], Larry Bradley[8], David T. Felson[4], Michael C. Nevitt[7], Irina Tolstykh[7] and Tuhina Neogi[3]. [1]Aalborg University, Aalborg, Denmark, [2]Birmingham VA Medical Center and University of Alabama, Birmingham, Minneapolis, MN, [3]Boston Univ Schl of Med, Boston, MA, [4]Boston University School of Medicine, Boston, MA, [5]Boston University School of Medicine, [6]Childrens Hospital and Harvard School of Medicine, [7]UCSF, San Francisco, CA, [8]University of Alabama, Birmingham, [9]University of Iowa

Objective: There may be racial/ethnic and sex differences in the pain experience of knee OA, which may be reflected in differences in somatosensory evaluations. Our objective was to assess differences in somatosensory findings between Caucasians and African-Americans (AA), and between men and women.

Methods: MOST is a cohort study of persons aged 50–79 years of age, with or at high risk of knee OA. At the 60-month clinic visit, participants underwent knee radiography, answered pain questionnaires, and had the following somatosensory assessments: static allodynia using a 26g monofilament, and hyperalgesia using a pin. Temporal summation (TS), an augmented pain response to repetitive mechanical stimuli thought to reflect central sensitization, was also assessed. These assessments were carried out separately over each patella and wrist. An abnormal response to 26g or pinprick was defined as the participant experiencing pain or a non-response on 3 out of 4 trials, respectively. TS was defined as being present when, after touching the skin with a 60g monofilament repeatedly at a frequency of 1Hz for 30 seconds, the subject reported increased pain or new pain at the site being tested. Univariate and multivariate-adjusted prevalences (age, BMI, clinic and race and sex, as applicable) of the somatosensory tests were obtained for each site and summated as being present overall at any site, stratified by race/ethnicity and gender.

Results: Of the 770 with somatosensory data, there were 652 Caucasians (438 women, 214 men) and 118 AAs (73 women, 45 men). Mean age, BMI and K-L grade was similar for all groups (Table 1).

Table 1. Clinical and demographic characteristics of study cohort

		University of Alabama (n = 371)			University of Iowa (n = 399)	
All subjects	White men (N = 125)	White women (N = 128)	Black men (N = 45)	Black women (N = 73)	White men (N = 89)	White women (N = 310)
Age, mean (SD), year	65.9 (8.3)	68.1 (7.2)	62.8 (7.0)	65.2 (8.0)	71.2 (7.9)	68.1 (7.9)
BMI, mean (SD), kg/m^2	30.8 (5.3)	28.5 (5.4)	31.3 (6.0)	32.6 (5.8)	30.3 (5.8)	30.2 (6.3)
K-L grade N (%)						
0–1	68 (54%)	57 (45%)	21 (47%)	26 (36%)	43 (48%)	159 (52%)
2	14 (11%)	28 (22%)	6 (13%)	15 (21%)	16 (18%)	68 (22%)
3–4	43 (34%)	43 (34%)	18 (40%)	32 (44%)	30 (34%)	82 (27%)

Adjusted prevalence of static allodynia with 26g was higher in African-American women and almost achieved statistical significance (p=0.06) (Table 2). Adjusted prevalences of the pin-prick and temporal summation somatosensory evaluations were not significantly different among the sex and racial groups.

Table 2. Age, BMI- and clinic-adjusted prevalence rates (95% CI) of pain and Temporal summation (*any site,* person-based)

	White men		White women		Black men		Black women		
	Prev (%)	95% CI	Prev (%)	95% CI	Prev (%)	95% CI	Prev (%)	95% CI	p-value
26 g[a]	3.3	1.6	5.2	3, 7	4.9	−3, 12	14.4	6.23	0.06
Pinprick	6.6	3, 10	7.5	5, 10	9.6	−1, 20	9	1, 17	0.91
Temporal summation	62.7	56, 69	57.7	53, 62	66.5	54, 79	64.6	54, 75	0.45

[a] Model was adjusted for sex, race, BMI and clinic site; additional adjustment for age not done since model became unstable and age was not significant for this test.
P-value is from an Analysis of variance

Adjustment for presence/absence of osteoarthritis did not impact the results for the pinprick and temporal summation tests; however this model did not converge for static allodynia for 26g.

Conclusions: African-Americans and women had greater prevalence of somatosensory abnormalities compared with Caucasians and men, but most of these differences were not statistically significant. This preliminary study is the first to demonstrate racial/ethnic difference in response to the 26g von Frey hair stimulus in patients with knee OA. Further exploration regarding factors that may contribute to such differences is warranted.

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1558

Relationship between Physical Activity and Health-Related Utility in Knee Osteoarthritis Patients. Larry Manheim[2], Jing Song[2], Rowland W. Chang[1] and Dorothy D. Dunlop[3]. [1]Northwestern Univ, Chicago, IL, [2]Northwestern University, [3]Northwestern University Medical School, Chicago, IL

Purpose: Cost Effectiveness analysis relies on health utility measurement to evaluate the relative effectiveness of many interventions. We examine the relationship between health-related utility and physical activity levels in persons with Knee Osteoarthritis (KOA), to address the following questions: 1) do individuals who meet Center for Disease Control (CDC) recommended levels of physical activity have higher levels of health-related utility? 2) is it necessary to meet CDC guidelines to have higher utility levels or is utility positively related to physical activity at more modest levels of physical activity?

Methods: This study uses baseline data from 143 subjects with radiographic knee OA (KL grade ≥2) enrolled in the IMPAACT study, a randomized controlled trial to evaluate a tailored physical activity intervention. The SF-36 health-related quality of life measure was used to derive the SF6-D utility measure over the follow-up period (3, 6 and 12 months) which yields values between zero (death) and one (perfect health). Baseline physical activity was assessed by accelerometers worn over one week. Each person completed a set of baseline questionnaires, used to measure subject demographics, comorbidities (based on reported medication use), BMI, disability level, and level of pain. The relationship of physical activity to subsequent health utility over one year was assessed using multiple regression with general estimating equations (GEE) multiple regression.

Results: Health-related utility was significantly higher for persons who met CDC guidelines (≥ 150 minutes of moderate/vigorous activity per week in bouts lasting more than 10 minutes), relative to those who were inactive. However, only 11% of individuals meet guidelines and 40% of the sample had no bouts of moderate/vigorous activity. We therefore asked whether higher levels of any intensity activity (as measured by accelerometer counts) were positively associated with higher utility. We found that even moving above the lowest quartile of accelerometer counts to the next quartile was associated with a significant increase in utility of.051 points (p=.025), after controlling for K-L grade, pain, number of comorbidities present, level of disability, and demographics. Among these other factors only level of pain remains a significant predictor of utility level when all variables are included in the regression.

Table. Partial Association of Physical Activity with Utility after controlling for Disease Severity, Pain, Comorbidities, Disability, Intervention, Demographics

Level of Physical Activity	Average Utility (Adjusted)	Partial Coefficient (Adjusted)	Significance Level
Lowest Quartile	0.765	reference group	
Lower Middle Quartile	0.816	+.051	p = .025
Higher Middle Quartile	0.838	+.073	p = .001
Highest Quartile	0.845	+.080	p = .003

Conclusion: Higher levels of physical activity at baseline were related to higher subsequent levels of health-related utility in KOA. This result holds for those meeting CDC guidelines. Importantly even persons not meeting guidelines but doing some activity had better utility that persons in the bottom activity quartile (largely inactive) Thus, even modest increases in physical activity levels may provide a significant improvement in health utility.

Disclosure: L. Manheim: NIH, 2; **J. Song:** NIH, 2; **R. W. Chang:** NIH, 2; **D. D. Dunlop:** NIH, 2.

1559

Reporting of the Recruitment Process in Randomized Clinical Trials of Biological Agents for the Treatment of Rheumatoid Arthritis. Ismail Simsek and Yusuf Yazici. NYU Hospital for Joint Diseases

Purpose: Before using the results of a randomized controlled trial (RCT) for treating an individual patient, a clinician must determine whether the patient differs from those who participated in the trial in a meaningful way. Therefore it is important to evaluate how the RCT sample was assembled from the general patient population. The trial recruitment process can be described with qualitative and quantitative data, both of which can contribute important information about the generalizability/external validity. The adequacy of reporting in RCTs has received increased attention and culminated in the publication of guidelines such as CONSORT. We tried to assess the adequacy of reporting of the recruitment process and quantify the levels of RA patients participating in RCTs of biological agents.

Methods: PubMed was searched for all reports of RCTs involving etanercept, infliximab, adalimumab, golimumab, certolizumab, abatacept and rituximab in RA patients in the English language published before 12/31/2009. Extension studies, interim analysis, and secondary analysis of previously published data were excluded as were phase I and phase II trials. Data recorded were: (1) eligibility fraction (proportion eligible of those screened), (2) enrolment fraction (proportion randomized of those eligible), (3) recruitment fraction (proportion of potential participants actually randomized), and (4) number of patients needed to be screened (NNS) in order to randomize one participant.

Results: A total of 45 RCTs were identified. Seventeen (37%) reported the number of patients who were evaluated by the investigators for eligibility, 14 (31%) reported the number eligible for participation, and all reported the actual number recruited. Only 9 (20%) of the RCTs reported recruitment process completely. Of the studies that reported quantitative recruitment information, the median eligibility fraction was 81% (IQR 71% to 91%), and the median enrolment fraction was 99% (IQR 82.25% to 100%). The median NNS was 1.23 (IQR 1.16 to 1.42), with most trials reportedly recruiting every patient screened for eligibility. We found no associations between provision of sufficient recruitment data and funding source, publication year, and the journal where the article was published.

Conclusions: A substantial majority of RCTs did not provide sufficient information about the patient recruitment process which makes assessments of external validity difficult. Furthermore, the rate of reporting of the recruitment process in this study was found to be lower as compared to similar studies conducted in different specialties or disease settings. Our finding of low NNS levels also suggests that once screened for eligibility patients are likely to be randomized. However, this finding needs to be treated with caution as it may actually present inadequate reporting of the eligible population

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1560

Rheumatologists Practise Evidence Based Medicine, an Observational Study. Stephen Hall[1], Adam Moreton[4], Kathryn A. Gibson[2], Barry A. Kane[2], Vivek Thakkar[2], J. Hanrahan[1], Evange Romas[1], Timothy Godfrey[1], Marie Feletar[1], Alexander Stockman[1], Jennifer Harmer[1], Rani Axtens[1], Peter Ryan[1], Andrew Gibson[1], Christopher Mack[1], Robert J. Moots[3] and Geraldine Hassett[2]. [1]Department of Medicine, Cabrini Health, Melbourne, Australia, [2]Rheumatology Department, Liverpool Hospital, Sydney Australia, [3]School of Clinical Sciences, University of Liverpool, Liverpool United Kingdom, Liverpool, United Kingdom, [4]School of Clinical Sciences, University of Liverpool, Liverpool United Kingdom

Background: Evidence-based medicine (EBM) is used to inform treatment guidelines and in decision-making about funding for medicines and procedures. The extent to which evidence exists and EBM is employed in clinical rheumatology practice is unclear.

Objectives: To assess the extent to which rheumatologists in office practice follow EBM in their treatment recommendations.

Methods: The medical records of 190 patients attending rheumatology clinics with participating physicians (Liverpool Hospital, Sydney, Australia, private practices in Melbourne, Australia and University Hospital Aintree, Liverpool, UK) on or after 2nd July 2007 were reviewed and interventions were identified for each diagnosis made. A standardized search protocol was utilized to identify randomized controlled trials (RCT) in Medline (1950– present) and EMBASE (1980–present) supporting these interventions. In addition the Cochrane Database of Systematic Reviews was searched. Where there was no RCT evidence to support a treatment recommendation a subsequent adjudication process was undertaken to assess if the recommendation was supported by expert opinion.

Results: A total of 332 interventions were recommended. This generated 251 literature searches. Approximately 50% of interventions in clinical rheumatology were supported by EBM. The adjudication process supported 64% of non EBM based recommendations. Only 20% of interventions were neither supported by EBM or at adjudication. This occurred more often for soft tissue and non-inflammatory conditions compared to inflammatory conditions and osteoporosis. Adherence to EBM was similar in the private and public sector in Australia and across the public sectors of Australia and the United Kingdom.

Conclusion: Approximately 50% of rheumatology practice is supported by RCT data. Where RCT data does not exist, expert opinion supports 64 % of the recommended interventions, thus only 20% of all interventions in rheumatology office practice lack evidence. The extent to which evidence exists varies across the rheumatic diseases. There is no difference in the rate of EBM across the public and private sectors of rheumatology.

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Screening and Treatment of Glucocorticoid Induced Osteoporosis in a Large U.S. National Pharmacy Database. Ryan C. Outman[2], Nathan J. Markward[1], Mona Khalid[1], Ronald E. Aubert[1], Jeffrey R. Curtis[2], Robert S. Epstein[1], Felix W. Frueh[1], Eric J. Stanek[1], Amy Steinkellner[1], Amy H. Warriner[2] and Kenneth G. Saag[2]. [1]Medco Health Solutions, Inc., [2]Univ of Alabama at Birmingham, Birmingham, AL

Statement of Purpose: Despite a significant associated fracture risk, previous population-based studies document low screening and treatment rates for individuals with glucocorticoid(GC)-induced osteoporosis (GIOP). Using data from a national pharmacy benefit manager, we evaluated the influence of physician specialty on the rates and predictors of bone mineral density (BMD) measurement and anti-osteoporotic prescriptions among patients who received 90 or more days of GC therapy between January 2004 and December 2006.

Methods: Using integrated medical and pharmacy data, we identified GC users and the physician that most frequently prescribed the GC prescriptions. In the 12 months following the 90 days of GC exposure, we also identified the presence of BMD tests and prescription medications commonly used to prevent or treat GIOP, including GIOP-specific therapies and hormone replacement therapy. BMD tests and GIOP prescription medications did not have to be ordered by the GC prescribing physician in order to be credited as having been done. Multivariable logistic regression was employed to examine the influence of physician specialty on BMD testing and GIOP prescribing patterns.

Summary of Results: 106,310 chronic GC users treated by 53,766 physicians were identified during the data extraction process and followed for 12 months after satisfying the 90-day exposure threshold. The mean age of the sample was 61 (SD = 18) years, and 59% were female. In the 12 months prior to satisfying the 90-day exposure threshold, GC-associated conditions and their relative frequencies included rheumatoid arthritis (6%), systemic lupus erythematosus (<1%), chronic obstructive pulmonary disease (5%), asthma (3%), and inflammatory bowel disease (<1%).

During the 12 month follow-up period, overall rates of BMD testing and any GIOP prescription medication were 4.6% and 23.5%, respectively. GIOP prescription medication use was 11.4% among women < 50, 32.3% among women 50–70, and 42.1% among women >70. BMD testing and GIOP medication use were significantly greater among women ≥ 50 (6.4 and 36.8%) compared to men (3.5% and 14.7%, $p < 0.001$) and women <50 (3.6% and 11.4%, $p < 0.001$).

After adjusting for patient age, gender, and GC-related baseline covariates, BMD testing was found to differ significantly by specialty of GC prescriber (internal medicine referent): endocrinology [OR = 1.61 (1.28–2.03)], gastroenterology [OR = 1.52 (1.27–1.81)], nephrology [OR = 1.78 (1.48–2.15)], and rheumatology [OR = 1.38 (1.26–1.51)]. GIOP medication use also differed by specialty (internal medicine referent): other [OR = 0.78 (0.75, 0.82)]; endocrinology [OR = 0.73 (0.64, 0.85)], gastroenterology [OR = 1.15 (1.05, 1.27)], nephrology [OR = 1.37 (1.23, 1.51)], pulmonology [OR = 1.34 (1.25, 1.45)], and rheumatology [OR = 1.59 (1.52, 1.67)].

Conclusions: Among high-risk individuals, both BMD screening and GIOP treatment rates remain low even through 2007, particularly for pre-menopausal women and men of all ages. Significant practice pattern variations among specialties persist. Developing interventions to improve GIOP management remains a high priority.

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Self-Management Strategies in Overweight/Obese Canadians with Arthritis. Sasha R. Bernatsky[1], Corneliu Rusu[2], Siobahn O'Donnell[2], Gillian A. Hawker[5], Crystal Mackay[4], Louise McRae[2], Mayilee Canizar[4] and Elizabeth M. Badley[3]. [1]McGill UHC/RVH, Montreal, QC, Canada, [2]PHAC, [3]University of Toronto, Toronto, ON, Canada, [4]University of Toronto, [5]Women's College Hospital, Toronto, ON, Canada

Purpose: To estimate the prevalence of being overweight/obese, among Canadians with arthritis, and to describe the arthritis self-management strategies among these individuals.

Methods: The 2009 Survey on Living with Chronic Diseases in Canada (SLCDC) was developed by the Public Health Agency of Canada in collaboration with Statistics Canada, to provide information on how arthritis affects Canadians, and how it is managed. A nationally representative sample of 4,565 Canadians age ≥20 years, who reported having been diagnosed with arthritis by a health professional in the 2008 Canadian Community Health Survey (CCHS) were interviewed. Data from the 2009 SLCDC, was linked with data from the 2008 CCHS to analyze self-management strategies (including exercise, weight control/loss, classes, community based programs) among overweight (BMI=25.0–29.9) or obese (BMI>30) Canadians with arthritis.

Results: The over-all response rate for the SLCDC survey was 78%. Within the SLCDC sample with arthritis(N= 4,565), the majority were female(63.2%), aged 45+(88.6%), reported post-secondary education(68.7%) and were unable to report type of arthritis(42.4%).

Almost a third (27.4%) of the 4,565 was obese, with an additional 39.9% overweight. The overweight/obese individuals were mostly (59.5%) female and aged >45(89.7%). Regardless of weight category, about 75% had accessed a health professional in the past year, to manage their arthritis. Just under half (49.5%) of the overweight/obese individuals reported being told by a health professional to exercise, and a similar number (45.5%) were told to control/lose weight. A slightly smaller percentage of the overweight/obese versus under/normal weight individuals (60.9% versus 67.1%, respectively) reported engaging in exercise to manage their arthritis symptoms. About 68% of overweight/obese individuals reported using weight control/loss to manage their arthritis symptoms.

In univariate analyses of overweight/obese individuals, we found no correlation between engaging in any arthritis self-management strategies and any of the following factors: age, income, marital status, region of residence, and time since diagnosis. Factors independently associated with not engaging in arthritis self-management strategies included: male sex; not having a

medical doctor; not taking medications; no reported recommendation by a health professional to exercise, control/lose weight or use assistive devices; the presence of co-morbidities; worse self-reported health; and less disability in activities of daily living.

Correlates of NOT engaging in ANY self-management activities, for overweight/obese (BMI>25) individuals with arthritis (N = 273)

Correlates	Crude RR	95% CI	Adjusted RR*	95% CI
Sex				
Female	Referent		Referent	
Male	1.64	1.12–2.40	1.71	1.16–2.52
Ethnicity				
Non-white	Referent		Referent	
White	3.48	1.49–8.15	2.87	1.07–7.74
Education				
Post-secondary	Referent		Referent	
Less than post-secondary	1.78	1.20–2.64	2.01	1.23–3.28
Medication use				
No medication	Referent		Referent	
Prescription meds only	0.62	0.35–1.12	0.91	0.71–1.16
Non-prescription meds only	0.38	0.24–0.61	0.90	0.68–1.19
Both	0.35	0.19–0.62	0.88	0.64–1.23
Any medication (excl. natural treatments)	0.43	0.28–0.64	0.90	0.68–1.19
Any medication (incl. natural treatments)	0.33	0.22–0.52	0.90	0.58–1.38
Knows type of arthritis				
Yes	Referent		Referent	
Doesn't know	1.50	1.01–2.24	1.47	1.1–1.95
Not receiving clinical recommendation to				
Exercise	3.09	2.02–4.72	1.26	0.61–2.62
Control/lose weight	2.47	1.52–4.03	1.31	1.07–1.60
Using assistive device	1.52	0.83–2.77	2.35	1.14–4.83
No recommendation at all	3.16	2.10–4.77	1.30	1.08–1.55
Co-morbidities				
Migraine	0.28	0.15–0.52	0.22	0.07–0.67
Ulcer	0.50	0.24–1.04	0.42	0.21–0.83
Self rated general health				
Fair or poor general health	0.69	0.45–1.07	0.74	0.57–0.97
Health somewhat worse/ much worse than 1 year ago	0.53	0.33–0.86	0.64	0.43–0.94
Satisfaction with life	0.54	0.27–1.01	0.46	0.22–0.95
Activity of Daily Living Limitations				
Severe limitation in at least one ADL	0.49	0.32–0.74	0.88	0.56–1.39
Medical doctor				
Has a medical doctor	0.39	0.23–0.66	0.79	0.67–0.92

RR = Relative Risk
* Adjusted for sex, age, race/ethnicity, education, marital status, income and region of residence.

Conclusion: Sub-sets of overweight/obese Canadians with arthritis are at risk for non-engagement in self-management activities. Ways that health professionals might encourage individuals with arthritis to engage in self-management may include providing more informed advice and targeted clinical recommendations.

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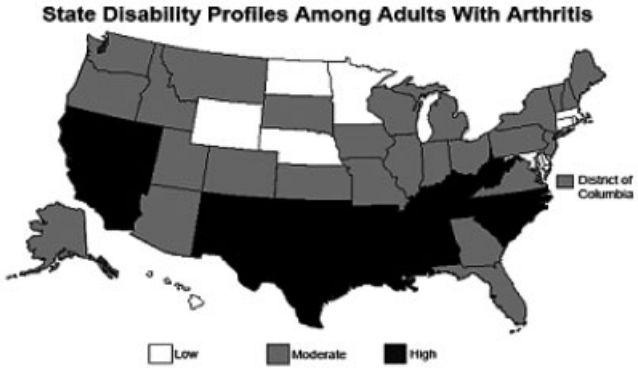
1563

State-Specific ICF Disability Profiles among US Adults with Arthritis. Jennifer M. Hootman[3], Kristina A. Theis[1], Julie Bolen[2] and Charles G. Helmick[1]. [1]CDC, Atlanta, GA, [2]CDC, [3]Centers for Disease Control, Kennesaw, GA

Background: Population level estimates of arthritis-related disability are needed to define the burden, identify target populations for intervention, and monitor effectiveness of public health programs. The International Classification of Function (ICF) is a standard framework used to describe health and disability and may be useful for population surveillance.

Methods: Data were from the 2009 Behavioral Risk Factor Surveillance System, an annual telephone health survey conducted in all 50 states and the District of Columbia (DC; n = 424,592 adults). Arthritis (ARTH) was defined as a 'yes' response to "Have you ever been told by a doctor or other health care professional that you have arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?". Three outcome measures, based on ICF domains, were created: 1) impairment = severe pain (PAIN), 2) limitation = activity limitation (AL), and 3) restriction = social participation restriction (SPR). PAIN was defined as 7 or higher on a 0–10 point scale. AL was defined as a limitation in usual activities due to arthritis. SPR was defined with a question asking about the extent that arthritis interfered with social activities such as shopping, going to movies or social gatherings. Respondents reporting "A lot" (versus "A little/Not at all") were defined as having SPR. State-specific prevalence estimates (%) and 95% confidence intervals (CI) among adults with arthritis were calculated for each of the ICF domains by state using statistical weights to account for the complex sample design. An overall state disability profile for each state was created using tertiles for each ICF domain. States in the highest tertile for all 3 ICF domains were classified as HIGH disability profile states and states in the lowest tertile for all 3 ICF domains were classified as LOW. All others were classified as MOD.

Results: Median prevalence for all 50 states/DC for each ICF domain were: PAIN = 23.9% (CI 22.3 – 26.2: state range 17.4% AK to 38.3% MS), AL = 44.6% (CI 43.5 – 46.1: state range 35.5% HI to 56.6% TN), and SPR = 14.8% (CI 14.0 – 15.9: state range 10.8% HI to 28.7% TN). Ten states (19.6%) were classified as having a LOW, 27 states (52.9%) were classified as MOD, and 14 states (27.5%: AL, AR, CA, KY, LA, MS, NV, NM, NC, OK, SC, TN, TX, WV) were classified as having a HIGH disability profile (figure). Tennessee, had the worst disability profile of all states/DC, ranking 50th in PAIN (35.7%), 51st in AL (53.6%) and 51st in SPR (14.8%). An estimated 14.5 million US adults with arthritis live in states with HIGH arthritis-related disability profiles.



Conclusions: These data identify states with poor disability profiles which may be high priority targets for widespread dissemination of evidence-based public health interventions that improve pain and function among adults with arthritis.

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Statistical Methods Analyzing Count Data with Excessive Zeros in Arthritis Research. Bin Zhang[3], Jingbo Niu[5], Yanyan Zhu[6], Tuhina Neogi[2], Ling Xu[1], David T. Felson[7], Michael P. LaValley[8] and Yuqing Zhang[4]. [1]Beijing, China, [2]Boston Univ Schl of Med, Boston, MA, [3]Boston Univ Schl of Medicine, Boston, MA, [4]Boston Univ School of Medicine, Boston, MA, [5]Boston University, Boston, MA, [6]Boston University, [7]Boston University School of Medicine, Boston, MA, [8]BU School of Public Health, Boston, MA

Background: Arthritis research data are often collected in multiple joints within a person (i.e., number of hand joints with Radiographic Osteoarthritis (ROA)) or multiple sub-regions of a joint (i.e., number of sub-regions with cartilage loss in a knee). It is common that the outcome measures contain excessive zeros (zero-inflated data), e.g., the majority of the study subjects have zero count of hand joint ROA. When assessing the relationship between outcome measure of interest (e.g., number of hand joint ROA) with risk factors (e.g., obesity), commonly used statistical methods, including Poisson regression and generalized estimating equations (GEE) model, fail to account for the zero-inflated data, resulting in not only producing biased effect estimates but also creating artificial association between disease outcomes and their risk factors.

Methods: We use zero-inflated models, mixture models that have two parts: one part deals with the excessive zeros and the other part with a usual random variable (RV) such as a negative binomial (NB), to analyze zero-inflated data. We simulated 1000 zero-inflated negative binomial RV Y, where Y=0 with proba-

bility only related to predictor x3, otherwise Y has NB distribution associated with predictors x1 and x2. We used 3 statistical models: the GEE model, the Zero-inflated Poisson regression model (ZIP), and the zero-inflated NB regression model (ZINB) to analyze the simulated data. We applied the same three models to examine the relation of body mass index (BMI) to the prevalence of ROA among participants in the Beijing Osteoarthritis Study.

Results: As shown in Table 1, the effect estimates (i.e., $\beta 1$, $\beta 2$, $\beta 3$) obtained from ZINB model is closer to true values than those from either GEE or ZIP model. Furthermore, GEE model generated a false association between X3 and Y, whereas no such an association was found using ZIP or ZINB models. Among participants of the BOA study, 70.8% of subjects had no ROA in any hand joints. The prevalence ratio or hand OA (PR) is significantly associate with BMI, per 5 unit BMI increase PR=1.2 (95% CI:1.12–1.28, P<0.001) from GEE model and 1.12 (95% CI: 1.03–1.22, P<0.01) from ZIP model, and no significant associate found, PR=1.10 (95% CI: 0.95–1.27, P=0.2) from ZINB model, adjusting for age and sex. A goodness-of-fit test suggests that the ZINB model should be used instead of the ZIP or Poisson regression models. Thus, the positive association between BMI and hand ROA obtained from GEE model may be false due to ignoring the zero-inflated phenomenon.

Table 1. Simulation Results

	$\beta 1$	$\beta 2$	$\beta 3$ (when Y is NB)	$\beta 3^*$ (when Y=0)
True Values	0.8	0.5	0	5
GEE	0.77 (0.73, 0.82)	0.39 (0.35, 0.44)	−0.73 (−0.77, −0.69)	Can not be estimated
ZIP	0.75 (0.71, 0.80)	0.44 (0.39, 0.49)	0.01 (−0.06, 0.07)	4.45 (3.74, 5.25)
ZINB	0.78 (0.70, 0.85)	0.47 (0.40, 0.54)	−0.01 (−0.11, 0.10)	5.01 (4.10, 5.92)

Conclusion: We demonstrated the superiority of zero-inflated models analyzing count data with excessive zeros. We show that zero-inflated models are important not only to discover the unbiased associations between outcomes and their risk factors but also to avoid introducing false association when there is none.

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The Association of Race with Gout: A Broadly Representative Inpatient Survey. Allan C. Gelber[1], Janet W. Maynard[2] and Carlton Haywood, Jr[2]. [1]Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD

Purpose: Gout is a leading cause of inflammatory arthritis. Established risk factors for gout include age, gender, hypertension and obesity. Relatively few studies have examined the association of race with gout status. We sought to determine, in a large, nationally representative survey of inpatient hospital stays, whether race was independently related to gout risk.

Method: We examined the 2004 Nationwide Inpatient Sample. In that calendar year, 37 states contributed data to the survey. For each hospital stay, one primary and 14 secondary ICD-9 diagnoses were recorded, as well as race, age, gender, socioeconomic status (SES) measures of health insurance and median household income for ZIP code. Hospital size and teaching status were recorded. We ascertained all hospital stays with a primary or secondary diagnosis of gout. The presence of co-morbid hypertension, obesity, acute and chronic renal insufficiency and sickle cell disease was identified. Our analyses were restricted to the 26 states that used race as a demographic code, and to patients aged 18–65 years. Using logistic regression, we examined the independent association of race with prevalent gout, with adjustment for demographic variables, co-morbidity profile, SES and hospital characteristics.

Results: A total of 2,332,974 hospital stays met the inclusion criteria. There were 18,851 (0.8%) hospitalizations in which a discharge diagnosis of gout was recorded. Overall, the study population was 62% female, 22.3% black and 77.7% white. Mean age was 43 years. In the dataset, 20% were receiving Medicaid, 29% had a household income <$36,000, 7% were diagnosed with obesity, 29% with hypertension, 2% with acute and 1.5% with chronic renal failure. These admissions were comprised of 47% urban teaching hospitals; 44% in the South, 26% in Northeast. Compared to the white patients, the risk of gout among the black patients in the survey is as follows:

Model	OR	95% CI
Race, unadjusted	1.44	1.40–1.49
Race, age-adjusted	1.71	1.66–1.76
Race, gender-adjusted	1.46	1.41–1.51
Race, hypertension-adjusted	1.14	1.11–1.18
Race, obesity-adjusted	1.43	1.39–1.48
Race, age, gender, hypertension, obesity	1.51	1.46–1.56
Race, age, gender, co-morbidity, SES, hospital profile-adjusted	1.51	1.45–1.56

Conclusion: In a broadly representative 2004 sample of US hospitalizations, black race was associated with a 50% increase in risk for coexistent gout. Clinicians evaluating hospitalized adult patients who manifest joint pain and swelling, ought to consider the greater burden of gout among the black segment of the American population.

Disclosure: A. C. Gelber: None; **J. W. Maynard:** None; **C. Haywood, Jr:** None.

1566

The Clinical and Economic Burden of Corticosteroid Adverse Events (AEs): A Systematic Literature Review. Evelyn F. Sarnes[2] and Maria E. Watson[1]. [1]GlaxoSmithKline, Research Triangle Park, NC, [2]Xcenda, Palm Harbor, FL

Background: Systemic corticosteroids are an important and commonly used therapy; however, their use must be balanced against a set of side effects. This study evaluated the clinical and economic burden of systemic corticosteroid AEs in a wide variety of patient populations. A secondary objective was to consider the clinical and economic impact of reducing daily corticosteroid doses.

Methods: A systematic review of 2007–2009 studies retrieved by a predefined search strategy in Medline, EMBASE, and Cochrane Library, as well as AHRQ, NICE, and NHS HEED (free text) was performed to supplement an existing literature review. Relevant articles (observational and intervention studies) evaluated incidence/relative risk of AEs following corticosteroid use or the relationship between dose/duration and AEs. Case studies, studies in infants, and studies with inhaled corticosteroids were excluded. Titles/abstracts of retrieved articles were screened for eligibility. A secondary search, based on citations from other systematic reviews and including pre-2007 articles, was conducted to obtain data on psychiatric conditions, infections, and peptic ulcers. Information about dose-response relationships was combined with cost data from the literature to estimate the cost implications of a dose reduction for two corticosteroid AEs.

Results: A total of 323 articles were evaluated from the primary search; 27 were included. Excluded articles did not focus on corticosteroid AEs (n=70), were case studies (n=50), evaluated corticosteroid efficacy (n=38), or evaluated therapy to alleviate corticosteroid AEs (n=13). The secondary search added 20 studies. Overall, 25 were retrospective in design, 13 were conducted in the US and 21 in Europe. The AEs for which the literature contained the greatest number of reports were psychiatric events (18 reports), infections (15), gastrointestinal (GI) conditions (14), and fracture (11). Common AEs (>30% incidence) with a greater number of reports were sleep disturbances, lipodystrophy, adrenal suppression, and hypertension. The incidence of fracture varied by location: wrist fracture, Colles' fracture, and lower limb fracture were generally low (incidence 3–5%). Vertebral fractures were more common (range, 21–30%). Severe GI AEs were less frequent (ulcers, 1–5%; bleeding, 3–5%). Despite wide variability in study design, population, daily dose, conditions treated, and treatment duration, most AEs (fracture, myocardial infarction (MI), weight gain, infections, glaucoma, and psychiatric events) demonstrated a dose-response pattern with increasing daily dose. Studies of fractures and MIs demonstrated the clearest dose-response relationship. As such, reducing daily dose requirements may reduce AE clinical and economic burden. For example, dose reduction from 7.5–15 mg/day to <7.5 mg/day may avoid 96 fractures per 10,000 elderly patients at $18,358 per fracture and a reduction from >10 mg/day to ≤10 mg/day avoid 19 MIs per 10,000 patients at $26,472 per MI (US $ 2009).

Conclusions: The clinical and economic burden of corticosteroid AEs is substantial; lowering the daily dose requirements may lower the incidence of many AEs.

Disclosure: E. F. Sarnes: GlaxoSmithKline, 5; **M. E. Watson:** GlaxoSmithKline, 3.

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The Cost-Effectiveness of Corticosteroid Injection of the Carpal Tunnel. Suzanne L. DeLea[1], Janet L. Poole[1], Natalia Chavez-Chiang[2], Wilmer L. Sibbitt[3] and Arthur D. Bankhurst[4]. [1]University of New Mexico, Albuquerque, NM, [2]University of New Mexico, [3]University of New Mexico HSC, Albuquerque, NM, [4]University of NM Med Ctr, Albuquerque, NM

Objective: Corticosteroid injection is a useful and low-cost therapy for carpal tunnel syndrome.This randomized controlled study addressed whether two different low-cost injection techniques affected the outcomes and cost-effectiveness of carpal tunnel injections.

Design: Prospective, randomized, controlled, single-blinded interventional trial.

Setting: Hospital outpatient musculoskeletal clinic.

Patients: 64 subjects with symptomatic carpal tunnel syndrome.

Interventions: 64 wrists with carpal tunnel syndrome were randomized to palpation-guided anatomic carpal tunnel injection with 80 mg triamcinolone acetonide by: 1) a conventional technique, or 2) injection by a mechanical syringe, the RPD (the reciprocating procedure device) syringe. A one-needle, two-syringe technique with hydrodissection by 1% lidocaine was used.

Main Outcome Measurements: Baseline pain by 10 cm Visual Analogue Pain Scale (10 cm VAS), procedural pain, pain at outcome (2 weeks and 6 months), responders, therapeutic duration, reinjection rates, total cost/patient/year, and cost/responder/year were determined.

Results: Both methods reduced pains cores by greater than 50% from baseline at 2 weeks ($p<0.001$). Relative to the conventional method, the mechanical syringe resulted in 62% greater reduction in injection pain ($p<0.02$), a 68% increase in responder rate ($p<0.02$), 50% reduction in non-responder rate ($p<0.02$), 57% increase in therapeutic duration ($p<0.001$), a 25% increase in time to next procedure, a 36% ($43 US) reduction in cost/patient/yr for a patient treated in a physician office ($p<0.001$), and a 34% reduction ($33 US) in cost/patient/year for a hospital outpatient ($p<0.001$) as well as reduced cost/responder/year ($p<0.001$).

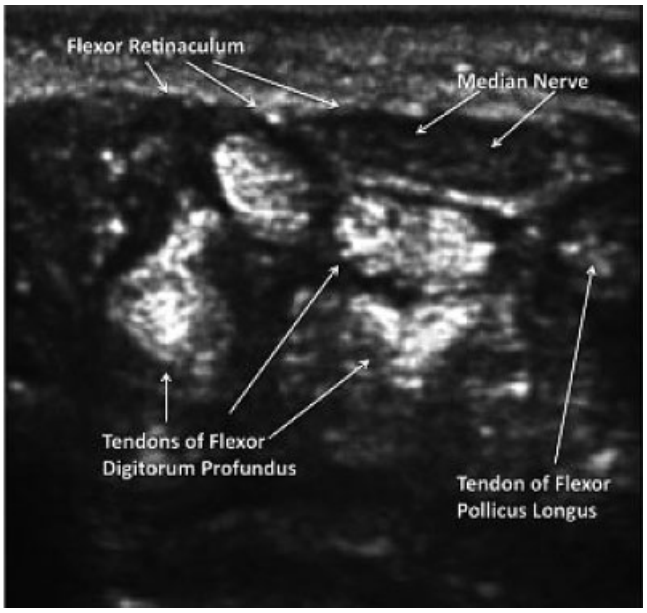
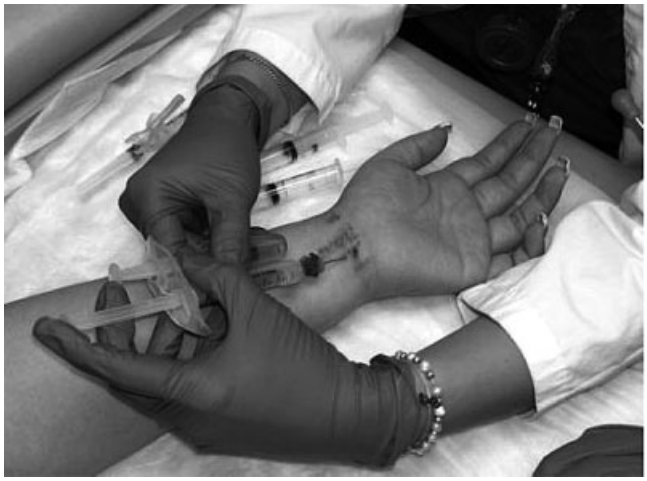


Figure 1.



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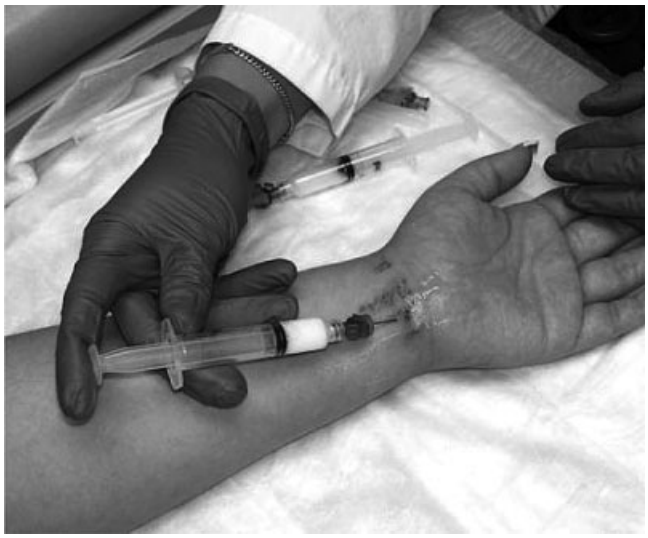

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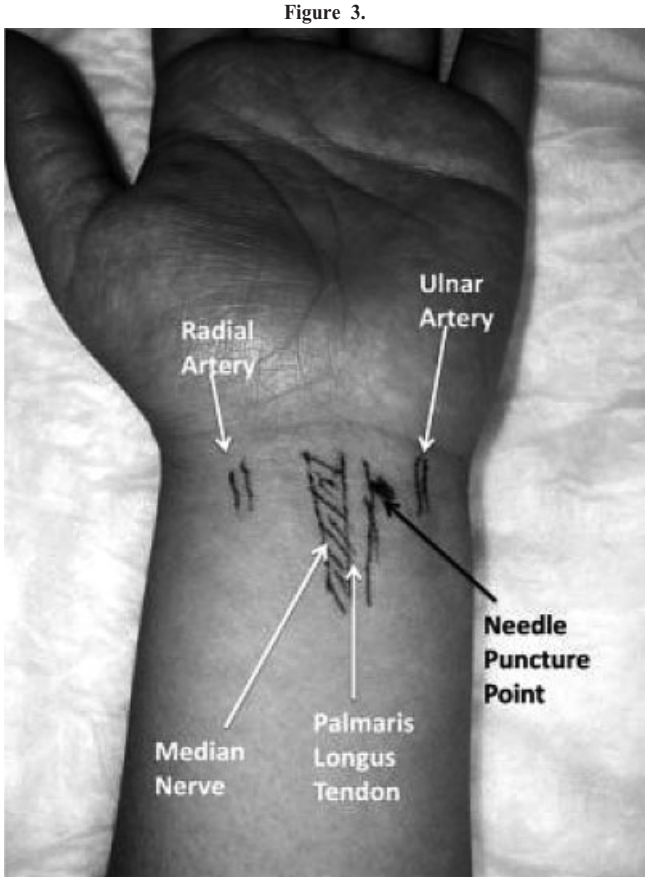

Figure 4.

Conclusion: Cost-effectiveness and outcomes of corticosteroid injection for carpal tunnel syndrome can be significantly improved by using low-cost alterations in technique.

Disclosure: S. L. DeLea: None; **J. L. Poole:** None; **N. Chavez-Chiang:** None; **W. L. Sibbitt:** Abbott Intravascular, Inc, 1, 9, Apple, Inc, 1, 9, Avanca Inc, 1, 9, Avanca Medical Devices, Inc, 1, 9, Avasca Medical, Inc, 1, 9, Avasca, Inc, 1, 9, Becton Dickinson, 9, Celgene, 1, Ferring Pharmaceuticals Inc., 9, Intellige; **A. D. Bankhurst:** None.

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The Prevalence and Characteristics of Fluorosis Causing Skeletal Deformities in Rural Tanzania. Helen G. Jarvis[2], Peta S. Heslop[2], John Kissima[1] and Richard Walker[3]. [1]Hai District Hospital, Kilimanjaro Region, Tanzania, East Africa, [2]Newcastle upon Tyne NHS Foundation Trust, Newcastle upon Tyne, United Kingdom, [3]Northumbria Healthcare NHS Foundation Trust, Tyne & Wear, United Kingdom

Introduction: Excessive ingestion of fluoride affects bone during growth causing a condition known as skeletal fluorosis (SF). This process can distort the congruence of joints, particularly weight bearing joints, leading to bone and joint pain. Previous small case series have reported rheumatological deformities in areas with high fluoride concentrations in the drinking water. Due to the harmful effects of excessive fluoride to teeth and bone the WHO (2004) recommended that fluoride levels in drinking water be < 1.5 mg/L. The area of Tanzania where the study was based had reported levels of fluoride as high as 35 mg/L in the ground water.

A survey was carried out to estimate the prevalence of SF in a Northern Tanzania village and the study was designed to focus on identifying those with deformity and disability due to SF.

Methods: Using census information a door to door survey was conducted to identify cases of SF. Based on literature review and expert opinion, a diagnosis of severe SF was made if the following were identified on clinical examination: abnormal coronal tibio-femoral angle, sabre tibia or juvenile kyphosis/scoliosis with no alternative cause. Cases were then examined for other clinical manifestations, and disability/pain levels were estimated using a 4 point Likert scale. Social & educational exclusion were also assessed as part of the estimate of disease burden.

Results: A population of 1435 were studied 762 (53%) Female & 673 (47%) Male, of whom 1135 (79%) were under 30 years of age. We identified 56 cases (22 (39%) female & 34 (61%) male) of severe SF (aged 2 – 30 yrs). This gives a crude prevalence of 3.9% of severe deforming disease.

52 (93%) had evidence of coronal tibio-femoral joint deformities - 45 valgus & 7 varus. Sabre tibia was identified in 18 (32%) and juvenile scoliosis/kyphosis in 3 (5%) of the cases. Combinations of the above diagnostic criteria were common with 2 cases having all 3 conditions.

Pain was reported in 37 (66%) cases using the ascending 4 point Likert severity scale. 25 (45%) reported moderate to severe pain & 36 (64%) reported limitation of normal activities. 97% had knee and lower limb pain with only 32% of those reporting pain in other skeletal sites.

17 (30%) felt their school attendance had been affected & 5 (9%) felt they were treated differently by their peers due to their SF.

Financial constraints meant only those with the worst deformities were referred for corrective surgery. 11 children have been operated on to date.

Conclusion: In this area with very high levels of fluoride in the ground water, SF is a common condition. The prevalence of nearly 4% in this village represents only the most severe end of the spectrum, being an estimate of the disability and burden that this condition causes in a community ingesting excessive amounts of fluoride. It appears that only the under 30's in the population have been affected by severe SF, most likely due to the time of construction of the deep wells in the area, which carry higher fluoride levels than surface water. Severe SF also seems to be more common in males than females, possibly due to hormonal effects. The study group is currently investigating why, despite endemic exposure, only a minority appear to develop severe deforming disease.

Disclosure: H. G. Jarvis: None; **P. S. Heslop:** None; **J. Kissima:** None; **R. Walker:** None.

1569

Thiazide and Loop Diuretics Are Associated with Incident Gout in the Atherosclerosis Risk in Communities (ARIC) Study. Mara A. McAdams[4], Janet W. Maynard[2], Allan C. Gelber[1], Alan N. Baer[3] and Josef Coresh[4]. [1]Baltimore, MD, [2]Johns Hopkins Univ, Baltimore, MD, [3]Johns Hopkins University, Baltimore, MD, [4]Johns Hopkins, Bloomberg School of Public Health

Background: While there is a clear association between diuretic use and the development of gout, it is unclear whether both thiazide and loop diuretics are associated with an increased incidence of gout. We quantified the association between incident gout and diuretic use, type of diuretic.

Methods: ARIC is a prospective population-based cohort study of 15,792 individuals recruited in 1987–1989 from four US communities. It consists of 1 baseline visit (visit 1) and 3 follow-up visits administered 3 years apart. At ARIC visit 4, participants were asked, "Has a doctor ever told you that you had gout?" Participants were excluded if they did not attend visit 4 or had gout prior to visit 1. At baseline, blood pressure values were measured. Participants were asked to bring all medications that they had taken in the past 2 weeks to the baseline visit. Medication data, including diuretic use and class, were obtained by trained interviewers reviewing prescription bottles. Hypertension (HTN) was defined by the report of a medication to treat HTN or a blood pressure measurement $> 140/90$ mm Hg.

We examined whether baseline diuretic use was associated with incident gout over 9 years of follow-up. We used logistic regression to calculate the odds of incident gout associated with diuretic use in the whole population and the subset with baseline HTN. All models were adjusted for age, sex, race, HTN and baseline body mass index, estimated glomerular filtration rate, diabetes, and protein and alcohol intake. The models for loop diuretics were also adjusted for CHF diagnosis.

Results: There were 10,872 participants who met the study criteria; 1,643 (15%) took a diuretic, 3,248 (30%) had HTN at baseline and 43% of the HTN patients were taking a diuretic. The study population was 57% female and 22% African-American. There were 286 gout cases. Per 1000 participants, the cumulative incidence of gout was 28 overall, 61 among those who reported diuretic use in the 2 weeks prior to the baseline visit, 21 for those not exposed to a diuretic, and 51 for those with HTN. Baseline use of any diuretic, including thiazide and loop diuretics, was associated with an approximately 2-fold increased risk of incident gout, after adjustment for confounders. Among the participants with HTN, the risk of gout was increased approximately 1.5-fold compared to non-diuretic users. Results were similar by sex and race, except for the association of loop diuretics (African-America, Adjusted OR=0.76, not significant) and (White, Adjusted OR= 3.6, p-value< 0.001).

Table. Odds of gout by diuretic use and class

Participants using diuretics (n=1,549) vs. participants not using diuretics, n=10,872 with 286 incident gout cases

	Any diuretic use	Thiazide	Loop
Gout	94	44	16
No Gout	1,549	799	158
Unadjusted OR	2.87 (2.23, 3.69)	2.24 (1.61, 3.11)	3.91 (2.30, 6.62)
Age adjusted OR	2.85 (2.21, 3.68)	2.21 (1.59, 3.08)	3.86 (2.28, 6.55)
Fully adjusted OR	2.26 (1.70, 3.00)	1.93 (1.35, 2.74)	2.14 (1.11, 4.14)

Participants with hypertension using diuretics (n=1,299) vs. participants not using diuretics, n=3,248 with 165 incident gout cases

	Any diuretic use	Thiazide	Loop
Gout	86	43	11
No gout	1,299	693	95
Unadjusted OR	1.50 (1.09, 2.05)	1.22 (0.85, 1.74)	2.25 (1.18, 4.28)
Age adjusted OR	1.50 (1.10, 2.06)	1.22 (0.85, 1.74)	2.27 (1.19, 4.33)
Fully adjusted OR	1.49 (1.06, 2.10)	1.44 (0.99, 2.10)	1.29 (0.57, 2.93)

Note: OR refers to odds ratios and we presented 95% Confidence Intervals. We did not calculate odds ratios for the exposure to thiazide diuretics because there was only one exposed case.

Conclusion: Our results suggest that diuretic use is associated with incident gout. Thiazide and loop diuretics were associated with twice the risk of gout. This study supports the previously reported association of diuretic use with gout and suggests that this association occurs with both loop and thiazide diuretics in a population based multi-ethnic sample reporting gout incidence.

Disclosure: M. A. McAdams: None; **J. W. Maynard:** None; **A. C. Gelber:** None; **A. N. Baer:** None; **J. Coresh:** None.

1570

Trends in Orthopedic Surgery Utilization among Patients with Rheumatoid Arthritis: A Focus on Surgery Type and Gender. Courtney A. Shourt[1], Cynthia S. Crowson[2], Sherine E. Gabriel[3] and Eric L. Matteson[4]. [1]Department of Medicine, Mayo Clinic College of Medicine, [2]Division of Biostatistics, Department of Health Science Research, Mayo Clinic College of Medicine, [3]Division of Epidemiology, Department of Health Science Research, and Division of Rheumatology, Mayo Clinic College of Medicine, [4]Division of Rheumatology, and Division of Epidemiology, Mayo Clinic College of Medicine

Objective: To describe current trends in arthritis related orthopedic surgery utilization amongst a population based cohort of patients with rheumatoid arthritis (RA).

Methods: A retrospective medical record review was performed of all incident cases of adult onset RA from a defined geographic population base who fulfilled criteria for RA in 1980–2007. Orthopedic surgeries occurring after the incidence date were recorded, including primary total joint arthroplasty (TJA), joint reconstructive procedures (JRP), soft tissue procedures (STP) and revision arthroplasty, classified according to joint involved (hip, knee, wrist, shoulder, elbow, hand, ankle, foot, cervical spine and temporomandibular). Cumulative incidence of surgery was estimated using Kaplan-

Meier methods. Time trends and gender differences were examined using Cox models.

Results: The study included 814 RA patients (mean age: 56 years; 68% female; mean follow-up 9.6 years). A total of 190 patients underwent ≥1 surgical procedures involving joints during follow-up. The cumulative incidence of any joint procedure at 10 years for 1980–1994 was 30.4% compared to 21.9% for 1995–2007 (p=0.08). The cumulative incidence of all joint surgeries was lower in the 1995–2007 cohort compared to the 1980–1994 cohort, with the greatest reduction in soft tissue procedures (synovectomies, tendon repairs, tendon transfers, meniscus repair, ligament release, cartilage repair), which decreased from 13.4% in 1980–1994 to 7.3% in 1995–2007 at 10 years after RA incidence (p=0.018). Knee surgeries were less common in patients diagnosed in 1995–2007 compared to those diagnosed in 1980–1994 (hazard ratio [HR]: 0.56; p=0.045), as were hand surgeries (HR: 0.45; p=0.059), but there was no change in hip surgeries (p=0.68). There were more surgeries preformed (across all surgery types) amongst female patients with a cumulative incidence of 29.4% at 10 years compared to 23.5% for men during the same time period (p=0.057).

Conclusion: The rates of arthritis related surgery continue to decrease for patients more recently diagnosed with RA, especially soft tissue procedures and knee surgeries. This trend is particularly noticeable in women. This decrease in rates may reflect improved treatments or secular trends in disease expression or changes in practice patterns.

Disclosure: C. A. Shourt: None; **C. S. Crowson:** None; **S. E. Gabriel:** None; **E. L. Matteson:** None.

1571

Understanding Billing Data: A Survey of Billing Process and Codes Used by Family Physicians for Rheumatological Conditions. Diane Lacaille, Jack Chang and Pamela Rogers. Arthritis Research Centre of Canada, Vancouver, BC, Canada

Objectives: Administrative data are increasingly used for research purposes. Accuracy of diagnostic codes used in billing data is a common concern, especially for data from family physicians (FPs). The objectives of our study were: 1) To understand the process used by FPs from different practice settings for billing and assigning diagnostic codes; 2) To identify the specific diagnostic codes commonly used by FPs for various rheumatologic diseases.

Methods: A sample of 343 FPs were randomly selected from the list of all FPs in the province, while ensuring a representative distribution of gender, time since graduation, and geographic location (health authority). FPs with specialized practices, in fully administrative roles, or not in active practice were excluded. Self-administered surveys were sent by fax. Reminders were sent to non-responders twice, at two week intervals. The survey elicited information about their practice setting, the process they used for billing and for assigning diagnostic codes, as well as information about their choice of diagnostic codes for selected rheumatologic conditions. Descriptive analysis was performed.

Results: Of the 343 FPs invited to participate, 74(5%) were ineligible, and 130 (48%) participated. The sample included 79% in full-time practice, 61% in urban areas, 67% with > 20 years since graduation and 37% who used electronic medical records (EMR). Results indicated that 67% of FPs select the diagnostic code themselves, 15% use EMR to assign the diagnostic code, and 10% have their MOAs assign the code. When coding themselves, 76% of FPs reported using a specific code for each type of arthritis, while 24% reported using the same code for all arthritis. Of those, commonly used codes included 781 (MSK symptom) [41%], 715 (OA) [22%], 716 (unspecified arthritis) [16%] and 714 (RA) [13%]. When patients present with multiple complaints, 46% of FPs reported submitting the code for the complaint which took the most time. When asked which code they used for specific types of arthritis, FPs provided the correct code for RA in 83% of respondents, OA (76%), Gout (83%), AS (63%), PsA (14%) with 23% using the code for psoriasis, SLE (13%). Subgroup analysis showed that practice setting (rural vs urban), but not other practice characteristics, influenced use of diagnostic codes. FPs in rural settings were more likely to use specific codes for each type of arthritis [86% vs 65% of urban FPs], and to select accurate codes (RA: 93% vs. 75%, rural vs. urban resp., OA: 85% vs. 69%, Gout: 83% vs. 60%, p<0.05).

Conclusion: Most FPs selected the diagnostic code themselves, use specific codes for each arthritis, and use the code for the complaint which took the most time. Selection of the accurate code for specific types of arthritis occurred in greater than 70% of respondents for OA, RA, and gout, but was inadequate for PsA and SLE. However, the use of a single code for all types of arthritis by nearly a quarter of FPs, with some using OA and RA, as well as misclassifications when specific codes were used, may lead to false positive cases of OA and RA. Further research is needed to validate diagnostic codes used by FPs in order to fully understand the impact of coding errors on estimates of prevalence.

Disclosure: D. Lacaille: None; **J. Chang:** None; **P. Rogers:** None.

1572

Urate-Lowering Therapy in Chronic Gout Results in Clinically Important Improvements in Health-Related Quality of Life—SF-36 Is Responsive to Change in Chronic Gout. Puja Khanna[2], Fernando Perez-Ruiz[1], Paul Maranian[2] and Dinesh Khanna[2]. [1]Hospital de Cruces, [2]UCLA

Purpose: SF-36 is a validated outcome measure to assess generic health-related quality of life (HRQOL) in patients with gout. We assessed HRQOL in patients with gout in an academic outpatient rheumatology setting.

Methods: SF-36 was administered at baseline, then at yearly intervals. Patients who had a gout flare within the past 1 month were excluded. We assessed statistical significance and the minimal clinically important differences (MCID) at the first and second year. Statistical significance was evaluated using paired t-test for changed scores of the SF-36 scales. MCID for SF-36 scales and summary scores was defined as improvement of ≥5 points and ≥2.5 points at 12 months, respectively. We assessed responsiveness to change (effect size) and interpreted it based on Cohen's criteria: 0.20–0.49 as small, 0.50–0.79 as moderate, and >=0.80 as large, and the predictors for improvement in the SF-36 scales and summary scores. We assessed improvement (defined as >=MCID) in 8 SF-36 scales and 2 summary scales. Independent variables included age, tophi (presence/absence), comorbidities (presence/absence), baseline joint involvement, baseline serum urate levels, change in serum urate level and number of flares from baseline to 12 months.

Results: Of 99 subjects, 96 were male, mean age was 57.1 years, disease dur was 8.2 years, 47% had associated comorbidities, 40% had tophi, and 64% had evidence of radiographic damage. Data was available for 77 patients at 1 year and 36 patients at 2 years. Patients were treated with urate lowering therapy (ULT) including allopurinol (N=64), benzbromarone (N=4), or combination therapy (N=1); only 7 patients were on oral colchicine. Baseline mean (SD) serum urate level was 8.9 (1.36) mg/dl and mean numbers of flares were 4.7 (4.5) over the last year. Patients with presence of tophi, polyarticular disease, and radiographic damage had lower SF-36 scores compared to patients without it. Urate-lowering therapies were associated with reduction in serum uric acid to 5.46 (1.1), (-3.44 (1.73); p< 0.001) and number of flares (-4.00 (4.32); p<0.001) over 12 months; and associated with a statistically significant and clinically meaningful improvement in the SF-36 scales and summary scores at 12 months (Table). Reduction in flares independently predicted improvements in SF-36 scales (bodily pain, physical functioning, and role physical) at 1 year after adjusting for the covariates (p values= 0.001–0.06). Improvement in SF-36 scores was maintained at 2 years.

SF-36	Baseline Mean (SD)	1-Year Mean (SD)	Effect Size#	% achieving MCID
Physical function	43.39 (11)	48.44 (8.33)*	0.48	34
Role Physical	43.68 (11.41)	49.44 (10.41)*	0.50	36
Bodily Pain	39.91 (11.23)	52.12 (10.77)*	1.09	69
General Health	43.04 (8.92)	47.12 (9)*	0.49	38
Vitality	50.74 (12.24)	54.97 (11.2)*	0.31	41
Social functioning	45.5 (11.89)	51.18 (8.82)*	0.40	53
Role emotional	48.98 (11.04)	51.69 (8.69)	0.20	22
Mental health	49.73 (11.92)	52.91 (10.51)	0.21	30
SF-36 PCS	40.37 (9.45)	48.48 (8.89)*	0.91	70
SF-36 MCS	52.16 (10.8)	54.15 (9.3)	0.08	38

* p<0.001

Conclusion: In this real-life observational cohort, appropriate gout specific-therapy was associated with statistical and clinically meaningful improvements in the number of flares and HRQOL at 1 year then maintained at 2 years. SF-36 is responsive to change with treatment in gout over time. Our data shows that SF-36 is responsive to change in chronic gout.

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1573

Validation of Diagnostic Codes for Subtrochanteric, Diaphyseal, and Typical Hip Fractures Using Administrative Claims Data. Pongthorn Narongroeknawin, Nivedita M. Patkar, Bita Shakoory, Archana Jain, Jeffrey R. Curtis, Elizabeth Delzell, Philip H. Lander, Robert Lopez-Ben, Michael J. Pitt, Monika M. Safford, David A. Volgas and Kenneth G. Saag. Univ of Alabama at Birmingham, Birmingham, AL

Background: As part of developing administrative claims-based algorithms for identifying subtrochanteric and diaphyseal fractures of the femur (SFF and DFF), we assessed the accuracy of hospital and physician diagnosis codes for these fractures. Algorithms that combined hospital discharge with surgeon's diagnosis codes to identify cases of these fractures yielded relatively high positive predictive values (PPV) and will be useful in future population-based observational studies.

Methods: Candidates for study inclusion were all patients with an ICD-9 diagnosis code for femoral fracture, at a University hospital from 01/2004 to 12/2008. Individuals with hospital discharge diagnosis for open femoral fracture and distal end femoral fractures were excluded because these fractures are usually caused by major trauma and not associated with longer term bisphosphonates use.

Based on the clinical history, radiology report, operative note, and discharge summary accounting for the fracture admission, patients were assigned to one of the following classifications: (1) SFF, defined as fracture at the region between the lesser trochanter and a point 5 centimeters distal; (2) DFF, defined as fracture at the region between subtrochanteric and supracondylar areas; or (3) "typical" hip fracture, other than SFF and DFF. We classified suspected SFF and DFF cases according to several alternative algorithms based on ICD-9 diagnosis codes, with the goal of identifying the algorithm that maximized PPV.

Result: We identified 137 persons with a suspected SFF and randomly selected 50 persons each with a suspected DFF or typical hip fracture. The PPV of case algorithms, which were varied based on the position and source of the diagnosis codes on medical claims, ranged from 69–89% for SFF, from 89–98% for DFF, and from 85–98% for typical hip fracture.

In a subgroup analysis, the PPVs of the various algorithms for SFF and typical hip fracture among patients age > 55 years and among patients without major trauma ICD-9 codes were the same as those in the primary analysis. In contrast, the PPVs of algorithms for DFF were lower for these subgroups than those in primary analysis. However, the number of confirmed DFF cases in these subgroups was small.

Conclusions: Administrative claims data-based algorithms that combined hospital discharge with surgeon's diagnosis codes to identify cases of SFF, DFF, and typical hip fracture yielded high PPVs. These claims algorithms will be useful in future population-based observational studies to evaluate the association between osteoporosis medications and subtrochanteric and diaphyseal fractures.

Table 1. Characteristic of Validation Sample

	All patients (n=235)	Subtrochanteric fracture[1] (n = 137)	Diaphyseal fracture[2] (n = 55)	Typical hip fracture[3] (n = 60)
Age (Mean ± SD)	48 ± 21	45 ± 20	41 ± 20	57 ± 23
Female (%)	36	32	38	43
Presence of major trauma code[4] (%)	71	81	87	53

[1] Subtrochanteric fracture (ICD-9; 820.22).
[2] Diaphyseal fracture (ICD-9; 821.00 and 821.01).
[3] Typical hip fracture (ICD-9; 820.00, 820.01, 820.02, 820.03, 820.09, 820.20, 820.21, and 820.8).
[4] Major trauma code (ICD-9; E800–E848, E881–E884, E908–E909, and E916–E928)

Table 2. Positive Predictive Value (PPV) of Various Case Identification Algorithms for Subtrochanteric, Diaphyseal, and Typical Hip Fractures

			Subgroup analyses					
	All patients		Patient age > 55 years		Patient without major trauma code**		Patient age > 55 years and without major trauma code**	
Case Identification Algorithm	Number of identified cases by different algorithms (%)*	PPV (95% CI)	Number of identified cases by different algorithms (%)*	PPV (95% CI)	Number of identified cases by different algorithms (%)*	PPV (95% CI)	Number of identified cases by different algorithms (%)*	PPV (95% CI)
Subtrochanteric Femoral Fractures								
• Any position on hospital discharge diagnosis list (primary or other)	137 (100)	69 (61–76)	43 (100)	72 (59–86)	33 (100)	76 (61–90)	22 (100)	73 (54–91)
• Primary hospital discharge diagnosis	107 (78)	74 (66–82)	37 (86)	78 (65–92)	28 (85)	82 (68–96)	19 (86)	79 (61–97)
• Surgeon's diagnosis on administrative claim	87 (64)	82 (73–90)	31 (72)	81 (67–95)	25 (76)	80 (67–93)	17 (77)	82 (64–93)
• Both primary discharge diagnosis AND surgeon's diagnosis	62 (45)	89 (81–97)	30 (70)	93 (84–100)	21 (64)	91 (78–100)	12 (55)	92 (76–100)
Diaphyseal Femoral Fractures								
• Any position on hospital discharge diagnosis list (primary or other)	55 (100)	89 (81–97)	12 (100)	67 (40–93)	9 (100)	78 (51–100)	5 (100)	60 (17–100)
• Primary hospital discharge diagnosis	35 (64)	94 (87–100)	8 (67)	80 (52–100)	7 (78)	86 (60–100)	4 (80)	75 (33–100)
• Surgeon's diagnosis on administrative claim	46 (84)	98 (93–100)	7 (58)	86 (60–100)	8 (89)	88 (65–100)	4 (80)	75 (33–100)
• Both primary discharge diagnosis AND surgeon's diagnosis	31 (56)	97 (90–100)	7 (58)	86 (60–100)	6 (67)	83 (54–100)	4 (80)	75 (33–100)
Typical Hip Fractures								
• Any position on hospital discharge diagnosis list (primary or other)	60 (100)	85 (76–94)	28 (100)	93 (83–100)	28 (100)	89 (78–100)	22 (100)	91 (79–100)
• Primary hospital discharge diagnosis	32 (53)	94 (85–100)	20 (71)	90 (77–100)	24 (86)	92 (81–100)	18 (82)	89 (74–100)
• Surgeon's diagnosis on administrative claim	49 (82)	98 (94–100)	26 (93)	96 (89–100)	26 (93)	96 (89–100)	21 (95)	95 (86–100)
• Both primary discharge diagnosis AND surgeon's diagnosis	29 (48)	97 (90–100)	19 (68)	95 (85–100)	22 (79)	95 (87–100)	19 (86)	95 (85–100)

*Compared to a case finding algorithm that accepted any SFF or DFF diagnosis on any position of hospital discharge diagnosis list
**Major trauma codes: E800-E848, E881-E884, E908-E909, and E916-E928.

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1574

Vitamin C Supplementation and Serum Uric Acid: A Meta-Analysis of Randomized Controlled Trials. Stephen P. Juraschek, Edgar R. Miller and Allan C. Gelber. Johns Hopkins Medical Institutions, Baltimore, MD

Background: Vitamin C is an essential micronutrient with uricosuric properties. Observational studies demonstrate an inverse association between levels of dietary or plasma vitamin C and serum uric acid (SUA). Thus far, clinical trials of vitamin C report inconsistent effects on SUA. The purpose of this meta-analysis was to determine the pooled effect of vitamin C on SUA culled from prior reports.

Methods: We conducted a meta-analysis of randomized controlled trials of vitamin C supplementation on SUA. A total of 1,988 publications, identified in MEDLINE, EMBASE, and CENTRAL databases, were subjected to the following inclusion criteria: (1) randomized controlled trials conducted on human subjects; (2) end-trial serum uric acid means and variance were reported; (3) oral vitamin C supplementation and a concurrent control group; and, (4) trial duration of at least one week. Trials that enrolled children or patients on dialysis or where vitamin C supplements were combined with other uricosuric agents were excluded. SUA effects were pooled by random-effects models and weighted by inverse variance.

Summary of Results: Thirteen trials met our eligibility criteria, totaling 545 participants. The median dose of vitamin C was 500 mg/d, trial size ranged from 8 to 184 participants, and median study duration was 30 days. Eight trials examined vitamin C as the only active intervention, whereas 5 trials administered vitamin C together with other vitamins, minerals or pharmacologic agents. The aggregate weighted effect of the 13 trials showed a SUA reduction of −0.33 mg/dL (95% CI: −0.66, 0.00; $P = 0.05$). Trials with a mean pretreatment SUA level above 4.85 mg/dL, the median value for these 13 trials, had a significantly greater SUA reduction in comparison to trials with mean pretreatment values ≤4.85 mg/dL ($P = 0.02$ in subgroup comparision). Notably, the pooled effects of trials with larger doses of vitamin C and those with vitamin C as the sole intervention showed greater significant reductions in SUA levels (Table).

Table. Vitamin C supplementation effects on serum uric acid - overall and subgroup analyses.

		Serum Uric Acid (mg/dL)	
	n	mean (95% CI)	P-value
All Trials (N = 13)	545	−0.33 (−0.66, 0.00)	0.05
Subgroup: Pretreatment Serum Uric Acid			
Trials with mean UA≤4.85 mg/dL (N=5†)	204	0.15 (−0.09, 0.39)	0.23
Trials with mean UA>4.85 mg/dL (N=5†)	252	−0.83 (−1.62, −0.04)	0.04
Subgroup: Vitamin C Dose			
Trials with dose <500 mg/d (N = 6)	203	0.09 (−0.17, 0.34)	0.52
Trials with dose ≥500 mg/d (N = 8*)	369*	−0.56 (−1.01, −0.11)	0.01
Subgroup: Intervention			
Only Vitamin C (N = 9*)	372*	−0.52 (−0.93, −0.10)	0.02
Vitamin C and other agents (N = 5)	200	0.12 (−0.15, 0.39)	0.38

N = Number of trials; n = Number of trial participants.
† Total number does not equal 13 since 3 trials did not report mean pretreatment SUA.
* One trial consisted of two distinct vitamin C intervention groups.

Conclusions: In this meta-analysis, vitamin C supplementation lowered SUA. Greater reductions in SUA occurred in trials that used high doses of vitamin C and in trials with subjects with higher pretreatment SUA levels. These data support consideration of vitamin C supplementation as a uricosuric agent in the prevention and control of gout.

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1575

What Kinds of Advice Do Health Food Store Employees and Pharmacists Provide to Consumers with Acute Low Back Pain? Jaya K. Rao[2], Dio Kavalieratos[1], Mary Roth[1], Morris Weinberger[1] and Timothy Carey[1]. [1]Chapel Hill, NC, [2]UNC Eshelman School of Pharmacy, Chapel Hill, NC

Background: Approximately 80% of adults experience at least 1 episode of acute low back pain (ALBP) during their lives. ALBP symptoms typically resolve in 4–6 weeks. Evidence-based guidelines recommend that physicians treat patients with ALBP conservatively with nonsteroidal anti-inflammatory drugs, avoid ordering imaging studies, and encourage usual activities as tolerated. Given that patients often use self-care strategies to treat pain, we examined the advice that health food store (HFS) employees and retail pharmacists provide for ALBP symptoms.

Methods: The study protocol was approved by the University of North Carolina Institutional Review Board. The actor, a 22 year-old Caucasian white male, visited 10 retail pharmacies and 10 HFSs in North Carolina during October 2009. He interacted with the HFS employees and pharmacists using the following standardized script: 1) his symptoms began 2 days ago and he was able to see a primary care physician (PCP) earlier that day; 2) the PCP followed ALBP guidelines and recommended ibuprofen every 6 hours; and 3) he was dissatisfied with the PCP's recommendations. He asked for general treatment recommendations, and specifically asked whether he needed to see a physician or other practitioner. He documented the recommendations on a data collection form following each encounter. We calculated the total monthly costs for each product recommended and examined whether the products had underlying evidence as a treatment for ALBP or potential side effects or interactions with prescribed medicines.

Results: Of the 6 pharmacists who recommended continuing ibuprofen, 2 reinforced a regular dosing schedule. Another 3 recommended changing to naproxen and 1 stated that the physician should have prescribed a muscle relaxant. Seven pharmacists suggested a physician visit but varied with respect to time frame; 4 recommended a visit if the symptoms lasted more than 2–3 days while 3 recommended a visit if the symptoms were not resolved within 1–2 weeks. Although 4 pharmacists said that imaging studies were not necessary, 3 recommended a radiographic study (1 specifically suggesting an MRI). Of the 10 HFS employees, 4 suggested continuing the ibuprofen; notably, 1 recommended increasing the dose to 800 mg every 6 hours. Nine HFS employees recommended various supplements and topical remedies with a total monthly cost ranging from $2 to $331. The recommendations included products that are safe but have no evidence to support their use for ALBP (e.g., glucosamine) and several that have known side effects (e.g., magnesium citrate) or could interact adversely with prescription medications (e.g., bromelain extract). Only 2 HFS employees suggested a physician visit, with one recommending having an MRI performed.

Conclusions: Pharmacists may inadvertently raise expectations regarding ALBP evaluation and symptom resolution while HFS employees may encourage consumers to purchase expensive products with no proven benefit for ALBP management. These results should be confirmed in a broader sample of pharmacists and HFS employees.

Disclosure: J. K. Rao: None; **D. Kavalieratos:** None; **M. Roth:** None; **M. Weinberger:** None; **T. Carey:** None.

1576

Who Falls? A Decade of Experience at a Musculoskeletal Specialty Hospital. Lisa A. Mandl[1], Michael Parks[2], Patricia Quinlan[2], Tina Bailey[2], Jacklyn Katz[2] and Steven Magid[2]. [1]Hospital for Special Surgery, New York, NY, [2]Hospital for Special Surgery

Summary: This study evaluates in-patients who fell at a musculoskeletal specialty hospital with no emergency room or trauma unit. Almost all admissions were for elective orthopedic procedures, a small percentage for non-critically ill rheumatic disease patients.

Methods: Retrospective review of all in-patient falls from 2000–2009. Falls were identified from the hospital's falls reporting database and ICD-9 discharge codes.

Results: There were a total of 868 in-patient falls in patients 18 years and over. The fall rate was 0.9 % of admissions, and 2.0 falls/1000 inpatient days. There were no significant trends in fall rate over time. Average age was 68 years, (range 18–93), 57.7 % were women. Among patients who fell, 97 (11.5%) had a lower extremity procedure, 156 (18.5%) had a spine procedure, 124 (14.7%) had a total hip replacement (THR), 322 (38.2%) had a total knee replacement (TKR) and 77 (8.9%) were admitted for other procedures or medical reasons. Twenty-six falls were second or third falls in the same patient during the same admission. Of the 842 first fall during an admission, 384 (45.1 %) involved using the bathroom and 145 (17.5 %) were in patients with a known history of previous falls. 110 first falls (13.1 %) resulted in injuries, of which 28 (3.3%) were serious, as defined by return to the operating room, transfer to a higher level of care, dislocation, fracture or intra-cranial bleed. Neither falls nor serious falls were significantly associated with day of the week or time of day. Patients with serious falls were more likely to fall earlier in their stay, (post-operative day 2.3 vs. 4.1; P-value 0.003) and have had a total hip replacement (p-value= 0.001). There was no significant association of serious falls with body mass index, age, gender, location in the hospital, day of the week or previous history of falling.

Discussion: Falls are avoidable events which can have devastating consequences. Most fall studies in the literature involve sick medical in-patients. Much less is known about falls in patients healthy enough for elective orthopedic surgery, or in non-critically ill rheumatology patients. This large series identifies bathroom related activities as high risk times for falling in these patients. Almost one fifth of patients were known to have fallen previously. This suggests the need for more effective fall prevention strategies in known high risk patients. The largest percentage of falls were in TKR patients, though serious falls were more common in THR patients. This is important, as the rates of both TKR and THR are projected to increase dramatically over the next two decades. THR patients are at higher risk for serious falls, and should be monitored closely, especially during the first 3 post operative days. These data can inform the creation of interventions to prevent falls and their consequences in this patient population.

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ACR Poster Session C
Genetics, Genomics and Proteomics: Rheumatoid Arthritis and SLE
Wednesday, November 10, 2010, 9:00 AM–6:00 PM

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***BLK* Confers a Risk for Renal Involvement in Japanese Patients with Systemic Lupus Erythematosus.** Kenichi Shimane[2], Yuta Kochi[5], Ryo Yamada[5], Yukinori Okada[1], Akari Suzuki[5], Keiko Myouzen[5], Tetsuya Horita[3], Tomonori Ishii[7], Michito Hirakata[4], Hirofumi Amano[6], Michiaki Kubo[1], Yusuke Nakamura[1], Naoyuki Kamatani[1] and Kazuhiko Yamamoto[8]. [1]CGM, RIKEN, Yokohama, Japan, [2]Department of Allergy and Rheumatology, Graduate School of Medicine, the University of Tokyo, Tokyo, Japan, [3]Hokkaido University Graduate School of Medicine, Sapporo, Japan, [4]Keio University School of Medicine, Tokyo, Japan, [5]Laboratory for Autoimmune Diseases, Center for Genomic Medicine, Institute of Physical Chemical Research (CGM, RIKEN), Tokyo, Japan, [6]School of Medicine, Juntendo University, Tokyo, Japan, [7]Tohoku University Graduate School of Medicine, Sendai, Japan, [8]Univ Tokyo Gr Schl of Med, Tokyo, Japan

Objectives: To find out whether 4 confirmed susceptibility genes to systemic lupus erythematosus (SLE), *BLK*, *STAT4*, *IRF5* and *TNFAIP3*, confer genetic predisposition to specific sub-phenotypes of SLE.

Methods: Our SLE case-control cohort consisted of 606 patients (mean age 43.4 years, 90.6% women) and 934 unrelated controls (mean age 52.6 years, 25.0% women), and they were all Japanese. We selected four single nucleotide polymorphisms (SNPs), rs13277113 (*BLK*), rs7574865 (*STAT4*), rs41298401 (*IRF5*) and rs2230926 (*TNFAIP3*), which are established genetic risk factors for SLE shared between Caucasian and Asian populations. We genotyped the SNPs using TaqMan assays. The difference of the genotype frequency was tested with the Chochran-Armitage trend test, using PLINK.

Results: We found a significant association of rs13277113 (*BLK*) with renal involvement (OR 1.48, 95%CI 1.14–1.93, p=0.0034) and a moderate association of rs41298401 (*IRF5*) with lupus anticoagulant (LAC) positivity

(OR 1.89, 95%CI 1.09–3.26, p=0.022). A stratified analysis between *BLK* and renal involvement by the morphologic classification (according to World Health Organization morphologic classification of lupus nephritis) indicated that rs13277113 (*BLK*) was more significantly associated with patients with class III and IV (OR 1.70, 95%CI 1.17–2.46, p=0.0057) than those with class I, II and V (OR 1.20, 95%CI 0.78–1.84, p=0.41), suggesting that BLK may be particularly involved in the progression of proliferative glomerulonephritis.

Conclusion: We demonstrated that polymorphisms in *BLK* and *IRF5* genes are associated with renal involvement and LAC positivity, respectively, in Japanese SLE patients. This suggests that disease susceptibility genes would effect on SLE sub-phenotype.

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A Comprehensive Replication Study and Functional Analysis of SLE Associated Variants in BLK, ATG5, PXK and SCUBE1. Angelica M. Delgado-Vega[6], Sergey Kozyrev[6], Johan Frostegård[4], Lennart Truedsson[5], Bernardo A. Pons-Estel[8], Sandra D'Alfonso[11], Torsten Witte[1], Bernard Lauwerys[9], Emoke Endreffy[12], László Kovács[12], Carlos Vasconcelos[2], Berta Martins da Silva[10], Javier Martin[3] and Marta E. Alarcón-Riquelme[7]. [1]Hannover Medical School, Germany, [2]Hosp Santo Antonio and ICBAS, Porto, Portugal, [3]Inst d Biomedicina y Parasitología López-Neyra, Granada, Spain, [4]Karolinska University Hosp at Huddinge, Stockholm, Sweden, [5]Lund U, Sweden, [6]Rudbeck Laboratory, Uppsala U, Sweden, [7]Rudbeck Laboratory, Uppsala U, Sweden. OMRF, OK. Andalucian Center f Genomics and Oncological Research Pfizer-University of Granada-Junta de Andalucia, Spain, [8]Sanatorio Parque, Rosario, Argentina, [9]U Catholique d Louvain, Bruxells, Belgium, [10]U do Porto, Porto, Portugal, [11]U Eastern Piedmont, Novara, Italy, [12]U of Szeged, Hungary

Background: The HapMap International project has provided an extensive catalogue of the common human genetic variation. It made possible the design of genome-wide association studies, which have radically contributed to the dissection of the genetic basis of SLE and multiple susceptibility variants have been identified. The 1000 genomes project, although not completed yet, is providing a deep source of newly identified variants that are ready to be used. In the present work, we have fine mapped four SLE-associated genes and imputed a handful of SNPs using these data, revealing novel potentially functional variants.

Methods: Fine mapping of BLK, ATG5, PXK and SCUBE1 was performed in the European multicenter collection "BIOLUPUS". Individuals with <90% of European ancestry identified by using PCA and STRUCTURE were removed as well as duplicated or related samples. Publicly available reference haplotypes and fine-scale recombination maps were downloaded from the 1000 genomes project (release August 2009) and HapMap phase 3 (CEU+TSI) for chromosomes 3, 6, 8 and 22. We combine these two reference panels and imputed the missing SNPs in our study data set by IMPUTEv2. Only SNPs for which the probabilities of each imputed genotype was >90% and the missing rate was <5% were included. A total of 299 SNPs in PXK, 60 SNPs in ATG5, 66 SNPs in BLK and 115 SNPs in SCUBE1 were tested for association in 1256 cases and 1576 controls, adjusting by the country of origin using GENABELv1.4–4 and PLINKv7. Multiple testing was corrected by genomic control and false discovery rate methods. The minimum set of SNPs explaining the association was calculated by multivariate logistic regression. Any SNP belonging to this set was typed, if it was an imputed SNP. A set of selected regions for each gene was re-sequenced in a number of individuals. Functional studies including expression and splicing analysis were performed.

Results: The only gene with genome-wide significance of association was BLK ($P = 6.5\times10^{-7}$ for the strongest SNP). The previously associated variants rs13277113 ($P = 1.58\times10^{-6}$) and rs2736340 ($P = 1.82\times10^{-6}$) ranked 2nd and 4th respectively. Conditional analysis suggested three independent groups of SNPs: one located in the promoter region (including rs13277113), another one in intron 1 and a third group of low frequency variants (MAF < 0.01) in the 3'UTR region.

In ATG5, the association was explained by two independent SNPs in the surroundings of exon 5. In PXK, a long haplotype of highly correlated SNPs in LD with the previously associated variant rs6445975 was delimited to the end of the gene. Association analysis with the levels of expression of these three genes is presented.

None of the SNPs in SCUBE1 reached significance after correction for multiple testing. Extremely high heterogeneity in the distribution of haplotypes and patterns of LD were observed among different countries.

Conclusions: We not only replicated the association of BLK, ATG5 and PXK but also present an extensive mapping of these genes. We narrowed down the associated regions and performed functional studies in order to understand the role of potentially causal variants on gene function.

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A High-Density Genome-Wide Association Study by the Sjögren's Genetics Network (SGENE) Identifies Both Novel Susceptibility Loci for Primary Sjögren's Syndrome and Overlapping Effects with Other Autoimmune Disorders. Christopher J. Lessard[3], Indra Adrianto[1], Kenneth Kaufman[1], Roland Jonsson[14], Gabor Illei[10], Maureen Rischmueller[12], Gunnel Nordmark[16], Xavier Mariette[13], Corrine Miceli-Richard[13], Marie Wahren-Herlenius[9], Torsten Witte[6], Michael Brennan[4], Roald Omdal[14], Fai Ng[11], Nelson Rhodus[15], Barbara Segal[7], R. Hal Scofield[2], Ben Rybicki for ACCESS[8], Courtney G. Montgomery[1], Juan-Manuel Anaya[5], John B. Harley[17] and Kathy L. Moser[2]. [1]Arthritis and Immunology Research Program, Oklahoma Medical Research Foundation, [2]Arthritis and Immunology Research Program, Oklahoma Medical Research Foundation and Department of Pathology, University of Oklahoma Health Sciences Center, [3]Arthritis and Immunology Research Program, Oklahoma Medical Research Foundation and Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [4]Carolinas Medical Center, [5]Center for Autoimmune Diseases Research (CREA), Universidad del Rosario, Bogota, Columbia, [6]Hannover Medical School, Germany, [7]Hennepin County Medical Center, Minneapolis, [8]Henry Ford Health System, [9]Karolinska Institute, Sweden, [10]National Institute of Dental and Craniofacial Research, NIH, [11]Newcastle University, England, [12]The Queen Elizabeth Hospital and Health Service, Australia, [13]Universite Paris-Sud, [14]University of Bergen, Norway, [15]University of Minnesota, [16]Uppsala University Hospital, Sweden, [17]US Department of Veterans Affairs Medical Center, Department of Medicine, University of Oklahoma Health Sciences Center, and Cincinnati Children's Hospital Medical Center

Background: Sjögren's syndrome (SS) is a clinically heterogeneous autoimmune disease characterized by exocrine gland dysfunction and involves both innate and adaptive immune responses. A complex genetic architecture has been hypothesized, however, genetic studies to date have been primarily limited to candidate genes approaches. We used high-density genotyping arrays to perform a genome-wide association (GWA) scan in an unbiased manner to identify SS susceptibility loci.

Methods: We have established the Sjogrens Genetics Network (SGENE) to assemble samples (currently >4000 subjects) for large-scale genetic studies. We used the Illumina OMNI1-Quad arrays containing >1.1×10E6 variants in a discovery cohort of 272 European-derived primary SS cases and 387 healthy controls. Stringent quality control criteria, adjustments for population stratification, and standard GWA statistical methodologies were used to compare allele frequencies between cases and controls. A total of ~774,000 single nucleotide polymorphisms (SNPs) were tested for association to SS in our final GWA dataset. For replication, we used a DNA pooling approach in an independent collection of cases and controls of European-decent, also genotyped using the OMNI1-Quad arrays. Weighted Z scores were used to determine meta p-values for combined discovery and replication data.

Results: The most significant region associated with risk of disease was the major histocompatibility complex (MHC) with 45 SNPs exceeding a genome-wide significance threshold of 5×10E-8, all of which replicated in our independent pooled samples. Within the MHC, peak significance was observed at HLA-DRA for rs9268832 (p=1.65×10E-10, odds ratio 2.3, CI: 1.8–3.0). Analysis in the replication cohort for rs9268832 resulted in p=1.61×10E-4, and an overall combined p=2.56×10E-13. Additional results across the extended MHC support association with multiple loci throughout this region. Evidence for novel genetic associations outside of the MHC were also observed. For example, association of SS with rs13282959 in both the discovery and replication cohorts was identified (meta p=1.93×10E-6). This SNP is located in a region of high regulatory potential near the musculin (MSC) gene. MSC is a multi-functional transcription factor involved in signaling pathways following B cell receptor activation. We specifically evaluated our data for evidence of association with ~30 loci previously established in systemic lupus erythematosus (SLE), a closely

related autoimmune disease. Association of IRF5 and TNIP1 was observed in both our discovery and replication cohorts. Support for other associated genes in both SLE and SS was observed for BANK1, PRDM1, JAZF1, STAT4, and IL12B.

Conclusions: This study represents the most comprehensive assessment of the genetic contribution to SS performed to date. We have identified and replicated numerous loci associated with disease, some of which have been previously associated with SLE and other related autoimmune diseases. Further characterization of these effects are warranted to precisely define causal variants and determine functional consequences that contribute to disease pathogenesis.

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An Immune Signature Based on Ex Vivo Responsiveness of Peripheral Blood Cells Is Associated with Radiographic Joint Damage in Rheumatoid Arthritis. John M. Davis III, Keith L. Knutson, Michael A. Strausbauch, Cynthia S. Crowson, Terry M. Therneau, Eric L. Matteson and Sherine E. Gabriel. Mayo Clinic, Rochester, MN

Purpose: In rheumatoid arthritis (RA), joint damage may occur even in patients with minimal disease activity. Thus, new techniques for determining the potential for future immune-mediated joint injury may facilitate targeting high-risk patients for aggressive therapy. The objective was to identify immune signatures of RA damage by broadly assessing ex vivo cytokine release by PBMC in response to stimulation.

Methods: We studied patients with early RA of <3 yrs duration, positive for rheumatoid factor or anti-citrullinated peptide antibodies. Radiography of the hands, wrists and feet was performed, and modified van der Heijde-Sharp (vdH-S) scores were determined. To establish immune signatures, we measured the release of 17 cytokines from PBMC in response to a panel of stimuli or in media alone using multiplexed immunoassays. The stimulation panel included anti-CD3/anti-CD28, CpG oligonucleotides (CpG), combined cytomegalovirus and Epstein Barr virus lysates (CMV/EBV), heat shock protein 60 (HSP60), phorbol myristate acetate with ionomycin (PMA/ionomycin), phytohemagglutinin (PHA), and combined Staphylococcal enterotoxins A and B (SEA/SEB). Mixed effects models were used to normalize the cytokine data and adjust for assay effects. Gradient boosting models (GBM) were used to predict the vdH-S score using all of the 136 stimulated cytokine concentrations and thereby derive a multi-cytokine prediction score (scale 0–100). Logistic regression models were used to determine the association of the GBM prediction score with the vdH-S score, dichotomized at the median, adjusting for clinical covariates.

Results: The study included 59 patients (median age: 54 yrs; 59% female; RA duration: 12.4 mo); 49 (84%) and 19 (24%) were taking methotrexate and biologics, respectively. The median vdH-S score was 18 units (interquartile range: 7, 37). In the GBM analysis, the production of the following cytokines (by descending relative influence for each stimulant) was associated with the vdH-S score, including: IL-12, IL-1β, and GM-CSF with CMV/EBV; IL-12, IL-10 and IL-4 with PMA/ionomycin; IL-6, IFN-g, and GM-CSF with anti-CD3/anti-CD28; IL-5, IL-12, and IL-10 with SEA/SEB; IL-12 with HSP60; IL-2, IL-4, and MCP-1 with CpG; GM-CSF and IL-5 with PHA; and finally, IL-7 and IL-8 in media alone; this model strongly correlated with the vdH-S score (Spearman correlation: 0.87). Cytokine production was generally increased with high vdH-S scores although GM-CSF, IL-2, IL-4 and MCP-1 were decreased under various stimulations. The multi-cytokine prediction score (per 10 units) was strongly associated with the presence of higher joint damage (vdH-S score $\geq$18 units) with an odds ratio of 1.28 (95% confidence interval: 1.11, 1.46; $p<0.001$) independent of covariates, including the use of methotrexate, biologics, and prednisone.

Conclusions: A PBMC-based immune signature, reflecting aberrant responsiveness of the peripheral innate and adaptive immune systems, is strongly associated with extent of radiographic joint damage in patients with early RA. Further studies are necessary to understand the biological implications of the findings and to define their clinical applicability.

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An Immune Signature Based on the Ex Vivo Responsiveness of Peripheral Blood Cells for Monitoring Disease Activity in Rheumatoid Arthritis. John M. Davis III, Keith L. Knutson, Michael A. Strausbauch, Cynthia S. Crowson, Terry M. Therneau, Eric L. Matteson and Sherine E. Gabriel. Mayo Clinic, Rochester, MN

Purpose: New techniques with enhanced capacity to detect systemic immune dysregulation are needed to enable tighter control of rheumatoid arthritis (RA). The objective was to identify an "immune signature" for predicting the level of disease activity in patients with RA by broadly assessing ex vivo cytokine release by PBMC in response to stimulation.

Methods: We conducted a correlative study of patients with early RA in an academic rheumatology practice. Data were collected for patient reported outcomes (PROs), including pain, morning stiffness, disability, and quality of life, using validated instruments. To establish immune signatures, we measured the release of 17 cytokines by PBMC in response to a panel of stimuli or in media alone using multiplexed immunoassays. The stimulant panel included anti-CD3/anti-CD28, CpG oligonucleotides (CpG), combined cytomegalovirus and Epstein Barr virus lysates (CMV/EBV), heat shock protein 60, phorbol myristate acetate with ionomycin (PMA/ionomycin), phytohemagglutinin, and combined Staphylococcal enterotoxins A and B. Mixed effects models were used to normalize the log-transformed cytokine data and adjust for assay effects. Factor analysis was used to combine multiple PROs into a single composite outcome. Gradient boosting models (GBM) were used to predict the PRO composite outcome using all of the 136 stimulated cytokine concentrations and thereby derive a multi-cytokine prediction score. Linear regression models were used to determine the associations of the score with validated disease activity measures, including the Disease Activity Score in 28 joints (DAS28), adjusting for clinical covariates.

Results: The study included 98 patients (63% female; mean age 56 yrs; mean RA duration 2.9 mo) with a total of 136 visits. In the factor analysis, pain levels influenced the PRO composite outcome most heavily. Among patients with high PRO composite scores, we observed that the release of T cell-derived cytokines, including IFN-γ, MIP-1β, IL-4, IL-5, IL-10, and IL-17, was significantly decreased. In contrast, we observed that the release of several innate cell-derived cytokines, including IL-1β, IL-6, and TNF-α, was significantly increased in these patients. In the GBM analysis, the most influential cytokines were MIP-1β, IL-7, IL-5, IFN-γ, and IL-13, and the most influential stimuli were CMV/EBV, CpG, PMA/ionomycin, and anti-CD3/anti-CD28. The multi-cytokine prediction score was confirmed to be associated with the PROs used to train the score and also with established disease activity measures, demonstrating evidence of criterion validity. The score (0 – 100) was strongly associated with the DAS28 (β coefficient: 0.25 per 10 units; standard error: 0.063; $p=0.0002$), independent of clinical covariates, including the use of methotrexate, biologics, and prednisone.

Conclusions: A PBMC-based immune signature, reflecting aberrant responsiveness of the innate and adaptive immune systems, is able to quantify the clinical activity of RA. If validated and standardized in future studies, this approach could enable more sensitive monitoring of RA activity, facilitating strategies of tight control and improved patient outcomes.

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Analysis of the Association of CDA (Cytidin Deaminase) (K27Q), TNF-α (-308G>A) and PTPN22 R620W Genetic Polymorphisms with Auto-Antibody Seropositive RA and the Response to B Cell Depletion. Barbara Tolusso[3], Fabio Di Pietro[7], Francesca Bobbio Pallavicini[4], Viviana Ravagnani[1], Maurizio Benucci[5], Edoardo Podesta'[2], Fabiola Atzeni[6], Valerio Napolioni[7], F. Carpi[7], Giusy Peluso[3], Francesca Faustini[3], Elisa Gremese[3], G. Biasi[1], Marianela Manfredi[5], Pier Carlo Sarzi Puttini[6], Bruno Lagana'[2], Carlomaurizio Montecucco[4] and Gianfranco Ferraccioli[3]. [1]Department of Clinical and Experimental Medicine, Section of Rheumatology & Internal Medicine, University of Verona, Verona, Italy, [2]Division of Clinical Immunology and Rheumatology, S. Andrea University Hospital, "Sapienza" University of Rome, II School of Medicine, Rome, Italy, [3]Division of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy, [4]Division of Rheumatology, University of Pavia, IRCCS S. Matteo Foundation, Pavia, Italy, [5]Rheumatology Unit, Department of Internal Medicine, Ospedale di S. Giovanni di Dio, Florence, Italy, [6]Rheumatology Unit, University Hospital L. Sacco, Milan, Italy, [7]School of Biosciences and Biotechnology, University of Camerino, Camerino (MC), Italy

Objective: To evaluate the genetic relationship between the two functional polymorphism of CDA (22G>A) and TNF-α (-308G>A) gene, and PTPN22 R620W respectively, in Rheumatoid Arthritis (RA) and their possible association with B cell depletion therapy.

Methods: One hundred and twenty three (82% female) RA patients who did not respond to previous DMARDs and/or TNFα blockers were enrolled in a multicenter italian study to evaluate the efficacy of RTX therapy. All RA were seropositive for at least one (RF-IgG,RF-IgA,RF-IgM,MCVA,ACPA) autoantibody. 181 healthy subjects living in the same geographical area entered in the study as a control group. DNA from patients and controls was genotyped for the PTPN22 R620W, TNFα-308 G/A and CDA K27Q polymorphisms by RLFP methods. The EULAR response criteria were used to assess the disease activity (DAS 44 ≤ 2.4: good response) at 6 months follow-up. Exact HWE tests were performed for each SNP independently among cases and controls. Logistic regression models (SAS V9.1.3) were used to assess the effects of each of the 4 SNPs on RA with adjusting for sex and age at disease onset. Multifactor dimensionality reduction (MDR,) was used to verify our interaction results. Models are evaluated on the testing balanced accuracy statistic (TBA), the cross-validation consistency (CVC) and the statistical significance of the model. These data were also analyzed using the G-MDR (V0.7) software package, an algorithm that includes adjustment for covariates (sex and age).

Results: All SNPs were in HWE except CDAK27Q (p=0.000011). Considering the TNFα −308A SNP, we showed an increased frequency of the allele A (19.8%) in the RA cohort compared to controls (9.1%; OR (95% CIs): 2.23 (1.40–3.60). The analysis of the CDA K27Q SNP showed a significant increased frequency of the genotype Q*/Q* (40.2%) and a decreased frequency of the genotype K*/Q* (31.2%) in RA patients compared to controls (Q*/Q*: 29.9%; OR: 1.58 (1.02–2.44); K*/Q*: 42.3%; OR: 0.62 (0.40–0.96). We found no difference in genotype distribution nor in allele frequencies of PTPN22 R620W between RA patients and controls. Based on the multilocus MDR approach, CDA K27Q SNP was the strongest risk factor for RA, with an average prediction accuracy of 57.9% (p=0.008). When we allowed for two genes in the analysis, the TNFα −308 G/A was identified in addition to CDA K27Q SNP and predicted disease status correctly 58.9% of the time (p=0.002); the prediction accuracy reached the value of 59.6% considering also the contribution of the PTPN22 R620W (p=0.001). Instead, the G-MDR method that includes sex and age in the analysis, showed that TNFα −308 G/A was the strongest risk factor for RA, with an average prediction accuracy of 57.6% (p<0.0001). No association was seen between PTPN22 R620W, TNFα-308 G/A and CDA K27Q polymorphisms and EULAR good response to RTX after 6th months FU.

Conclusions: Aggressive-progressive RA prone to receive RTX associates to −308 allele*A of the TNFα gene which is linked to high TNFalpha synthesis and to the QQ CDA genotype which is linked to a lower inhibition of the GM-CSF synthesis.

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Association of *PPP2CA* Polymorphisms with SLE Susceptibility in Multiple Ethnic Groups. Wenfeng Tan[15], Jian Zhao[15], Yun Deng[15], Kenneth M. Kaufman[2], Jennifer A. Kelly[1], Sang-Cheol Bae[5], Deh-Ming Chang[9], Yeong Wook Song[13], Chack-Yung Yu[14], Robert P. Kimberly[11], Marta E. Alarcón-Riquelme[12], John B. Harley[4], Chaim O. Jacob[17], Timothy J. Vyse[6], Timothy B. Niewold[16], Patrick M. Gaffney[10], Kathy L. Moser[10], Judith A. James[10], Gary S. Gilkeson[7], Diane L. Kamen[8], Jennifer M. Grossman[15], Bevra H. Hahn[15], George C. Tsokos[3] and Betty P. Tsao[15]. [1]Arthritis and Immunology Program, Oklahoma Medical Research Foundation, [2]Arthritis and Immunology Program, Oklahoma Medical Research Foundation and US Department of Veterans Affairs Medical Center, [3]Beth Israel Deaconess Medical Center, Harvard Medical School, [4]Cincinnati Children's Hospital Medical Center and US Department of Veterans Affairs Medical Center, [5]Hanyang University, Korean, [6]Imperial College London, Hammersmith Hospital, London, UK, [7]Medical University of South Carolina, [8]Medical University of South Carolina, [9]National Defense Medical Center, Taipei, Taiwan, [10]Oklahoma Medical Research Foundation, [11]On Behalf of PROFILE Investigators, University of Alabama, [12]On Behalf of the BIOLUPUS and GENLES Networks, Uppsala University, Sweden, Center for Genomics and Oncological Research, Granada, Spain, Oklahoma Medical Research Foundation, [13]Seoul National University, Seoul, Korea, [14]The Ohio State University, [15]University of California, Los Angeles, CA, [16]University of Chicago, [17]University of Southern California

Purpose: *PPP2CA* encodes the most highly expressed catalytic subunit α of protein phosphatase 2A (PP2A), which comprises a family of serine/threonine protein phosphatase with various important roles in regulation of NF-κB, MAPK and WNT signaling pathways, as well as cell growth and division. Abnormal expression of PP2A in T cells from SLE patients results in the decreased production of IL-2, suggesting the involvement of PP2A in the abnormal immune regulation in SLE patients (JCI, 115, 3193, 2005). Here we examined the association of *PPP2CA* variants with SLE.

Methods: We genotyped a panel of 18 SNPs spanning a 32kb region from *PPP2CA* promoter to 3.2kb downstream (including 1 at promoter, 15 at intron and 2 at downstream) in six populations: African-Americans and Gullahs (AA&Gullah) (1,651 cases, 1,962 controls), Asians (1,272 cases, 1,270 controls), European Americans (EA) (3,980 cases, 3,546 controls), Hispanic and Native Americans (Hisp&NA) (1,508 cases, 812 controls) using Illumina iSelect system. Additionally, ~400 ancestry informative markers were used to control population admixture and to eliminate genetic outliers. Chi-square and Mantel-Haenszel test were performed to compare the allelic difference and conduct the trans-ethnic meta-analysis.

Results: Multiple SNPs of *PPP2CA* showed significant association with SLE in Asians, EA and Hisp&NA but not in AA&Gullah. Two SNPs (rs7704116 at intron 2 and rs10491322 at the 3′ downstream) showed consistently strong association with SLE across Asian, EA and Hisp&NA, which were in almost complete linkage disequilibrium (LD) (r^2 = 0.98–0.99) with each other in each population. Of note, rs7704116 showed the strongest association signal with SLE in Asians and Hisp&NA and the smallest *P* value after Meta-analysis of genotype data in Asian, EA, Hisp&NA and AA&Gullah populations ($p_{Meta} = 3.8 \times 10^{-7}$, OR = 1.21[1.12–1.30]) (Table 1). One 32kb haplotype block spanning from promoter to 3′UTR downstream of *PPP2CA* was constructed based on the genotyping data of 18 SNPs in Asian, EA, Hisp&NA and AA&Gullah populations, which led to the identification of a common risk haplotype (GGCAAAAC-GAAAAAAAAG) strongly associated with SLE ($p_{Meta} = 2.3 \times 10^{-7}$, OR= 1.28 [1.13–1.31]) (Table 1).

Table 1. Associations of rs7704116 and common risk haplotype with SLE in multiple ethnic groups

SNP/Haplotype	Position	Population	Number of subjects Cases	Controls	MA	MAF Cases	Controls	*P* value	OR (95% CI)	Meta-analysis *P* value	OR (95% CI)
rs7704116	Intron 2	Asian	1272	1270	A	0.07	0.04	8.1×10^{-5}	1.64 [1.28–2.11]	3.8×10^{-7}	1.21 [1.12–1.30]
		European	3971	3536	A	0.08	0.07	5.8×10^{-4}	1.24 [1.1–1.4]		
		Hisp&NA	1507	810	A	0.19	0.15	3.4×10^{-3}	1.28 [1.08–1.5]		
		AA&Gullah	1651	1962	A	0.13	0.13	0.68	1.03 [0.9–1.18]		
			Haplotype frequencies								
GGCAAAACGAAAAAAAAG	–	Asian	1272	1270	–	0.06	0.04	2×10^{-4}	1.59 [1.2–2.0]	2.3×10^{-7}	1.28 [1.13–1.31]
		European	3971	3536		0.09	0.08	0.001	1.22 [1.1–1.4]		
		Hisp&NA	1507	810		0.23	0.18	0.02	1.29 [1.1–1.5]		
		AA&Gullah	1651	1962		0.12	0.12	0.48	1.05 [0.9–1.2]		

Conclusions: This study provides evidence that *PPP2CA* represents a novel locus predisposing to SLE susceptibility in Asian, European, Hispanic and Native American populations. The common risk haplotype shared in these populations is likely to carry one or more underlying causal variant(s) that increase risk for the development of SLE.

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Association of Variants in the *TLR7-TLR8* Region with Systemic Lupus Erythematosus in Non-Asian Populations. Yun Deng[8], Jian Zhao[8], Wenfeng Tan[8], Kenneth M. Kaufman[2], Elizabeth E. Brown[7], Jeffrey C. Edberg[7], Diane L. Kamen[6], Gary S. Gilkeson[10], Chaim O. Jacob[10], Robert H. Scofield[2], Robert P. Kimberly on behalf of PROFILE Investigators[7], Carl D. Langefeld[12], Jennifer A. Kelly[1], Marta E. Alarcón-Riquelme on Behalf of the BIOLUPUS and GENLES Networks[3]. John B. Harley[4], Timothy J. Vyse[5], Barry I. Freedman[11], Patrick M. Gaffney[2], Kathy L. Moser[2], Judith A. James[2], Timothy B. Niewold[9], Jennifer M. Grossman[8], Rita M. Cantor[8], Bevra H. Hahn[8] and Betty P. Tsao[8]. [1]Arthritis and Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Arthritis and Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK; University of Oklahoma Health Sciences Center, Oklahoma City, OK; US Department of Veterans Affairs Medical Center, Oklahoma City, OK, [3]Center for Genomics and Oncological Research, Granada, Spain, [4]Cincinnati Children's Hospital Medical Center and US Department of Veterans Affairs Medical Center, Cincinnati, OH, [5]Imperial College London, Hammersmith Hospital, London, United Kingdom, [6]Medical University of South Carolina, Charleston, SC, [7]University of Alabama, Birmingham, AL, [8]University of California, Los Angeles, CA, [9]University of Chicago, Chicago, IL, [10]University of Southern California, Los Angeles, CA, [11]Wake Forest University Baptist Medical Center, NC, [12]Wake Forest University Health Sciences, NC

Objectives: Our previous study identified the G allele of an X-linked *TLR7* SNP (rs3853839, located at 3'UTR) associated with increased expression levels of *TLR7* and SLE susceptibility in 9,274 Eastern Asians ($p = 6.5\times10^{-10}$) that had a stronger male effect. In this study, we sought to further characterize and localize SLE-associated SNPs of *TLR7* and its functionally related gene *TLR8* (17-kb downstream of rs3853839) in non-Asian populations.

Methods: A total of 47 SNPs, spanning the ~55kb genomic region of *TLR7-TLR8*, were genotyped on a customized Illumina array in a collection of case-control samples including European Americans (EA, 3930 cases vs. 3477 controls), African Americans & Gullahs (AA&Gullah, 1674 cases vs. 1915 controls), and Hispanics & Native Americans (Hisp&NA, 1479 cases vs. 800 controls). Additionally, ~400 ancestry informative markers were genotyped to control population stratification and remove genetic outliers for analysis. Association analysis of each SNP was performed using PLINK and conditional analysis was conducted to distinguish independent signals from associated SNPs. We used Q statistic to test the heterogeneity of OR between males and females, and Mantel-Haenszel test to generate a trans-ethnic meta-analysis *P* value.

Results: Significant associations of SNPs ($P < 0.05$) with SLE in each ethnic group were observed at *TLR7* region after Bonferroni correction, including 3 SNPs in EA, 1 SNP in AA&Gullah and 1 SNP in Hisp&NA. The following conditional analysis revealed the previously identified *TLR7* 3'UTR SNP (rs3853839) as the only independent variant across all 3 populations, exhibiting the strongest association ($P = 1.5\times10^{-6}$ in EA, 1.4×10^{-3} in AA&Gullah and 2.8×10^{-6} in Hisp&NA, Table 1). Trans-ethnic meta-analysis yielded a *P* with genome-wide significance ($P = 1.05\times10^{-12}$, OR = 1.26), confirming our previous finding in Eastern Asians. However, unlike the Asian sample where both sexes showed association, the evidence for this SNP conferring risk to SLE was only observed in female non-Asian datasets.

Table 1. Association of rs3853839 with SLE in multiple ethnic groups

Ethnicity	Panels	Sex	Case/ Control	G Allele Frequency Case	Control	*P*	OR (95% CI)
Eastern Asian	Combined	M	358/1550	0.89	0.77	1.3×10^{-6}	2.33 (1.64–3.30)
		F	3976/3390	0.80	0.77	1.2×10^{-7}	1.24 (1.14–1.34)
		All	4334/4940	0.81	0.77	**6.5×10^{-10}**	**1.27 (1.17–1.36)**
European American	Replication	M	338/1137	0.198	0.201	0.9	0.99 (0.73–1.34)
		F	3592/2340	0.203	0.165	3.9×10^{-7}	1.28 (1.17–1.41)
		All	3930/3477	0.202	0.172	**1.5×10^{-6}**	**1.25 (1.14–1.37)**
AA&Gulah	Replication	M	131/573	0.214	0.157	0.1	1.46 (0.91–2.35)
		F	1543/1342	0.196	0.166	4.1×10^{-3}	1.22 (1.07–1.40)
		All	1674/1915	0.196	0.165	**1.4×10^{4}**	**1.23 (1.08–1.41)**
Hsp&NA	Replication	M	114/73	0.421	0.479	0.43	0.79 (0.44–1.43)
		F	1365/727	0.446	0.366	6.3×10^{-7}	1.40 (1.23–1.60)
		All	1479/800	0.445	0.371	**2.8×10^{-6}**	**1.36 (1.20–1.55)**

Conclusion: We replicated the association between rs3853839 and SLE with genome-wide significance in EA, AA&Gullah, and Hisp&NA populations, showing *TLR7* as a common risk locus for SLE in multiple ethnic groups.

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Association of Variants in the *TNFAIP3* Region with Systemic Lupus Erythematosus in a Multi-Ethnic Study. Indra Adrianto[5], Christopher J. Lessard[8], Kenneth M. Kaufman[9], Juan-Manuel Anaya[12], Marta E. Alarcón-Riquelme on Behalf of the BIOLUPUS and GENLES Networks[6]. Sang-Cheol Bae[1], Elizabeth E. Brown for PROFILE[13], Barry I. Freedman[18], Gary S. Gilkeson[4], Chaim O. Jacob[16], Judith A. James[8], Robert P. Kimberly[13], Javier Martin[3], Joan T. Merrill[8], Timothy B. Niewold[15], So-Yeon Park[1], Bernardo A. Pons-Estel[10], Betty P. Tsao[14], Timothy J. Vyse[2], Carl D. Langefeld[19], Mary B. Humphrey[11], John B. Harley[17], Kathy L. Moser[8], Courtney G. Montgomery[7] and Patrick M. Gaffney[7]. [1]Hanyang University, Seoul, Republic of Korea, [2]Imperial College London, [3]Instituto de Parasitologia y Biomedicina López-Neyra, CSIC, Granada, Spain, [4]Medical University of South Carolina, [5]Oklahoma Medical Research Foundation, Oklahoma City, OK, [6]Oklahoma Medical Research Foundation; Center of Genomics and Oncological Research (GENyO), Granada, Spain, [7]Oklahoma Medical Research Foundation; Co-Senior Authors, [8]Oklahoma Medical Research Foundation; The University of Oklahoma Health Sciences Center, [9]Oklahoma Medical Research Foundation; The University of Oklahoma Health Sciences Center; Oklahoma City VA Medical Center, [10]Sanatorio Parque, Rosario, Argentina, [11]The University of Oklahoma Health Sciences Center, [12]Universidad del Rosario, Colombia, [13]University of Alabama at Birmingham, [14]University of California, Los Angeles, [15]University of Chicago, [16]University of Southern California Keck School of Medicine, [17]US Department of Veterans Affairs Medical Center; Cincinnati Children's Hospital Medical Center, [18]Wake Forest University Baptist Medical Center, [19]Wake Forest University Health Sciences

Background: Systemic lupus erythematosus (SLE) is a complex autoimmune disease with varied and potentially severe clinical manifestations affecting multiple organs. Prevalence of this disease varies between genders and among age-groups and ethnicities. SLE affects women nine times greater than men and is more common in non-Caucasians than in Caucasians. Recent studies indicate that genetic variants in the region of tumor necrosis factor alpha-induced protein 3 (*TNFAIP3*) are associated with SLE in subjects of European and Asian ancestry. *TNFAIP3* encodes a zinc-finger protein called A20, a critical regulator of inflammatory signaling pathways. To further characterize and localize the effect of *TNFAIP3*, we genotyped and imputed single-nucleotide polymorphisms (SNPs) within and flanking *TNFAIP3* in multiple populations: European, African-American, Asian including Korean, Hispanic enriched for Amerindian-European admixture, and Gullah populations.

Methods: Using a custom designed SNP panel for the Illumina iSelect system, we genotyped 127 SNPs in and around *TNFAIP3* and 343 ancestry-informative markers (AIMs) in a total of 8922 SLE unrelated cases and 8077 controls. Then, using HapMap Phase III and 1000 Genomes Project data we imputed a minimum of 274 additional SNPs for each of the populations (the number varied based on linkage disequilibrium structure). We converted the posterior probabilities to the most likely genotypes with a threshold of 0.8 and removed imputed SNPs with less than 90% average certainty of the most probable genotypes. We assessed single marker association to SLE using logistic regression with sex, global and local ancestry adjustments under additive, dominant, and recessive models.

Results: Association analysis identified risk haplotypes in Europeans and Asians likely to harbor a causal variant. Further haplotype comparisons across populations revealed a variant that likely explains the majority of the genetic association between SLE and *TNFAIP3* identified in our study populations with $P=1.96 \times 10E-8$, OR=1.69, 95% CI=1.41–2.04 in Europeans, $P=3.30 \times 10E-9$, OR= 2.26, 95% CI=1.73–2.97 in Asians, and $P=1.24 \times 10E-9$, OR=2.53, 95% CI=1.88–3.41 in Koreans alone. No significant association was found in other populations.

Conclusion: These results support genetic association with SLE in the region of *TNFAIP3*, unique to Europeans and Asians and further demonstrate the complexity of identifying associations across different populations. Sequencing and functional studies are necessary to validate this variant and determine the contribution of *TNFAIP3* to SLE.

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Association of Variants in the NF-kB Regulatory Pathway Loci with Systemic Lupus Erythematosus in Multiple Populations. Graham Wiley[6], Indra Adrianto[8], Jennifer A. Kelly[5], Kenneth M. Kaufman[11], Juan-Manuel Anaya[13], Marta E. Alarcón-Riquelme on Behalf of the BIOLUPUS and GENLES Networks[7]. Sang-Cheol Bae[1], So-Young Bang[1], Elizabeth E. Brown for PROFILE[14], Barry I. Freedman[19], Gary S. Gilkeson[4], Chaim O. Jacob[17], Judith A. James[10], Robert P. Kimberly[14], Javier Martin[3], Joan T. Merrill[10], Timothy B. Niewold[16], Bernardo A. Pons-Estel[12], Betty P. Tsao[15], Timothy J. Vyse[2], Carl D. Langefeld[20], John B. Harley[18], Kathy L. Moser[10], Courtney G. Montgomery[9] and Patrick M. Gaffney[9]. [1]Hanyang University, Seoul, Republic of Korea, [2]Imperial College London, [3]Instituto de Parasitologia y Biomedicina López-Neyra, CSIC, Granada, Spain, [4]Medical University of South Carolina, [5]Oklahoma Medical Research Foundation, [6]Oklahoma Medical Research Foundation, Oklahoma City, OK, [7]Oklahoma Medical Research Foundation; Center of Genomics and Oncological Research (GENyO), Granada, Spain, [8]Oklahoma Medical Research Foundation; Co-First Authors, [9]Oklahoma Medical Research Foundation; Co-Senior Authors, [10]Oklahoma Medical Research Foundation; The University of Oklahoma Health Sciences Center, [11]Oklahoma Medical Research Foundation; The University of Oklahoma Health Sciences Center; Oklahoma City VA Medical Center, [12]Sanatorio Parque, Rosario, Argentina, [13]Universidad del Rosario, Colombia, [14]University of Alabama at Birmingham, [15]University of California, Los Angeles, [16]University of Chicago, [17]University of Southern California Keck School of Medicine, [18]US Department of Veterans Affairs Medical Center; Cincinnati Children's Hospital Medical Center, [19]Wake Forest University Baptist Medical Center, [20]Wake Forest University Health Sciences

Background: The transcription factor NF-kB is an important factor in inflammation and the immune response. Unrestrained NF-kB response has previously been associated with autoimmune disease, sepsis, and some cancers. It is therefore not surprising that NF-kB signaling is tightly regulated within the cell through a pathway of protein-protein interaction and post-translational protein modification. One key component of this pathway is the *TNFAIP3* complex consisting of *TNFAIP3*, *TNIP1*, *TNIP2*, *TAX1BP1*, *ITCH*, and *RNF11*. This complex, along with the ubiquitin-conjugating enzyme *UBE2L3*, deactivates NF-kB pathway proteins through deubiquitation of K63 polyubiquitin chains and subsequently targets those proteins for degradation via K48 ubiquitination. Recent GWAS have revealed that genetic variants in the *TNFAIP3*, *TNIP1*, and *UBE2L3* regions are associated with systemic lupus erythematosus (SLE) in subjects of European and Asian ancestry. SLE is an autoimmune disease characterized by loss of tolerance to self-antigens and dysregulated interferon responses. To further characterize and localize the effect of the *TNFAIP3* regulatory complex, we genotyped and imputed single-nucleotide polymorphisms (SNPs) within and flanking *TNIP1* on 5q33, *TNIP2* on 4p16, *UBE2L3* on 22q11, *TAX1BP1* on 7p15 in multiple populations: African-Americans (1,569 cases/1,893 controls), Asians (1,328 cases/1,348 controls), Europeans (4,248 cases/3,818 controls), Gullah (155 cases/131 controls), and Hispanics enriched for Amerindian-European admixture (1,622 cases/887 controls).

Methods: Using the Illumina iSelect system, we genotyped a total of 231 SNPs in and around those loci and 343 ancestry-informative markers (AIMs). We then imputed untyped SNPs at those loci using HapMap Phase III and 1000 Genomes Project data. We converted the posterior probabilities to the most likely genotypes with a threshold of 0.8 and removed imputed SNPs with less than 90% average certainty of the most probable genotypes. We assessed single marker association to SLE using logistic regression with sex and global ancestry adjustments under additive, dominant, and recessive genetic models.

Results: We observed strong associations between SLE and multiple SNPs within *TNIP1* in Europeans, Hispanics, African-Americans, and Asians ($P_{combined}=5 \times 10E-8$) with the strongest signal at rs7708392 ($P_{combined}=2.53 \times 10E-19$). We also identified strong associations within *UBE2L3* in Europeans, Asians, African-Americans and Hispanics with the most significant association at rs7444 ($P_{combined}=1.25 \times 10E-14$).

Conclusions: These results establish that variants within *TNIP1* and *UBE2L3* contribute to differential risk of SLE in multiple populations. Further functional studies will be required to determine the precise variant(s) influencing SLE risk.

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Association Study of the *ILAK1* Gene with Susceptibility to Systemic Lupus Erythematosus and Systemic Sclerosis. Yuko Ota[3], Yasushi Kawaguchi[1], Manabu Kawamoto[2], Kae Takagi[2], Akiko Tochimoto[2], Yasuhiro Katsumata[2], Takahisa Gono[2], Sayumi Baba[2], Yuko Okamoto[2] and Hisashi Yamanaka[4]. [1]Tokyo Women's Medical Univ, Tokyo, Japan, [2]Tokyo Women's Medical Univ, [3]Tokyo Women's Medical University, Tokyo, Japan, [4]Tokyo Womens Med Univ, Shinjuku-ku, Tokyo, Japan

We explored whether single nucleotide polymorphisms (SNPs) in the *Interleukin-1 receptor associated kinase-1*(*IRAK1)* gene contribute to systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) susceptibility in the Japanese population. Two hundred forty-four patients with SLE, 180 patients with SSc and 268 healthy controls (HC) were enrolled in this study. Four SNPs (rs2239673, rs763737, rs7061789, and rs5945174) in the *IRAK1* gene were determined by allelic discrimination with the use of a specific TaqMan probe and PCR restriction fragment length polymorphism (PCR-RFLP). Association measured using either $\chi 2$ or Fisher's exact test at the allelic and genotypic levels. Because *IRAK1* is located on chromosome Xq28, cases and controls were stratified by gender and measured for each stratum.

In patients with SLE, the most common clinical manifestations in this study were nephritis (45%), cytopenia (32%), and neuropsychiatric manifestations (30%). The prevalence of butterfly rash was 17%, arthritis was 25%, serositis was 7%, and antiphospholipid antibody syndrome was 5%.

Both alleles and genotypes of all of the four SNPs in *IRAK1* gene showed strong associations with SLE in female cohort ($P < 0.0002$; odds ratio = 1.9), although there were no associations between alleles and genotypes in the SNPs with whole SLE and in male cohort. In SLE, there were significant correlations between the allele of each SNP and nephritis. There were also significant differences in the frequencies of genotype of the SNPs between patients with butterfly rash or cytopenia and HC. In the frequency of genotype of rs5945174, there was a significant difference between patients with nephritis and HC. In patients with SSc, there were no association in the alleles and genotypes of the four SNPs in the *ILAK1* gene.

In haplotype analyses, GGGG haplotype (defined as "G" at rs2239673, "G" at rs763737, "G" at rs5945174, "G" at rs7061789) was associated with susceptibility to Japanese patients with both SLE and SSc. The p value for association reached to $10^{-8}$and 10^{-2} respectively.In this study, we confirmed the association between an SNP in the *IRAK1* gene and susceptibility to SLE in female Japanese population. Several autoimmune disorders, including multiple sclerosis, rheumatoid arthritis, SLE and SSc are more common in women than men. Several mechanisms have been proposed as explanations for this gender bias. IRAK1, an X chromosome gene may have a critical role in the pathogenesis of SLE and SSc.

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Combining Genetic and Environmental Risk Factors To Model RA Susceptibility. Lori B. Chibnik[3], Bo Ding[7], Brendan T. Keenan[4], Katherine P. Liao[2], Karen H. Costenbader[1], Lars Klareskog[6], Lars Alfredsson[7] and Elizabeth W. Karlson[5]. [1]Brigham & Women, Boston, MA, [2]Brigham & Women's Hosp, Boston, MA, [3]Brigham and Women's Hospital, Boston, MA, [4]Brigham and Women's Hospital, [5]Brigham and Womens Hosp, Boston, MA, [6]Karolinska University Hospital, Stockholm, Sweden, [7]Karolinska University Hospital

Background: Cumulative genetic risk scores (GRSs) have shown promise in modeling rheumatoid arthritis (RA) susceptibility. In addition, many gene-environment interactions (GEIs) have been significant factors in RA risk. We combine a GRS and GEIs to develop the best model for RA risk.

Methods: We studied models of RA risk in two cohorts, the U.S. Nurses' Health Studies (NHS) and the Swedish Epidemiologic Investigation of RA (EIRA). We created a weighted GRS using 31 non-HLA single nucleotide polymorphisms at validated RA risk loci, where the weight for each risk allele is the log of the odds ratio based on published GWAS or meta-analysis. In addition, we genotyped HLA-DRB1 locus with subjects coded as having 0, 1 or 2 copies of shared epitope (SE) alleles. Based on previously found significant interactions, we included two additional polymorphisms, GSTT1-null and HMOX1. Smoking was the main environmental factor for GEI (dichotomized as $\leq$ 10 pack-years vs. $>$ 10 pack-years). Parallel analyses were performed among (1) 371 Caucasian seropositive (CCP+ and/or RF+) cases and 551 controls from NHS and (2) 987 Caucasian ACPA positive cases and 958 controls from EIRA to develop the best model in each dataset. We began with a base model including year of birth and smoking (plus sex and region of Sweden in EIRA). Hierarchical models adding the most significant factors were compared to the previous and base models using pseudo R^2 for parsimony and area under the ROC curve (AUC) and the Integrated Discrimination Improvement (IDI, which quantifies the overall improvement in sensitivity and specificity) for discrimination.

Results: The mean (SD) age of diagnosis of RA was 57 (10) in NHS and 50 (12) in EIRA. For NHS, the base model produced an AUC of 0.578. Adding the GRS and HLA to the model increased the AUC to 0.669. The IDI between the 2 models was 0.07 (0.05–0.08), indicating a significant improvement (null IDI = 0). Our best performing model contained the GRS and GEIs between smoking and HLA, GSTT1-null and HMOX1 and had an AUC of 0.700 and IDI of 0.10 (0.07–0.12) compared to the base model and 0.03 (0.02–0.04) as compared to the model with GRS and HLA. For EIRA, the base model produced an AUC of 0.630. Adding the GRS and HLA to the model increased the AUC to 0.733. The IDI between the 2 models was 0.11

(0.10–0.13). Adding the GEIs between smoking and HLA did not significantly improve the model (AUC = 0.734, IDI = 0.001 [−0.003–0.003]), compared to the model with GRS, clinical factors and HLA. Inclusion of other covariates did not improve the models in either cohort.

Conclusion: Inclusion of GEIs significantly improves the discriminative ability of models predicting RA risk in NHS but not EIRA. These conflicting results emphasize the importance of developing models separately in different populations. However, further work to discover genetic, environmental and GEI factors is needed before these models are used in clinical settings.

Table. Summary Measures for Selected Models in the US Nurses' Health Study and Swedish Epidemiologic Investigation in RA

	NHS[1]			EIRA[2]		
Model	AUC[3]	IDI[4] (95% CI) compared to Base	IDI[4] (95% CI) compared to Base+GR5+ HLA-SE	AUC[3]	IDI[4] (95% CI) compared to Base	IDI[4] (95% CI) compared to Base+GRS+ HLA-SE
Base[5]	0.578	N/A	N/A	0.630	N/A	N/A
Base + GRS[8] + HLA-SE[7]	0.669	0.07* (0.05–0.08)	N/A	0.733	0.11* (0.10–0.13)	N/A
Base + GRS + GEIs[8]	0.700	0.10* (0.07–0.12)	0.03 (0.02–0.04)	0.734	0.11* (0.10–0.13)	0.001 (−0.003–0.003)

[1] NHS: Nurses' Health Study; [2] EIRA: Epidemiologic Investigation in RA; [3] AUC: Area Under Receiver Operating Characteristic Curve
[4] IDI: Integrated Discrimination Improvement; [5] Baseline Model includes year of birth and heavy smoking in NHS and year of birth, heavy smoking, sex, and geographical region of Sweden for EIRA; [6] GRS: Genetic Risk Score; [7] HLA-SE: Human Leukocyte Antigen Shared Epitope
[8] Gene-Environment Interactions include main effects and product terms in model; NHS: GEI between smoking and HLA, GSTTI-null and HMOX1; EIRA: GEI between smoking and HLA
* $p < 0.01$

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Contribution of *VpreB1* Gene Copy Number Variation to the Risk of Rheumatoid Arthritis. Seung-Cheol Shim[2], Mi-Kyoung Lim[2], Dong-Hyuk Sheen[2] and Yeun-Jun Chung[1]. [1]Catholic University, Seoul, Korea, Republic of, [2]Eulji University, Daejeon, Korea, Republic of

Background: Copy number variation (CNV), especially in the genomic loci harboring dosage-sensitive genes, has been reported to affect susceptibility to diverse autoimmune diseases. In human, a copy number loss of 22q11.2, a region harboring pre-B cell receptor gene (*VpreB1*), has been suggested to be associated with chronic autoimmune arthritis. Recently, mice lacking surrogate light chain encoded by λ5 and *VpreB1* has been reported to harbor high levels of autoantibodies, and showed evidence of escape of pre-B cells expressing prototypic autoantibody heavy chains from negative selection, leading to mature autoantibody secreting $CD21^{-}CD23^{-}$ B cells in their serum.

Objective: To investigate whether CNV of the *VpreB1* associates with susceptibility to rheumatoid arthritis (RA), and whether RA patients have a significantly higher frequency of $CD21^{-}CD23^{-}$ B cells in the peripheral blood than healthy controls.

Methods: We evaluated the copy numbers of the *VpreB1* in an independent cohort of 229 cases and 233 controls using genomic quantitative real-time PCR. We also performed fluorescence in-situ hybridization analysis targeting *VpreB1* locus (22q11.22) and diploid control locus of the same chromosome arm (22q13.1). Next, we explored the frequency of B cell subsets in the peripheral blood from RA patients and controls, and further characterized $CD21^{-}CD23^{-}$ B cells using FACS.

Results: The median gene dose of *VpreB1* in the study population was two. The proportion of the individuals with <2 copy of *VpreB1* was significantly higher in RA patients than in controls (10.9% *vs* 0.9%, $p<0.0001$), while that of the individuals with >2 copy was lower in RA patients (1.7% in RA *vs* 18.9% in controls, $p<0.0001$).

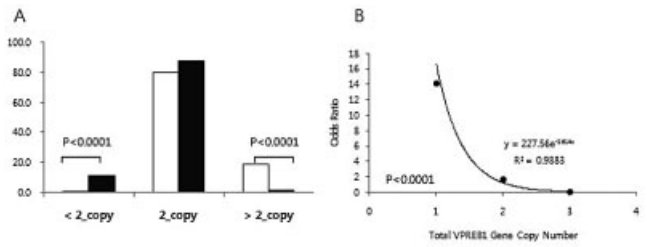

Figure 1.

VpreB1 copy number < 2 was associated with an increased risk of RA in which the odds ratio (OR) was 11.5 (95% CI 2.7–49.3). The OR for RA in individuals with >2 copies was significantly lower than that with 2 copies (OR=0.1, 95% CI 0.03–0.3). We also found that the proportion of $CD21^{+}CD23^{+}$ cells was significantly lower in RA patients than in controls (26.2% *vs* 34.9%, $p=0.005$), while that of $CD21^{-}CD23^{-}$ cells was significantly higher in RA (11.9% in RA *vs* 5.7% in controls, $p=0.002$).

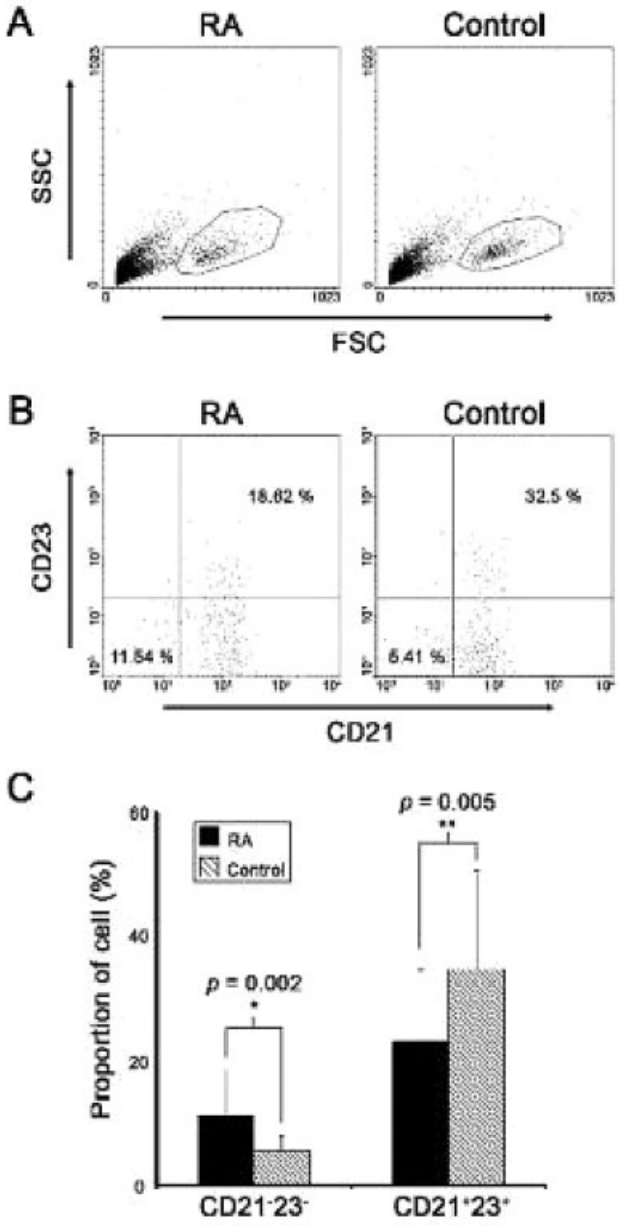

Figure 2.

The majority (73%) of $CD21^{-}CD23^{-}$ B cells were $CD38^{-}CD27^{+}$, a phenotype compatible with switch memory B cells.

Conclusions: This study provides evidence that low copy number of the *VpreB1* is a RA susceptibility genetic variant which could be involved in B cell dysregulation in this disease. These findings could help understanding the pathogenesis of RA and other autoimmune disorders in which aberrant B cell regulation plays an essential role.

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1590

Early Disease Onset Is Predicted by a Higher Genetic Risk for Lupus and Is Associated with a More Severe Phenotype in Lupus Patients. Ryan Webb[3], Jennifer A. Kelly[3], Emily C. Somers[7], Travis Hughes[3], Kenneth M. Kaufman[4], Elena Sanchez[3], Swapan K. Nath[3], Gail Bruner[3], Marta E. Alarcon-Riquelme[5], Gary S. Gilkeson[2], Diane L. Kamen[2], Bruce C. Richardson[6], John B. Harley[1] and Amr H. Sawalha[8]. [1]Cincinnati Children's Hospital Medical Center, VAMC, Oklahoma City, OK, [2]Med Univ of South Carolina, Charleston, SC, [3]Oklahoma Medical Research Foundation, [4]Oklahoma Medical Research Foundation, University of Oklahoma, US Department of Veterans Affairs Medical Center, [5]Oklahoma Medical Research Foundation, Uppsala University, Uppsala, Sweden, [6]University of Michigan, Ann Arbor, MI, [7]University of Michigan, [8]University of Oklahoma, US Department of Veterans Affairs Medical Center, Oklahoma Medical Research Foundation, Oklahoma City, OK

Purpose: Systemic lupus erythematosus (SLE) is a chronic, multi-organ, autoimmune disease that affects people of all ages and ethnicities. Herein, we explore the relationship between the age at disease onset and many of its diverse manifestations. We further determine the relationship between age of disease onset and genetic risk in SLE patients.

Methods: We explore the relationship between the age at disease onset and SLE manifestations in a multi-ethnic cohort of 1,317 patients. SLE patients were genotyped across 19 confirmed genetic susceptibility loci for SLE. Logistic regression was used to determine the relationships between the number of risk alleles present and age of disease onset.

Results: Childhood-onset SLE had higher odds of proteinuria, malar rash, anti-dsDNA antibody, hemolytic anemia, arthritis, and leukopenia (odds ratios = 3.03, 2.13, 2.08, 2.50, 1.89, 1.53, respectively, and p-values <0.0001, 0.0004, 0.0005, 0.0024, 0.011, and 0.045, respectively). In females, the odds of having cellular casts were 2.18 times higher in childhood-onset versus adult-onset SLE ($p=0.0027$). With age of onset ≥ 50, the odds of having proteinuria, cellular casts, anti-nRNP antibody, anti-Sm antibody, anti-dsDNA antibody, and seizures were reduced. Instead, late adult-onset SLE patients have higher odds of developing photosensitivity compared with early adult-onset patients (onset ≥ 18 and <50 yrs). Importantly, each SLE-susceptibility risk allele carried within the genome of SLE patients increased the odds of having a childhood-onset disease in an ethnicity-specific manner: each risk allele increased risk by an average of 48% in Gullah, and 25% in African-Americans, but this was not significant in Hispanic and European-American lupus patients.

Conclusions: We report and quantify for the first time the genetic contribution towards predicting early-onset disease in SLE patients. Furthermore, we report a more severe SLE phenotype in patients with an early-onset disease in a large multiethnic cohort, independent of gender, race, and disease duration.

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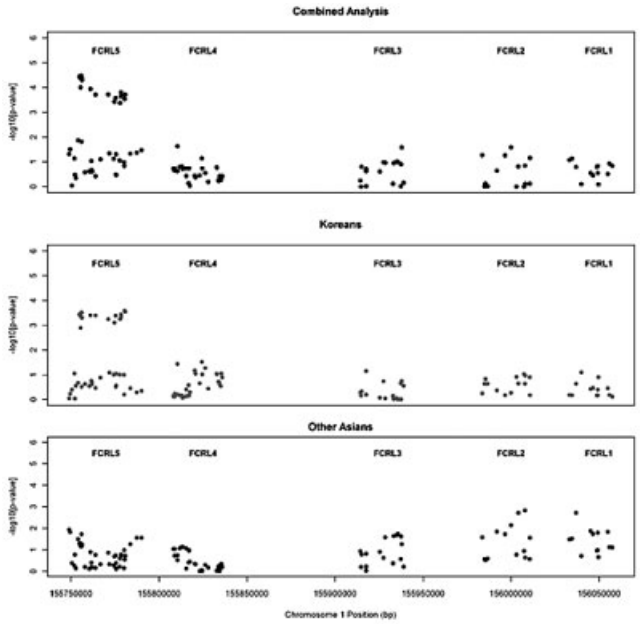
1591

Ethnic Specific Genetic Associations within the FCRL Gene Cluster in SLE. Nickolas M. Pajewski[15], Carl D. Langefeld[23], Kenneth M. Kaufman[11], Adrienne Williams[23], Mary Comeau[23], Graciela S. Alarcon[2], Michelle A. Petri[1], Rosalind Ramsey-Goldman[7], John D. Reveille[18], Luis M. Vila[17], Marta E. Alarcon-Riquelme on Behalf of the BIOLUPUS and GENLES Networks[10]. Juan-Manuel Anaya[19], Sang-Cheol Bae[3], Susan A. Boackle[21], Lindsey A. Criswell[14], Barry I. Freedman[23], Patrick M. Gaffney[9], Gary S. Gilkeson[5], Peter K. Gregersen[6], John B. Harley[16], Chaim O. Jacob[22], Judith A. James[9], Joan T. Merrill[9], Kathy L. Moser[9], Timothy B. Niewold[20], Robert Hal Scofield[8], Anne M. Stevens[12], Betty P. Tsao[13], Timothy J. Vyse[4], Elizabeth E. Brown[15], Robert P. Kimberly[15] and Jeffrey C. Edberg[15]. [1]Timonium, MD, [2]Oakland, CA, [3]Hanyang Univ Medical Center, Seoul, Korea, Republic of, [4]Imperial College London, [5]Med Univ of South Carolina, Charleston, SC, [6]N Shore Univ Hosp Rsch Ctr, Manhasset, NY, [7]Northwestern University, Chicago, IL, [8]Oklahoma Med Res Foundation, Oklahoma City, OK, [9]Oklahoma Med Research Foundation, Oklahoma City, OK, [10]Oklahoma Medical Research Foundation, Uppsala, Sweden, [11]Oklahoma Medical Research Foundation; The University of Oklahoma Health Sciences Center; Oklahoma City VA Medical Center, [12]Pediatrics, U. of Washington, Seattle, WA, [13]UCLA School of Medicine, Los Angeles, CA, [14]UCSF-Box 0500, San Francisco, CA, [15]Univ Alabama Birmingham, [16]Univ of OK Hlth Sci Ctr, Oklahoma City, OK, [17]Univ of PuertoRico Schl of Med, San Juan, PR, [18]Univ Texas Health Sci Ctr, Houston, TX, [19]Universidad del Rosario, Colombia, [20]University of Chicago, Chicago, IL, [21]University of Colorado-Denver SOM, Aurora, CO, [22]USC School of Medicine, Los Angeles, CA, [23]Wake Forest University Health Sciences

Background: The FCRL gene cluster in humans on chromosome 1q23.1 encodes 5 proteins that share a common ancestor with the classical Ig-binding Fc receptors. Each of the FCRL1–5 gene products are expressed by B cells but vary in their distribution on different subpopulations while FCRL3 is also found on NK and T cell subsets. Despite the similarity to the classical FCR, no definitive data demonstrate binding of Ig but very recent studies suggest binding of MHC and MHC-like molecules. A functional promoter variant in the FCRL3 locus has been inconsistently associated with SLE.

Methods: We have performed a large case-control association study (n= (cases:controls) 3938:3491/1527:1811/961:336/1265:1260 European-American (EA)/African-American (AA)/Hispanic (Hisp)/Asian) with 123 SNPs that span 5 FCRL genes (FCRL1–5) on chrm 1q23.1. SNPs were selected from variants identified in a re-sequencing project and were genotyped on a custom iSelect array (Illumina) as part of a large SLEGEN consortium experiment. Logistic regression models were used to test for association adjusting for population structure through principal components analysis and gender.

Results: In the Korean population (cases=640; controls=740), we detected association within the FCRL5 gene with strongest association at rs1571967 (intronic SNP)($p=3.6\times10\text{-}4$, OR=0.61[0.47–0.80]). This SNP was replicated in an independent collection of Asian case/control samples from North America (n=625/520) (combined $p=3.6\times10^{-5}$, OR=0.66 [0.54–0.80]).



We also observed independent association at 2 non-synonymous SNPs in the FCRL5 gene in the Asian population (peak association at rs6679793, combined $p=2.0\times10^{-4}$, OR=0.69 [57–0.84]). No evidence of association within FCRL3 (including the previously associated −169 promoter SNP, rs7528684) was observed. No significant associations ($p<0.005$) were detected in the FCRL1–5 genes in the EA, AA and Hisp populations.

Conclusions: Together, these results demonstrate an association in the FCRL5 gene with SLE in Asians. FCRL5 is known to bind a viral MHC class I-like molecule and is likely to be involved in regulating innate immunity. The identification of non-synonymous SNPs in FCRL5 that associate with SLE in Asian populations provides the opportunity to explore the impact of genetic variation in regulating immune responses in autoimmunity.

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European Genetic Ancestry Protects Against the Development of Renal Disease in Systemic Lupus Erythematosus. Ilana B. Richman[7], Kimberly E. Taylor[7], Sharon A. Chung[6], Laura Trupin[7], Michelle A. Petri[4], Edward H. Yelin[6], Robert R. Graham[3], Annette T. Lee[1], Timothy W. Behrens[2], Peter K. Gregersen[5], Michael F. Seldin[9] and Lindsey A. Criswell[8]. [1]Feinstein Insititute Med Rsch, Manhasset, NY, [2]Genentech Inc, South San Francisco, CA, [3]Immunology Biomarkers Group, Genentech, South San Francisco, [4]Johns Hopkins University School of Medicine, Timonium, MD, [5]N Shore Univ Hosp Rsch Ctr, Manhasset, NY, [6]Rosalind Russell Medical Research Center for Arthritis, Division of Rheumatology, University of California, San Francisco, San Francisco, CA, [7]Rosalind Russell Medical Research Center for Arthritis, Division of Rheumatology, University of California, San Francisco, [8]UCSF-Box 0500, San Francisco, CA, [9]University of California, Davis

Background: African Americans, Asians, and Hispanics with systemic lupus erythematosus (SLE) are at greater risk of developing renal disease than Caucasians. The extent to which genetic or environmental factors contribute to these disparities remains uncertain. We hypothesized that in a multiethnic SLE case series, European genetic ancestry would be protective against the development of renal disease. We further hypothesized that any protective effect of ancestry may be partially attributable to variation in specific genes associated with renal disease in SLE.

Methods: This was a cross-sectional study of 1,910 adults with SLE enrolled in two SLE case collections. Clinical data and confirmation of SLE diagnosis were obtained by chart review. Self-reported socioeconomic data were available for a subset of participants. All participants were genotyped for a set of 116 single nucleotide polymorphisms (SNPs) informative for continental ancestry. A subset of participants was also genotyped for 80 SNPs in 14 candidate genes for renal disease in SLE and had HLA typing available. Continental ancestry was estimated for each participant using the program STRUCTURE, assuming 5 populations. We used logistic regression to test the association between European ancestry and renal disease, adjusting for disease duration and sex. Subsequent analyses assessed whether also adjusting for other continental ancestries, educational attainment, or SNPs in genes associated with renal disease in SLE attenuated the relationship between European ancestry and renal disease.

Results: Genetic ancestry estimation for 1910 SLE cases demonstrated that participants had on average 62.4% European, 15.8% African, 11.5% East Asian, 6.5% Amerindian, and 3.8% South Asian ancestry. Among participants, 34.4% (n=656) had a history of renal disease. After adjustment for ancestry, SNPs in *IRF5* (rs4728142), *BLK* (rs2736340), *STAT4* (rs3024912), *ITGAM* (rs9937837)and *HLA-DRB1*0301* and *DRB1*1501* were associated with renal disease in SLE ($p<0.05$). In multivariable logistic regression, a 10% increase in European ancestry was associated with a 15% reduction in the odds of having renal disease after adjustment for disease duration and sex (OR 0.85, 95% CI 0.82–0.87, p=1.9e-30). Adjusting for other genetic ancestries, educational attainment, or SNPs associated with renal disease did not substantively alter this relationship (Table).

Table. Association between European Ancestry and Renal Disease among SLE Cases

Model	N	OR for 10% ↑ in Euro Ancestry	95% CI	p-value
European ancestry + disease duration, sex (Model 1)	1820	0.85	0.82–0.87	1.9e–30
Model 1 + other genetic ancestries	1820	0.82	0.77–0.87	3.1e–13
Model 1 + educational attainment	1129	0.83	0.80–0.86	5.5e–24
Model 1 + *IRF5* (rs4728142), *BLK* (rs2736340), *STAT4* (rs3024912), *HLA DRB1*0301, *1501,* other genetic ancestries†	753	0.82	0.69–0.98	0.032

† Only SNPs with $p < 0.05$ in multivariable models were retained in the final model

Conclusions: European ancestry is protective against the development of renal disease in SLE, an effect independent of other genetic ancestries, common risk alleles, and socioeconomic status.

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1593

Fine Mapping and Expression Studies Point to KIF5A as the Gene Responsible for Association of the 12q13 Locus with Rheumatoid Arthritis. Annie McClure, Steve Eyre, Wendy Thomson, Jane Worthington and Anne Barton. The University of Manchester, Manchester, United Kingdom

Background: A region on chromosome 12q13 was shown to have modest association with rheumatoid arthritis (RA) in the Wellcome Trust genome-wide association study (GWAS) of seven common diseases. Two parallel studies have since confirmed this as a RA susceptibility locus in UK and US populations (rs1678542 $P=1.3\times10^{-7}$ and $P=5.4\times10^{-6}$, respectively) and the same SNP has also been associated with type 1 diabetes (T1D). Variants mapping to nearby genes have also been associated with T1D and multiple sclerosis. The associated variant, rs1678542, is located in intron 15 of *KIF5A*. KIF5A is a microtubule motor protein involved in the transport of neurofilaments and expression was reported to be confined to neurons. However other ubiquitous kinesin family members have been shown to be involved in cell motility and intracellular transport of HLA-class II molecules.

Objectives: The aim of the current study was to investigate the 12q13 region further to identify the most likely RA susceptibility gene in the region.

Methods: A region of ~400kb surrounding the associated variant on 12q13 was selected for fine mapping. Tag SNPs were chosen to capture all the known variation across the region ($r2 > 0.8$). Any SNPs showing larger effect sizes than rs1678542 were then genotyped in a larger, independent validation cohort of 3633 RA cases and 2908 controls.

To investigate the expression of KIF5A, RNA was extracted from the blood of 52 RA patients and cDNA was synthesised. Whole blood RNA samples were selected to represent the range of possible genotypes at rs1678542 (major allele homozygous n=20, heterozygous n=19, minor allele homozygous n=13). KIF5A is known to be expressed in the brain so RNA was extracted from mouse brain to act as a positive control. Primers were designed to amplify KIF5A in human and mouse transcriptomes. The expression of two housekeeping genes (GAPDH and ACTIN) was also measured in order to normalise KIF5A expression. QRT-PCR was carried out using the ABI 7500.

Results: In a fine-mapping cohort of 1,000 RA cases and 1,000 controls, 5 tag SNPs were identified that exhibited greater effect sizes than rs1678542. These 5 SNPs and rs1678542 were then genotyped in the larger validation cohort. Only rs1678542 remained significantly associated (p=0.004, OR 0.90 95%, CI 0.84–0.97). QRT-PCR of KIF5A confirmed its expression in whole blood. Correlation of expression with genotype at rs1678542 by linear regression showed a significant trend in expression by genotype (1×10^{-3}). Individuals homozygote for the protective major allele had reduced KIF5A expression when compared to individuals who were heterozygote or homozygote for the minor allele at rs1678542.

Conclusion: After fine mapping of the region, association remains strongest with the original SNP identified in the WTCCC GWAS mapping to the KIF5A gene. The demonstration of expression of KIF5A in whole blood improves its potential for involvement in RA pathogenesis. Furthermore we present the first evidence of a correlation between KIF5A expression and genotype at a SNP associated with RA. The next step will be to validate this correlation using allele specific expression.

Disclosure: A. McClure: None; **S. Eyre:** None; **W. Thomson:** None; **J. Worthington:** None; **A. Barton:** None.

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Fine Mapping and Trans-Ethnicity Genotyping in IL2/IL21 Establish the Genetic Association between IL21 and Systemic Lupus Erythematosus. Travis Hughes[7], Xana Kim[7], Jennifer A. Kelley[7], Kenneth M. Kaufman[9], Carl D. Langefeld[17], Julie Ziegler[17], Robert P. Kimberly[10], Jeffrey C. Edberg[15], Rosalind Ramsey-Goldman[5], Michelle A. Petri[1], John D. Reveille[14], Javier Martin[3], Elizabeth E. Brown[11], Luis M. Vila[13], Judith A. James[6], Gary S. Gilkeson[4], Kathy L. Moser[6], Patrick M. Gaffney[6], Joan T. Merrill[6], Timothy J. Vyse[2], Marta E. Alarcon-Riquelme[8], Swapan K. Nath[7], John B. Harley[12] and Amr H. Sawalha[16]. [1]Timonium, MD, [2]Imperial College, Rheumatology Section, Hammersmith Hospital, [3]Instituto de Parasitología y Biomedicina López-Neyra, Consejo Superior de Investigaciones Científicas, [4]Med Univ of South Carolina, Charleston, SC, [5]Northwestern University, Chicago, IL, [6]Oklahoma Med Research Foundation, Oklahoma City, OK, [7]OMRF, [8]OMRF, Center for Genomics and Oncological Research Pfizer, University of Granada, Junta de Andalucia, Uppsala, Sweden, [9]OMRF, OUHSC, VAMC, [10]Univ Alabama at Birmingham, Birmingham, AL, [11]Univ Alabama at Birmingham, [12]Univ of OK Hlth Sci Ctr, Oklahoma City, OK, [13]Univ of PuertoRico Schl of Med, San Juan, PR, [14]Univ Texas Health Sci Ctr, Houston, TX, [15]University of Alabama at Birmingham, Birmingham, AL, [16]University of Oklahoma Health Sciences Center, OMRF, VAMC, Oklahoma City, OK, [17]Wake Forest University Health Sciences

Purpose: Genetic association of the IL2/IL21 region at 4q27 has been previously reported in lupus and a number of autoimmune and inflammatory diseases. Herein, using a very large cohort of lupus patients and controls, we localize this genetic effect to the IL21 gene.

Methods: We genotyped 45 tag SNPs across the IL2/IL21 locus in two independent lupus cohorts. We studied a European-derived cohort consisting of 4,248 lupus patients and 3,818 healthy controls, and an African-American cohort of 1,569 patients and 1,893 healthy controls. Genetic association between the genotyped markers was determined, and pair-wise conditional analysis was performed to localize the genetic effect in the IL2/IL21 locus in lupus.

Results: We establish and confirm the genetic association between IL2/IL21 and lupus in two independent lupus cohorts. Using conditional analysis and utilizing trans-ethnicity genotyping, we localize the genetic effect for the first time in this locus to two SNPs; rs6835457 located in the 3'UTR flanking region of IL21 (Pmeta=2.51E-06), and rs907715 located within IL21 (Pmeta=1.74E-06).

Conclusion: Our data identify IL21 as a lupus susceptibility gene within the IL2/IL21 linkage disequilibrium block. This localization might be relevant to other autoimmune and inflammatory disease with a reported association in the IL2/IL21 genetic locus.

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Fine Mapping of NMNAT2 for Association with SLE Susceptibility: A Multiethnic Case-Control Study. Jian Zhao[13], Carl D. Langefeld[16], Kenneth M. Kaufman[2], Jennifer A. Kelly[1], Patrick M. Gaffney[1], Kathy L. Moser[1], Marta E. Alarcón-Riquelme on Behalf of the BIOLUPUS and GENLES Networks[3]. Timothy J. Vyse[5], Chaim O. Jacob[14], Robert P. Kimberly[15], Jeffrey C. Edberg[15], Elizabeth E. Brown on Behalf of PROFILE investigators[11], Lindsey A. Criswell[7], John B. Harley[4], Deh-Ming Chang[6], Yeong Wook Song[9], Chack-Yung Yu[10], Bernardo Pons-Estel[8], Jennifer M. Grossman[12], Rita M. Cantor[12], Bevra H. Hahn[12] and Betty P. Tsao[12]. [1]Arthritis and Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Arthritis and Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK; US Department of Veterans Affairs Medical Center, Oklahoma City, OK, [3]Center for Genomics and Oncological Research, Granada, Spain, [4]Cincinnati Children's Hospital Medical Center and US Department of Veterans Affairs Medical Center, Cincinnati, OH, [5]Imperial College London, Hammersmith Hospital, London, United Kingdom, [6]National Defense Medical Center, Taipei, Taiwan, [7]Rosalind Russell Medical Research Center for Arthritis, University of California, San Francisco, CA, [8]Sanatorio Parque, Rosario, Argentina, [9]Seoul National University, Seoul, Korea, [10]The Ohio State University, Columbus, OH, [11]University of Alabama, Birmingham, AL, [12]University of California, [13]University of California, Los Angeles, CA, [14]University of Southern California, Los Angeles, CA, [15]US Department of Veterans Affairs Medical Center, Oklahoma City, OK, [16]Wake Forest University Health Sciences, NC

Background: NMNAT2, one of the three Nicotinamide mononucleotide adenylyl transferases, is a central enzyme of the NAD biosynthesis pathway mainly expressed in Golgi-complex with a known function of delaying axon degeneration. In this study, we sought to replicate a putative association at rs2022013 in *NMNAT2* from the SLEGEN genome-wide association study (GWAS) conducted in women of European ancestry (Harley et at, 2008) not yet exceeding the stringent threshold for genome-wide significance (typically $P<5\times10^{-8}$).

Methods: A total of 24 SNPs, spanning the genomic region of *NMNAT2*, were genotyped on a customized Illumina array. Additionally, ~400 ancestry informative markers were used to control population admixture and to eliminate genetic outliers. The association of *NMNAT2* SNPs with SLE was tested in a collection of 15,424 case-control samples consisting of European Americans (EA), African Americans and Gullahs (AA&Gullah), Asians and Hispanic and Native Americans (Hisp&NA). We performed Chi-square test to compare the allelic difference between cases and controls, likelihood ratio test to distinguish independent signals from associated SNPs, and Mantel-Haenszel test to conduct the trans-ethnic meta-analysis.

Result: Among the 16 association signals observed in EA (3477 vs. 3470 case-control samples independent of SLEGEN GWAS), we replicated the association of rs2022013 ($P=9.5\times10^{-7}$, OR=0.84) and identified 4 independent SLE-associated SNPs located in intron 1 of *NMNAT2* (long isoform) with the strongest signal at rs12146097 ($P=1.6\times10^{-9}$, OR=1.34). Allelic association detected in EA was partially extended to Hisp&NA (5 SNPs with allelic *P* from 0.018 to 7.8×10^{-4}, 1508 vs. 812) but not to AA&Gullah (1680 vs. 1953). Rs607332 (within intron 6) exhibited the strongest signal in AA&Gullah ($P=0.0013$, OR=0.9) and Hisp&NA ($P=2.9\times10^{-4}$, OR=0.8) but had no association in EA, which indicated specific associations of *NMNAT2* SNPs in various populations. No SNP showed significant association with SLE in Asians (1272 vs. 1270). The most significant meta-analysis *P* value of 4 ethnic groups was detected at rs12146097 ($P=1.25\times10^{-9}$, OR=1.29).

Conclusion: We provided independent evidence that *NMNAT2* predisposes to susceptibility to SLE with genome-wide significance. Trans-ethnic fine mapping showed *NMNAT2* SNPs had different association patterns among multiple ethnic groups. Our data suggested the novel role of NAD biosynthesis in the pathogenesis of SLE.

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1596

Gene-Interactions Influence Methotrexate Efficacy in Rheumatoid Arthritis: Analysis of 62 SNPs Panel in a Monocentric Cohort of Rheumatoid Arthritis Affected Patients. Thomas Barnetche[1], Caroline Rooryck-Thambo[4], Christophe Hubert[3], Christophe Richez[2], Benoit Arveiler[4] and Thierry Schaeverbeke[2]. [1]Bordeaux University Hospital, Rheumatology Department, Bordeaux, France, [2]Bordeaux University Hospital, Rheumatology Department, [3]Genomics-Transcriptomics Facility, Bordeaux, [4]Human Genetics Laboratory EA4137, University Victor Segalen Bordeaux 2

Purpose: Methotrexate (MTX) is one of the most widely used disease-modifying antirheumatic drugs (DMARDs) for the treatment of rheumatoid arthritis. No single genetic marker allows predicting response to the treatment. Here, we aimed to establish gene-gene epistatic interactions to predict MTX response therapy. SNPs were selected in proteins and enzymes that step in folate, purine and adenosine pathways, and also in several transporters that participate to MTX cellular absorption and elimination.

Method: A sample of 222 RA affected patients treated with low dose of MTX (7,5mg to 25mg with oral, intra-muscular or subcutaneous administration) was included in a monocentric study. Efficacy to MTX was assessed using EULAR response criteria and/or physician's assessment. A panel of 62 SNPs was analyzed for each patient. Univariate analysis in genotypes and allele frequencies was performed. Then gene-gene interactions were studied using Multifactor Dimensionality Reduction (MDR). MDR is considered as a non-parametric approach to detect non-linear interactions between binary variables that influence a binary outcome. This method reduces the dimensionality of genotypes predictors from N-dimensions to one dimension in pooling multilocus genotypes into high-risk and low risks MTX response groups. The robustness and significance of the model were tested through cross validation consistency (CVC, 10-fold).

Results: The MDR method highlights that MTX response (about 67% in this sample) is related with epistatic interactions among variants in ABCC3 (ATP-binding cassette, sub-family C) efflux transporter (rs739921 [C/G], rs4148412[C/T]), ABCC5 efflux transporter (rs4148575 [C/T]) and adenosine monophosphate deaminase 1 (rs2268699 [A/C]). Testing accuracy was 0.635 and CVC was 10/10. Carriers of a predisposing genotype combination were 22.14-fold more likely to respond to MTX than those without (CI95%: 9.76–50.21; $p<0.0001$). Sensitivity was 73%, specificity was 89% and accuracy was 78%. Univariate analysis revealed independent association for only two of these four SNPs: rs4148412[C/T] (ABCC3) and rs2268699 [A/C] (AMPD1) ($p<0.05$).

Conclusion: These data indicate that epistatic interactions in MTX pharmacology pathway influence the treatment response. Further studies are needed to confirm the role of genetic variants in ABCC transporters in MTX response, and to determine the exact functional impact of this genetic model.

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1597

Genome-Wide Association Study for Rheumatoid Arthritis in the Korean Population Points to Population-Specific Candidate Loci as Well as Overlap with European Susceptibility Loci. Jan Freudenberg[2], Hye-Soon Lee[4], H. D. Shin[7], B. D. Han[5], Y. M. Kang[6], S. C. Shim[1], Y. K. Sung[4], CB Choi[4], Annette Lee[3], Peter K. Gregersen[2] and S. C. Bae[4]. [1]Eulji University Hospital, [2]Feinstein Institute for Medical Research, Manhasset, NY, [3]Feinstein Institute for Medical Research, [4]Hanyang University Hospital for Rheumatic Diseases, [5]Korea National Institute of Health, [6]Kyungpook National University School of Medicine, [7]Sogang University

We have carried out a genome-wide association study (GWAS) in Korean individuals in order to identify susceptibility loci for Rheumatoid Arthritis (RA). We generated high quality genotypes for 441398 SNPs in 801 cases of RA and 757 controls. Genome-wide significance (P<5*e-08) was attained by markers from the MHC-region and from the *PADI4* gene. We then selected and analyzed 79 markers from 46 loci for replication in an independent sample of 718 cases and 719 controls. The combined analysis of genotypes from both stages did not reveal any additional loci with genome-wide significance. However, the replication data showed nominal association signals (P<5*e-02) for markers from 11 out of the 46 replicated loci, greatly exceeding random expectation. Genes that were most significant in the replication stage and in the combined analysis include the known European RA loci *BLK*, *AFF3* and *CCL21*. Thus, in addition to the previously associated *STAT4* alleles, variants at these three loci may contribute to RA not only among Europeans, but also among Asians. In addition, we observed replication signals near the genes *PTPN2, FLI1*, *ARHGEF3, LCP2*, *GPR137B*, *TRHDE*, and *CGA1*. Based on the excess of small P-values in the replication stage, we estimate that more than half of these loci are genuine RA susceptibility genes. Finally, we systematically analyzed the presence of association signals in Koreans at established European RA loci. This showed a significant enrichment of European RA loci among Korean RA loci.

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Genome-Wide Copy-Number-Variation Study in Chinese Han Population Identifies Deletion of LCE3C_LCE3B as Susceptibility Factor for Rheumatoid Arthritis. Xiaolan Lu[2], Jianping Guo[3], Ru Li[3], Xia Liu[3], Zuowei Wu[4], Jinxia Shi[3], Xinyu Wu[3], Yingni Li[3], Yi Zhao[3], Chun Li[3], Sisi Pan[3], Lei Zhu[3], Jing He[3], Xu Liu[3], Wenjun Chen[1], Baoli Zhu[4] and Zhanguo Li[3]. [1]Beijing Institute of Genomics, Chinese Academy of Sciences, [2]Department of Rheumatology and Immunology, People's Hospital Peking University, Beijing, China, [3]Department of Rheumatology and Immunology, People's Hospital Peking University, [4]Institute of Microbiology, Chinese Academy of Sciences

Objective: To identify susceptibility genes concerning copy number variations (CNVs) in rheumatoid arthritis (RA) and to determine whether the RA risk CNVs are specifically associated with certain subsets of RA.

Methods: We first conducted a genome-wide CNV analyses by array comparative genomic hybridization (aCGH), and further characterized the association between the CNV of the late cornified envelope (LCE) genes, LCE3C_LCE3B and RA in a case-control cohort (518 RA patients and 507 controls). All samples were directly genotyped for the presence or absence of LCE3C_LCE3B alleles by PCR. The cases were classified based on their HLA–DRB1 genotypes, anti-citrullinated protein antibodies (ACPAs) and rheumatoid factor (RF) status, as well as clinical features.

Results: In aCGH study, we identified LCE3C_LCE3B as a candidate risk factor for RA (Log2 ratio = 1.50 ± 0.92). In replication study, we further demonstrated that the deletion of LCE3C_LCE3B was associated with RA (allele analysis: p = 3.03×10-3; OR 1.30, 95%CI 1.09–1.56; genotype analysis: p = 2.02×10-3; OR 1.58, 95%CI 1.02–2.45), with the specificities in anti-cyclic citrullinated peptide antibody (anti-CCP) positive (p = 0.03; OR 1.40, 95%CI 1.01–1.94), RF negative (p = 0.04; OR 1.78, 95%CI 1.04–3.06), anti-keratin antibody (AKA) negative (p = 6.68×10-3; OR 1.51, 95%CI 1.01–2.26), and rheumatoid nodules (RNs) negative subsets (p = 0.01; OR 1.52, 95%CI 1.08–2.13).

Conclusion: Our study demonstrated that LCE3C_LCE3B-del was a novel susceptibility factor for RA in Chinese Han population, and the LCE3C_LCE3B-del association with RA was significantly relevant to HLA–DRB1 shared epitope (SE), anti-CCP, RF and AKA status.

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Genome-Wide Pathway Analysis Identifies Oxidative Stress Related Gene MSRA as Rheumatoid Arthritis Susceptibility Locus. Jose Ezequiel Martin[5], Behrooz Z. Alizadeh[10], Miguel A. Gonzalez-Gay[4], Alejandro Balsa[2], Dora Pascual-Salcedo[2], Benjamín Fernández-Gutiérrez[1], Enrique Raya[3], Lude Franke[9], Ruben Van't Slot[11], Marieke J. H. Coenen[7], Piet van Riel[8], T. R. D. J. Radstake[8], B. P. C. Koeleman[11] and Javier Martin[6]. [1]Hospital Clinico San Carlos, Dept. of Rheumatology, Spain, [2]Hospital La Paz, Madrid, Dept. of Rheumatology, Spain, [3]Hospital Universitario Clinico San Cecilio, Dept. of Rheumatology, Spain, [4]Hospital Xeral-Calde, Dept. of Rheumatology, Lugo, Spain, Spain, [5]Instituto de Parasitologia y Biomedicina Lopez-Neyra, CSIC, Armilla, Granada, Spain, [6]Instituto de Parasitologia y Biomedicina Lopez-Neyra, CSIC, Spain, [7]Radboud University Nijmegen Medical Center, Department of Human Genetics, The Netherlands, [8]Radboud University Nijmegen Medical Center, Department of Rheumatology, The Netherlands, [9]University Medical Center Groningen, Dept. Human Genetic, The Netherlands, [10]University Medical Centre Groningen, Dept. of Epidemiology, [11]University Medical Centre Utrecht, Dept. Medical Genetics, The Netherlands

Objective: Genome-wide association studies (GWASs) carried out in rheumatoid arthritis (RA) have led to the discovery of several genetic associations with this disease. Still, the current associated genetic variations can explain only part of the genetic risk involved in RA, and it is well recognised that these GWASs are likely underpowered to detect all common disease variants. Therefore, we explored the genomic regions showing low-significance associations in previous GWASs of RA.

Methods: To reduce the false-positive signal fraction, we exploited pathway analysis to prioritise regions containing genes most likely to be implicated in RA. We hypothesised that true disease genes would be in a similar pathway. Therefore, genes from similar pathways but located in different regions were prioritised for replication using Prioritizer software. 384 genetic variants selected from previous RA GWASs were tested in a Spanish case/control discovery cohort comprising 376 RA patients and 478 healthy controls for replication. Statistically significant associations were further validated in replication cohorts from Spain and Netherlands, up to a total of 1,818 RA patients and 2,498 controls.

Results: We detected a novel genetic association between RA and the MSRA gene (rs10903323, $P = 2.91\times10^{-5}$, OR = 1.51) in the Spanish combined population. This association was further tested in our independent Dutch replication cohort. Combined analysis showed an overall association of MSRA with RA ($P = 2.19\times10^{-4}$, OR = 1.28).

Conclusion: Novel association in the MSRA gene related to oxidative stress is described herein and support a major role for this process in RA.

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Identification of Genetic Markers of Rheumatoid Arthritis Severity by Genome-Wide Association Studies. Sebastien Viatte[1], Darren Plant[2], John Bowes[2], Deborah Symmons[2], Jane Worthington[2] and Anne Barton[1]. [1]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [2]Arthritis Research UK Epidemiology Unit, The University of Manchester

Introduction: The largest genetic risk to develop rheumatoid arthritis (RA) arises from a group of alleles of the HLA DRB1 locus ("shared epitope"). Recent genome wide and candidate gene association studies have identified over 30 confirmed single nucleotide polymorphisms (SNPs) predisposing to disease (susceptibility loci). However, the genetic variants identified so far do not predict clinical outcomes, such as erosions, disability or response to treatment, well. We therefore sought to identify genetic markers of outcome of disease severity, in patients with recent-onset inflammatory polyarthritis (IP).

Methods: The Norfolk arthritis register (NOAR) is a primary care-based inception cohort of subjects with inflammatory polyarthritis recruited at symptom onset and followed prospectively. Demographic and clinical data

are recorded at inclusion and at yearly assessments thereafter. Serologic status (anti citrullinated protein antibodies (ACPA)) is determined at study entry. A subset of 372 patients was genotyped for 370,404 single nucleotide polymorphisms (SNPs) by genome-wide array (Illumina). The association of SNP markers with clinical and radiological markers of disease severity was investigated using the presence of erosions by 5 years as the primary outcome measure. Adjustment for the presence of ACPA, a known marker of disease severity, and for receiving disease modifying anti-rheumatic medications was incorporated into the analysis.

Results: At baseline 84% of the 372 genotyped patients satisfied the 1987 ACR criteria for RA; and 62% carried at least one copy of an HLA-DRB1 allele known to confer susceptibility to RA. 48% were erosive by 5 years. Genome-wide association studies revealed a number of SNPs with evidence for association with erosions by year 5 of follow-up (p-values $< 5.9\times10^{-6}$ for SNPs mapping to SLC15A4 (chr. 12), XIRP2 (chr. 2) and HLA-DQ (chr. 6)) or with the extent of radiological damage quantified by the Larsen score (5 SNPs mapping to MTMR7, $p=4.4\times10^{-8}$). Logistic regression analysis within the genotyped NOAR dataset confirmed the known strong association between positivity for ACPA and erosions, and showed a weaker but independent association between HLA-DRB1 susceptibility alleles and erosions.

Discussion: We have found a set of SNPs with strong evidence for association with radiological damage by 5 years. Genotyping of these candidate SNPs is currently underway in an independent cohort. The identification of genetic predictors of severity at presentation could be used to predict which patients are likely to develop erosive disease, and it may be possible to target these patients for more aggressive treatment earlier in their disease course. If replicated, these genetic markers may improve the predictive value of ACPA in identifying patients likely to experience a severe disease course and pave the way for a more personalised approach to medicine.

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1601

Identification of KIAA Proteins in Immune Complex Proteome from Juvenile Idiopathic Arthritis and Systemic Lupus Erythematosus. Anil Chauhan[2], Brooke Gilliam[2], Catherine P. Riley[1], Jiri Adamec[1] and Terry L. Moore[3]. [1]Purdue University, [2]Saint Louis University, [3]St Louis University, St Louis, MO

Purpose: Biomarkers discovered by proteome analysis are not only useful for patient stratification but for monitoring therapeutic responses and understanding of disease pathogenesis. Biological fluids such as plasma although a good source of information, present a technical challenge due to at least ten orders of magnitude dynamic range of protein concentration. Protein and peptide immuno-affinity pre-fractionation coupled with mass spectometry (MS)-based proteomics have been used for biomarker discovery; however a prior knowledge of the disease association is required. Thus we wanted to develop a proteomic approach that is capable of identifying low abundance disease associated proteins as a possible biomarker candidate. We achieved this by combining receptor affinity for isolation of immune complexes (ICs) with downstream coupling to nano-LC/MS-MS.

Methods: Fifteen IC samples from juvenile idiopathic arthritis (JIA) and systemic lupus erythematosus (SLE) patients were purified using receptor affinity columns and then fractionated on a Criterion XT Bis Tris precast 4–20% polyacryamide gel. Thereafter, each sample protein lane was cut into 5 equal pieces. Tryptic peptides from these samples were then developed on a nanoLC-Chip system (1100 Series LC, Agilent) and separated on the on-chip C-18 reversed phase ZORBAX 300SB-C18 ($0.075\mu m \times 150$ mm; Agilent). The NanoLC-MS chromatograms were acquired in positive ion mode with a capillary voltage of 1850 V, an end plate offset of 500 V, dry gas at 300°C and 4 L/min. Spectra were acquired for 350–2000 m/z at a scan speed of 8,100 m/z/s with 0.15 s maximum accumulation time.

Results: We identified a total of 873 proteins from ICs purified from the fifteen samples. The ICs from the JIA patients showed more proteins associated with cell adhesion, proliferation, protein transport, and ATP biosynthetic process, while the SLE group with cytoskeleton organization, signal transduction, T cell activation, and intracellular and signaling cascade. A number of proteins that are known target of post translational modifications in autoimmune response were also identified. The common proteins present in these ICs were complement proteins, fibrinogen, apolipoprotein A-I, cartilage acidic protein, and S100 calcium-binding proteins. The SLE-ICs showed a large number of nuclear proteins such as zinc finger proteins including 652, 644, 133, and matrin type 5. In addition, ICs from JIA and SLE showed the presence of T cell receptor beta chains, suggesting an active role for T cells. KIAA proteins are proteins encoded by large cDNA identified by Kazusa cDNA project. They display multiple domains that suggset their involvement in interactions with other biological molecules. We observed two unique sets of KIAA proteins one associated to JIA and other with SLE. There are 2031 KIAA cDNA entries in HUGE database that are being characterized (http://www.jp/huge/ppi).

Conclusion: We show a successful approach to identify low abundance antigens from ICs.The IC proteome shows more proteins unique to individuals rather than disease group. The presence of KIAA proteins in the ICs suggest their role in disease pathogenesis and as a new potential biomarker group.

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1602

Major Histocompatibility Complex Associations with Thrombosis and Antiphospholipid Antibody Production in Systemic Lupus Erythematosus. Rachel Kaiser[4], Sharon A. Chung[4], Kimberly E. Taylor[5], Suzanne L. May[2], Patricia P. Ramsay[2], Hong L. Quach[2], Diana L. Quach[2], Julie A. Lane[1], Janelle A. Noble[1], Michael F. Seldin[3], Lisa Barcellos[2] and Lindsey A. Criswell[6]. [1]Children's Hospital Oakland Research Institute, [2]UC Berkeley, [3]UC Davis, [4]UCSF, San Francisco, CA, [5]UCSF, [6]UCSF-Box 0500, San Francisco, CA

Purpose: Thrombosis occurs at a younger age and at an increased frequency in systemic lupus erythematosus (SLE) compared to the general population. Known risk factors such as antiphospholipid antibodies (aPL) incompletely explain outcomes in this complex phenotype. The major histocompatibility complex (MHC) has the strongest association with SLE but associations with subphenotypes are less well-established due in part to linkage disequilibrium in the region. Prior studies in Caucasians suggest that *HLA-DRB1* allele frequencies differ between SLE patients with and without aPL, and that DR4 and DR7 may be associated with anticardiolipin autoantibodies (aCL). We investigated the association of *HLA-DRB1* and other MHC loci (independent of *HLA-DRB1)* with thrombosis and aPL production in SLE.

Methods: We genotyped 909 SLE cases of European descent for 2360 single nucleotide polymorphisms (SNPs) across 4.9 Mb of the MHC using the Illumina Combined MHC panel. These cases were also genotyped for *HLA-DRB1* and 384 ancestry informative markers. Thrombotic events (deep venous thrombosis, myocardial infarction, stroke, pulmonary embolism, retinal vein thrombosis, recurrent miscarriage) and aPL status (aCL IgG and IgM, lupus anticoagulant (LAC)) were obtained from medical record review. Associations with *HLA-DRB1* alleles were identified using a relative predispositional effects (RPE) method. SNPs associated with aPL and thrombosis were identified using forward selection with conditional logistic regression based on haplotypes implemented in WHAP.

Results: We genotyped 1974 SNPs and 640 SLE cases after stringent quality control criteria were applied and subjects with <90% northern European ancestry were removed. Five percent of the subjects were LAC positive, 33% were aCL positive, 35% were positive for at least one of these aPLs, and 24% experienced at least one thrombosis. *HLA-DRB1*0701* was associated with thrombosis in a global X^2 test and in a multivariate model adjusting for age, gender, smoking history, disease duration, nephritis history, aPL, Northern European ancestry and medications (including immunodmodulators and hydroxychloroquine) (OR 2.06, 95%C.I. 1.09–3.90, p=0.027). No *DRB1* associations were found with aPL (global χ^2 p>0.05). Conditional logistic regression identified associations independent of *HLA-DRB1* in or near the BAT3-MDC1-HCP5 region with thrombosis (OR=2.53, haplotype specific $p=1.35\times10^{-10}$) and in or near the BTNL2-HLA-E-HLA-B region with aPL (OR 4.50, haplotype specific $p=6.80\times10^{-5}$).

Conclusions: *HLA-DRB1*0701* is associated with thrombosis in SLE but no *HLA-DRB1* associations were found with aPL, possibly due to a lack of power to detect an association. We also identified several MHC associations with thrombosis and aPL independent of the *HLA-DRB1* locus. Interestingly, these associations were in Class I and III in addition to the previously associated Class II loci. Furthermore, these associations were different for the outcomes of thrombosis and aPL. Thrombosis risk in SLE may be explained in part by MHC genetic variation.

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1603

MMEL1 and CDK6 Are Associated with ACPA Positive and RF Positive Rheumatoid Arthritis. Marthe Thoresen Mæhlen[1], Tore K. Kvien[3], Till Uhlig[2] and Benedicte A. Lie[4]. [1]Dept. of Rheumatology, Diakonhjemmet Hospital, 2. Institute of Immunology, Oslo University Hospital, Oslo, Oslo, Norway, [2]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [3]Diakonhjemmet Hospital, Oslo, Norway, [4]Institute of Immunology, Oslo University Hospital, Oslo, Norway

Background: Genes play an important role in the aetiology of rheumatoid arthritis (RA), and recent genome wide association studies have reported several new SNPs to be associated with RA. Some of these have been replicated. However, further studies are needed to establish whether these are true risk loci.

Objective: Investigate whether 11 candidate SNPs (in KIF5A, REL, CCL21, PRKCQ, STAT4, CTLA4, MMEL1, CDK6, TRAF1, OLIG3-TNFAIP3 (2 SNPs)) are associated with RA and autoantibody production in the Norwegian population.

Method: DNA from 950 Norwegian RA patients and 1130 Norwegian controls were genotyped with TaqMan assays (Applied Biosystems). All 11 SNPs had >98% genotyping success rate and all genotypes were in Hardy-Weinberg equilibrium. χ^2 tests were used to test for associations. For the SNPs that were not associated with RA, we calculated the power in our dataset to detect an association using *Power and Sample Size program, version PS 3.0.14*. These calculations were based on odds ratios and minor allele frequencies published in a recent meta-analysis (Stahl, E.A. *et al Nat. Genet,* 2010).

Results: The major allele of MMEL1 and minor allele of CDK6 were both significantly associated with RA (table). The associations were restricted to ACPA positive and RF positive RA. The minor allele of STAT 4 was significantly associated with ACPA positive RA only. None of these 3 SNPs were associated with ACPA negative or RF negative RA. The remaining eight SNPs showed no significant association with RA in our Norwegian cohort.

Gene	Patients	Minor allele	MAF case	MAF control	Allele test	OR 95% CI	P-value
MMEL1	ALL	C	0.298	0.334	T/C	1.18 (1.03–1.35)	0.01
MMEL1	ACPA +	C	0.276	0.334	T/C	1.30 (1.11–1.53)	0.001
MMEL1	RF +	C	0.251	0.334	T/C	1.45 (1.26–1.78)	>0.001
CDK6	ALL	G	0.262	0.227	G/C	1.20 (1.04–1.39)	0.01
CDK6	ACPA +	G	0.274	0.227	G/C	1.28 (1.09–1.52)	0.003
CDK6	RF+	G	0.278	0.227	G/C	1.31 (1.10–1.56)	0.003
STAT4	ALL	T	0.239	0.223	T/G	1.10 (0.95–1.27)	0.22
STAT4	ACPA+	T	0.253	0.223	T/G	1.18 (1.0–1.40)	0.05

Conclusion: We replicated the proposed associations between MMEL1 and CDK6 with RA. In addition we demonstrated that CDK6 and MMEL1 are associated to both ACPA positive and RF positive RA. Further we confirmed that STAT4 is associated with ACPA positive RA. We found no association with eight SNPs, however due to moderate to low risk in other populations, we may have had insufficient power to detect an association.

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1604

Multiple Expanded B-Cell Clones Are Already Present in Early Rheumatoid Arthritis: Results of a Comparison between Early and Longstanding Disease Using High Throughput Sequencing Technology. Marieke E. Doorenspleet[2], Stefano Alivernini[2], Marjolein J. de Hair[2], Paul L. Klarenbeek[2], Marieke M. Herenius[2], Marleen G. van de Sande[2], Barbera D. van Schaik[1], Rebecca E. Esveldt[2], Antoine H. van Kampen[1], Danielle M. Gerlag[2], Frank Baas[3], Paul P. Tak[2] and Niek de Vries[2]. [1]Dept. of Clinical Epidemiology, Biostatistics and Bioinformatics Academic Medical Center-University of Amsterdam, [2]Div. Clinical Immunology and Rheumatology Academic Medical Center-University of Amsterdam, Amsterdam, The Netherlands, [3]Laboratory for Genome Analysis Academic Medical Center-University of Amsterdam

Background: B-cells play an important role in the pathogenesis of rheumatoid arthritis (RA) but their exact role remains unclear. We previously found that expanded B-cell clones can be detected in inflamed synovial tissue (ST) of patients with longstanding RA. These clones were either absent or of very low frequency in peripheral blood (PB), suggesting local retention and/or proliferation in the synovium. Here we examined whether oligoclonal B-cell expansions can be detected in early stages of RA.

Objectives: Compare expanded B-cells in paired samples (ST and PB) during different stages of disease using novel high throughput sequencing technology.

Methods: We included 2 anti-CCP+ patients with active RA. Patient 1 (pt1) was DMARD naïve and had a disease duration less than 1 year. Patient 2 (pt2) had active disease despite methotrexate treatment and had a disease duration of more than 10 years (longstanding RA). mRNA was isolated from paired samples (ST biopsies from arthritic ankle/knee and PB, respectively). Linear amplification was performed with primers for all V(ariable)-families of the receptor heavy-chain. The amplified products contain the Complementarity Determining Region 3 (CDR3), which can be used as a 'fingerprint' for each clone. The samples were analyzed using a Genome Sequencer (454/Roche). The frequency of clones was determined by custom bioinformatics algorithms identifying the CDR3-region of each receptor (up to 1 million receptors at once). Clones with a frequency of ≥1% were arbitrarily considered as highly expanded.

Results: In the longstanding RA-patient 15 highly expanded B cell clones were detected in the ST. Of interest, we also detected 14 highly expanded clones in the ST of the early RA patient. In both patients the highest frequency observed was 7%, and none of the highly expanded clones had a clearly higher frequency than the other clones. The oligoclonal pattern observed was defined by distinctly different CDR3 sequences and use of different gene segments in both patients. In the PB samples of both patients only few expanded clones were found (5 and 6 highly expanded clones, respectively). However, most clones that were highly expanded in ST could also be detected in the PB of both patients, albeit at very low frequencies (less than 0,05% in both patients). In contrast, highly expanded clones from the PB were not at all found in ST. Comparing both patients, the highly expanded clones were all different.

Conclusion: This is the first analysis of B-cell clones in ST and PB samples comparing RA patients with different disease duration, using novel HTS technology. Our data suggest that oligoclonal B-cell expansions can already be detected in early stages of RA. This suggests that multiple epitopes might already be involved in so-called early RA.

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1605

New HLA-DRB1 Classifications in Association with Rheumatoid Arthritis for Global Application: Beyond the Conventional Shared Epitope Hypothesis. So-Young Bang[1], Hye-Soon Lee[1], Ji-Seon Lee[1], Eun-Mi Kim[1], Kyung Wha Lee[2] and Sang-Cheol Bae[1]. [1]Department of Rheumatology, Hanyang University Hospital for Rheumatic Disease, Korea, Republic of, [2]Hallym Institute for Genome Application, Hallym University Sacred Heart Hospital, Korea, Republic of

Objectives: The HLA-DRB1 shared epitope (SE) hypothesis does not wholly explain HLA contribution to rheumatoid arthritis (RA) susceptibility. Different classification systems have been proposed, but few have been validated in non-Caucasians. Here, we investigated the relevance of recent HLA-DRB1 allele classifications of RA susceptibility and protection in a large Asian cohort of RA patients and controls.

Methods: All 2,601 unrelated Korean subjects including 1,482 patients with RA and 1,119 unaffected controls were genotyped. Four-digit level HLA-DRB1 typing was performed by direct DNA sequence analysis. HLA-DRB1 alleles were grouped according to the Tezenas du Montcel and Mattey classification systems.

Results: Based on Tezenas du Montcel classification, S_2/S_{3P} genotype was associated with the greatest risk for RA, with an OR (95% CI) of 15.30 (4.79–48.93). We confirmed our previous finding that DRB1*0901 was the second significant risk allele for RA in the Korean population [OR 1.83 (1.53–2.19), $P = 4.37 \times 10^{-11}$]. The HLA-DRB1 alleles were reanalyzed according to our modified classification system including DRB1*0901 [S_4 (^{67}F^{70}RRRAE^{74})]. Interestingly, S_2/S_{3P} and S_4/S_{3P} genotypes were associated with the higher risk for RA compared with conventional classification. Additionally, the SE/D^{70+} genotype was associated with lower risk for RA, compared with the SE/D^{70-} genotype using the Mattey classification system.

RA risk for genotypes according to our modified HLA-DRB1 classification system*

Genotype	No. (%) of controls (n=1,119)	No. (%) of RA cases (n=1,482)	OR (95% CI)	*P*
S_2/S_3*	4 (0.36)	26 (1.75)	21.96 (6.82–70.73)	3.87×10^{-27}
S_4/S_3*	36 (3.22)	149 (10.05)	11.91 (7.59–18.68)	1.20×10^{-20}
S_3*/S_3*	3* (3.13)	190 (12.82)	11.90 (7.69–18.43)	1.20×10^{-28}
S_4/S_4	11 (0.98)	31 (2.09)	6.46 (2.91–14.35)	4.44×10^{-4}
S_3*/L	311 (27.79)	602 (40.62)	4.41 (3.47–5.60)	6.00×10^{-34}
S_2/L	11 (0.98)	20 (1.35)	2.61 (1.09–6.24)	0.03
S_4/L	148 (13.23)	203 (13.70)	2.59 (1.91–3.51)	9.82×10^{-10}
L/L	563 (50.31)	258 (17.41)	reference	—

*Logistic regression analysis adjusted for age and sex. All odds ratios (OR) 95% confidence intervals (95% CI), and P values were calculated by comparing each group with the reference group. DRB1 alleles were divided into three susceptible *0401). S_3* ("RRAA/" *0101, *0102, *0404, *0405, *0408, *0410, *0445, *1001, *1402 and *1406) and S_4 ("*10^{-10}RRRAE/*" *0901)] and low risk (L, others) alleles. S_2/S_2 and S_2/S_4 genotypes were not observed in Korean populations.

Conclusions: All susceptible alleles, except *0901, were classified as S_2 or S_{3p} using the Tezenas du Montcel criteria. We propose that an appropriate HLA classification system including DRB1*0901 is required in populations with DRB1*0901 as an RA susceptibility allele. An appropriate HLA-DRB1 model should aid in clarifying the roles of these alleles in RA.

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1606

Pre Analytical Effects of Serum Collection and Handling in Quantitative Immunoassays for Rheumatoid Arthritis. Ferhan Qureshi[3], William Manning[3], Scott Eastman[3], Wayne Hu[3], Michael Centola[6], Mary Turner[7], Craig W. Carson[5], Ana A. Kumar[4], Linda A. Zacharias[2], Claire Alexander[3], Doug Haney[3], Guy Cavet[3] and Lyndal K. Hesterberg[1]. [1]Crescendo Bioscience, Inc., South San Francisco, CA, [2]Crescendo Bioscience, Inc., Edmond, OK, [3]Crescendo Bioscience, Inc., [4]OK Arthritis Center, Edmond, OK, [5]Oklahoma Arthritis Ctr, Edmond, OK, [6]Oklahoma Med Research Foundation, Oklahoma City, OK, [7]Oklahoma Medical Research Foundation

Background: Pre-analytical variables related to serum processing and handling can have significant influences on the results obtained in quantitative protein immunoassays. Understanding the impact of these variables is critical for assay development, validation, and commercial testing. The effect of 2 routine serum collection methods (on the clot with ambient temperature shipping vs. centrifuged with cold chain shipping) and 2 serum handling variables (time before assay and freezing) were examined in a novel, validated, 12-biomarker RA disease activity test (DA Test) and up to 15 additional proteins being evaluated as predictors of structural damage progression in Rheumatoid Arthritis (RA).

Method: To evaluate serum collection variables, multiple matched sets of Becton Dickinson Serum Separator Transport Tubes (BD SST™) were drawn from 10 RA patients, with varying disease activity. One set of tubes from each individual was processed per manufacturer's instructions followed by overnight shipment in a temperature controlled (2–8°C) package ("Cold chain"). A matched tube from each individual was simultaneously shipped overnight at ambient temperature while remaining on the clot (e.g. not centrifuged; OTC). Upon arrival, the OTC tube was centrifuged and all samples were aliquoted for analysis in single-plex ELISAs and mutli-plex Meso Scale Discovery immunoassays.

To evaluate post-processing serum handling effects, matched aliquots of serum were held at multiple temperatures (−80°C, −20°C, 4°C and 25°C) for extended periods of time before assaying to generate a DA Test score which was then compared to the scores obtained in a baseline measurement. Additionally, multiple aliquots of serum (including both pools and individuals) were subjected to 3 successive freeze thaw cycles at −80°C prior to analysis by immunoassay.

Results: Significant differences in analyte concentrations were seen in >45% (13/27) of the analytes between the 2 collection methods. Twelve of thirteen biomarkers levels increased in the OTC samples, while one decreased. Of the 13 biomarkers with significant changes, 5 had poor correlation within the 10 RA patient samples ($R^2 < 0.7$) compared to the centrifuged, cold chain samples. The individual DA Test scores varied widely, (−16% to 126%), confirming the value of onsite centrifugation and cold chain shipping. The impact of serum storage (post-processing) at the various temperatures tested and multiple freeze thaw cycles on biomarker levels was minimal. Additional studies, to characterize combinations of multiple pre-analytical variables are currently being designed.

Conclusion: Serum collection, processing and handling methods have a significant impact on the measurable serum protein levels. These results illustrate the importance of characterizing pre-analytical variability to ensure test accuracy and for using robust serum processing and handling procedures for development, validation, and clinical testing with biomarker assays including the DA Score.

Disclosure: F. Qureshi: Crescendo Bioscience, Inc., 3; **W. Manning:** Crescendo Bioscience, Inc., 3; **S. Eastman:** Crescendo Bioscience, Inc., 3; **W. Hu:** Crescendo Bioscience, Inc., 3; **M. Centola:** Crescendo Bioscience, Inc., 3, 5, 9, OMRF, 3, 5, 9; **M. Turner:** Crescendo Bioscience, Inc., 3, 5, OMRF, 3, 5; **C. W. Carson:** None; **A. A. Kumar:** None; **L. A. Zacharias:** None; **C. Alexander:** Crescendo Bioscience, Inc., 3; **D. Haney:** Crescendo Bioscience, Inc., 3; **G. Cavet:** Crescendo Bioscience, Inc., 3; **L. K. Hesterberg:** Crescendo Bioscience, Inc., 3.

1607

Serum TNFα and IL-6 Concentrations in Systemic Lupus Erythematosus, Rheumatoid Arthritis and Controls Are Associated with Polymorphisms in *PTPN2*, *IRF5*, *INFG*, and *NOD2*. Joseph F. Solus[3], Young Hee Rho[3], Annette M. Oeser[4], Cecilia P. Chung[2], Chun Li[3], Jeffrey R. Smith[3] and C. Michael Stein[1]. [1]Vanderbilt University Medical Center, Nashville, TN, [2]Vanderbilt University Medical Center, Baltimore, MD, [3]Vanderbilt University Medical Center, [4]VUMC 23rd Ave South Pierce, Nashville, TN

Purpose: Elevated serum concentrations of inflammatory mediators are characteristic of autoimmune inflammatory disease. Genetic variation contributes to the regulation of inflammation. We examined the hypothesis that indicators of inflammation in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are associated with a subset of genetic polymorphisms previously implicated in the etiology and pathology of inflammatory autoimmune disease.

Method: Serum TNFα and IL-6 concentrations were measured by multiplex ELISA (Millipore Corp.) in patients with SLE (n=148) or RA (n=166) and in control subjects without inflammatory rheumatic disease (n=177). Candidate genes were chosen from publications reporting association with autoimmune or inflammatory disease. Genotypes for 345 SNP markers from 75 genes were determined using Golden Gate assay (Illumina Inc.). Association was calculated by linear regression of $\log_{10}$-transformed data using an additive genetic model.

Results: TNFα concentrations were higher in patients with SLE (median 4.8, IQR [3.1–7.9] pg/ml) and RA (5.5 [2.8–11.0] pg/ml) than controls (2.8 [2.1–3.9] pg/ml). IL-6 concentrations were higher in patients with SLE (5.7 [2.3–22.4] pg/ml) and RA (13.8 [4.4–43.0] pg/ml) than controls (2.9 [1.0–11.5] pg/ml), and were higher in RA than SLE (all $p<0.001$). Several genetic variants were associated with markers of inflammation. TNFα was associated with *IRF5*(rs10488631) in SLE ($p=0.01$) and controls ($p=0.001$) but not in RA, and with *IFNG*(rs2069727) in SLE ($p=0.007$) but not in RA and controls. TNFα was associated with *PTPN2*(rs2542151), *DRB1*(rs3021304) and *NOD2*(rs5743291) in RA ($p=0.001$, 0.001, 0.009), and in controls with *NOD2* ($p=0.01$), but not in SLE. The top rank order for associations with IL-6 were *TYK2*(rs280523) and *IL10*(rs1800890) in SLE ($p=0.005$ for each), *DRB1*(rs3021304) and *NOD2*(rs748855) in RA ($p=0.0005$, 0.001), and *MMP7*(rs12285347, rs17098318) in controls ($p=0.002$, 0.009). Several other associations for IL-6 were of nominal significance ($p<0.01$). The analysis of all samples as a single group revealed *PTPN2* as the top rank order association for both TNFα and IL-6 ($p<0.0001$, $p=0.0006$). A possible interaction between *PTPN2* and disease status was observed for TNFα ($p=0.03$) but not for IL-6 ($p=0.9$).

Conclusion: An *IRF5* polymorphism previously associated with susceptibility to lupus and other autoimmune disease was associated with serum TNFα concentrations in SLE patients and controls but not in RA, suggesting that the mechanism of regulation of TNFα through interferon regulatory factor 5 is retained in SLE but is disrupted or obscured by other factors in RA. An analogous situation may exist for regulation of TNFα and IL-6 in patients with RA or SLE and healthy controls through *PTPN2, NOD2,* and *IFNG*.

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1608

SLE-Associated Genetic Variants Influence Gene Expression in Patients. Hatice Bilgic[4], Thearith Koeuth[5], Joseph C. Wilson[5], Ward Ortmann[1], Michelle Petri[2], Peter Gregersen[3], Timothy Behrens[1] and Emily C. Baechler[5]. [1]Genentech, Inc., [2]Johns Hopkins School of Medicine, [3]The Feinstein Institute for Medical Research, [4]University of Minnesota, MN, [5]University of Minnesota

Background: SLE is a complex disorder which is likely to be affected by multiple biological pathways. Mapping the genetic influences of individual genes and or/pathways that contribute to disease may reduce complexity and increase the power to identify genetic risk factors that cause SLE. Recent genome-wide genetic association studies in SLE have identified numerous single nucleotide polymorphisms (SNPs) conferring risk to lupus. We hypothesized that some of these genetic variants will correlate with gene expression phenotypes in SLE. Uncovering these SNP/transcript associations may permit a better understanding of the genetic underpinnings of human SLE, and the identification of novel targets for therapy.

Methods: We studied 309 Caucasian SLE patients enrolled from the Hopkins Lupus Cohort via the Autoimmune Biomarkers Collaborative Network. Gene expression levels were quantified in peripheral blood cells of SLE patients with the Illumina WG-6 BeadChip expression arrays. Any gene that had a detection p-value >0.1 (not expressed) for $>95\%$ of samples was removed from analysis. For the remaining genes, the expression values in individual samples that had detection $p>0.1$ had were replaced with the minimum detectable ($p<0.1$) expression value for that gene. This resulted in 24,849 probes for further analyses. Type I interferon (IFN) gene signature scores were calculated from the expression of 70 IFN-inducible genes. DNA samples from the same subjects were genotyped on Illumina HumanHap 550K Genotyping BeadChip and subjected to standard data quality filters. We selected 34 SNPs previously shown to be associated with SLE and interrogated the correlation of genotype with gene expression using Pearson correlation and one-way ANOVA.

Results: In this discovery cohort, we identified putative cis-associations between blood cell gene expression levels and SNPs in or near 3 genes (BLK, KLK1, and UBE2L3) for which there is a priori evidence of genetic association with disease. Two SNPs upstream of BLK (rs2736340, rs13277113) were significantly correlated with BLK transcript levels ($r=-0.21$, $p=0.0002$; ANOVA $p\leq0.001$). SNP rs266858 is in the kallikrein gene cluster on chromosome 19, near the SLE-associated KLK1 gene. This SNP was significantly correlated with KLK1 transcript levels ($r=0.16$, $p=0.006$; ANOVA $p=0.001$). A SNP within the gene that encodes the ubiquitin-conjugating enzyme UBE2L3 (rs5754217) was significantly correlated with UBE2L3 gene expression ($r=0.39$, $p<0.0001$; ANOVA $p<0.001$). We also identified significant correlations between the type I IFN gene score and SLE-associated SNPs in/near ATG5 ($p=0.0004$), COPS8 ($p=0.01$), PHRF1 ($p=0.01$), PRDM1 ($p=0.004$), PTPN22 ($p=0.04$), and STAT4 ($p=0.005$).

Conclusions: Our initial findings suggest that several cis interactions between SLE-associated alleles and transcript levels, and that SLE SNPs may influence the type I IFN signature. A complete validation analysis is required to identify the most promising genetic effects for further study.

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1609

Stratification of Rheumatoid Arthritis Patients into Disease Subtypes with Clinical Implications. Glynn Dennis, Cecile Holweg, Jason Hackney, Houston Glibert, Wei Yu Lin, Lauri Diehl, Judith Endres, David Fox, Mike Townsend and Flavius Martin. Genentech

Purpose: The study aimed to identify molecular subtypes of rheumatoid arthritis (RA) that differ in their biological composition and response to therapy.

Methods: Genome-wide transcriptional profiles for 81 synovial tissue samples obtained by surgery from 50 active RA patients fulfilling the 1987 ACR criteria were stratified by bootstrapped hierarchical clustering. Statistically supported sample subtypes were further characterized by significance analysis of microarrays and pathway analysis. Platform independent validation of subtypes was performed by immunohistochemistry, fluorescence-based cell sorting and semi-quantitative polymerase chain reaction. Subtype-intrinsic gene signatures were tested for their ability to classify external data using linear discriminant analysis. Protein biomarker assays measured the association between serum proteins and response to rituximab.

Results: Multi-scale bootstrapped hierarchical clustering of 81 samples inferred four molecular subtypes of RA. Each subtype represented a discrete transcriptional program that reflected differences in tissue cellularity and biological composition. Diffusely infiltrated tissues were assigned to one of two subtypes characterized by fibroblast-like transcriptional programs that differed slightly, but significantly, in their pathway composition. Tissues with substantial immune infiltration were assigned to one of two immunoregulatory subtypes distinguishable by either a potent B cell signature or a broad inflammatory signature reflecting various myeloid and T cell transcriptional programs. Predictive gene signatures for each subtype accurately classified institutionally independent microarray profiles of histologically similar samples. Protein-based assays of B cell signature genes in a large placebo-controlled study of rituximab in RA revealed a combinatorial relationship between low levels of certain B cell biomarkers in serum and a poor clinical response to B cell depleting therapy.

Conclusions: We reduced RA tissue heterogeneity down to 4 discrete molecular subtypes and provided subtype-intrinsic gene signatures that were able to accurately classify independently derived external data. The unique cellular and biological composition of each subtype suggests that molecular stratification of RA patients has the potential to improve clinical trial design and therapeutic intervention by identifying those patients that are most likely to benefit from a given therapy.

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1610

The Associations between RA Genetic Risk Alleles and Seropositive but Non-Erosive Rheumatoid Arthritis. Katherine P. Liao, Jing Cui, Michael E. Weinblatt, Christine Iannaccone, Nancy Shadick, Robert M. Plenge, Daniel H. Solomon and Elizabeth W. Karlson. Brigham and Women's Hospital, Boston, MA

Background: Presently, little is known about the subgroup of subjects with seropositive rheumatoid arthritis (RA) who never develop bone erosions in contrast to those with erosions that remain stable or progress despite treatment. Our objective was to determine whether specific RA genetic risk alleles were associated with remaining erosion-free in a longitudinal RA cohort.

Methods: Our study was conducted in a prospective observational cohort of >1100 RA patients recruited from the outpatient practice of an academic medical center. We included patients with bilateral hand radiographs obtained at baseline and at 2 yr follow-up with formally assessed Sharp scores. The primary outcome was erosion-free status at recruitment and at 2 yr follow-up. We genotyped 31 validated RA risk alleles in a seropositive (RF+ or anti-CCP+) subset of this cohort.

To assess whether individual risk alleles for seropositive RA were also associated with erosion-free status, we tested each polymorphism using a log additive model (0, 1, 2) in a logistic regression adjusted for significant clinical predictors of erosion-free status. The significant clinical predictors were determined in a previous study: younger age at RA onset, male gender, and shorter RA duration. We quantified the association between risk alleles and erosion-free status using odds ratios (OR), 95% confidence intervals (CI) and p-values from the logistic regression models.

Summary Three hundred-three RA subjects in the cohort had Sharp scores and genotype information; 18% were erosion-free at recruitment and 2 year follow-up: 75% female, mean age at RA onset of 44.3 yrs (SD 10.1) and mean RA duration of 8 yrs (SD 8); 94.6% were anti-CCP+, 83.6% were RF+, and 76.6% had ≥ 1 copy of the HLA-shared epitope (HLA-SE). In the erosive group, 84% were female, with mean age at RA onset of 41.8 yrs (SD 14) and mean RA duration of 18 yrs (SD 12.3). There was no significant difference between anti-CCP status, methotrexate and anti-TNF use at baseline between the erosion-free group and those with erosions.

Two alleles were independently associated with erosion-free status after adjusting for clinical factors (age at RA onset, gender, RA duration): *REL* (rs13031237, T allele) with erosion-free status and *KIF5A* (rs775322, T allele) with not remaining erosion-free (Table 1). Neither allele reached statistical significance after Bonferroni correction. The HLA-SE was not associated with erosion-free status in this seropositive cohort.

Table 1. Association between *REL* and *KIF5A* with erosion-free status in seropositive RA adjusted for clinical predictors of erosion-free status.

Variables	Clinical model* + *REL*			Clinical model* + *KIF5A*		
	OR	95% CI	p-value	OR	95% CI	p-value
Age at RA onset (every 5 yrs)	0.77	0.66, 0.90	0.0001	0.78	0.67, 0.91	0.0013
Male gender	2.87	1.25, 6.58	0.013	2.81	1.23, 6.42	0.015
RA duration (yrs)	0.86	0.82, 0.91	<0.0001	0.87	0.83, 0.91	<0.0001
Risk allele	1.95	1.19, 3.17	0.0076	0.54	0.33, 0.88	0.013

* Clinical model includes age at onset, gender, and RA duration.

Conclusion: *REL* which encodes a component of the osteoclastogenesis pathway may predict erosion-free status in seropositive RA beyond significant clinical predictors. *KIF5A*, whose role in RA is unclear, was associated with erosive disease in this small study. Larger studies in independent cohorts are needed to confirm these associations.

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1611

TNIP2 Is Associated with Joint Destruction in Patients with Rheumatoid Arthritis. Taku Suzuki[2], Katsunori Ikari[2], Koichiro Yano[2], Yoshiaki Toyama[1], Atsuo Taniguchi[2], Hisashi Yamanaka[2] and Shigeki Momohara[2]. [1]Department of Orthopaedic Surgery, Keio University, [2]Institute of Rheumatology, Tokyo Woman's Medical University, Japan

Background: Recently a large-scaled meta-analysis of genome-wide association studies (GWAS) and replication studies identified novel rheumatoid arthritis (RA) risk loci in European descent populations; CD2/CD58 (rs11586238), CD28 (rs1980422), PRDM1 (rs548234), TAGAP (rs394581), PTPRC (rs10919563), RAG1-TRAF6 (rs540386), PTPN2 (rs7234029), PLCL2 (rs4535211), CD247 (rs1773560), ICAM1-ICAM3 (rs892188), NHLH2 (rs4272626), TNIP2 (rs231707), REL (rs13017599), and BLK (rs13277113).

The aim of this study was to investigate the genetic association of these reported 14 genes and joint destruction in Japanese RA patients.

Materials and Methods: DNA samples of 1504 Japanese patients were collected from the IORRA (Institute of Rheumatology RA cohort) DNA collection (84% of the patients were female, 87% were anticyclic citrullinated peptides (ACPA) antibody positive, 88% were rheumatoid factor positive and the mean age of the patients was 59.3 years). Of the patients, Sharp/ van der Heijde score (SHS) of the hands at 5-year disease duration, which represents joint destruction, could be measured in 628 patients.

Tested SNPs on the genes were selected based on the published studies (1–3). Genotyping was performed using the TaqMan assay according to the manufacture's instructions (Applied Biosystems, Japan). Multiple regression analysis was performed with SHS (hands) as a dependent variable, and as independent variables, the number of HLA-DRB1 alleles encoding the shared epitope (SE), the number of the risk alleles of RA-susceptible genes, sex, ACPA, and age of onset. The analysis was performed using the R software package.

Results: Sex (female, $P = 1.3\times10^{-4}$), age of onset (younger, $P = 1.3\times10^{-4}$), the number of SE ($P = 0.034$), the risk allele of TNIP2 ($P = 0.0092$) had impact on radiographic joint damage in Japanese RA patients while the other RA-susceptible genes did not show any association with the joint destruction.

Conclusions: We identified TNIP2 as a genetic factor for the joint destruction in RA patients.

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1612

Trait-Stratified Genome-Wide Association Study Identifies Novel and Diverse Genetic Associations with Serologic and Cytokine Phenotypes in Systemic Lupus Erythematosus. Silvia N. Kariuki[4], Beverly S. Franek[4], Akaash A. Kumar[4], Jasmine Arrington[4], Racheal A. Mikolaitis[2], Tammy O. Utset[4], Meenakshi Jolly[2], Mary K. Crow[1], Andrew D. Skol[3] and Timothy B. Niewold[4]. [1]Hospital for Special Surgery, Mary Kirkland Center for Lupus Research, New York, NY, [2]Rush University, Section of Rheumatology, Chicago, IL, [3]University of Chicago Pritzker School of Medicine, Section of Genetic Medicine, Chicago, IL, [4]University of Chicago Pritzker School of Medicine, Section of Rheumatology and Gwen Knapp Center for Lupus and Immunology Research, Chicago, IL

Introduction: Systemic lupus erythematosus (SLE) is a highly heterogeneous disorder. SLE-associated autoantibodies and high serum interferon alpha (IFN-α) are important heritable phenotypes in SLE which are correlated with each other, and play a role in disease pathogenesis. We set out to detect genetic factors associated with autoantibody profiles and serum IFN-α in SLE.

Methods: SLE patients were stratified by extremes of phenotype in serology and serum IFN-α for a case-case genome-wide association study. Single nucleotide polymorphisms (SNPs) in seven loci were selected for follow up in a large independent cohort of 450 SLE patients and 522 controls using a multi-step screening approach based on novel metrics and expert database review. The seven loci were: LRRC20, PPM1H, LPAR1, ANKS1A, PTPRM, EFNA5, and VSIG2.

Results: SNPs in the LRRC20, PPM1H, LPAR1, ANKS1A, and VSIG2 loci each demonstrated strong association with a particular serologic profile (all OR>2.2 and $p<8\times10^{-4}$). Each of these serologic profiles was associated with increased serum IFN-α. SNPs in PTPRM and LRRC20 were associated with increased serum IFN-α independent of serologic profile ($p=3.2\times10^{-6}$ and $p=5.0\times10^{-3}$ respectively). None of the SNPs were strongly associated with SLE in case-control analysis, suggesting that the major impact of these variants will be upon subphenotypes in SLE.

Conclusions: This study demonstrates the power of using serologic and cytokine subphenotypes to elucidate genetic factors involved in complex autoimmune disease. The distinct associations observed emphasize the heterogeneity of molecular pathogenesis in SLE, and the need for stratification by subphenotypes in genetic studies.

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ACR Poster Session C
Imaging of Rheumatic Disease II: Ultrasound, PET, Capillary Microscopy and Molecular Imaging
Wednesday, November 10, 2010, 9:00 AM–6:00 PM

1613

[^{18}F]PEG-Folate: A New Potential Macrophage PET Tracer for Imaging of Arthritis. Conny J. van der Laken[3], Inge de Greeuw[2], Yoony Y. J. Gent[4], Karin Weijers[4], Alexandre E. Voskuyl[4], Gerrit Jansen[4], Ben A. C. Dijkmans[4], Adriaan A. Lammertsma[2], Phil S. Low[1], Sumith Kularatne[1], Albert D. Windhorst[2] and Carla F. M. Molthoff[2]. [1]Dept. of Chemistry, Purdue University, [2]Dept. of Nuclear Medicine & PET Research, VU Medical Center, Amsterdam, [3]Dept. of Rheumatology, VU Medical Center, Amsterdam, The Netherlands, [4]Dept. of Rheumatology, VU Medical Center

Background: Previous studies in rheumatoid arthritis (RA) patients have shown clear visualization of arthritis with Positron Emission Tomography (PET) and (18)F-fluorodeoxyglucose ([^{18}F] FDG). We found more specific imaging of arthritis with macrophage targeting, using the PET tracer, [^{11}C](*R*)PK11195[1]. Due to the relatively high level of non-specific binding of [^{11}C](*R*)PK11195 in surrounding tissues, we developed another macrophage PET tracer, [^{18}F]PEG-folate, with potential superior imaging characteristics. Our previous work has shown that the folate receptor (FR-β) on activated macrophages may be an attractive target for imaging of arthritis[2].

Objective: Pilot study to investigate the potential of [^{18}F]PEG-folate PET to image arthritis in a rat model.

Methods: FR binding affinity for F-PEG-folate relative to folic acid and the circulating plasma folate [6S]-5-methyltetrahydrofolate was assessed by FACS analysis and binding competition with Folate-FITC. Five Wistar rats were immunized with methylated bovine serum albumin (mBSA) and adjuvans. At day 21, arthritis was induced with an intra-articular injection (ia) of mBSA in the right knee. At day 30, 4 rats were injected with 20 MBq [^{18}F]PEG-folate and 1 rat with 10 MBq [^{18}F]FDG, followed by PET imaging during 2 hrs. Following imaging, rats were sacrificed to obtain ex vivo tissue biodistribution and (immuno)histopathological analysis.

Results: FR binding affinity for F-PEG folate was just 1.2-fold lower than for folic acid, but 5-fold higher than for [6S]-5-methyltetrahydrofolate. In all rats with induced arthritis, histopathology showed a macrophage-rich inflammation in the synovial tissue of the affected joint, resembling synovitis in RA patients. [^{18}F]PEG-folate cleared rapidly from the circulation, with levels decreasing from 2.1%ID/g at 1 min post-injection (p.i.) to 0.01 %ID/g at 1 hr p.i., 30 times lower than blood levels of [^{18}F]FDG at 1 hr p.i. On [^{18}F]PEG-folate PET images, the arthritic joints were clearly depicted. Inflamed-to-control knee ratios of [^{18}F]PEG-folate increased continuously up to 2.3 at 1 hr p.i and 2.6 at 2 hr p.i. In contrast, ratios of [^{18}F]FDG declined over time to 1.3 at 1 hr. Ex vivo tissue biodistribution data also revealed uptake of [^{18}F]PEG-folate in spleen, skin, fat and lymph nodes, suggesting binding to locally present (activated) macrophages in these tissues. This finding was confirmed by in vivo blockade of folate receptors by injection of i.v. glucosamine-folate prior to injection of [18FPEG-folate which significantly reduced uptake of [18F]PEG-folate in these tissues.

Conclusion: These first pilot data show that [^{18}F]PEG-folate may be a promising PET tracer for imaging arthritis by targeting of macrophages in synovial tissue. Further explorative rat studies, including comparison with [^{11}C](*R*)PK11195, are in progress and will be followed by investigation in humans.

References:

1. Van der Laken CJ, et al. Arthritis Rheum. 2008;58:3350–5.
2. van der Heijden JW, et al. Arthritis Rheum. 2009;60:12–21.

Disclosure: C. J. van der Laken: None; **I. de Greeuw:** None; **Y. Y. J. Gent:** None; **K. Weijers:** None; **A. E. Voskuyl:** None; **G. Jansen:** None; **B. A. C. Dijkmans:** None; **A. A. Lammertsma:** None; **P. S. Low:** Endocyte, 5; **S. Kularatne:** None; **A. D. Windhorst:** None; **C. F. M. Molthoff:** None.

1614

Asymptomatic Hyperuricemia: Ultrasonographic Findings. Carla Solano[3], Pedro José Rodríguez-Henríquez[4], Fritz Hofmann[4], Araceli Bernal[4], Norma Marín-Arriaga[4], Alberto Gabriel López-Reyes[4], Luis Guirado[1], Angelica Vargas-Guerrero[1], Luis Amezcua-Guerra[1], Marwin Gutierréz[5], Cristina Hernández-Díaz[4], Manuel Martínez-Lavín[1] and Carlos Pineda[2]. [1]Instituto Nacional de Cardiología, Mexico, [2]Instituto Nacional de Rehab, Mexico City, Mexico, [3]Instituto Nacional de Rehabilitación, El Salvador, [4]Instituto Nacional de Rehabilitación, Mexico, [5]Universitá Politecnicá delle Marche Ospedale "A Murri", Italy

Background: Musculoskeletal ultrasound (US) is a low-cost, widely accessible, non-invasive technique, which allows a multiplanar, real-time evaluation of joints without the use of ionizing radiation. Its use has recently been expanded to the evaluation of inflammatory arthritides, including gout. Ultrasonographic characteristics of gout are already well defined; however, the findings in asymptomatic patients have not been thoroughly described. US have shown to be superior in detecting changes in gouty arthritis than other imaging techniques.

Objective: To characterize the morphostructural abnormalities detected by US associated with the deposition of crystals in articular and extra-articular tissues of patients with asymptomatic hyperuricemia.

Methods: Men and women older than 18-years with asymptomatic hyperuricemia (serum uric acid ≥7.0 mg/dL and no joint complaints), without urate-lowering therapy; and normouricemic subjects without articular symptoms (control group) were recruited after informed consent was obtained. US scans of the femoral cartilage and tendons in the knee, tendons at the ankle, Achilles tendon and first metatarsophalangeal (1st MTP) joint were obtained. OMERACT definitions for US pathology were applied; tendinopathy: was defined as a loss of the fibrilar pattern, intratendinous tophi and/or calcifications.

Results: Demographics: 97 subjects were enrolled; 45 hyperuricemic and 52 normouricemic control subjects with a median age of 56 and 47.3 years. The average uric acid level in the hyperuricemic group was 8.17mg/dL (±0.95), see Table 1.

Table 1.

Variable	Hyperuricemia (n=45)	Normouricemia (n=52)	P
Age, years	56 ± 17.2	47.3 ± 10.9	0.003*
Male	30	35	0.9**
Uric Acid, mg/dL	8.17 ± 0.95	5.47 ± 0.90	<0.0001*

* Unpaired t test
** Chi-square test

In the hyperuricemic group tendinopathy was found in the posterior tibial tendon $p < 0.05$, as well as the presence of double contour sign in the 1st MTP joint $p < 0.0001$.

Table 2.

Variable	Hyperuricemia	Normouricemia	P
Osteophytes	12	8	Ns
Erosions	7	6	Ns
Power Doppler	0	0	Ns
Synovitis	32	25	Ns
Double contour sign	24	1	<0.0001

* All analyses were performed by chi-square tests.

Conclusion: Asymptomatic hyperuricemic patients show US morphostructural changes similar to those with established gout. Results confirm the notion that urate crystals are present in articular tissues before gout is clinically evident and may give further support for the use of urate-lowering therapy in asymptomatic hyperuricemic patients.

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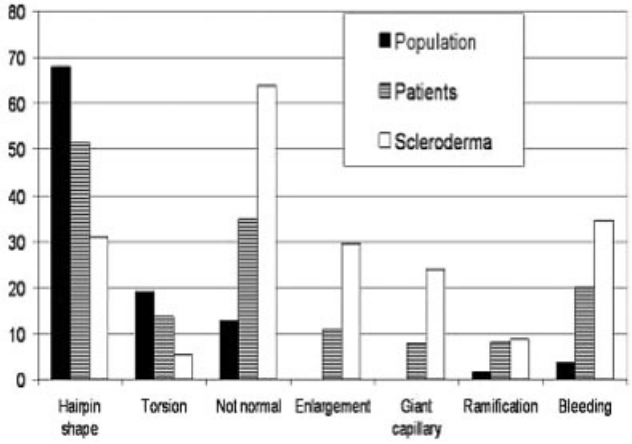
1615

Capillary Microscopy—A Cross-Sectional Study in the Population. Oliver Sander[1], Moritz Schroeder[3], Benedikt Ostendorf[1], Jutta Richter[1], Matthias Reppel[3], Hasan Acar[2], Martina Blumenroth[4] and Matthias K. Schneider[1]. [1]Dept. Rheumatology, Heinrich-Heine University, Duesseldorf, Germany, [2]Dept. Rheumatology, Heinrich-Heine University, [3]Heinrich-Heine University Duesseldorf, [4]Rheumazentrum Rhein-Ruhr

Objective: Application of capillary microscopy in the general population.

Method: Our mobile campaign for rheumatic diseases (RheumaTruck) visited 26 sites in the metropolitan region Rhine-Ruhr. The visitors could participate in different tests (including capillary microscopy of fingers III-V of both hands with standardized image documentation). Demographic data, self reported symptoms based on the connective tissue screening questionnaire (CSQ), and an ad hoc diagnosis by a rheumatologist were documented. 110 outpatient visitors of the rheumatologic department were documented the same way and served as controls. The capillary images were assessed by an experienced examiner semi quantitatively regarding density, edema, bleeding, hairpin shape, caliber equalization, enlargement, giant capillaries, ramification, bushy capillaries, elongation, torsion, flow properties and filling. The results were combined with the other collected data and analyzed statistically.

Results: 3196 visitors were counted. 754 visitors underwent capillary microscopy to availability of the device (mean age 54 years, 75% female, 10,000 images evaluable). Capillary microscopy and evaluation took 1 to 2 minutes each. The costs were restricted to the purchase of the device. 8% of the sample were not assessable. 68% of the capillaries showed the normal hairpin form, torsion (17%), ramification (3%), elongation (2%), enlargement (1%) was seen in the others. Hemorrhage was seen in 5% of subjects; 4 giant capillaries were detected. Hairpin shape was seen in only 52% of the rheumatologic outpatients and 31% of patients with known systemic sclerosis. Those had higher counts of divergences, esp. giant capillaries.



There are no gender differences in the capillary morphology. The number of normal capillaries decreases slightly with age (71% in the under-30s to 65% among 70–80 year olds). A previous described association of tortured capillaries and psoriasis (in the personal and family medical history) could not be confirmed. A new diagnosis of systemic sclerosis was not identified. In fibromyalgia, the rate of normal hairpin shape capillaries was with a rate of 79% significant higher than the average for the visitors. Raynaud's phenomenon was associated with altered blood flow and capillary filling, but no detectable differences in the morphology.

Conclusion: The expected high rate of inconspicuous findings in the visitors was confirmed, contrasting the observations in patients with rheumatic diseases. Raynaud's phenomenon was detectable by altered fillings and blood flow. The capillary microscopy is suitable for the application in larger populations.

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1616

Concordance between Ultrasound Readers Determining Presence of Monosodium Urate Crystal Deposition in Knee and Toe Joints. Rennie N. G. Howard[2], Michael H. Pillinger[2], Soterios Gyftopoulos[2], Ralf G. Thiele[4], Christopher Swearingen[3] and Jonathan Samuels[1]. [1]New York University Hospital for Joint Disease, New York, NY, [2]NYU Langone Medical Center, NYU Hospital for Joint Diseases, New York, NY, [3]University of Arkansas for Medical Sciences, Little Rock, AR, [4]University of Rochester, Rochester, NY

Background: Determination of monosodium urate (MSU) deposition in joints by musculoskeletal ultrasound (MSK-US) could have implications for uric acid (UA) management in patients with gout and possibly asymptomatic hyperuricemia (AH). Recently, criteria for sonographic diagnosis of MSU crystal deposition have been developed, but reproducibility of readings using these criteria has not been well established.

Methods: We consecutively recruited male patients ages 55–85 during primary care visits to an urban VA hospital. We assessed all patients for gout by ACR criteria, and obtained serum UA levels. Patients were divided into 3 groups: gout, AH (no gout, UA $\geq$ 6.9 mg/dL), and controls (no gout, UA $\leq$ 6.8 mg/dL). 50 patients (14 with gout, 17 with AH, and 19 controls) returned for subsequent evaluation which included MSK-US of knees and 1st metatarsalphalangeal (MTP) joints to evaluate for the double contour sign (knees) and tophi (MTPs). All images were read blindly by two observers trained in rheumatology and MSK-US. Kappa statistics were used to estimate the amount of agreement between ultrasound measures scored by the two raters. We also calculated the total percent of observations in agreement.

Results: Evidence of MSU crystal deposition was found in the same 10 patients by both observers (6 gout, 3 AH, 1 control), and in 3 additional patients by one of the observers (1 gout, 2 AH). These findings were further analyzed by site. MSU crystal deposition was identified in a total of 14 common joints by both observers, and in 4 additional joints by the first observer and 6 additional joints by the second observer. Percentage agreement and kappa statistics for our three primary ultrasound measures were as follows; total joints (n=200, 95% agreement, kappa 0.709), femoral articular cartilage (n=100, 95% agreement, kappa 0.679) and 1st MTPs (n=100, 95% agreement, kappa 0.734). Additional analyses by left and right side are shown in the table below. Ratings on only 10 out of 200 joints were in disagreement.

Site	# of Joints Assessed	# of Joints Affected Rater 1	# of Joints Affected Rater 2	% Agreement	Kappa (95% CI)
Femoral Articular Cartilage	**100**	**8**	**9**	**95**	**0.679 (0.415, 0.943)**
-Right	50	6	6	96	0.832 (0.649, 1.000)
-Left	50	2	3	94	0.370 (−0.188, 0.928)
First MTP	**100**	**10**	**11**	**95**	**0.734 (0.512, 0.956)**
-Right	50	5	6	98	0.890 (0.701, 1.000)
-Left	50	5	5	92	0.556 (0.168, 0.944)
Total Joints	**200**	**18**	**20**	**95**	**0.709 (0.539, 0.880)**

Conclusions: Both percentage agreement and agreement beyond chance between the raters (as estimated by kappa statistics) were very high for the three ultrasound measures. These findings support the use of MSK-US as a reliable modality for detecting MSU deposition. Since MSU deposition is an indication for urate lowering, this type of imaging could be performed noninvasively at the bedside or in the clinic to help direct therapy in gout patients, with possible implications for treatment in AH patients as well should these findings be reproducible in larger cohorts.

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1617

Demonstrating Musculoskeletal Ultrasound Competency in a Valid and Reliable Way. Eugene Y. Kissin[4], Jingbo Niu[5], Ralf G. Thiele[11], Midori Jane Nishio[1], Jay B. Higgs[13], Janak R. Goyal[10], Daniel G. Malone[12], David A. Bong[2], Amy M. Evangelisto[3], Wolfgang A. Schmidt[7], Peter Balint[8], Carlos Pineda[6] and Gurjit S. Kaeley[9]. [1]Lafayette, CA, [2]Bruce, WI, [3]Arthritis Rheumatic & Back Disease Association, Philadelphia, PA, [4]Boston University, Boston, MA, [5]Boston University, Boston, MA, [6]Institutu Nacional de Rehab, Mexico City, Mexico, [7]Medical Center for Rheumatology Berlin-Buch, Berlin, Germany, [8]National Institute of Rheumatology and Physiotherapy, Budapest, Hungary, [9]University of Florida College of Medicine, Ponte Vedra Beach, FL, [10]University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Perth Amboy, NJ, [11]University of Rochester, Rochester, NY, [12]University of Wisconsin, Madison, WI, [13]Wilford Hall Medical Center/Brooke Army Medical Center, San Antonio, TX

Purpose: The amount of training needed to become competent in musculoskeletal ultrasound (MSUS) is debatable, and a valid exam to determine competency in MSUS is needed. While others have previously established training and testing procedures, no one has yet documented MSUS test reliability or validity. We aim to develop a reliable and valid MSUS test.

Methods: USA rheumatology fellows who had participated in an 8 month, standardized, MSUS curriculum completed an exam of MSUS consisting of multiple choice questions (MCQs), and practical scanning (PrE) of normal anatomy.

10 faculty members (> 4 years of practical and teaching experience in MSUS courses) individually submitted 250 MCQs covering 8 peripheral joint regions and typical rheumatic conditions. As a group, the faculty excluded 143 MCQs that were unclear or irrelevant to rheumatology. Remaining MCQs were tested in 2 groups: 3 rheumatologists without MSUS training, to exclude MCQs answered correctly by all 3, and 5 rheumatologists expert in MSUS to exclude MCQs answered incorrectly by 3 of 5, resulting in 76 MCQs on the exam.

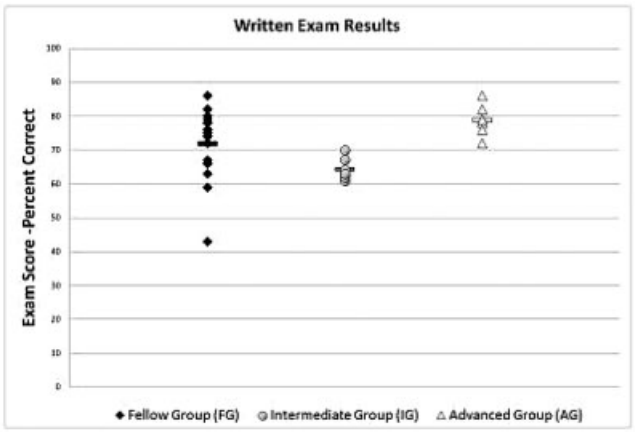
To validate the MCQ exam, 3 additional groups completed it: rheumatologists who finished an intermediate course of training through the Mexican School of Musculoskeletal Ultrasound (Intermediate Group (IG), n=7), rheumatologists with > 2 years of experience in MSUS from both Mexico and the USA (Advanced Group (AG), n=7), and USA fellows (Fellow Group (FG), n=19).

All Fellows and 2 MSUS faculty members took an 8-station PrE for scanning technique in all 8 joint areas. Faculty graded images from the PrE, blinded to source, on a 5 point scale based on predefined quality measures.

Results: The MCQ exam was reliable (Cronbach's a= 0.76) and discriminated between IG and AG (median score 63% vs. 79%, p=0.003 Wilcoxon). The FG median MCQ test score exceeded that of the IG (72% vs. 63%, p=0.02 Wilcoxon), but had the greatest range - from worse than the IG to better than the AG (Figure 1). Fellows and faculty median PrE scores were

not significantly different (2.4 vs. 2.8, p=0.18), but 2 fellows scored significantly lower than the faculty members. PrE and MCQ results correlated well (Spearman r=0.63, p=0.004).

Conclusions: A written and practical exam proved moderately reliable and valid in a comparison of practitioners of varying levels of training. The correlation between results of the two exam parts adds further validity. Most fellows who completed an 8 month MSUS training program achieved similar essential MSUS knowledge to the advanced MSUS group (MCQ), and similar basic scanning technique to their mentors (PrE), thus demonstrating basic competence. However, fellow test results varied significantly despite completion of a standardized teaching program. Given the variability in achieving MSUS competency after uniform training, requisite MSUS experience should be based on outcome testing rather than a fixed time period of education.



Disclosure: E. Y. Kissin: None; **J. Niu:** None; **R. G. Thiele:** None; **M. J. Nishio:** None; **J. B. Higgs:** None; **J. R. Goyal:** None; **D. G. Malone:** None; **D. A. Bong:** None; **A. M. Evangelisto:** None; **W. A. Schmidt:** None; **P. Balint:** None; **C. Pineda:** None; **G. S. Kaeley:** None.

1618

Effect of Musculoskeletal Ultrasound (MSKUS) Examination on Therapeutic Decision Making in Inflammatory Arthritis. Arnold Ceponis[2], John J. Cush[1] and Arthur Kavanaugh[3]. [1]Baylor Research Institute, Dallas, TX, [2]Division of Rheumatology, Allergy and Immunology, University of California San Diego, San Diego, CA, [3]University of California-San Diego, La Jolla, CA

Background: MSKUS is a sensitive and specific imaging modality with growing utilization in rheumatology. However, the impact that MSKUS examination may have on therapeutic decision making in the management of inflammatory arthritis is unknown.

Methods: Rheumatologists were presented with online survey including 4 standard clinical vignettes (3 RA and 1 PsA), and were asked to make management decisions before and after data from joint ultrasound was reported. Physician demographics, use and familiarity with MSKUS were also surveyed.

Results: Of the 332 respondents (mean age 53.7 yrs), who answered the survey, 30% reported performing MSKUS, 25% send patients to imaging centers, 34% reported being familiar, but not performing MSKUS themselves, and 29% were not familiar with /never using MSKUS. Confidence that MSKUS can detect active synovitis using power Doppler (PD) or visualization of synovial tissue/fluid was expressed by 59% and 78%, respectively, and for detection of enthesitis by 56% of respondents.

When presented with 4 clinical scenarios, the addition of typical data from MSKUS was shown to potentially have a very significant impact on rheumatologists' specific treatment plans ($p < 0.0001$). Case 1: for an obese RA patient on MTX 20 mg/wk with a high tender joint count, but equivocal clinical synovitis and lack of erosions on x-ray, a lack of synovial hypertrophy and hyperemia on MSKUS significantly decreased the number of respondents intending to add/increase prednisone (10% pre-MSKUS *vs* 3% post, $p < 0.00001$), DMARD (51% pre *vs* 27% post, $p < 0.0001$), or biologics (74% pre *vs* 35% post, $p < 0.0001$). Case 2: significantly more respondents chose to escalate treatment with prednisone (5% pre-MSKUS *vs* 10% post, $p < 0.001$), DMARD (36% pre *vs* 68% post, $p < 0.0001$) or biologics (9% pre *vs* 61% post, $p < 0.0001$) in a patient with early RA without x-ray erosions and low joint count after MSKUS showed erosions and more abundant synovitis on gray scale and PD. Case 3: in polyarticular PsA on MTX 15 mg/wk and a TNF-inhibitor without clinically active peripheral synovitis, but tender unilateral Achilles, a finding of bilateral Achilles paratenonitis and enthesitis by MSKUS prompted respondents to escalate prednisone (3% pre-MSKUS *vs* 11% post, $p < 0.0001$), DMARD (22% pre, *vs* 50% post, $p < 0.0001$) or escalate/change a biologic (8% pre *vs* 34% post, $p < 0.0001$). Case 4: no significant changes in therapy (prednisone, $p > 0.63$, DMARD, $p > 0.14$, or biologic, $p > 0.70$) occurred when MSKUS results were similar to those of clinical examination in severe active RA.

Lack of training, followed by reimbursement uncertainty and time concerns were reported as major barriers for MSKUS utilization among rheumatologists.

Conclusions: In specific clinical settings, typical results from MSKUS, can significantly impact therapeutic decision making. The most pronounced influence of the MSKUS examination was seen on the decisions to use biologic agents. This data is being validated in an ongoing clinical study using real time MSKUS on actual RA patients in a clinic setting.

Disclosure: A. Ceponis: None; **J. J. Cush:** None; **A. Kavanaugh:** None.

1619

Enthesopathy Detected by 18-Fluorodeoxyglucose Positron Emission Tomography in Patients with Polymyalgia Rheumatica. Hiroyuki Yamashita[2], Kazuo Kubota[1], Yuko Takahashi[3], Hiroshi Kaneko[3] and Akio Mimori[3]. [1]Department of Radiology, National Center for Global Health and Medicine, [2]Division of Rheumatic Diseases, National Center for Global Health and Medicine, Shinjuku-ku, Tokyo-to, Japan, [3]Division of Rheumatic Diseases, National Center for Global Health and Medicine

Background: Polymyalgia rheumatica (PMR) is characterised by acute-onset proximal muscle pain and stiffness in patients over 50 years of age, and is diagnosed by excluding other disorders that cause similar complaints. Although the exact pathology of PMR is unknown, synovitis and bursitis are also common in this disease. Magnetic resonance imaging (MRI) or ultrasonography frequently reveals inflammation of the tenosynovial sheaths on the patients' hands or feet. A study of PMR using 18-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) documented involvement of the spinous processes. Here, we present additional PET/CT findings in PMR.

Patients and Methods: Thirteen consecutive patients with PMR admitted to our institute between August 2007 and April 2010 were enrolled in the study. The number of the patients and the mean age ± SD was 13 and 76.2±6.5 years (range, 66–87), respectively.The diagnosis was based on the criteria of PMR of Chuang *et al.* and the exclusion of other inflammatory diseases. All 13 patients underwent FDG-PET/CT before starting steroid therapy. One patient also had clinical temporal arteritis.

Results and Discussion: FDG uptake was detected in the large joints and spinous processes in accordance with previous reports, and these sites were positive in 85% (11/13) and 54% (7/13) of the patients, respectively. In addition, muscle-tendon attachment sites in 69% (9/13) of the patients were FDG-positive, *i.e.*, a majority of our PMR patients had enthesopathy. Of the large joints, the shoulders (11/11), hips (11/11), and knees (7/11) were the main affected sites. The enthesopathy was predominantly detected in the ischial tuberosities (9/9) and greater trochanter of the femur (8/9). Some of the FDG-positive lesions were detected on MRI, and the ratio of positive results in patients examined was 4/4 in the large joints, 1/1 in enthesopathy, and 0/2 in the spinous processes. Large vessel involvement was detected in two patients as multiple FDG uptake lesions. Of these, one patient had clinical symptoms of temporal arteritis, while the other was completely asymptomatic for the vasculitis. Enthesopathy in the patients was difficult to detect on physical examination because of overlapping myalgias or arthralgias. PET/CT may be useful for evaluating organ involvement in PMR patients.

Conclusion: FDG-PET/CT shows that not only inflammation of the spinous processes and large joints but also enthesopathy may be common in polymyalgia rheumatica.

Disclosure: H. Yamashita: None; **K. Kubota:** None; **Y. Takahashi:** None; **H. Kaneko:** None; **A. Mimori:** None.

1620

Erosive Osteoarthritis Is Not Associated with Invading Synovial Tissue: An Ultrasound Study. Ralf G. Thiele[1], Laura A. Paxton[3], Bethany A. Marston[2], Darren Tabechian[4] and Allen P. Anandarajah[1]. [1]University of Rochester, Rochester, NY, [2]University of Rochester, Rochester, NY, [3]University of Rochester, North Chili, NY, [4]University of Rochester School of Medicine, Rochester, NY

Background: In patients with osteoarthritis, bony defects in small joints of the hand can occasionally be seen with conventional radiography (CR). Such a condition may be called erosive osteoarthritis (EOA). Swelling may occur, and the term "inflammatory osteoarthritis" is occasionally used. The degree of actual synovial proliferation remains unclear. It also remains unclear if bony defects of EOA are associated with synovial proliferation, similar to rheumatoid arthritis (RA).

Objectives: To assess if synovial proliferation and synovial hyperemia can be detected sonographically in EOA.

Methods: 1091 US studies obtained over 16 months were reviewed. All US studies were performed by a rheumatologist certified in musculoskeletal US, with >15 years of US experience. Studies were performed using a Toshiba Xario US machine with an 18 MHz linear transducer with differential tissue harmonic imaging and high-sensitivity Doppler capability, and a SonoSite M-Turbo machine.

Patients with a CR diagnosis of EOA were identified. For the diagnosis of EOA, the radiologist's final assessment was counted.

US studies of joints in which EOA had been described by CR were assessed for the following:

1. Effusion, defined as a distension of the hyperechoic, fibrous joint capsule by anechoic synovial fluid; 2. Synovial proliferation, defined as hypo- to hyperechoic tissue within the joint cavity and emanating from the hyperechoic, fibrous capsule; 3. Synovial hyperemia, defined as a pulsatile Doppler signal within the joint capsule, associated with synovial tissue. Doppler signals were graded as follows: 0 = no signal; 1 = single vessel dots; 2 = confluent Doppler signals occupying less than half of the identified synovial tissue; 3 = confluent Doppler signals occupying more than half of the identified synovial tissue.

US studies of 13 RA patients were randomly selected and scored as a comparison group.

Results: Results were available for 13 EOA patients and 21 joints: DIP, n = 15; PIP, n = 6 (13 RA patients: MCP, n = 104; PIP, n = 104).

Effusions were seen in 4/21 (19%) joints in EOA and 67/208 (32%) joints in RA. When effusions in EOA patients were seen, they were seen over the volar aspects of DIP and PIP joints, or immediately adjacent to bone spurs, where the spurs mechanically distended the joint capsule. Synovial proliferation was seen in 2/21 (9.5%) joints in EOA and 120/208 (58%) in RA. The degree was minimal in all cases of EOA. Only a concentric proliferation of the synovial lining was seen, but no invading pannus tissue was appreciated in EOA. Doppler scoring was 0 in 19/21 (90.5%) or 1 in 2/21 (9.5%) in EOA and 3 in 28/208 (13.5%), 2 in 52/208 (25%), 1 in 30/208 (14%) and 0 in 98/208 (47%) in RA.

Conclusion: In this US study, synovial changes were found to be fundamentally different in EOA and RA. Increases in synovial fluid around bone spurs in EOA did not have an inflammatory character. Synovial proliferation in EOA was, in stark contrast to RA, minimal. Similarly, synovial hyperemia was rarely seen in EOA, while this is common feature of RA. Invading synovial tissue was not seen adjacent to bony defects in EOA. Using sensitive US technology, synovial proliferation and hyperemia were not characteristic of EOA.

Disclosure: R. G. Thiele: SonoSite, 8, 9; **L. A. Paxton:** None; **B. A. Marston:** None; **D. Tabechian:** None; **A. P. Anandarajah:** None.

1621

Evaluation of the 7-Joint Ultrasound Score (US7) by Detailed Joint Region-Analysis of an Arthritis Patient Cohort over One Year. Sarah Ohrndorf[3], Beatrice Halbauer[3], Lydia Naumann[3], Ekkehart Dietz[2], Gerd R. Burmester[1] and Marina Backhaus[4]. [1]Charite-University Medicine, Berlin, Germany, [2]Department of Medical Statistics Charité, Berlin, Germany, [3]Department of Rheumatology and Clinical Immunology, University Hospital Charité, Berlin, Germany, [4]University Medicine Berlin: Campus Charité Mitte, Berlin, Germany

Purpose: To evaluate the 7-joint ultrasound score (US7) by joint region-analysis of a cohort of arthritis patients over one year.

Methods: US7 examines the clinically dominant wrist, MCP and PIP II and III, MTP II, and V joints for synovitis, tenosynovitis/paratenonitis and erosions. Synovial inflammation is scored semi-quantitatively (grade 0–3) by grey scale (GS) and vascularity by power Doppler (PD) ultrasound (US), respectively. Tenosynovitis/paratenonitis and erosions are scored qualitatively (grade 0–1) by GS US.

Forty-five patients with RA (84.4%), PsA (13.3%) and AS with peripheral joint involvement (2.2%) with a mean disease duration of 9.0 years (SD 7.9, range 7.5 mths-47.6 years) were included and examined before (baseline) and after 3, 6 and 12 months (t3, t6 and t12) starting or changing therapy (DMARD±TNFinh.).

A detailed US7 analysis was performed for the baseline examination, referring to each examined joint region.

Results: N=45 patients with longstanding arthritis were recruited from the rheumatology Outpatient Clinic of the Charité-University Hospital Berlin, Germany.

The *initial* joint region-analysis resulted in 95.6% involved wrists from dorsal, of which grade 2 was most often detected (48.9%). Furthermore, erosions in this joint region were detected in 68.9% of patients, respectively. Wrist joints from palmar also showed synovitis in 88.9% with nearly the same number each for grade 1 (40%) and grade 2 (37.8%). Here, erosions were deteced in 57.8%. Tenosynovitis of the extensor carpi ulnaris tendon being considered as an early finding in RA, was just found in 40% with a PD activity in 6.6%.

GS synovitis was evaluated in 95.6% both in MCP joint II and III from palmar. Most erosions in the MCP joint II were detected from radial (68.9%) in comparison to palmar (44.4%) and dorsal (48.9%). In the MTP joint V 75.6% erosions were seen from lateral.

With regards to paratenonitis, MCP joint II showed changes in 4.4% of patients, and MCP joints II only in 2.2%.

Conclusion: Synovitis in GS US was more often detected in the wrist from dorsal than from palmar. Tenosynovitis of the extensor carpi ulnaris tendon is often involved in RA and could be presented by GS US in 40%, respectively. Most erosions were found in the lateral scan of the MTP joint V and the radial scan of the MCP joint II. The detailed joint region-analysis showed that paratenonitis was a rare finding with the consequence that paratenonitis might not be a necessary component in the US7.

Disclosure: S. Ohrndorf: None; **B. Halbauer:** None; **L. Naumann:** None; **E. Dietz:** None; **G. R. Burmester:** None; **M. Backhaus:** None.

1622

Fluorescence Imaging of Articular Proteinase Activities and Osteoblast Activity Showed Treatment Response to Anti-Interleukin-1 Antibodies in a Mouse Model of Collagen-Induced Arthritis. Fons A. J. van de Loo, Eline Vermeij, Onno J. Arntz, Marije Koenders and Wim B. van den Berg. Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Objective: To monitor the response of anti-IL-1$\alpha\beta$ antibody treatment on collagen-induced arthritis (CIA) using cathepsin- and matrix metalloproteinase (MMP) cleavable near-infrared probes, and a probe of osteoblast activation.

Methods: CIA was induced in male DBA1/J mice by immunization with bovine collagen-type II. Mice received either anti-IL-1$\alpha\beta$ sera (200 μl i.v.) or normal rabbit serum as a control at day 21. Ten days later, probes were injected i.v. and 6 hours later mice were imaged using the IVIS Lumina (Caliper Life Sciences). Thereafter, ankle and knee joints were dissected and processed for RNA, histology or X-ray. The ProSense 680 probe (VisEn Medical Inc, Bedford, USA) becomes activated upon enzymatic cleavage by cathepsins (B, K, L, S, D), collagen degrading lysosomal cysteine proteinases. The MMPSense 680, can be activated by different MMPs (2,3,9,13), known to degrade collagen and proteoglycans during arthritis. OsteoSense 680 is a fluorescent biphosphonate that binds to hydroxyapetite, a biomarker for osteoblast activation. Gene expression profiling was done of synovial biopsies from (non)-inflamed knees of untreated mice (MOE430_2 oligonucleotide array, Affymetrix, CA). Ankle joints were X-ray photographed and analyzed using a stereo microscope and scored on a scale ranging from no damage (0) to complete bone destruction (5).

Results: Inflamed synovia of CIA showed enhanced expression of the extracellular matrix degrading enzymes cathepsin-K (13-fold, osteoclasts specific gene), cathepsin-S (9-fold, specific for monocytes), MMP-13 (50-fold), MMP-3 (22-fold), MMP-14 (9-fold), MMP9 and MMP-2 (4-fold). Genes related to bone destruction as cathepsin K (13-fold), TGFβ1 (5-fold), TRAP5 (9-fold) and RANKL (10-fold) were upregulated as were also the

osteoblast specific enzymes osteocalcin (10-fold) and periostin (7-fold). The signal of ProSense and MMPSense in both knees and paws correlated with joint inflammation and cartilage destruction, but only the MMPSense and not the ProSense correlated with chondrocyte death, a marker of irreversible cartilage destruction. Anti-IL-1$\alpha\beta$ antibody treatment alleviated CIA and markedly diminished the ProSense and MMPSense imaging signal. OsteoSense signal was increased during inflammation and was higher in mice showing mild bone loss as measured by X-ray and was significantly lower in the anti-IL-1 treated mice.

Conclusion: The correlation of both ProSense and MMPSense to inflammation and destruction is in line with the upregulation of Cathepsins and MMP's during CIA, and the connective tissue destructive properties of these enzymes. Interestingly, only the MMPSense signal correlated with chondrocyte death and we speculate that MMPs are directly involved as both MMP9 and 13 have galectin-3 as a substrate, an anti-apoptotic protein in chondrocytes. The OsteoSense signal in CIA showed that new bone formation by osteoblasts occurred under mild bone loss conditions. Imaging of these three probes is a sensitive method to measure joint inflammation, connective tissue destruction and repair, and overall is fluorescence imaging a valuable tool to monitor a treatment response.

Disclosure: F. A. J. van de Loo: None; **E. Vermeij:** None; **O. J. Arntz:** None; **M. Koenders:** None; **W. B. van den Berg:** None.

1623

High Reliability of Nailfold Videocapillaroscopy—An Outcome Measure for Systemic Sclerosis-Related Microvsacular Disease? Herman Hofstee[4], Erik Serné[4], Chris Roberts[2], Roger Hesselstrand[1], Agneta Scheja[1], Tonia Moore[3], Marie Wildt[1], Joanne Manning[2], Anton Vonk Noordegraaf[4], Alexandre Voskuyl[4] and Ariane Herrick[2]. [1]Lund University, Sweden, [2]The University of Manchester, United Kingdom, [3]The University of Manchester, United Kingdom [4]VU University Medical Center, Amsterdam, The Netherlands

Background: Systemic sclerosis (SSc)-related structural microvascular abnormalities can be directly visualised using the non-invasive technique of nailfold capillaroscopy. Computerised techniques combined with high magnification videocapillaroscopy bring the potential of capillaroscopy being not only a diagnostic tool but also an outcome measure in longitudinal studies of SSc-related microvascular disease, including studies of treatment response. Good reliability is a necessary prerequisite for a test to be a valid clinical or research tool. The aim of our study was to investigate the inter- and intra-observer reliability of both qualitative and quantitative nailfold capillaroscopic parameters.

Methods: Mosaic nailfold images were acquired from the non-dominant ring finger of 10 healthy controls, 10 patients with primary Raynaud's phenomenon, and 30 with SSc using a computerised videocapillaroscopy system (magnification 300x). Each image was assessed 'blindly' by 6 observers (2 from each of 3 centres from 3 different countries). Images were graded for both qualitative (including capillary architecture, avascularity, haemorrhages, and tortuous, ramified, bushy and bizarre loops) and quantitative parameters (including number of mega- and giant capillaries, capillary density, and capillary dimensions). Inter-and intra-rater reproducibility were assessed for (a) ordered categorical scores (qualitative and quantitative) using a weighted kappa co-efficient with quadratic weights and (b) quantitative measurements using intra-class correlations.

Results: These are summarised in the table.

	Inter-observer reliability	Intra-observer reliability
Weighted Kappa of ordered categories (95% CI)		
Architecture	0.72 (0.55, 0.82)	0.75 (0.64, 0.83)
Avascularity	0.61 (0.37, 0.75)	0.74 (0.62, 0.82)
Haemorrhage	0.56 (0.16, 0.79)	0.73 (0.57, 0.86)
Tortuous	0.39 (0.25, 0.50)	0.68 (0.60, 0.76)
Ramified	0.58 (0.30, 0.73)	0.73 (0.59, 0.84)
Bushy	0.73 (−0.02, 0.90)	0.80 (0.58, 0.94)
Bizarre	0.21 (0.00, 0.32)	0.76 (0.55, 0.92)
Mega capillary	0.76 (0.64, 0.84)	0.87 (0.82, 0.91)
Giant capillary	0.84 (0.71, 0.92)	0.92 (0.87, 0.96)
Intra-class correlation coefficient of quantative measurements (95% CI)		
Density	0.87 (0.88, 0.92)	0.92 (0.91, 0.97)
Apex	0.94 (0.93, 0.97)	0.97 (0.96, 0.99)
Arterial	0.88 (0.87, 0.93)	0.96 (0.95, 0.99)
Venous	0.91 (0.90, 0.96)	0.96 (0.95, 0.99)
Total width	0.94 (0.93, 0.97)	0.98 (0.98, 0.99)

Inter- and intra-observer reliability of quantitative parameters showed substantial to almost perfect agreement. Certain qualitative parameters (architecture, avascularity, haemorrhage, ramified, and bushy capillaries) showed moderate to substantial inter-observer agreement and substantial intra-observer agreement, whereas other parameters including tortuous and bizarre capillaries showed moderate to poor inter-observer agreement.

Conclusions:

1) All quantitative and some qualitative parameters are highly reliable in terms of inter- and intra-observer agreement.

2) Other qualitative parameters, including tortuosity, are less reliable.

3) Capillaroscopy is likely to be a useful diagnostic tool and an outcome measure in studies of SS-related microvascular disease, provided that parameters selected are those with high reliability.

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1624

Hypodermal Compressibility as a Diagnostic Test for Eosinophilic Fasciitis. Eugene Y. Kissin[1], Michael R. York[2] and Robert W. Simms[3]. [1]Boston University, Boston, MA, [2]Boston University Medical Ctr, Boston, MA, [3]Boston University School of Medicine, Boston, MA

Purpose: Eosinophilic fasciitis (EF) is an autoimmune, fibrotic disorder that presents with painful swollen extremities. Though there are clinical characteristics that may distinguish it from diffuse systemic sclerosis (dSSc), frequently a deep wedge biopsy of the skin and fascia is felt to be necessary to confirm the diagnosis. We sought to determine whether high resolution B-mode ultrasound could distinguish forearm involvement by EF from similar fibrotic diseases such as systemic sclerosis, and diabetic cheiroarthropathy (DMc), and from controls with normal skin and fascia.

Methods: Consecutive patients with clinically diagnosed EF, DMc, dSSc, and fibromyalgia (FM) (FM with normal skin and subcutaneous tissue) were recruited from a rheumatology clinic over a period of 2 years to undergo ultrasound evaluation of the forearm. A GE LOGIQ e ultrasound unit with an L12 probe was used to evaluate the more clinically affected mid-dorsal forearm. The hypodermal tissues between the deep dermal interface and the muscle edge at the groove formed between the extensor digitorum and extensor carpi radialis was evaluated in short axis for the following variables: tissue depth with no transducer pressure (gel layer used to "float" the transducer to avoid any pressure), tissue depth with maximal tissue compression by transducer, and tissue echogenicity measured by densitometry (NIH Image). Dermal thickness was also measured. Tissue compressibility was calculated as (non-compressed tissue depth–compressed tissue depth)/non-compressed tissue depth. Statistical analysis was by T-test.

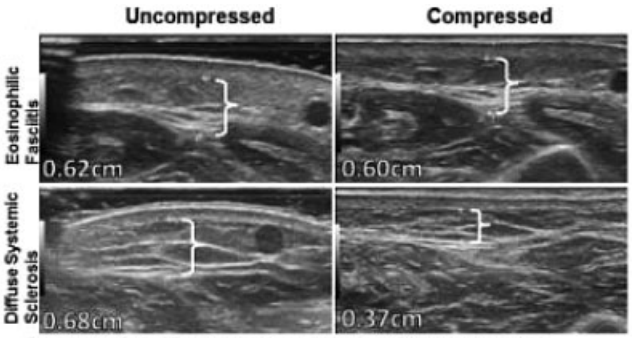
Results: The following numbers of patients were studied in each group: EF–8, dSSc–23, DMc–8, FM–8. Hypodermal percent compressibility was significantly less in EF compared with the other groups (means ± SD): EF–9 ± 7, dSSc–30 ± 13 ($p<0.004$ vs. EF), DMc–29 ± 20 ($p<0.02$ vs. EF), and FM–29 ± 14 ($p<0.003$ vs. EF) (figure). Hypodermal atrophy, measuring less than 4mm in thickness, was apparent in patients with EF–3/8 (38%), dSSc–7/23 (30%), and DMc–4/8 (50%), but not FM–0/8 (0%). DMc or dSSc patients only had < 20% hypodermal compressibility if they also had hypodermal atrophy, while all but one EF patient had compressibility of less than 20% regardless of hypodermal atrophy. Hypodermal tissue average echogenicity did not differ between the 4 groups (EF=155 ± 21 densitometry units (du), dSSc=145 ± 16 du, DMc=157 ± 12 du, FM=149 ± 17 du, p=NS). Dermal thickness also did not vary significantly between the 4 groups (EF=1.3mm ± 0.2, dSSc=1.4mm ±0.3, DMc=14mm ±0.3, FM 13mm ±0.3, p=NS).

Hypodermis Compression Test for Eosinophilic Fasciitis

Patient group	Hypodermal % compression	Hypodermis <4mm thick (% of patients)	Hypodermis echogenicity
Eosinophilic Fasciitis (n=8)	9 ± 7	38	155 ±21
Diffuse systemic sclerosis (n=23)	30 ± 13 p<0.004*	30	145 ±16
Diabetic (n=8) cheiroarthropathy	29 ± 20 p<0.02*	50	157 ±12
Fibromyalgia (control) (n=8)	29 ± 14 p<0.003*	0	149 ±17

A. comparison of hypodermis in patient groups. * P for comparison with eosinophilic fasciitis. Echogenicity measured in densitometry units.

Figure 1.



B. representative B-mode ultrasound images from a patient with eosinophilic fasciitis and with diffuse systemic sclerosis.

Figure 2.

Conclusions: Ultrasound can easily measure hypodermal compressibility. Our data suggest that reduction in hypodermal compressibility to less than 20% in non-atrophied hypodermis can be used to distinguish EF from dSSc and DMc, potentially obviating the need for wedge biopsy.

Disclosure: E. Y. Kissin: None; **M. R. York:** None; **R. W. Simms:** None.

1625

Novel PET/MR Fusion Imaging and Quantification of Knee Synovitis in Rheumatoid Arthritis. John T. Ryan[4], C. T. Ng[1], Aisling Kennedy[2], Robert G. Gibney[1], Oliver Fitzgerald[1], Patrick C. Brennan[5], Eric Heffernan[1], Jonathan McNulty[3], Louise Rainford[3], Ursula Fearon[1] and Douglas Veale[1]. [1]Dublin Academic Medical Centre, Dublin, Ireland, [2]Dublin Academic Medical Centre, [3]University College Dublin, [4]University of Sydney, Lidcombe, NSW, Australia, [5]University of Sydney

We recently identified hypoxia and altered blood vessel stability in the rheumatoid arthritis (RA) joint suggesting the vessels are dysfunctional, as they do not match metabolic demand. PET/CT imaging is recognized as an important advance in health care and research. In this study we aim to develop an innovative imaging approach to visualize and quantify synovial tissue (ST) blood flow and metabolic activity in inflamed joints of RA patients.

RA patients with an active knee joint synovitis were recruited and underwent clinical assessment prior to contiguous imaging initially with MR, then PET/CT followed by a needle videoarthroscopy, ST biopsy and pO2 measurement (novel LICOX probe). The PET radiotracer - Fluorodeoxyglucose (18F) was used and image-data intensity resolution was optimised for ST. These images exhibit the qualities of MRI with higher intensity regions in the areas of ST inflammation with extra heat-map information from the PET imaging. Semi-quantitative scoring of the MRI datasets was performed using the RAMRIS score. ST biopsies were stained for CD3+ (T cells), CD68+ (macrophages), and Factor VIII/ SMA (Blood vessel maturity) and NCAM expression.

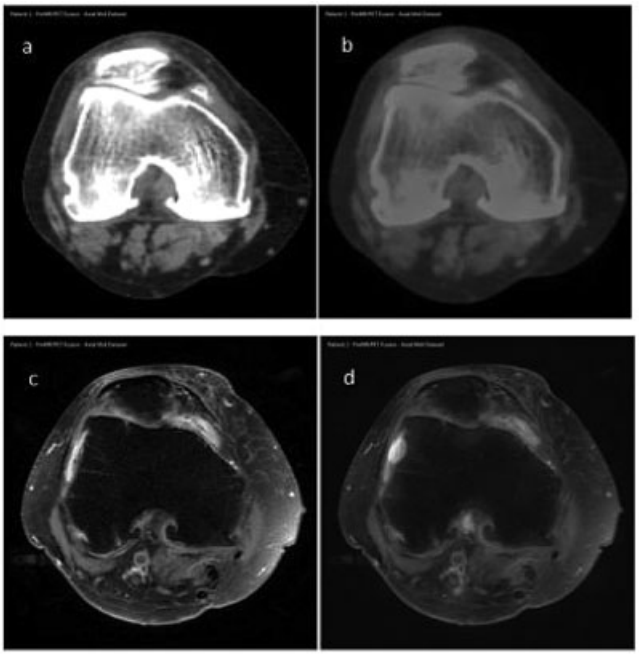


Figure 1. (a) Axial CT slice, (b) Axial PET/CT, (c) Axial contrast-enhanced MRI, (d) PET/MR fusion image.

RA patients (n=9) have completed combined scanning/arthroscopy protocols. Proof-of-concept images and quantitative assessments have been developed (Fig. 1, 2). Fig. 1a and b show the CT and PET/CT scans, 1c shows MR and the PET/MR fusion image is shown in Fig 1d. Evaluation of disease activity, blood flow or metabolic activity is not possible in Fig 1a or 1c, while Fig. 1b only provides information of metabolic activity. Fig. 1c does illustrate areas of high signal representing inflammation. Fig. 2 shows the contrast of PET imaging of an inflamed knee compared to the uninflamed contralateral knee and good PET/MRI structural agreement. A region of interest (ROI) was evaluated (n=3) of the target and the opposite knee to calculate a ratio of affected:unaffected. A significant correlation was found between PET activity with MRI score ($r = 0.9986$, $p < 0.0001$), with low tpO2 in vivo levels (xyz), while an inverse relationship was found with blood vessel maturity and stability, reflected by factor VIII/ SMA and NCAM expression on ST immunohistology of the blood vessels ($r = -0.99$, $p < 0.0001$).

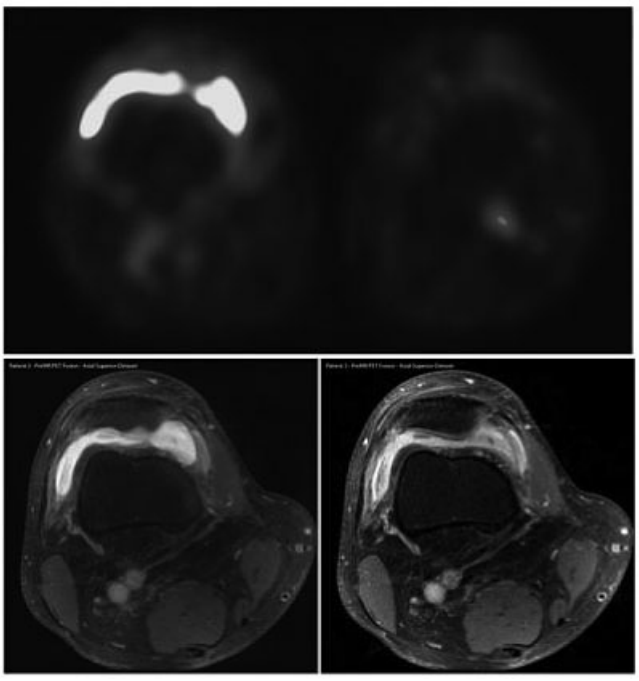


Figure 2. PET image of affected side versus unaffected contralateral side (top). Structural agreement of PET with MRI (bottom).

This is the first description of hybrid PET/MRI fusion imaging of inflamed joint in RA. The preliminary data suggest a close correlation between measures of inflammation, blood flow and metabolic activity. The potential correlation with cellular and molecular biomarkers suggests this novel imaging protocol may be extremely powerful in assessing response to therapies in vivo.

Disclosure: J. T. Ryan: None; **C. T. Ng:** None; **A. Kennedy:** None; **R. G. Gibney:** None; **O. Fitzgerald:** None; **P. C. Brennan:** None; **E. Heffernan:** None; **J. McNulty:** None; **L. Rainford:** None; **U. Fearon:** None; **D. Veale:** Abbott Laboratories, 2, Amgen Inc., 8, Centocor, Inc., 2, GlaxoSmithKline, 2, Mundipharma, 2, 8, Opsona, 2, 8, Pfizer Inc, 8, Schering-Plough, 8, Wyeth Pharmaceuticals, 2, 8.

1626

Outcomes and Cost-Effectiveness of Carpal Tunnel Injections Using Sonographic Needle Guidance. Natalia R. Chavez-Chiang[2], Suzanne Delea[1], Wilmer L. Sibbitt[3], Arthur D. Bankhurst[4] and Hillary Norton[2]. [1]University of New Mexico, Albuquerque, NM, [2]University of New Mexico, [3]University of New Mexico HSC, Albuquerque, NM, [4]University of NM Med Ctr, Albuquerque, NM

Objective: This randomized controlled study addressed whether sonographic needle guidance affected the outcomes of corticosteroid injection for carpal tunnel syndrome.

Methods: 76 symptomatic carpal tunnels were randomized to injection by conventional palpation-guided or sonographic image-guided injection enhanced with a one-handed RPD (the reciprocating procedure device) syringe. A one needle, two-syringe technique was used where sonographic-guided hydrodissection with 1% lidocaine with a first syringe was performed followed by injection with 80 mg of triamcinolone acetonide.

Baseline pain, procedural pain, pain at outcome (2 weeks and 6 months), responders, therapeutic duration, reinjection rates, total cost, and cost per responder were determined.

Results: There were no complications in either treatment group. Relative to conventional palpation-guided methods, sonographic guidance for injection of the carpal tunnel resulted in 77.1% reduction in procedural pain ($p<0.001$), a 63.3% reduction in pain scores at outcome ($p<0.002$), 84.6% increase in the responder rate ($p<0.001$), 51.6% reduction in the non-responder rate ($p<0.001$), a 71.0% increase in therapeutic duration ($p < 0.001$), a 59.3% ($150) reduction in cost/responder/year for a hospital outpatient ($p<0.001$) and a 20.8% reduction in cost/patient/year for a hospital outpatient ($p<0.001$).

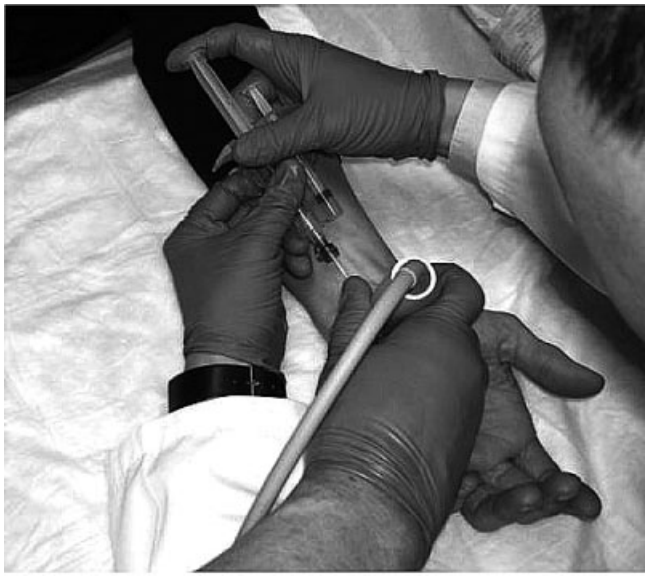


Figure 1.

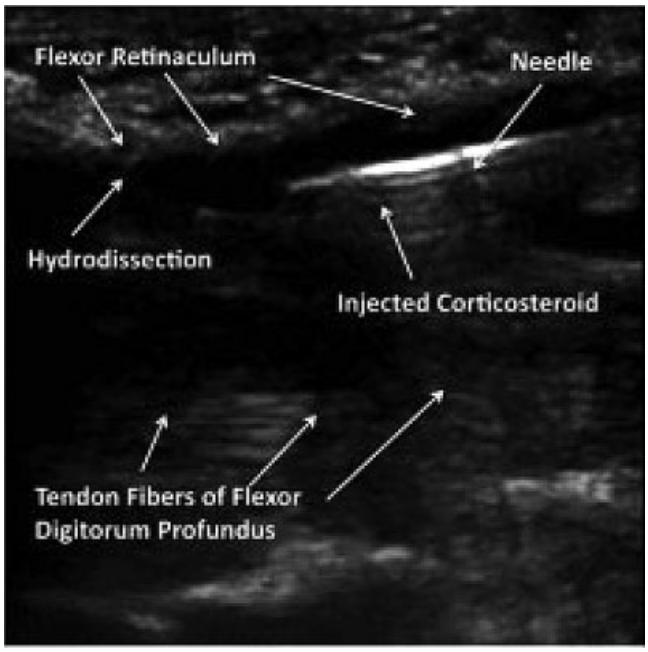


Figure 2.

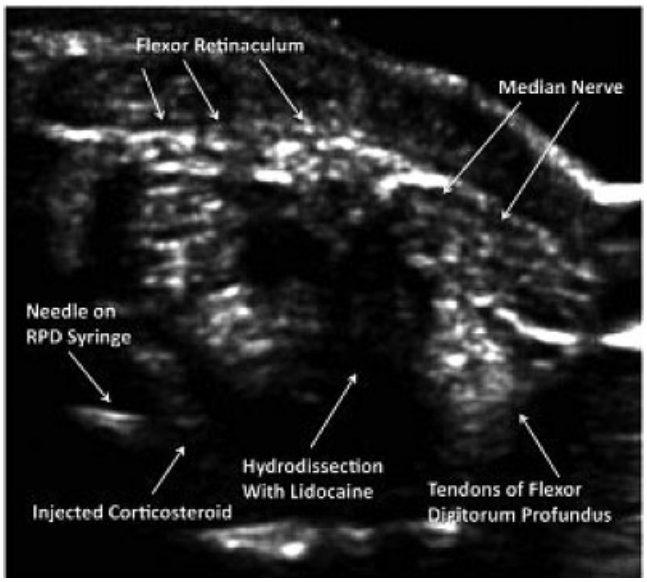


Figure 3.

Conclusion: Sonographic needle guidance improves the performance, clinical outcomes, and cost-effectiveness of injection of the carpal tunnel.

Disclosure: N. R. Chavez-Chiang: None; **S. Delea:** None; **W. L. Sibbitt:** Apple, 1, 2, 5, Avanca Inc, 1, 2, 5, Avanca Medical Devices, 1, 2, 5, Avasca Inc, 1, 2, 5, Avasca Medical, 1, 2, 5, Becton Dickinson, 5, Celgene, 1, Ferring Pharmaceuticals Inc., 5, Intelligence managment solutions, 1, 2, 5; **A. D. Bankhurst:** None; **H. Norton:** None.

1627 WITHDRAWN

1628

Potential Use of Matrix Metalloproteinase-13 Fluorogenic Probe for Imaging Osteoarthritis Development *In Vivo*. Sung Jae Choi[2], Young Ho Lee[2], Jong Dae Ji[2] and Gwan Gyu Song[1]. [1]Korea Univ College of Med, Seoul, Korea, Republic of, [2]Korea Univ College of Medicine, Korea, Republic of

Objective: the early detection of osteoarthritis (OA) is currently a key challenge in the field of rheumatology. Biochemical studies of OA have indicated that matrix metalloproteinase-13 (MMP-13) plays a central role in cartilage degradation. In this study, we describe the potential use of a dark-quenched fluorogenic MMP-13 probe to image MMP-13 in both *in Vitro* and rat models *in Vivo*.

Method: the imaging technique involved using a MMP-13 peptide substrate, near-infrared (NIR) dye, and a NIR dark quencher. This compound is composed of (i) Cy5.5, which was used as the near-infrared (NIR) dye (ex/em; 675/695), (ii) a short peptide sequence, G*PLGMRG*LGK, which was used as the MMP-13 cleavable substrate, and (iii) black hole quencher-3 (BHQ-3), which was used as the NIR dark-quencher specific for Cy5.5 (abs. 650 nm). The quenching properties of the probe were analyzed and visualized using a spectrofluorometer with a fixed excitation wavelength of 675 nm and a Kodak Image Station 4000MM equipped with filter for Cy5.5.

Results: OA-induced cartilage produced strong NIR fluorescence signals that were clearly visualized in the fluorescent images (1.30.2, 3.3 0.7, and 7.4 1.4-fold vs normal side for 0, 6, and 8 weeks, respectively; $n = 3$). NIR fluorescence signals in the eight-week OA rat had a 2.2-fold increase relative to the six week OA rat. Furthermore, the histological section of the normal cartilage showed a smooth articular surface with clear demarcation between the cartilage and subchondral bone the results from this study demonstrate that the use of a dark-quenched fluorogenic probe allows for the visual detection of MMP-13 *in* V*itro* and in OA-induced rat models. In particular, by targeting this OA biomarker, the symptoms of the early and late stages of OA can be readily monitored, imaged, and analyzed in a rapid and efficient fashion.

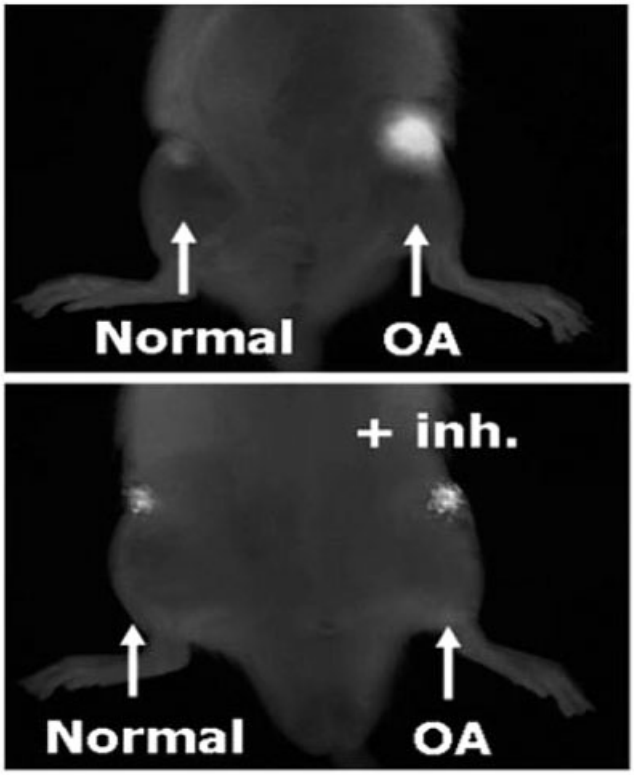


Figure 1. In Vivo imaging of upregulated MMP-13 in OA-induced cartilages 1 hour after intracartilage-injection of probe 1.

Conclusion: we anticipate that this simple and highly efficient fluorogenic probe will assist in the clinical management of patients with OA, not only for early diagnosis but also to assess individual patient responses to new drug treatments.

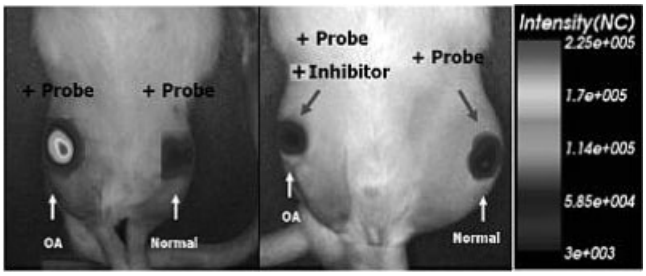


Figure 2. In ViVo NIR fluorescence tomographic images of normal and OA cartilage after local injection of probe 1 with or without the addition of the MMP-13 inhibitor in eight week OA-induced rat model.

Disclosure: S J. Choi: None; **Y. H. Lee:** None; **J. D. Ji:** None; **G. G. Song:** None.

1629

Psychometric Properties of Synovitis Assessed in Rheumatoid Arthritis: Improved Intraobserver Reliability of Ultrasound vs. Clinical Evaluation in an Ancillary Study of the "Etanercept Versus DMARDs" Randomized, Prospective, Multicentre Study. Peter Mandl[5], Peter V. Balint[5], Yves Brault[4], Marina Backhaus[9], Maria Antonietta D'Agostino[7], Walter Grassi[1], Desiree M. Van Der Heijde[3], Eugenio De Miguel[8], Richard J. Wakefield[6], Isabelle Logeart[4] and Maxime Dougados[2]. [1]Clinica Reumatologica, Università Politecnica delle Marche, Jesi, Ancona, Italy, [2]Hospital Cochin, Paris, France, [3]Leiden University Medical Center, Meerssen, The Netherlands, [4]Pfizer, La Défense, Paris, France, [5]Rheumatology Department III, National Institute of Rheumatology and Physiotherapy, Budapest, Pest, Hungary, [6]Rheumatology Department, University of Leeds, Chapel Allerton Hospital, Leeds, United Kingdom, [7]Rheumatology Department, Versailles-Saint Quentin en Yvelines University; APHP, Ambroise-Paré Hospital, Boulogne-Billancourt, France, [8]Rheumatology Unit, La Paz University Hospital, Madrid, Spain, Spain, [9]University Medicine Berlin: Campus Charité Mitte, Berlin, Germany

Objectives: To propose different global ultrasound (US) and Power Doppler ultrasound (PD) scoring systems for measuring synovitis in rheumatoid arthritis (RA), with regard to the optimal number of joints to be evaluated. To evaluate for each proposed scoring system intra-observer reliability, face validity and discriminant capacity of US and PD synovitis versus clinical synovitis.

Methods: This 52-week, prospective, open-label, randomized, parallel-group, multicenter, outpatient study was conducted in RA subjects with moderate disease receiving etanercept combined with methotrexate (ETN+MTX) or various DMARDs. Due to early termination of the study, analyses were restricted to data collected from screening to the week-12 visit period. To study selected global scoring systems for clinical, US and PDUS techniques, 42 joints were evaluated: 28 joints (DAS28 joints), bilateral metatarsophalangeal, ankle and talonavicular joints using either a binary count (yes/no) or a 0–3 semiquantitative score. A total of 66 different scoring systems were evaluated consisting of 11 different joint combinations, clinical, US and PDUS derived data, including both counts and scores. Intra-observer reliability was calculated at several timepoints by intraclass correlation coefficient (ICC) and standard error of measurement. Face validity was evaluated as the degree of association between CRP or ESR and each scoring system; correlation was assessed at screening (Pearson's). To calculate discriminant capacity of scoring systems, the ETN+MTX and the conventional DMARD groups were evaluated separately and the difference in SRM was calculated.

Results: 66 patients were randomized in the study; 62 patients (mean age 53.8 years, 80.6% female, mean disease duration: 8.8 years) were included in the modified intention to treat population with 30 patients receiving various DMARDS, and 32 receiving ETN+MTX. Reliability was better for US and PD than for clinical evaluation of synovitis in stable subjects between baseline and screening visit ranging from 0.6–0.95 and 0.56–0.93 vs. 0.33–0.75 (respective ICC values of US, PD, clinical indices). Face validity was similar between the techniques. Difference in discriminant capacity (difference of difference in SRM between treatment groups) of US and PD vs. clinical synovitis, was −0.25 (−0.96/0.64) and 0.08 (−0.37/0.59) (median, range) respectively in the baseline to 12 weeks period. No relevant differences in psychometric properties were observed regarding the number and specific localizations of the evaluated joints between the different scoring systems but with a trend in favor of better performance while referring to PD indices.

Conclusion: This study suggests that US and PD have not only similar but better reliability than generally used clinical indices for evaluating synovitis in RA. PD was also found to have better discriminant capacity than clinical synovitis for distinguishing between treatment arms. Such findings were observed for the different tested scoring systems suggesting that a simplified scoring system referring to the PD findings might be sufficient; these findings require further evaluation in larger study populations.

Disclosure: P. Mandl: Wyeth Pharmaceuticals, 5; **P. V. Balint:** Wyeth Pharmaceuticals, 5; **Y. Brault:** Pfizer Inc, 3; **M. Backhaus:** None; **M. A. D'Agostino:** None; **W. Grassi:** None; **D. M. Van Der Heijde:** Abbott Laboratories, 5, Amgen Inc., 5, Bristol-Myers Squibb, 5, Centocor, Inc., 5, Chugai, 5, Merck Pharmaceuticals, 5, Novartis Pharmaceuticals Corporation, 5, Pfizer Inc, 5, Roche, 5, sanofi-aventis, 5, Schering-Plou; **E. De Miguel:** Abbott Laboratories, 2, 5, 8, Roche, 8, Schering-Plough, 8, Wyeth Pharmaceuticals, 2, 8; **R. J. Wakefield:** None; **I. Logeart:** Pfizer Inc, 3; **M. Dougados:** Abbott Laboratories, 1, 2, AstraZeneca, 1, 2, Bristol-Myers Squibb, 1, 2, Pfizer Inc, 1, 2, Roche, 1, 2, UCB, Inc., 1, 2.

1630

Sensitivity and Specificity of the Physical Examination Compared to Ultrasound in Identifying Knee and Ankle Arthritis in JIA.

Ginger L. Janow[3], Vikash Panghaal[2], Terry L. Levin[2] and Norman T. Ilowite[1]. [1]Children's Hospital Montefiore, Bronx, NY, [2]Department of Radiology, Montefiore Medical Center, [3]Division of Pediatric Rheumatology, Children's Hospital Montefiore, New York, NY

Background: JIA can be an extremely debilitating disease of childhood with significant physical, psychological and financial costs to affected children. Early identification of active arthritis and treatment are crucial to the prevention of long term joint damage and disability. There is significant inter-user variability in the physical examination diagnosis of active arthritis, even among experienced pediatric rheumatologists. Ultrasound (US) with power Doppler has been shown to be a helpful tool in assessing joint involvement and has the capability to identify sub-clinical disease. Use of US in all children with JIA may not be justifiable because of the cost.

Objective: (1) To determine the sensitivity and specificity of physical examination for identifying synovitis in knee and ankle joints of children with juvenile idiopathic arthritis. (2) To identify patients who would benefit most from additional screening via ultrasound.

Methods: A total of 22 patients with JIA were referred for ultrasound. Bilateral knees and ankles were examined using US with and without power Doppler in a blinded manner. Active arthritis on physical examination was defined as non bony swelling (criteria 1) or limitation of motion with either pain on motion or tenderness (criteria 2). Active arthritis on ultrasound was defined as synovial hyperplasia, effusion or increased vascularity on power Doppler. Eighty-eight joint assessments were completed by both a pediatric rheumatologist and a radiologist. Rheumatologist assessments were collected via chart review.

Results: Physical exam had a sensitivity of 61%, a specificity of 75%, positive predictive value of 71% and negative predictive value of 66% as compared to US. When the definition of clinical synovitis was restricted to include only joints that met both of the clinical criteria (1 and 2), the specificity improved to 90%, with a decrease in sensitivity to 50 %. Overall, the physical exam was more specific for identifying synovitis in the ankle than knees (specificity of 81% and 58% respectively).

Discussion: These data support the use of US to assess joints that do not meet both of the clinical criteria. Addtionally, the physical exam is less sensitive for identifying knee arthritis which could support further US screening of these joints. Prudent use of ultra-sound in situations where the physical exam is less reliable could help identify sub-clinical disease and improve long-term outcomes.

Disclosure: G. L. Janow: None; **V. Panghaal:** None; **T. L. Levin:** None; **N. T. Ilowite:** None.

1631

The Comparison of Ultrasound & Physical Findings (CUSP) Remission Study—Ultrasound Remission Is Attained in Only 20% of Patients on Anti-TNF Therapy.

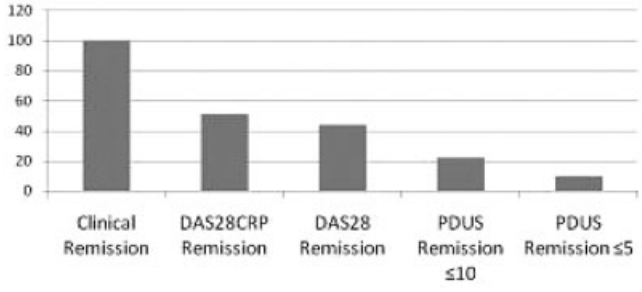
Joanne M. Kitchen[1], Bernadette M. Lynch[3], Oliver M. FitzGerald[2], Douglas J. Veale[3] and David Kane[1]. [1]Adelaide and Meath Hospital, Dublin, Ireland, [2]St Vincents Univ Hospital, Ranelagh Dublin, Ireland, [3]St Vincents Univ Hospital, Dublin, Ireland

Background: Studies show persistent inflammation on imaging in a proportion of patients in clinical remission on traditional DMARDs. This study aimed to evaluate clinical remission in patients on anti-tumour necrosis factor alpha (anti-TNF) drugs using objective measurement with DAS scores & ultrasound scoring using gray scale (GS) & power Doppler (PD) imaging.

Methods: Patients with Rheumatoid (n=29) and Psoriatic arthritis (n=12) on anti-TNF therapy & deemed by their supervising clinician to be in remission were assessed. Patient joint counts were performed. C-reactive protein (CRP) was measured and DAS28CRP was calculated. Visual analogue scales (VAS) (pain, general wellbeing) & Health Assessment Questionnaires (HAQ) were completed. Ultrasound examination of the DAS28 joint set and of the ankles and metatarsophalangeal joints was performed (GE Logiq 9) with a high frequency (15MHz) linear array transducer. GS and PD synovitis were graded using an established semi-quantitative scale (0–3).

Results: The mean disease duration was 9.9 years (range 2–30) & mean patient age was 56 years (range 33–75). Average duration of biologic therapy was 31.5 months (4–67) and 95% were on their first biologic. Mean DAS28CRP was 2.57 (1.35–4.85) while mean DAS28 was 2.74 (0.91–4.9). 21/41(51%) of patients were in DAS28CRP remission, 14 had low disease activity (DAS28CRP >2.6, <3.2) while 5 patients had active disease. Mean HAQ score was 0.58 (0–1.63). 34/41 (83%) had GS synovitis of at least Grade 2 in one joint, while the remainder (7/41, 17%) had Grade 3 synovitis in at least one joint. All patients had positive PD signal in at least one joint. Mean total score of PD was 19 (range 2–64). 22/41 (54%) patients had Grade 2 PD and 4/41 (10%) had grade 3 PD. If PD remission was defined as PD total score of 10 or less, 9/41 pts (22%, mean 6.4, range 2–10) fulfilled criteria. If PD remission was defined as PD total score of 5 or less, 4/41 pts (10%, mean 3.75, range 2–5) fulfilled criteria. GS and PD synovitis scores were significantly positively correlated with DAS28CRP (r=0.575 and r= 0.793 respectively, p<0.01 for both).

Percentage of patients in Remission



Conclusion: Ninety percent (37/41) of patients in clinical remission & 81% (17/21) of patients in DAS remission on anti-TNF show persistent inflammation on GS & PD imaging. Standard clinical assessment alone is

insufficient to determine remission in patients on anti-TNF therapy. Formal DAS28 scores should be performed routinely to ensure therapeutic response is adequate. Ultrasound assessment of remission reveals ongoing inflammation in patients in clinical remission.

Disclosure: J. M. Kitchen: Abbott Laboratories, 2; **B. M. Lynch:** None; **O. M. FitzGerald:** Abbott Laboratories, 2, 5, 8, Bristol-Myers Squibb, 2, Pfizer Inc, 5, 8; **D. J. Veale:** Abbott Laboratories, 2, 5, 8, Centocor, Inc., 5, 8, GlaxoSmith-Kline, 2, 5, 8, Mundipharma, 2, 8, Opsona, 2, 8, Pfizer Inc, 5, 8, Schering-Plough, 5, 8, Wyeth Pharmaceuticals, 2, 5, 8; **D. Kane:** None.

1632

The Power Doppler Ultrasonography Score from 24 Synovial Sites or 6 Simplified Synovial Sites, Including the Metacarpophalangeal (MCP) Joints, Reflects Well the Clinical Disease Activity and Serum Biomarkers in Patients with Rheumatoid Arthritis. Atsushi Kawakami[1], Shin-ya Kawashiri[1], Naoki Iwamoto[1], Mami Tamai[1], Hideki Nakamura[1], Junko Kita[1], Akitomo Okada[1], Tomohiro Koga[1], Satoshi Yamasaki[1], Tomoki Origuchi[1] and Katsumi Eguchi[2]. [1]Nagasaki University, Nagasaki, Japan, [2]Sasebo City General Hospital, Sasebo, Nagasaki, Japan

Purpose of Study: We evaluated the significance of the power Doppler ultrasonography (PDUS) score by comparing it with serum biomarkers and clinical disease activity.

Methods: We measured the PDUS scores of 24 synovial sites in 12 joints in 22 RA patients. For convenience, the PDUS scores of 6 synovial sites in 6 joints were also examined. Both PDUS scores included the metacarpophalangeal (MCP) joints. Each joint was scored for a power Doppler (PD) signal on a scale from 0 to 3. The PDUS scores are the sums of the PD signal scores for the 24 synovial sites or the 6 synovial sites. On the same day, serum variables as well as clinical disease activity were evaluated. Serum variables included vascular endothelial growth factor (VEGF), matrix metalloproteinase-3 (MMP-3), MMP-9 and tissue inhibitor of metallo-proteinases-1 (TIMP-1). The clinical disease activity included the disease activity score of 28 joints (DAS28), the simplified disease activity score (SDAI) and the clinical disease activity score (CDAI).

Results: The PDUS scores from the 24 joint sites were significantly positively correlated with tender joints counts, swollen joint counts, DAS28, SDAI, CDAI and serum biomarkers including MMP-3, VEGF and TIMP-1, whereas it did not correlate with MMP-9. Accordingly, the PDUS scores from the 6 synovial sites greatly correlated with those from the 24 joint sites. Clinical disease activities as well as serum variables were also clearly correlated with the PDUS scores from the 6 synovial sites.

Conclusions: The standard as well as the simplified PDUS scores well reflected clinical disease activity and serum variables, including angiogenic factors. Our data reaffirm the utility of ultrasonography for monitoring disease activity in patients with RA.

Disclosure: A. Kawakami: None; **S.-y. Kawashiri:** None; **N. Iwamoto:** None; **M. Tamai:** None; **H. Nakamura:** None; **J. Kita:** None; **A. Okada:** None; **T. Koga:** None; **S. Yamasaki:** None; **T. Origuchi:** None; **K. Eguchi:** None.

1633

The Role of Ultrasound in B Mode and Power Doppler Sonography in the Diagnosis of Enthesitis in Children. Dana Toib[1], Anthony R. French[1], Nirvikar Dahiya[2], William D. Middleton[2], Richard Brasington[1] and Andrew J. White[1]. [1]Washington Univ Schl of Med, St Louis, MO, [2]Washington Univ Schl of Med

Purpose: Enthesitis is a distinctive feature of Juvenile SpA (JSpA). Recently, ultrasound in B mode and power Doppler sonography has been suggested to be a valuable tool in the assessment of enthesitis. The aim of this study was to compare the physical exam (PE) with ultrasonography (US) in the assessment of enthesitis in children.

Methods: 20 JSpA patients, 19 polyarticular/pauciarticular JIA patients, 8 adolescent patients with idiopathic arthralgias and 9 healthy pediatric controls underwent US exam of 16 peripheral entheses using Terason t3000 equipment with 12-MHz linear array transducer. The US images were interpreted independently by two radiologists and abnormalities were quantified using a modification of the Madrid sonographic enthesitis index (MASEI). Entheseal PE was completed independently by two pediatric rheumatologists. Current treatment, inflammatory markers and CHAQ scores were recorded on all patients.

Results: Sonographic evidence of enthesitis was most common in the JSpA group (53% of patients; 6.9% of examined entheses), but was also found in all other study groups, including pauciarticular/polyarticular JIA (37% of patients; 5.0% of entheses), idiopathic arthralgias (38% of patients; 2.7% of entheses) and healthy controls (28% of patients; 2.1% of entheses).

PE evidence of enthesitis was most common in the idiopathic arthralgias group (56% of patients; 18.4% of entheses), followed by the JSpA group (43% of patients; 7.8% of entheses) and the polyarticular/pauciarticular JIA group (26% of patients; 3.0% of entheses). None of the healthy controls had PE evidence of enthesitis.

Sonographic severity of enthesitis was highest in the JSpA group with an enthesitis score of 4.7, followed by 1.6 in the polyarticular/pauciarticular JIA group, 1.1 in the idiopathic arthralgias group and 0.8 in healthy controls.

Follow-up PE and US were performed on two of the JSpA patients who had the highest US enthesitis scores and were the only patients who at the initial study visit time were untreated or treated only with NSAIDs. Repeat US revealed resolution of entheseal vascularization and development of calcifications consistent with post-inflammatory changes corresponding with clinical improvement. The PE did not correlate with these changes.

Agreement on presence of enthesitis between two examiners in PE and US were 26% and 41% respectively. Agreement on presence of enthesitis between PE and US was only 3%.

Neither the PE nor the US enthesitis scores correlated with other measures of disease activity including white blood cell count, hemoglobin, platelet count, ESR, CRP or CHAQ score.

Conclusions: US detected the highest frequency of enthesitis among the JSpA group whereas PE detected the highest frequency of enthesitis among the idiopathic arthralgias group. Agreement on presence of enthesitis between PE and US was poor. US interobserver agreement was limited, but superior to that of the PE. Sonographic findings consistent with mild enthesitis were found in healthy controls. These findings suggest that although US might have a role in the diagnosis of enthesitis in children, it should be used cautiously due to a limited inter observer reliability and specificity.

Disclosure: D. Toib: None; **A. R. French:** None; **N. Dahiya:** None; **W. D. Middleton:** None; **R. Brasington:** None; **A. J. White:** None.

1634

Ultrasound Bone Erosions—Their Morphological Basis Obtained by High-Resolution Micro-Computed Tomography Imaging. Stephanie Finzel[2], Sarah Ohrndorf[1], Matthias Englbrecht[2], Christian M. Stach[2], Janin Messerschmidt[1], Georg Schett[3] and Marina Backhaus[4]. [1]Charite University Hospital, Berlin, Germany, [2]Department of Internal Medicine 3, University of Erlangen-Nuremberg, Erlangen, Germany, [3]Friedrich Alexander Univ, Erlangen, Germany, [4]University Medicine Berlin: Campus Charité Mitte, Berlin, Germany

Objectives: To validate, whether bony lesions appearing in high-resolution ultrasound (HRUS) are true bone erosions.

Methods: In total, 26 individuals (14 with rheumatoid and 6 with psoriatic arthritis as well as 6 healthy controls) were assessed for bone erosions at the radial, palmar and dorsal side of the MCP2 and the palmar and dorsal sides of the MCP3 and MCP4 joint. All patients received a HRUS and for validation of results a micro-computed tomography scan (μCT). The prevalence (0/1) and severity of bone erosions obtained in HR US and μCT were recorded and compared.

Results: Overall there was a good correlation between the severity of US erosions and μCT erosions ($r = 0.463$, $p < 0.0001$).

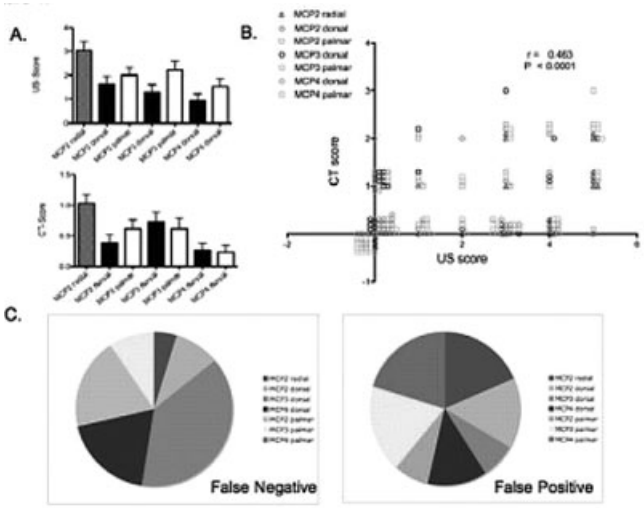


Figure 1.

False-negative (US 1/ μCT 0) results were obtained in only 10% of the joint regions and were mostly due to small erosive lesions at the dorsal sides of the MCP joints. False-positive results were more frequent (28%) and primarily based on vascular bone channels at the palmar sides of the MCP joints as well pseudo-erosions created by osteophytes.

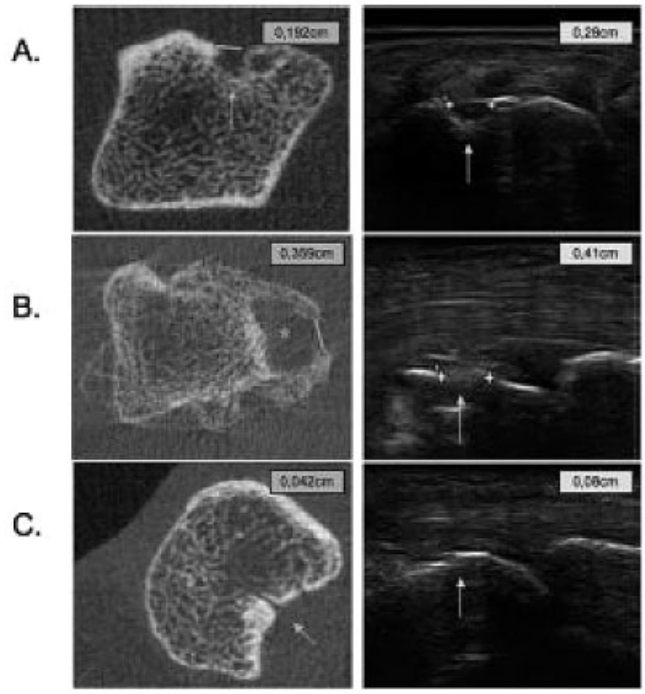


Figure 2.

Conclusions: These data show that the majority of erosion in the US was indeed based on true bone erosions with a cortical break. The sensitivity of US for detecting bone erosions was high and there was a good correlation between the severity of bone erosions in the US and the μCT imaging. Specificity of US for bone erosions was substantially lower, suggesting that smaller US lesions do not always refer to true breaks in the cortical bone surface.

Disclosure: S. Finzel: None; **S. Ohrndorf:** None; **M. Englbrecht:** None; **C. M. Stach:** None; **J. Messerschmidt:** None; **G. Schett:** None; **M. Backhaus:** None.

1635

Ultrasound Lung Comets. Validity, Reproducibility and Feasibility of a Simplified Assessment of Pulmonary Interstitial Fibrosis in Connective Tissue Disorders. Marwin Gutierrez[1], Fausto Salaffi[1], Marina Carotti[3], Marika Tardella[1], Chiara Bertolazzi[1], Elisabetta Bichisecchi[3], Mara Giorgi[3], Alarico Ariani[1], Carlos Pineda[2], Emilio Filippucci[1] and Walter Grassi[1]. [1]Clinica Reumatologica, Università Politecnica delle Marche, Jesi, Ancona, Italy, [2]Instituto Nacional de Rehabilitacion, Mexico City, Mexico, [3]S.O.D Radiologia Clinica, Dipartimento di Scienze Radiologiche, Ospedale Riuniti, Ancona.

Objective: To investigate the validity, reproducibility and feasibility of a simplified ultrasound lung comets (ULC) assessment compared with a comprehensive assessment of pulmonary interstitial fibrosis in patients with connective tissue disorders (CTD).

Methods: A total of 36 consecutive patients (32 female, 4 male, mean of age: 58.5 years, mean of disease duration: 60 months) with diagnosis of CTD (28 with systemic sclerosis, 2 with Sjögren's syndrome, 1 with undifferentiated CTD, 2 with anti-synthetase syndrome, 2 with dermatomyositis and 1 with mixed CTD) of Rheumatology Department of Università Politecnica delle Marche were enrolled in this study. The inclusion criteria were: previous diagnosis of CTD according to international criteria and a high resolution computed tomography (HRCT) performed no longer than 10 days prior to the beginning of the study. Each patient underwent a chest ultrasound exam by a rheumatologist experienced in ultrasound blinded to the HRCT findings, using a MyLab 70 XVG (Esaote Spa, Genoa-Italy) equipped with a 2–7 MHz multifrequency convex transducer. Both comprehensive, as previously proposed (1, 2) and simplified ULC assessments were scanned. The simplified ULC assessment included 14 sites bilaterally: third para-sternal, fifth mid-clavicular, anterior axillary, medial axillary and posterior axillary, and eighth sub-scapular and para-vertebral intercostal spaces. These sites were chosen on the basis of both the width of the acoustic window and the prevalence of ULC. The number of ULC was summed for each intercostal space and the total was scored using the following semiquantitative scoring (0= < 5; 1= 5–15; 2= 16–30; 3= >30 ULC) (3). For criterion validity, HRCT was considered the gold standard and an experienced radiologist interpreted it, adopting the topographic semiquantitative score proposed by Warrick et al. Inter and intra-observer reliability, with an other rheumatologist sonographer with less experience in the field of ultrasound, was also investigated.

Results: A total of 1440 sites were evaluated by ultrasound. A highly significant agreement between the comprehensive and simplified ULC assessment was found (chi-square, p=0.0001). A significant positive correlation was also found between the simplified ULC assessment and Warrick scores (Spearman rank test, rho= 0.656, p< 0.0001). The concordance correlation coefficient values for the inter and intra-observer were in a range from 0.832 to 0.956 and 0.786 to 0.943 (p < 0.0001), respectively. Finally, there was a relevant difference in time spent on comprehensive (mean 20.6 minutes) with respect to the simplified (mean 7.4 minutes) ULC assessment.

Conclusion: Our results provide evidence in favour of the validity, reproducibility and feasibility of a simplified 14 sites ULC assessment as an adjunct method to assess pulmonary interstitial fibrosis in patients with CTD.

Gargani L et al. Ultrasound lung comets in sistemic sclerosis: a chest sonography hallmark of pulmonary interstitial fibrosis. Rheumatology 2009;48:1382-7.

Lichtenstein D et al. The comet-tail artifact: an ultrasound sign of alveolarinterstitial syndrome. Am J Respir Crit Care Med 1997;156:1640-6.

Disclosure: M. Gutierrez: None; **F. Salaffi:** None; **M. Carotti:** None; **M. Tardella:** None; **C. Bertolazzi:** None; **E. Bichisecchi:** None; **M. Giorgi:** None; **A. Ariani:** None; **C. Pineda:** None; **E. Filippucci:** None; **W. Grassi:** None.

1636

Use of Musculoskeletal Ultrasound in Diagnosis of Early Inflammatory Arthritis: Are Limited Joint Surveys Adequate? Paramvir Sidhu, Jeffrey Lisse, Rafael Grau, Eric P. Gall and Mihra Taljanovic. University of Arizona, Tucson, AZ

Objectives:

1. To study the impact of using musculoskeletal ultrasound in diagnosis of early inflammatory arthritis.

2. To examine feasibility of using limited form of musculoskeletal ultrasonography for diagnosis of early inflammatory arthritis without significantly compromising diagnostic accuracy.

Subjects: Patients with clinical suspicion of inflammatory arthritis but non-diagnostic work up including RF, CCP antibodies, ESR, CRP and plain radiographs.

Methods: 80 patients underwent comprehensive musculoskeletal ultrasound of 22 joints of hands & wrists (bilateral PIP, MCP & wrist joints) from year 2003 to 2010. Parameters analyzed at imaged joints included synovial thickening,

increased vascularity and erosions. Retrospective review of this imaging data as well as clinical data including age, sex, serological status (RF & CCP antibody positivity), inflammatory markers (ESR & CRP) and final diagnosis was performed.

Results:

Total Patients	80
Clinical Data Available	53
Female	65
Male	15
Age	19 to 82 yrs (Median Age = 52)
RF positive	6
CCP antibody positive	4
Elevated ESR	10
Elevated CRP	9

	Synovial Thickening		Increased Vascularity		Erosions	
Joints	Right	Left	Right	Left	Right	Left
2nd MCP	40	43	35	33	25	25
3rd MCP	32	31	28	22	21	17
5th MCP	22	26	15	12	9	11
Wrist	28	29	26	30	4	1

There were 48 patients with synovial thickening and increased vascularity and 35 patients with erosions at one or more joints. Changes suggestive of inflammatory arthritis were most commonly seen at 2nd & 3rd MCP and wrist joints. Thirty patients were found to have synovial thickening, 25 increased vascularity and 13 erosions at one or more joints despite having negative RF & CCP antibodies and normal inflammatory markers (ESR & CRP). Fourteen patients were given final diagnosis of inflammatory arthritis primarily based on musculoskeletal ultrasound results and all 14 had synovial thickening and increased vascularity at one or more of 2nd & 3rd MCP and wrist joints.

Conclusions: 1. Musculoskeletal ultrasound is a very useful tool in diagnosis of early inflammatory arthritis in clinical practice.

2. Brief musculoskeletal ultrasound, restricted to just 6 joints (bilateral 2nd & 3rd MCP and wrist joints) instead of 22 joints, can be used to make the diagnosis of early inflammatory arthritis without significantly compromising diagnostic accuracy and thus reducing time required to perform the exam.

Disclosure: P. Sidhu: None; **J. Lisse:** None; **R. Grau:** None; **E. P. Gall:** None; **M. Taljanovic:** None.

1637

Utility of Ultrasound in the Diagnostic Assessment of Shoulder Pain in Polymyalgia Rheumatica: Results from an International, Prospective, Multi-Center Longitudinal Study. ACR–EULAR Study Group for Development of Classification Criteria for PMR. Wolfgang A. Schmidt[17], Marco A. Cimmino[9], Peter Mandl[18], Peter V. Balint[1], Annamaria Iagnocco[22], Richard J. Wakefield[20], Michael Schirmer[4], Carlo Salvarani[10], Artur Bachta[16], Maria C. Cid[15], Christina Duftner[8], Christian Dejaco[12], Georgina Espígol-Frigolé[2], Pierluigi Macchioni[10], Zsuzsa Schmidt[18], Novák P. Kaposi[19], Gyula Poór[18], Elizabeth Nordborg[23], Haner Direskeneli[11], Sibel Z. Aydin[11], Colin Pease[20], Khalid Ahmed[13], Mehrdad Mazlumzadeh[7], Andy Abril[5], Neil Gonter[21], Hilal Maradit-Kremers[3], Cynthia S. Crowson[3], Bhaskar Dasgupta[14] and Eric L. Matteson[6]. [1]3rd Rheumatology Department, National Institute of Rheumatology and Physiotherapy, Budapest, [2]Center for Diagnosis Imaging, Hospital Clínic, Montserrat del Amo, Barcelona, Spain, [3]Department of Health Sciences Research, Mayo Clinic, Rochester, MN, [4]Department of Internal Medicine I, Medical University Innsbruck, Innsbruck, Austria, [5]Department of Internal Medicine, Division of Rheumatology, Mayo Clinic, Jacksonville, FL, [6]Department of Internal Medicine, Division of Rheumatology, Mayo Clinic, Rochester, MN, [7]Department of Internal Medicine, Division of Rheumatology, Mayo Clinic, Scottsdale, AZ, [8]Department of Internal Medicine, General Hospital of the Elisabethinen, Klagenfurt, Austria, [9]Department of Internal Medicine, University of Genova, Genova, Italy, [10]Department of Rheumatology, Arcispedale S. Maria Nuova, Reggio Emilia, Italy, [11]Department of Rheumatology, Marmara University Medical School, Istanbul, Turkey, [12]Department of Rheumatology, Medical University, Graz, Graz, Austria, [13]Department of Rheumatology, Princess Alexandra Hospital, Harlow, United Kingdom, [14]Department of Rheumatology, Southend University Hospital, Essex, United Kingdom, [15]Department of Systemic Autoimmune Hospital Clinic Provincial, Barcelona, Spain, [16]Deptartment of Internal Medicine and Rheumatology, WIM CSK MON, Warszawa, Poland, [17]Immanuel Krankenhaus Berlin: Medical Center for Rheumatology Berlin-Buch Berlin, Berlin, Germany, [18]National Institute of Rheumatology and Physiotherapy, Budapest, Hungary, [19]Radiology Department, National Institute of Rheumatology and Physiotherapy, Budapest, Hungary, [20]Rheumatology and Rehabilitation Research Unit, University of Leeds, Leeds, UK, [21]Rheumatology Associates of North Jersey, Teaneck, NJ, [22]Rheumatology Unit, Clinica e Terapia Medica Department, Sapienza Università di Roma, Policlinico Umberto I, Rome, Italy, [23]Sahlgren University Hospital, Department of Rheumatology, Göteborg, Sweden

Objective: To evaluate the performance of musculoskeletal ultrasound (US) in the initial assessment and follow up of patients over the age of 50 years presenting with recent onset bilateral shoulder pain.

Methods: US of shoulder and hips was performed in 89 patients with an initial diagnosis of new onset PMR, 117 control subjects with newly diagnosed conditions mimicking PMR presenting with recent onset of bilateral shoulder pain (includes 37 subjects with new onset rheumatoid arthritis (RA), 30 subjects with other shoulder conditions) and 21 controls without shoulder conditions. All subjects were ≥50 years of age. US evaluations were performed using a standardized protocol developed as part of a 6-month prospective study and included assessment of subdeltoid bursitis, biceps tenosynovitis, glenohumeral or hip synovitis and trochanteric bursitis. A preceding training and standardization exercise of US operators at different sites in the study demonstrated very good intercenter comparability of results.

Results: Patients with PMR were more likely to have abnormal US findings in the shoulder (particularly subdeltoid bursitis and biceps tenosynovitis), and somewhat more likely to have abnormal findings in the hips than control subjects as a group. PMR could not be distinguished from RA on the basis of US, but could be distinguished from non-RA shoulder conditions and subjects without shoulder conditions.

Ultrasound Findings	PMR (N = 89)	Controls with shoulder conditions (N = 117)	RA with shoulder involvement (N = 37)	Non-RA Shoulder Condition (N = 30)	Controls without shoulder conditions (N = 21)
at least ONE shoulder with subdeltoid bursitis, biceps teno-synovitis or glenohumeral synovitis	85%	72%*	84%	63%**	19%**
BOTH shoulders with subdeltoid bursitis, biceps teno-synovitis or glenohumeral synovitis	62%	49%	73%	27%**	0%**
at least ONE shoulder with subdeltoid bursitis or biceps tenosynovitis	84%	67%**	76%	57%**	19%**
BOTH shoulders with subdeltoid bursitis or biceps tenosynovitis	60%	43%*	60%	23%**	0%**
at least ONE hip with synovitis or trochanteric bursitis	35%	20%*	23%	9%*	0%**
BOTH hips with synovitis or trochanteric bursitis	17%	9%	5%	3%	0%*
at least ONE shoulder and ONE hip with findings as above	33%	15%**	19%	7%**	0%**
BOTH shoulder and BOTH hips with findings as above	10%	8%	5%	3%	0%

*$p < 0.05$; **$p < 0.01$ compared to PMR

Conclusions: In this largest and first multicenter study of US in PMR, most subjects with PMR have abnormal findings on shoulder US. US had limited value in distinguishing PMR from RA, but had value in discriminating PMR from other conditions associated with shoulder pain. US of the shoulders and hips may have added value for diagnosis of PMR.

Disclosure: W. A. Schmidt: None; **M. A. Cimmino:** None; **P. Mandl:** None; **P. V. Balint:** None; **A. Iagnocco:** None; **R. J. Wakefield:** None; **M. Schirmer:** None; **C. Salvarani:** None; **A. Bachta:** None; **M. C. Cid:** None; **C. Duftner:** None; **C. Dejaco:** None; **G. Espígol-Frigolé:** None; **P. Macchioni:** None; **Z. Schmidt:** None; **N. P. Kaposi:** None; **G. Poór:** None; **E. Nordborg:** None; **H. Direskeneli:** None; **S. Z. Aydin:** None; **C. Pease:** None; **K. Ahmed:** None; **M. Mazlumzadeh:** None; **A. Abril:** None; **N. Gonter:** None; **H. Maradit-Kremers:** None; **C. S. Crowson:** None; **B. Dasgupta:** None; **E. L. Matteson:** None.

ACR Poster Session C
Infection-Related Rheumatic Disease Poster
Wednesday, November 10, 2010, 9:00 AM–6:00 PM

1638

A Comparison of the Presentation, Synovial Fluid Analysis, and Treatment Course in Children and Adults with Lyme Arthritis. Brian E. Daikh[4], Fred Emerson[3], F. Lee Lucas[2], Robert Smith[1] and Carol McCarthy[1]. [1]Maine Medical Center, [2]Maine Medical Center Research Institute, [3]Maine Medical Partners, [4]Rheumatology Associates PC, Portland, ME

In the northeastern United States, Lyme arthritis is an increasingly recognized form of monoarticular inflammatory arthritis in both the pediatric

and adult population. We have observed that some cases of pediatric Lyme arthritis may be confused with septic arthritis leading to unnecessary hospitalization and surgical drainage. We wondered how frequently this occurs in children and whether there are differences between the pediatric and adult population in the presentation and management of Lyme arthritis.

Methods: Charts of pediatric and adult patients evaluated for Lyme arthritis by rheumatologists and pediatric infectious disease specialists in Portland, ME between January 2002 and July 2008 were reviewed. Patients included for analysis had documented synovitis and positive Lyme serology. Data on clinical presentation, synovial fluid and peripheral blood results, treatment, and clinical course were extracted and subjected to statistical analysis.

Results: 29 adults and 50 children met inclusion criteria and were studied. Children were more likely than adults to present acutely ($p = 0.01$). They were less likely to be weight bearing ($p = 0.04$), had a higher mean synovial fluid WBC count ($p = 0.00004$), were more likely to be hospitalized ($p = 0.02$) and were more likely to have a suspected septic arthritis ($p = 0.02$), although there was no statistical difference between the two groups with respect to surgical intervention. In contrast, adults received more oral antibiotic courses ($p = 0.006$). They were less likely to have normal function within four weeks of initiating antibiotic treatment ($p = 0.0002$), were more likely to have intravenous antibiotics in subsequent treatment courses ($p = 0.01$), and were more likely to be diagnosed with a persistent arthritis ($p = 0.0007$).

Conclusions: The presentation of Lyme arthritis in children and adults in our study population differed in the acuity of presentation and subsequent management. Children were more frequently hospitalized for suspected septic arthritis whereas adults were more often managed in the outpatient setting. Yet children tended to have more prompt resolution of their synovitis and received less treatment overall. The clinical spectrum of Lyme arthritis is variable, ranging from chronic indolent synovitis to acute monoarticular arthritis mimicking septic arthritis. In the appropriate geographic and clinical setting, Lyme arthritis should be considered in children presenting with acute monoarticular arthritis. Considering the diagnosis early may prevent hospitalization and needless intervention including surgical drainage.

Disclosure: B. E. Daikh: None; **F. Emerson:** None; **F. L. Lucas:** NCI, 9, NICHD, 9; **R. Smith:** None; **C. McCarthy:** None.

1639

Autoantibodies to a Novel Cytoplasmic Rod/Ring Structure Target CTP/GTP Synthetic Pathway in HCV Infection after Interferon/ Ribavirin Therapy. Wendy C. Carcamo[2], Angela Ceribelli[3], Jason Y. F Chan[3], Westley H. Reeves[2], Giovanni Covini, Carlos A. Von Muhlen[1], Liu Chen[3], Minoru Satoh[2] and Edward K. L. Chan[2]. [1]Metanalysis, Porto Alegre, Brazil, [2]University of Florida, Gainesville, FL, [3]University of Florida

Purpose: Autoantibodies (aab) can be important disease markers and basic research tools in molecular and cell biology. Cytoplasmic antigenic structures identified by ANA screening consisting of rods and rings (RR) are novel subcellular structures. The current aim is to identify clinical occurrences associated with RR aab, elucidate the antigenic targets and their biologic function.

Methods: Sera collected from multiple clinical centers were analyzed by HEp-2 slides as well as other mammalian cell lines for the presence of anti-RR. Positive samples were then analyzed by immunoprecipitation of ^{35}S-labeled K562 cell extracts. Identity of candidate antigens associated with RR was validated by co-staining with established specific antibodies.

Results: Anti-RR recognized cytoplasmic rods of 3–10μm in length and rings with ~2–5μm in diameter in HEp-2 cells, distinct from all known aab reported to date. A total of 80 anti-RR samples were identified, clinically linked to Hepatitis C virus (HCV), mostly after interferon-alpha/ribavirin (IFN/R) therapy. Clinical data were available from 23 Italian anti-RR+ patients: 15 HCV+, 6 HCV-, and 2 unknown. Prevalence of anti-RR did not correlate with specific HCV genotypes: *Type 1* (6/15), *2a* (3/15), *3* (1/15), and *4* (1/15). 14/15 HCV+ were treated with IFN/R therapy, indicating a strong link of RR aab to this therapy. 75% (9/12) of HCV with anti-RR had no response to IFN/R therapy, suggesting anti-RR may be associated with poor response. The 6 HCV(−)RR+ patients had no common diagnosis. However, prevalence of anti-RR in general hepatic disease population was low (3.5%, ~35/1000), indicating that HCV infection alone seldom induces anti-RR aab. In an autoimmune disease center setting, prevalence of anti-RR was also very low: only 2 SLE patients were identified among >2,000 in database. Analysis of the 2 SLE patients over 3-yr span was available. Interestingly, patient #1 had HCV(*3a*) and anti-RR was detected within 4 mo after IFN/R treatment. This patient was unresponsive and treated again with IFN/R after 6 mo. Liver function then normalized and anti-RR disappeared. Patient #2 had anti-Sm/RNP, anti-phospholipid aab with lupus nephritis, but was apparently HCV- and had stable anti-RR for at least 2 yrs. About a third of anti-RR+ sera immunoprecipitated 55kDa doublets. Candidate 55kDa antigens cytosine triphosphate synthase (CTPS1) and inosine monophosphate dehydrogenase 2 (IMPDH2) were identified to be highly enriched in RR. Multiple inhibitors of these enzymes were shown to be sensitive inducers of RR formation in all mammalian cell types analyzed.

Conclusion: CTPS1 and IMPDH2 are key enzymes in CTP and GTP synthesis respectively, inhibitors to which were demonstrated to induce RR formation. Development of anti-RR is most common in HCV+ patients with IFN/R treatment, but anti-RR may be found in HCV- patients. Ribavirin is a sensitive inhibitor of IMPDH2 enzymatic activity, may thus lead to aberrant RR formation, and trigger aab production during HCV treatment. Anti-RR production in other systemic diseases remains unclear.

Disclosure: W. C. Carcamo: None; **A. Ceribelli:** None; **J. Y. F Chan:** None; **W. H. Reeves:** None; **G. Covini:** None; **C. A. Von Muhlen:** None; **L. Chen:** None; **M. Satoh:** None; **E. K. L. Chan:** None.

1640

Chloroquine (CQN) Is Not Superior to Meloxicam (MCAM) in the Treatment of Early Persistent 'Musculoskeletal Pain and Polyarthralgias' (MSK-P) Following Chikungunya (CHIKV): A Non Commercial Investigator Initiated Community Based Controlled Drug Study. Arvind Chopra[2], Manjit Saluja[3] and Anuradha Venugopalan[1]. [1]Center for Rheumatic Diseases, [2]Center for Rheumatic Diseases, Pune, India, [3]Center for Rheumatic Diseases

CHIKV is predominantly a self limiting short duration febrile severe arthralgia illness.Though experimentally demonstrated (Sourisseau. PLoS Pathog 2007; 3(6):e89: 804), therapeutic role for CQN is flimsy. A CQN trial (CuraChik: NCT00391313) was abandoned. CQN was used rampantly in the recent India CHIKV epidemic(Chopra. Arthritis Rheum 2008; 58(9): 2921). We carried out an exploratory study during the epidemic.

Methods: 509 cases of CHIKV were identified in a survey of 1450 population in village Bavi (Sholapur, West India). Acute cases received symptomatic measures. 70 consenting patients (62 women, median age 50 years) with persistent MSK-P (minimal duration 4 weeks, active painVAS > 40 mm) and seropositive anti-CHIKV IgM/IgG antibody were enrolled into randomized, single blind (doctor) parallel efficacy two arm (CQN=38, MCAM=32) trial of 24 weeks duration; CQN phosphate (250 mg od) and meloxicam (MCAM, 7.5 mg od). Rescue analgesic(paracetamol) was monitored. MSK-P could not be further classified. 43 patients showed minimal few site synovitis/ tenosynovitis. We visited homes monthly, to complete trial procedures/assessments. Pain VAS (primary efficacy) and ACR efficacy measures (+ Indian version HAQ) were recorded. Besides routine laboratory investigations, selected cytokines [IL-6, γ-Interferon, TNF- α, CXCL-10/IP-10, and IL-13) were assayed and geometric mean (Fig 2) computed; pre-epidemic controls were used. XRays were not taken. An intention to treat analysis (last observation carried forward, ANOVA) was completed;significant $p < 0.05$ with CI (95% confidence interval). At baseline, the groups matched well.

Results: The mean change from baseline to completion for efficacy and cytokines did not differ significantly between the groups [Difference for pain VAS: CI −0.8, 1.3]. Paracetamol consumption was almost similar.

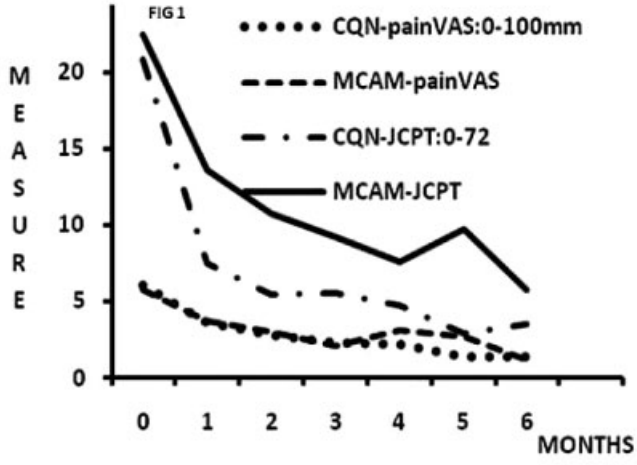


Figure 1.

Fig. 1 shows mean painVAS and pain/tender joint count. Amongst completers, beyond 3 months study, pain was aymptomatic, mild and moderately severe in 37%, 52% and 11% trial patients respectively; corresponding 42%, 42% & 15% for CQN. Seven patients withdrew but none due to AE. Five patients reported mild AE (usually dyspepsia; none skin/eye).

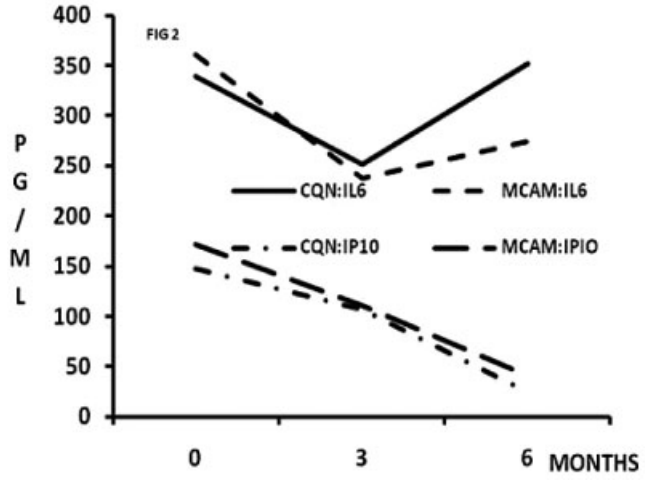


Figure 2.

Though decreased from baseline, cytokines remained elevated (above control) at 24 weeks endpoint.

Conclusion: In this first ever truly community based drug intervention trial, CQN did not offer any therapeutic advantage over symptomatic NSAID in the long term treatment of early persistent MSK-P following CHIKV. Despite clinical relief, cytokines (especially IL-6) remained elevated and this may implicate long term prognosis.

Disclosure: A. Chopra: None; **M. Saluja:** None; **A. Venugopalan:** None.

1641

Clinical Features of Acute Human Parvovirus B19 in Adults: What We Could Learn from It? Hideto Oshikawa[1], Makiko Yamamoto[2], Akira Jibatake[2], Kiyoharu Muranaka[2], Kazuki Yoshida[2], Masako Utsunomiya[2], Tatsuo Kobayashi[2], Mitsumasa Kishimoto[3] and Kazuo Matsui[2]. [1]Department of Rheumatology, Kameda Medical Center, Kamogawa City, Chiba, Japan, [2]Department of Rheumatology, Kameda Medical Center, [3]St Luke's International Hospital, Japan

Background: Human parvovirus (HPV) B19 infection in adults often mimics rheumatic disease such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA).

Purpose: To investigate the clinical features of acute HPV B19 infection in adults and examine the rate of patients who fulfill the classification criteria for SLE or RA.

Methods: Retrospective chart review of adult patients with newly-diagnosed acute HPV B19 infection from April 2006 to April 2010 was performed in a community-based hospital in Japan. The diagnosis was made with the positive serum anti-HPV B19 IgM antibody.

Results: Of the thirty-five patients diagnosed as acute HPV B19 infection, 24 patients (68.5%) were female and the mean age was 38.6 years. Nearly half of the patients (48.5%) had a history of recent sick contact with people who had a clinical manifestation of viral infection. The predominant signs and symptoms were: arthralgia/arthritis (85.7%), skin rash (60%), edema (54.2%), fever (51.4%), and lymphadenopathy (31.4%). Seventeen patients (48.5%) were diagnosed during the spring and 9 patients (25.7%) in the summer.

The involved joints were the hand (72.7%), followed by knee (63.6%), wrist (54.5%), elbow (54.5%), and ankle (45.4%). The most frequent type of arthritis was polyarthritis (81.8%), followed by oligoarthritis (18.2%). Monoarthritis was not seen in our study.

The following abnormal laboratory findings were observed: positive anti-nuclear antibody (ANA) (95.2%), lymphocytopenia (81.2%), elevated lactate dehydrogenase (68.7%), hypocomplementemia (50%), and anemia (21.2%). Rheumatoid factor and anti-CCP antibody were not detected in patients who were tested (22 and 10 patients).

Four patients (11.4%) fulfilled the 1997 revised ACR SLE Criteria and 9 patients (25.7%) fulfilled the preliminary 2010 SLICC/ACR SLE Criteria. Of 11 patients with physician identified arthritis, none fulfilled the 1987 ACR RA Criteria, and 4 patients (36.3%) fulfilled the 2010 ACR/EULAR RA Criteria. Three patients fulfilled the both new SLE and RA criteria.

During the mean follow-up of 5.6 weeks (range 0–42), the mean duration of arthritis was 22 days (range 11–36). As for treatment, NSAIDs were used in 11 patients (31.4%), and acetaminophen in 10 patients (28.5%).

Conclusion: HPV B19 infection in adults, often present with acute polyarthritis and skin rash accompanied with lymphocytopenia, hypocomplementemia, and positive ANA. About one-third of adult patients with acute HPV B19 infection fulfill the criteria for SLE or RA, or both. We should consider the possibility of HPV B19 infection in the differential diagnosis of SLE or early onset RA.

Disclosure: H. Oshikawa: None; **M. Yamamoto:** None; **A. Jibatake:** None; **K. Muranaka:** None; **K. Yoshida:** None; **M. Utsunomiya:** None; **T. Kobayashi:** None; **M. Kishimoto:** Abbott Immunology Pharmaceuticals, 9, Bristol-Myers Squibb, 9, Chugai, 9, Eisai, 9, Mitsubishi-Tanabe Pharma, 9, Takeda Pharmaceutical Co Ltd, 9, Wyeth Pharmaceuticals, 9; **K. Matsui:** Abbott Immunology Pharmaceuticals, 9, Chugai, 9, Eisai, 9, Mitsubishi-Tanabe Pharma, 9, Takeda Pharmaceutical Co Ltd, 9, Wyeth Pharmaceuticals, 9.

1642

Cytokines in Chikungunya (CHIKV): Storm in a Teacup or Winds before the Storm. Arvind Chopra[2] and Anuradha Venugopalan[1]. [1]Center for Rheumatic Disease, Pune, India, [2]Center for Rheumatic Diseases, Pune, India

CHIKV is an acute severe (polyarthralgias) self limiting arboviral illness. 10% cases develop chronic RMSK. We witnessed a wide spectrum of inflammatory arthritis following CHIKV in our referral practise (Chopra. Arthritis Rheum 2008;58(9):2921). During the epidemic (2006), we completed a cross section house- house 1192 rural population (West India) survey in 10 weeks and identified 509 clinical cases (86% symptomatic);225 cases (81% symptomatic) consented blood investigations and are the basis of current report.

Methods: Clinical, diagnosis was substantiated by serology (49% IgM and 62% IgG CHIKV antibodies; immunochromatographic and IIF). Persistent RMSK cases followed upto 18–21 months. Lab investigations (inlcuding RF, CRP, ANA, CCP) repeated at predetermined timepoints: malaria and dengue excluded. None showed throbocytopenia. IL-6 (51.12 pg/ml), IL-13 (181.44 pg/ml), TNF-α (32.29 pg/ml), IFN-γ (3.12 pg/ml), and CXCL10/ IP-10 (3.16 pg/ml) assayed by standard ELISA; geometric means from healthy control (pre-epidemic) shown in parenthesis.

Observations: Post onset, 65% cases recovered within one month. None died. Rest suffered from predominantly (86%) persisted non-specific polyarthralgias (NSA). Overt synovitis/ tenosynovitis was mild and uncommon. 18% and 12% cases remained symptomatic at 6 and 12 months respectively. IgM response vanished by 6 months while IgG rising titer was demonstrated till study completion. Cytokine profile shown in the figures.

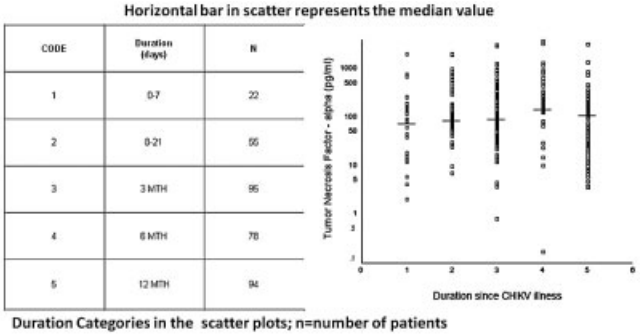


Figure 1.

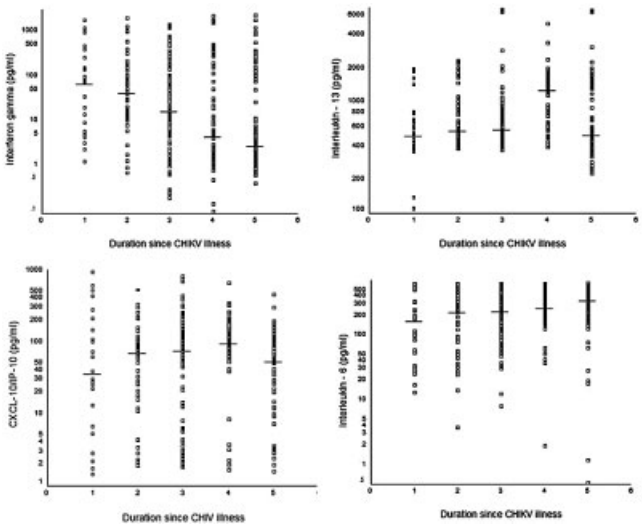


Figure 2.

The cytokine upsurge persisted irrespective of symptom resolution or the type of RMSK (NSA/OA/Inflammatory/soft tissue rheumatism). An early robust IFN -γ response was often associated with early resolution. High IL-13 was often evident in patients with chronic RMSK. Though conjointly elevated in early illness, a disconnect was observed between IL-6 (remained high) and C-Reactive Protein (low levels) during follow up. The overall seropositivity of autoantibodies was low (<5%).

Conclusions: This daunting community study of CHIKV epidemic demonstrates an intense proinflammatory cytokine milieu during early and persistent phase (RMSK) despite an overall benign clinical profile. It may be linked with persistence of RMSK. We continue to follow this story and hope to unravel the long term implication of this intriguing arbovirus.

Disclosure: A. Chopra: None; **A. Venugopalan:** None.

1643

Geographic Distribution of Endemic Fungal Infections among Older Americans. John W. Baddley[3], Kevin L. Winthrop[1], Nivedita M. Patkar[3], Elizabeth Delzell[4], Fenglong Xie[4], Lang Chen[4] and Jeffrey R. Curtis[2]. [1]Oregon Health Sciences University, [2]University of Alabama-Birmingham, Birmingham, AL, [3]University of Alabama at Birmingham, Birmingham, AL, [4]University of Alabama at Birmingham, Birmingham, AL

Background: Histoplasmosis (histo), blastomycosis (blasto) and coccidioidomycosis (cocci) are major endemic fungal infections in the U.S. and have been associated with use of biologics for arthritis. Data regarding the epidemiology and geographic distribution of endemic fungal infections in older adults are limited. Identifying geographic areas with a relatively high incidence of endemic fungal infection may impact diagnostic or prevention measures in older adults receiving biologics.

Methods: We evaluated a 5% sample of national Medicare data for years 1999–2008. Fungal infections were identified by ICD-9 codes (histo, 115.x; blasto, 116.0; cocci, 114.x). A case required one inpatient claim or at least two outpatient claims at least 7 days apart but within 90 days. Co-morbidities were identified by ICD-9 codes and defined as one physician claim within 6-months prior to the index case date. We calculated national, regional and state-based incidence rates (per 100,000 person-years) and determined mortality 90-days post diagnosis date.

Results: Five-hundred fifteen cases (241 histo; 218 cocci; 56 blasto) were identified. Mean age was 77.7 years and 53.8% were male. Regional variation was evident (Figures 1, 2), with histo and blasto incidence higher in southern and midwestern states; and cocci incidence higher in the Southwest US. Of all histo cases, 3.8% had an underlying diagnosis of rheumatoid arthritis (RA); 5.2% of cocci cases had underlying RA. Ninety-day mortality was highest (12.5%) in histo patients.

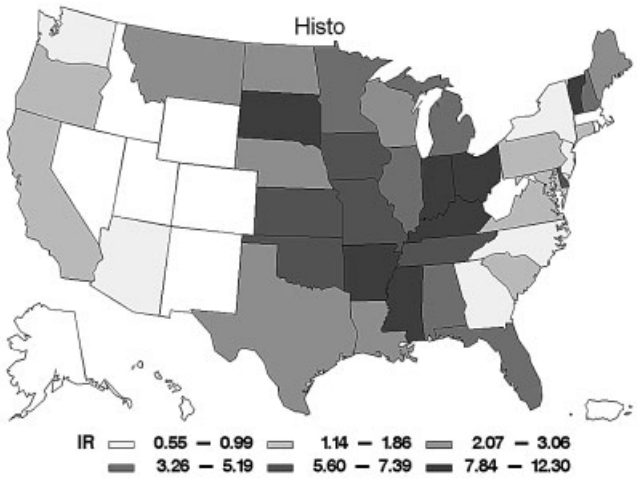


Figure 1. Geographic distribution of histo (rates per 100,000 person years).

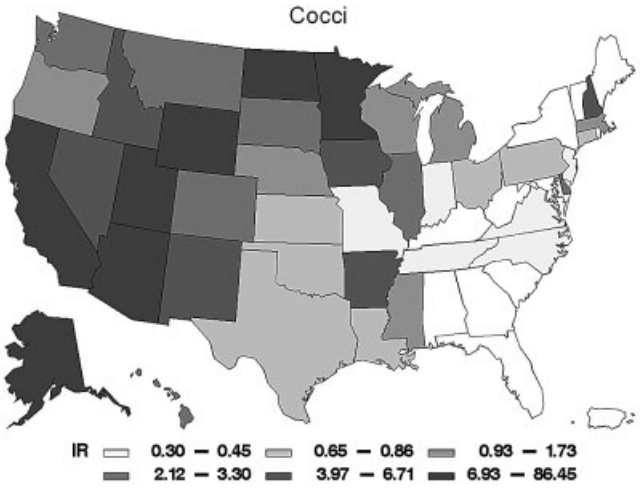


Figure 2. Geographic distribution of cocci (rates per 100,000 person years).

Conclusion: Histoplasmosis is the most common endemic fungal infection among older Americans. Geographic distribution for these mycoses is evident; however, it is important to note that cases occur outside of endemic areas. Histo and blasto incidence rates were higher in southern and midwestern states; and cocci incidence was higher in the Southwest US. Knowledge of areas of increased risk may impact diagnostic or prevention measures in older adults with inflammatory conditions and those receiving biologics.

Disclosure: J. W. Baddley: None; **K. L. Winthrop:** None; **N. M. Patkar:** None; **E. Delzell:** None; **F. Xie:** None; **L. Chen:** None; **J. R. Curtis:** None.

1644

Identification of *Borrelia Burgdorferi* in Brazil: The Etiologic Agent of Brazilian Lyme Disease-Like Syndrome (Baggio-Yoshinari Syndrome). Elenice Mantovani, Roberta G. Marangoni, Giancarla Gauditano, Virgínia L. N. Bonoldi and Natalino H. Yoshinari. Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo

Background: Baggio-Yoshinari Syndrome (BYS) is a new tick-borne infection, similar to Lyme Disease (LD) described in the northern hemisphere, except for essential differences in epidemiological, clinical and laboratory findings. The difficulty in identifying the BYS causative agent has delayed the dissemination of knowledge about this emerging zoonosis. The purpose of this study was identify the etiologic agent of BYS using a conserved gene that synthesizes the flagellar hook (flgE) of *Borrelia burgdorferi* sensu lato by molecular typing method based on Polymerase Chain Reaction (PCR).

Methods: Eight patients fulfilling the BYS diagnostic criteria were selected from November 2008 to October 2009. The patients had to present erythema migrans and positive epidemiologic history. Thirty healthy individuals, without history of tick bite or risk areas exposure, were included in the control group. The blood samples were collected and stored in −20°C. The DNA was extracted by commercial Kits. The PCR assay was performed targeting the gene flgE followed by sequence analysis.

Results: PCR targeting the gene flgE, which amplifies a fragment of ~470pb, showed positivity in 4 samples (50%). Sequences disclosed 99% of homology to *B. burgdorferi* flagellar hook protein (flgE) gene (L43849). All samples of the control group were negative for the primers used in this study. Partial sequences (flgE 470) of *Borrelia burgdorferi* flagellar hook protein generated in this study were deposited into GenBank and assigned nucleotide accession no. HM245929.

Conclusions: By the first time, we identified *B. burgdorferi* in South America and possibly in southern hemisphere. We also conclude that spirochete *B. burgdorferi* can cause two different clinical entities, Lyme disease in United States of America and Eurasia and Baggio-Yoshinari Syndrome in Brazil.

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1645

Prevalence, Impact and Risk Factors for Musculoskeletal Pain among HIV Infected Adults: An Epidemiologic Study. Karen Walker-Bone[1], Edwina Lawson[2], Duncan Churchill[2], Yvonne Gilleece[2], Martin Fisher[2] and Caroline Sabin[3]. [1]Brighton & Sussex Medical School, Brighton, United Kingdom, [2]Brighton & Sussex University Hospitals NHS Trust, [3]University College, London

Background: HIV is a global pandemic. Since the advent of antiretroviral therapies (HAART), mortality has been dramatically reduced in the western world but HIV-infected adults are living longer to acquire comorbidities. This cross-sectional epidemiologic study investigated the prevalence of musculoskeletal pain among a large cohort of HIV-infected adults.

Methods: Outpatient attendees at an HIV Unit in the UK were surveyed over a 6-month period. A questionnaire enquiring about demography, regional and widespread pain, symptoms of musculoskeletal disease (e.g. pain, swelling, rashes, sicca symptoms, fracture) was administered by trained nurses.

Results: In total 1050 HIV-infected adults were approached from whom 859 (82%) useable replies were received. 90% of the respondents were male, mean age 42 years, mean duration HIV infection 6 years. 76% were current users of HAART. In total, 539 (63%) reported pain lasting > 1 day in past month; 431 reported chronic musculoskeletal pain (> 3 months). The mean duration of chronic pain was 4.5 years. Pain was significantly increased in older age groups ($p=0.002$). Women reported pain more frequently than men throughout the age range, had higher mean pain scores ($p=0.022$) and were significantly more likely to take painkillers most days ($p<0.0001$). HIV patients with pain were significantly less likely to be working ($p=0.0001$). Back, shoulder and neck were the most common sites of regional pain. Current users of ARVs were significantly more likely to report pain in the past month, swollen joints and use of analgesics and were more disabled. Symptomatic HIV patients (stage 2 and 3) were significantly more likely to report pain and disability than asymptomatic (stage 1). In mutivariate analyses, significant predictors of pain were: age, duration of HIV infection and use of protease inhibitors.

Conclusions: Musculoskeletal pain is common amongst HIV-infected adults, particularly women. As in uninfected patients, psychosocial factors are importantly associated but so are HIV factors including duration of infection and exposure to Protease Inhibitors. Musculoskeletal pain impacts significantly in this population causing disability and sickness absence and reduced quality of life.

Disclosure: K. Walker-Bone: None; **E. Lawson:** None; **D. Churchill:** None; **Y. Gilleece:** None; **M. Fisher:** None; **C. Sabin:** None.

1646

Surrogate Markers of B-Cell Non-Hodgkin Lymphoma in Patients with Hepatitis C Virus-Related Cryoglobulinemia Vasculitis. Guillaume Geri[2], Benjamin Terrier[2], Oren Semoun[1], David Saadoun[2], Damien Sène[2], Hélène Merle-Beral[2], Frédéric Charlotte[2], Lucile Musset[2], Mathieu Resche-Rigon[1] and Patrice Cacoub[2]. [1]INSERM URMS 717, Paris 7, Paris, France, [2]Pitié-Salpetrière Hospital, Paris, France

Background: Hepatitis C virus (HCV) is associated with mixed cryoglobulinemia (MC) vasculitis and B-cell non-Hodgkin lymphoma (B-NHL), with a risk for B-NHL 35-fold higher in HCV-MC patients than the general population. However, no surrogate markers associated with the presence of B-NHL are available in HCV-MC vasculitis patients in clinical daily practice.

Methods: 104 HCV-MC vasculitis patients (including 20 with B-NHL) were included. The main clinical and biological markers associated with the presence of B-NHL were evaluated.

Results: Main epidemiological and virologic features were similar between patients with and without B-NHL. Patients with B-NHL compared to those without showed higher rates of poor general status (40 vs 16.7%; $p=0.032$), purpura (90 vs 66.7%; $p=0.05$), renal involvement (50 vs 28.6%; $p=0.11$), and cardiac involvement (15 vs 0%; $p=0.0006$). Patients with B-NHL showed higher median cryoglobulin level (1.44 vs 0.67 g/L; $p=0.0004$), and lower median C4 (0.025 vs 0.06 g/L; $p=0.001$) and gammaglobulin levels (5.3 vs 13.3 g/L; $p<0.0001$) than patients without B-NHL. Free light chain kappa/lambda ratio was more frequently abnormal in patients with than those without B-NHL (64.3 vs 33.3%, $p=0.10$). In multivariate analysis, only gammaglobulin level was associated with the presence of B-NHL [OR 0.77 (95% CI −0.44; −0.13), $p=0.0006$]. Using receiving operating characteristics curves, the optimal cut-off value for gammaglobulin level was 9 g/L, with sensitivity, specificity, positive and negative predictive values for the presence of B-NHL of 75, 82, 50 and 93%, respectively.

Conclusion: In HCV-MC patients, low gammaglobulin level (< 9g/L) is strongly associated with the presence of B-NHL.

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1647

The Diagnosis of Reactive Arthritis in the Real World and Factors That Might Contribute to Its Under/Misdiagnosis. Jenny Lin[2], Anjali G. Shetty[2] and John D. Carter[1]. [1]Univ of South Florida, Tampa, FL, [2]University of South Florida

Purpose: Epidemiological data indicate that reactive arthritis (ReA) is under/misdiagnosed. Most epidemiologic studies demonstrate that ReA is the second most prevalent type of spondyloarthritis (SpA) with one study suggesting it is the most common. Other data demonstrate that the incidence of ReA should rival that of rheumatoid arthritis. A breadth of clinical experience, however, suggests that rheumatoid arthritis (RA) and other types of SpA are diagnosed far more often than ReA. The purpose of this study was to see how often rheumatologists diagnose ReA and determine factors that might contribute to this under/misdiagnosis.

Methods: We designed an internet survey that was sent to rheumatologists worldwide. The aims of this 26 question internet survey were twofold: to determine how often practicing rheumatologists diagnose ReA compared to other types of SpA and RA, and to uncover factors that might lead to this under/misdiagnosis. The survey was sent out to random rheumatologists who are registered with the American College of Rheumatology.

Results: The survey was delivered to 3,200 rheumatologists and 377 replied (11.8% response rate). Of the rheumatologists who replied 257/377 (68.2%) were male, 289/377 (76.7%) spend at least half there time in clinical care, 271/377 (71.9%) see at least 100 patients per month, 300/377 (79.6%) have been in clinical practice longer than 5 years since completion of their fellowship, and 256/377 (67.9%) practice in the U.S. In adult patients with new-onset diagnoses (disease duration <6 months), RA was the most common diagnosis followed by psoriatic arthritis (PsA), ankylosing spondylitis (AS), undifferentiated spondyloarthritis (uSpA), ReA, and inflammatory bowel disease related SpA; in patients with a disease duration of > 6 months, the order in decreasing frequency was RA followed by PsA, AS, uSpA, IBD related SpA, and ReA. PsA sine psoriasis was diagnosed only slightly less often than ReA in patients with disease duration of <6 months and at a nearly identical rate to ReA in patients >6 months disease duration. RA patients are more likely to have a monoarthritis or oligoarthritis if they are seronegative. Patients with inflammatory arthritis are queried about the possibility of preceding sexually transmitted diseases and dysentery, but they are more likely to be asked about the latter. Keratoderma blennorrhagicum is rarely diagnosed with 283/377 (75.1%) of respondents stating that they diagnose this in 0–10% of ReA patients; yet palmoplantarpustular psoriasis with arthritis is diagnosed nearly as often as ReA with an average of 4.4 vs. 6.13 cases per year respectively. Radiographic and advanced imaging work-up performed for ReA is the same as other types of SpA. There does not appear to be an

overreliance on the HLA-B27 antigen or the complete triad of symptoms to make the diagnosis of ReA.

Conclusion: Rheumatologists diagnose RA far more often than any type of SpA. ReA, specifically, is the second least commonly diagnosed type of SpA in acute patients and the most infrequent diagnosis in those with chronic SpA. ReA patients could be misdiagnosed as seronegative RA, PsA sine psoriasis, or palmoplantarpustular psoriasis with arthritis.

Disclosure: J. Lin: None; **A. G. Shetty:** None; **J. D. Carter:** NIH, 2.

1648

The Infectious Risk of the Lower Respiratory Tract Is Increased in Patients with Rheumatic Diseases Treated by Biologic DMARDs, in Particular in Case of Pre-Existing Colonisation. Guillaume Geri, Sabrina Dadoun, Simon Paternotte, Maxime Dougados and Laure Gossec. Cochin Hospital, Paris, France

Introduction: Bronchiectasis is frequently associated (up to 30%) with chronic inflammatory rheumatic diseases and leads to repeated infectious events of the lower respiratory tract. Objective: To evaluate the risk of infectious events lower respiratory tract in patients treated with biologic disease modifying anti-rheumatic drugs for chronic inflammatory rheumatic diseases.

Methods: Monocenter, retrospective systematic study of all patients with a chronic inflammatory rheumatic disease and with concomitant bronchiectasis, seen at least twice in the department between 2000 and July 2009. An episode of infection was defined as an infection necessitating prescription of antibiotics for pulmonary purposes. Pre-existing bacteriologic colonization of the lower respiratory tract was collected at each time point. Univariate and multivariate analyses were performed to pick up predictive factors of the number of infectious respiratory events.

Results: 47 patients were included (mean age 64.1±9.1 years, 33 (70.2%) women), with a mean follow-up per patient of 4.3±3.1 years, i.e., 194 patients-years of follow-up totalizing 98 treatment periods. Rheumatoid arthritis was the main rheumatic disease (90.1%). The mean number of infectious events was 0.7±1.0 event per patient-year. The factors predicting infections were the type of treatment (biologic vs synthetic disease-modifying treatments), with an odds ratio of 8.7 (95% confidence interval: 1.7–43.4) and bronchial colonization by any germ (odds ratio 7.4, 2.0–26.8). Five patients had previous colonization (by: Pseudomonas aeruginosa (60%), Staphylococcus aureus (20%) or Haemophilus influenza (20%)).

Conclusion: Infectious risk was much higher in patients treated with biologic DMARDs than in those with non-biologic DMARDs. Bronchial colonisation was an important and independent risk factor, including if the colonization was by usual germs. Physicians should regularly monitor for colonization during biologics treatment.

Disclosure: G. Geri: None; **S. Dadoun:** None; **S. Paternotte:** None; **M. Dougados:** None; **L. Gossec:** None.

1649

Usefulness of Procalcitonin Measurement in Differentiating between Activity of Systemic Autoimmune Disease and Bacterial Infection. Olga Sleglova[3], Helena Dejmkova[4], Jana Uhrova[2] and Jaromir Belacek[1]. [1]Department of Biostatistics, 1. Medical Faculty, Charles University, Prague, Czech Republic, [2]Institute of Clinical Biochemistry, Prague, Czech Republic, Czech Republic, [3]Institute of Rheumatology, Prague, Czech Republic, [4]Institute of Rheumatology, Prague, Czech Republic

Objective: To evaluate the usefulness of testing for serum procalcitonin (PCT) in the differential diagnosis of infectious complications and acute disease exacerbation in patients with systemic autoimmune diseases.

Methods: 125 patients with systemic autoimmune diseases who were admitted to the inpatient department for suspected acute infection or acute exacerbation of their disease were prospectively tested for PCT concentrations. Concurrently, the levels of C-reactive protein (CRP), white blood cell counts (WBC), C3 and C4 complement components were established. The group of patients with infection comprised of two subgroups: with systemic and localised infection. Control group included 87 ambulatory patients with autoimmune diseases without any signs of deterioration.

Results: The serum PCT levels were significantly higher in patients with infections than in patients with an active systemic disease (PCT mean ± SEM 4.560 ± 1,513 vs. 0,254 ± 0,029, p< 0,001). The levels of CRP and white blood cell counts were also higher in patients with infections; the differences between C3 and C4 complement component values were not statistically significant. PCT serum concentrations were not elevated in any of the patients included in control group, and they were not affected by the current corticosteroids or immunosuppressive treatment. The sensitivity of the PCT test for an infectious complication (cut-off value = 0.5ng/ml) was 52.4%, specificity 94.0% and diagnostic accuracy 80.2%. The area under ROC curve for PCT was 73.21%.

Conclusion: The increased serum PCT levels demonstrate good specificity for the evidence of infection in patients with systemic diseases. The sensitivity of PCT serum values is lower and it is therefore suitable to complement the assessment with another high-sensitivity indicator, such as CRP.

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ACR Poster Session C
Miscellaneous Rheumatic and Inflammatory Diseases II
Wednesday, November 10, 2010, 9:00 AM–6:00 PM

1650

Adalimumab Therapy in 18 Patients with Severe Hidradenitis Suppurativa. Orlando Pompei Fernández[5], Ricardo Blanco Alonso[5], Ignacio Villa[4], Marcos Gonzalez López[2], Hector Fernández LLaca[1], M. Del Carmen González-Vela[3], Mario Agudo Bilbao[6], Cristina Martinez Dubois[6], Victor M. Martinez-Taboada[7], M. Enriqueta Peiro Callizo[5], Jose Luis Peña Salgredo[5], Alfonso Fernando Corrales Martinez[5] and Miguel Angel Gonzalez-Gay Mantecon[5]. [1]Department of Dermatology, Hospital Universitario Marqués de Valdecilla, Santander, Cantabria, [2]Department of Inmunology, Hospital de Liencres, Santander, Cantabria, [3]Department of Pathology, Hospital Universitario Marqués de Valdecilla, [4]Department of Rheumatology, Hospital Sierrallana, [5]Department of Rheumatology, Hospital Universitario Marqués de Valdecilla, Santander, Cantabria, Spain, [6]Department of Rheumatology, Hospital Universitario Marqués de Valdecilla, Santander, Cantabria, [7]Department of Rheumatology, Hospital Universitario Marqués de Valdecilla, Santander, Spain

Objective: Several case-reports describing successful response to TNF-α antagonists in patients with hidradenitis suppurativa (HS), especially with infliximab and etanercept, have been reported. However, most of them had a short follow-up, showed limited efficacy and/or unacceptable side effects. Our aim was to evaluate the efficacy and safety of adalimumab therapy in 18 patients with refractory HS.

Methods: All of them fulfilled the following criteria: (1) HS resistant to standard medical treatments; (2) lack of response to at least 1 systemic immunomodulating drug; (3) multifocal active HS. In all cases Adalimumab therapy (40 mg subcutaneously every-other-week) was started. If HS was not adequately controlled, adalimumab dosage was increased up to 40 mg/week. If persistent clinical remission was achieved adalimumab therapy was gradually decreased to a minimum dose of 40 mg every 3 weeks. Quality of life was assessed using the Dermatology Life Quality Index (DLQI).

Results: 18 patients (9W:9M) (mean age, 45.17±15.8 years) with severe HS (mean disease duration, 19.83 ± 17.3 years) were studied. In 6 patients HS was associated with other conditions; SLE (2 cases), rheumatoid arthritis (2 cases), idiopathic monoarthritis (1 case), and psoriasis (1 case). Five patients had initially been treated with infliximab and 1 with etanercept. All these 5 patients were switched to adalimumab due to inefficacy. At 1st month 13, 4 and 1 patient achieved high, moderate and none improvement in suppurative symptoms, respectively. The 6 patients with associated diseases also experienced improvement of these conditions. After a mean follow-up of 92 ± 88 weeks adalimumab efficacy was maintained. Adalimumab was well-tolerated. The most frequent side-effect was mild to moderate pain at injection site, and only 1 patient developed a severe facial skin reaction.

Conclusions: Adalimumab seems to be an effective and safe treatment in refractory HS. These promising results warrant the need of prospective controlled study.

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1651

Association of Langerhans Cell Histiocytosis with Erdheim-Chester Disease: How Close Monocyte/Macrophage and Dendritic Cell Lineages Are? Baptiste Hervier, Frrederic Charlotte, Olivier Hermine, Antoine Neel, Nicole Brousse, Aude Rigolet, Christian De gennes, Eric Hachulla, Xavier Girerd, Antoine Dupuy, Zahir Amoura and Julien Haroche. CHU Pitié Salpetrière, APHP, Paris, France, French Reference Center for Lupus

Objectives: Histiocytoses are a heterogeneous group of diseases that can be classified into either Langerhans cell histiocytosis (LCH) or non-Langerhans cell histiocytosis. The latter includes Erdheim-Chester disease (ECD). This study investigated the clinical association between LCH and ECD.

Methods: This retrospective study included 16 patients (10 males, 6 females, median age 41 years) treated at twelve different university hospitals between 1970 and 2010. Inclusion criteria were biopsy-proven LCH in association with two or more diagnostic signs of ECD.

Results: LCH and ECD were diagnosed simultaneously in 4/16 cases, whereas LCH preceded ECD in 12/16 cases. The median time interval was 7.5 years (range 2–22) in these cases. Major organs involved in LCH were the bones (n=12), skin (n=8) and lungs (n=3). ECD mainly affected the large vessels (n=11), bones (n=11) and retroperitoneum (n=9). Non-biopsy proven central nervous system (n=6) and pituitary gland (n=6) involvement also occurred. No specific histologic features were identified in the 65 biopsies studied, including platelet-derived growth factor receptor β expression. Between one and four lines of treatment were required in nine patients diagnosed with LCH. Nine patients were treated with interferon α-2a after the diagnosis of ECD was made. A partial improvement occurred in all assessable patients concerning ECD (n=5) and/or LCH (n=2). These 16 patients were compared with a monocentric cohort of 48 ECD patients; the only difference between the groups was a lower frequency of bone involvement in ECD patients with concomitant LCH (9/13 vs 47/48, $p<0.003$).

Conclusions: This study suggests that a pathogenic link exists between LCH and ECD. Although the mechanisms responsible for both diseases remain unknown, the present association could argue for transitions between monocyte/macrophage and dendritic cell lineages.

The patient characteristics of LCH in association with ECD were similar to those in patients with LCH alone, whereas bone involvement may have been less common in ECD when it was in association with LCH. Clinicians should be aware of this association and should consider the possibility of ECD in patients with LCH, especially in the case of treatment resistance.

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1652

Blinded Multi-Rater Evaluation of Diagnosis and Candidate Classification Criteria for Polymyalgia Rheumatica (PMR). ACR–EULAR Study Group for Development of Classification Criteria for PMR. Eric L. Matteson[5], Marco A. Cimmino[7], Hilal Maradit-Kremers[1], Carlo Salvarani[8], Michael Schirmer[3], Wolfgang A. Schmidt[13], Maria C. Cid[12], Christian Dejaco[10], Pierre Duhaut[20], Zsuzsa Schmidt[14], Annamaria Iagnocco[18], Artur Bachta[2], Carlotta Nannini[19], Fabrizio Cantini[19], Victor Martínez-Taboada[21], Haner Direskeneli[9], Sibel Z. Aydin[9], Raashid Luqmani[15], Colin Pease[16], Mehrdad Mazlumzadeh[6], Kenneth Calamia[4], Clement J. Michet[5], Andy Abril[4], Neil Gonter[17], Cynthia S. Crowson[1], Rickey Carter[1] and Bhaskar Dasgupta[11]. [1]Department of Health Sciences Research, Mayo Clinic, Rochester, MN, [2]Department of Internal Medicine and Rheumatology, WIM CSK MON, Warszawa, Poland, [3]Department of Internal Medicine I, Medical University Innsbruck, Innsbruck, Austria, [4]Department of Internal Medicine, Division of Rheumatology, Mayo Clinic, Jacksonville, FL, [5]Department of Internal Medicine, Division of Rheumatology, Mayo Clinic, Rochester, MN, [6]Department of Internal Medicine, Division of Rheumatology, Mayo Clinic, Scottsdale, AZ, [7]Department of Internal Medicine, University of Genova, Genova, Italy, [8]Department of Rheumatology, Arcispedale S. Maria Nuova, Reggio Emilia, Italy, [9]Department of Rheumatology, Marmara University Medical School, Istanbul, Turkey, [10]Department of Rheumatology, Medical University, Graz, Graz, Austria, [11]Department of Rheumatology, Southend University Hospital, Essex, United Kingdom, [12]Department of Systemic Autoimmune Hospital Clinic Provincial, Barcelona, Spain, [13]Immanuel Krankenhaus Berlin: Medical Center for Rheumatology Berlin-Buch Berlin, Berlin, Germany, [14]National Institute of Rheumatology and Physiotherapy, Budapest, Hungary, [15]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Oxford University, Oxford, UK, [16]Rheumatology and Rehabilitation Research Unit, University of Leeds, Leeds, UK, [17]Rheumatology Associates of North Jersey, Teaneck, NJ, [18]Rheumatology Unit, Clinica e Terapia Medica Department, Sapienza Università di Roma, Policlinico Umberto I, Rome, Italy, [19]Rheumatology Unit, Ospedale Misericordia e Dolce, Prato, Italy, [20]Service de Medecine Interne, Amiens, France, [21]Servicio de Reumatología, Hospital Universitario Marques de Valdecilla, Facultad de Medicina, Universidad de Cantabria, Santander, Spain

Objective: To assess multi-rater discrimination of polymyalgia rheumatica (PMR) from other conditions mimicking PMR.

Methods: A total of 23 investigators were asked to blindly rate 10 PMR cases and 20 controls derived from a large prospective study of candidate criteria for PMR. Investigators were asked to review the clinical features, examination findings (ie restricted shoulder/hip movement, synovitis), inflammatory markers (ESR/CRP), serology for RF and anti-CCP, the steroid response (categorized as rapid, complete, sustained). Each criteria was rated on a 5-point scale reflecting the degree of confidence of a PMR diagnosis (1=strongly influences diagnosis of PMR to 5=strongly influences the diagnosis was not PMR). After all criteria were rated, investigators were asked to provide a diagnosis of PMR or other condition and indicate whether they would enter such a subject in a clinical trial for PMR. To assess the diagnostic accuracy of each candidate criteria, the mean rating across all raters was taken. This composite score was then used to determine the areas under the ROC curve (AUC), denoted as the c-statistic. Patients were categorized into 3 groups based on raters' misclassification rates. Group 1: greater than 50% misclassified; Group 2: 20–50% misclassified, Group 3: less than 20% misclassified.

Results: Missclassification proportion was ≥20% in 10 patients. Factors that contributed to misclassification in Group 1 (n=3, 1 case, 2 controls) were normal ESR and/or CRP, poor or ill- sustained steroid response and RF positivity without peripheral synovitis. In Group 2 (n=7: 4 cases, 3 controls), misclassification was related to persistent synovitis, no complete/sustained steroid response, RF or CCP positivity and low baseline ESR and/or CRP. The AUC c-statistic suggested that gender, duration of symptoms, systemic symptoms such as weight loss, neck pain, limitation of movement and serum electrophoresis were unhelpful in discriminating cases from controls (c-statistic < 0.8 in all). Bilateral hip pain, morning stiffness, ESR and CRP levels (pre and especially post steroid), steroid response were good discriminators of cases from controls (c-statistic > 0.8 in all, table).

Candidate Criteria	PMR Cases M (SD)	Controls M (SD)	P value*	C-statistic	95% CI C-Statistic
Bilateral pelvic girdle aching	1.8 (1.1)	3.3 (1.1)	0.01	0.80	(0.54, 0.92)
Morning stiffness >45 min	1.7 (1.0)	3.0 (1.4)	<0.01	0.87	(0.63, 0.96)
Abnormal CRP at baseline	1.8 (0.9)	3.2 (1.4)	<0.01	0.81	(0.58, 0.92)
Abnormal ESR at 26 weeks	2.3 (1.0)	3.2 (0.8)	<0.01	0.89	(0.64, 0.97)
Abnormal CRP at 26 weeks	2.2 (0.9)	3.1 (1.1)	<0.01	0.85	(0.62, 0.94)
Rapid steroid response	2.6 (1.5)	4.6 (0.6)	<0.01	0.99	(0.90, 1.00)
Complete steroid response	2.2 (1.4)	4.5 (0.7)	<0.01	0.98	(0.84, 1.00)
Sustained steroid response	2.6 (1.4)	4.3 (0.7)	<0.01	0.99	(0.90, 1.00)

*P value from a Wilcoxon rank sum test for difference in rating scores between PMR cases and controls. Scores tested are mean score across the 23 raters, further averaged by case (n = 10) and control (n = 20).

Conclusions: The verification exercise showed the stepped diagnostic process and most candidate criteria items performed well in discriminating PMR cases from controls. However, a significant proportion of cases/controls were difficult to classify. Questions such as whether PMR may not always adequately respond to steroids and whether polymyalgic RF positive disease without peripheral synovitis can occur need further investigation.

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1653

Bone Events in Type 1 Gaucher Disease before and during Treatment. Jerome Stirnemann[2], Djazia Heraoui[1], Corine Vincent[3], Olivier Fain[2], Bruno Fantin[1], France Mentre[3] and Nadia Belmatoug[1]. [1]APHP-Referral Center of Lysosomal Diseases (RCLD), Clichy, France, [2]APHP-Referral Center of Lysosomal Diseases (RCLD), Bondy, France, [3]INSERM, Paris, France

Introduction: Gaucher disease (GD), a rare autosomal-recessive disorder, is due to a deficiency of a lysosomal enzyme (glucocerebrosidase) and is characterized by liver and spleen enlargement and severe bone complications. Enzyme replacement therapy (ERT), available since 1991 (alglucerase then imiglucerase), is the reference treatment. Bone complications generally decline after 2 years of ERT. However, no data are available on main bone events (BE) (avascular necrosis, bone infarcts, pathologic fractures) occurring during treatment. Several biomarkers (chitotriosidase, ferritin, angiotensin

converting enzyme and tartrate-resistant acid phosphatase) are elevated during GD evolution

The aim of this study was to retrospectively evaluate the frequency of bone events (BE) during 2 periods, diagnosis to first treatment and the latter to the closing date.

Methods: BE of 62 treated patients followed at Beaujon Hospital, Clichy, France, were described with Kaplan–Meier curves and linear-mixed models were used to evaluate their biomarker changes.

Results: BE occurred before treatment (54 events in 21 patients) but also during treatment (12 events in 10 patients), with respective frequencies (95% confidence interval) at 10 years of 22.4% (13.3–36.3) and 20.0% (10.2–36.9). Figure 1 represents the first BE in the 62 Gaucher-disease between diagnosis and first treatment during the first 30 years of follow-up; Figure 2 represents the first BE in these 62 patients receiving ERT between first treatment and closing date during 15 years of follow-up.

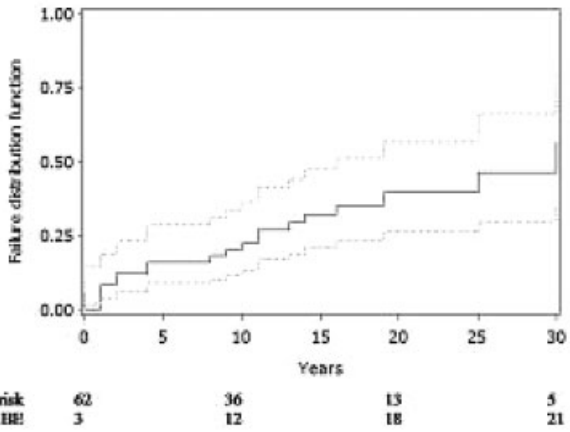

Figure 1. Bone events (BE) in the 62 Gaucher-disease patients between diagnosis and first treatment during the first 30 years of follow-up.

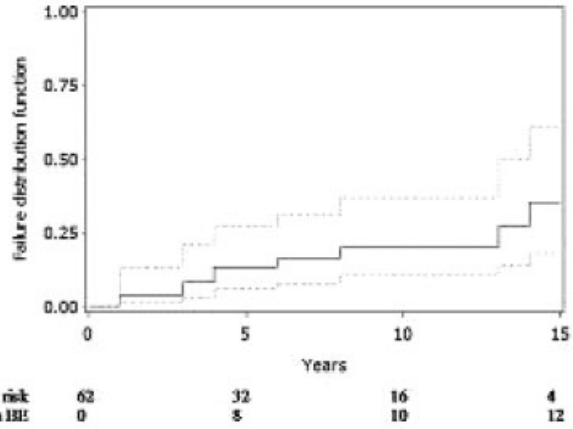

Figure 2. Bone events (BE) in the 62 Gaucher-disease patients between first treatment and closing date during 15 years of follow-up.

The 54 BE before treatment onset were [n (%)]: 28 (52%) avascular necroses, 7 (13%) bone infarcts, 12 (22%) pathologic fractures and 7 (13%) vertebral compression fractures. The 12 BE that occurred under treatment were [n (%)]: 3 (25%) avascular necroses, 4 (33%) bone infarcts with clinical bone crises and 5 (42%) pathologic fractures. The probability of suffering an BE by 10 years (95% CI) was 22.4% (13.3%-36.3%) before treatment and 20.0% (10.2%-36.9%) under ERT.

High ferritin levels and low platelet counts at treatment onset were significantly associated with BE during treatment (P=0.019 and P=0.039, respectively).

Conclusions: Bone complications could occur without but also under ERT (about 20% at 10 years). Platelet counts and ferritin levels at treatment onset at start of treatment seem to predict BE during treatment.

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1654

Development of Classification Criteria for Polymyalgia Rheumatica (PMR): Results from an International, Prospective, Multi-Center Longitudinal Study ACR—EULAR Study Group for Development of Classification Criteria for PMR.

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Objective: To develop ACR/EULAR classification criteria for PMR by assessing the performance of candidate criteria in a prospective longitudinal study of patients presenting with new onset bilateral shoulder pain.

Methods: Candidate inclusion/exclusion criteria for classification of PMR and assessment of steroid response were defined through a consensus conference and a wider Delphi survey. These criteria were then evaluated in a 6-month prospective study of patients ≥50 years of age including subjects with a diagnosis of new onset PMR and controls with newly diagnosed conditions mimicking PMR (i.e. new onset rheumatoid arthritis (RA), connective tissue diseases, shoulder conditions, fibromyalgia, osteoarthritis, etc.) presenting with recent onset of bilateral shoulder pain. All subjects were evaluated at baseline and week 26 resulting in reclassification of 9 PMR subjects and 4 controls. Data collection included clinical signs and symptoms, lab results, treatment details, ultrasound (US) evaluation, MHAQ, SF36, and pain rating. The c-statistic (i.e. area under receiver operating characteristic curve) was used to assess the ability of each criterion to discriminate controls from PMR subjects (based on diagnosis at week 26).

Results: Disease features present in >80% of the 92 PMR subjects were ≥2 weeks duration of symptoms, bilateral shoulder pain, morning stiffness >45 min duration and elevated c-reactive protein (CRP) or erythrocyte sedimentation rate (ESR). 73% of PMR subjects presented with all 3 features, while only 29% of the 131 controls had all 3. Features that best discriminated RA from PMR were peripheral synovitis, abnormal rheumatoid factor (RF) or anti-citrullinated protein antibody (ACPA) and hip pain/limited range of motion (c-statistic ≥ 0.7). Features best discriminating shoulder conditions from PMR were hip pain/limited range of motion, morning stiffness and elevated CRP/ESR (c-statistic ≥ 0.7). A scoring algorithm was developed and included morning stiffness >45 min (2 points), abnormal CRP/ESR (2 points), hip pain/limited range of motion (1 point),

abnormal RF or ACPA (-2 points), and other joint pain (-1 point). A score ≥ 3 had 76% sensitivity and 77% specificity for discriminating all controls from PMR. The specificity was higher (91%) for discriminating shoulder conditions from PMR and lower (71%) for discriminating RA from PMR. US findings were somewhat useful in discriminating PMR from shoulder conditions, but not from RA.

Conclusions: Patients ≥50 yrs old presenting with bilateral shoulder pain can be classified as having PMR in the presence of morning stiffness>45 min, elevated CRP/ESR and new hip pain in the absence of peripheral synovitis or positive RA serology.

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1655

Different Diagnostic Criteria in the Diagnosis of Polymyalgia Rheumatica. Samy Zakout and John R. Kirwan. University of Bristol, Bristol, United Kingdom

Background: Patients with polymyalgia rheumatica (PMR) are often treated in the community. General practitioners (GPs) may refer for rheumatological opinion in situations of diagnostic uncertainty or disease relapse, but PMR often presents a diagnostic dilemma as the differential diagnosis is wide. Published diagnostic criteria are primarily used for research or to distinguish between rheumatic diseases. Their sensitivity and specificity in a routine referral clinic are not known.

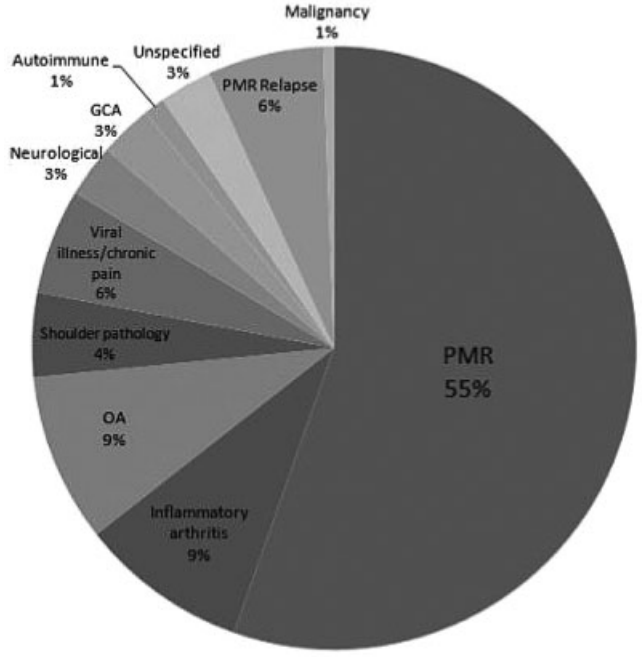
Objective: To explore how PMR diagnostic criteria perform when applied to patients with or without PMR, diagnosed on clinical grounds in a routine hospital outpatient department.

Methods: A hospital-based PMR rapid access clinic was established in our rheumatology department in July 2007. The aim of this clinic is to see new patients with suspected PMR within 2 weeks of referral. The diagnosis of PMR was made on clinical grounds. Published criteria were consulted at the time of this analysis.

Diagnostic criteria used are those of Bird[2], Hunder[2], Healey[3] and Hazleman[2].

Sensitivity and specificity of each of the diagnostic criteria were then calculated. The results of applying two criteria consecutively were also explored.

Results: 182 patients were referred over 28 months. 171 patients attended their hospital appointments. Patients with relapse were excluded from the analysis of the diagnostic criteria which were applied to 94 patients with a diagnosis of new PMR and 66 with an alternative diagnosis. Only half of the patients had new PMR (figure 1).



The ability of different criteria to identify PMR and non-PMR patients as well as sensitivity and specificity are shown in figure 2.

PMR Patients*

	All criteria	Bird, Hazleman & Healey	Bird & Hazleman	Bird & Hunder	Bird only	No criteria
No of pts	37	11	4	5	33	4
Percentage	39.3%	11.7%	4.3%	5.3%	35.1%	4.3%

Non-PMR Patients*

	All criteria	Bird & Hunder	Bird only	No criteria
No of pts	1	5	39	21
Percentage	1.5%	7.6%	59.1%	31.8%

*No patients met further combinations.

Sensitivity and Specificity

Criteria	Bird	Hunder	Healey	Hazleman
True positive	90	53	48	41
False positive	45	6	1	1
True negative	21	60	65	65
False negative	4	41	46	43
Sensitivity	95.7%	56.4%	51.1%	43.6%
Specificity	31.8%	90.9%	98.5%	98.5%

If patients are first classified as PMR using Bird criteria and are then rejected if they fail the Hazleman or Healey criteria, both high sensitivity (95.7%) and high specificity (98.5%) are achieved.

Conclusion: There is a clear potential for improving diagnostic accuracy using a rapid access PMR clinic where the diagnosis can be made or ruled out in most patients in one or two visits. No criteria have both high sensitivity and high specificity for identifying clinically diagnosed PMR in a routine referral clinic but a combination of criteria applied consecutively may offer an advantage.

References:

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2. Salvarani, C., et al., Medical progress – Polymyalgia rheumatica and giant-cell arteritis. New England Journal of Medicine, 2002. 347(4): p. 261–271.

Disclosure: S. Zakout: None; **J. R. Kirwan:** None.

1656

Diseases Associated with Positive NOD2/CARD15 Gene Mutations: Blau's Syndrome Versus an Intermediate Subset of Blau's Syndrome and Crohn's Disease. Qingping Yao[4], Lan Zhou[3], Philip Cusumano[2] and Le-Chu Su[1]. [1]The Department of Gastroenterology, Cleveland Clinic, Cleveland, OH, [2]The Department of Internal Medicine, Cleveland Clinic, Cleveland, OH, [3]The Department of Neurology, Cleveland Clinic, Cleveland, OH, [4]The Department of Rheumatic and Immunologic Diseases, Cleveland Clinic, Cleveland, OH

Purpose: Blau's syndrome is an autosomal dominant autoinflammatory disease, characterized by dermatitis, arthritis, and uveitis. Since the report in 1985, the clinical features of the disease have chiefly derived from studies of the pediatric population. Fevers, eruptions, and internal organ involvement have been reported as well. However, sporadic adult onset Blau's syndrome has rarely been seen in the medical literature. NOD2/CARD15 gene mutations have been associated with both Crohn's disease and Blau's syndrome. It is hypothesized that an intermediate subset of Blau's syndrome and Crohn's disease could be present but no similar reports have appeared. A small case series are presented herein to expand the clinical spectrum of the diseases.

Method: Four adult patients were referred to the Department of Rheumatology at the Cleveland Clinic between January 2009 and April 2010 for unclear diagnoses. These patients were also seen by internists and consulted by other specialists. The medical records of the patients were reviewed and relevant clinical and laboratory data was excerpted and analyzed. The blood specimens of the patients were tested for NOD2/CARD15 gene mutations.

Results: We report 4 patients with clinical features of autoinflammatory diseases and positive NOD2/CARD15 gene mutations. The mean age was 45.5 (age 28 to 55), disease duration was 3.1 (0.5 to 7 yrs), with 3 female and 1 male, and 3 cases were Caucasian with 1 Jewish. Three of them presented with rash, 1 had subacute spongiotic dermatitis with superficial perivascular lymphoplasmacytic infiltrate, 1 had palisaded neutrophilic and granulomatous

dermatitis, and 1 had pigmented purpuric dermatitis and mesenteric granulomatous lymphadenitis. Three patients developed low to high grade fevers, 3 developed polyarthritis, with 1 patient with a history of bilateral total hip replacements, and 3 had ocular symptoms with a case of documented iritis. Of the 3 patients with abdominal pain and diarrhea, 2 carried the diagnosis of Crohn's disease with reports of colonoscopic evidence of cryptitis, and 1 had normal endoscopy. One case was found to have small fiber neuropathy. Therapeutically, 3 patients were treated with oral glucocorticoids, with response, 1 was treated with TNF blockers (infliximab and adalimumab) with some response, and 1 responded well to anakinra.

Conclusion: Adult onset patients with positive NOD2/CARD15 gene mutations may present with atypical clinical features of Blau's syndrome, and some features may be shared by Crohn's disease. Given the shared phenotype and genotype by Crohn's disease and Blau's syndrome, a subset of these two diseases, intermediate syndrome, may be entertained.

Disclosure: Q. Yao: None; **L. Zhou:** None; **P. Cusumano:** None; **L.-C. Su:** None.

1657

Efficacy and Safety of Thalidomide on Mucocutaneous Symptoms: A Systematic Review and Meta-Analysis. Juan A. Martinez Lopez[3], Estibaliz Loza[3], Jesús Maese[3], Maria Rosario Rodriguez Moreno[2], Maria Piedad Rosario Lozano[3] and Loreto Carmona[1]. [1]Fundación Española Reumatol, Madrid, Spain, [2]Hospital Virgen de las Nieves, Granada, Spain, [3]Sociedad Española de Reumatología, Madrid, Spain

Background: Adverse events lead to the suspension of thalidomide's commercial use in many states. However, it has immunomodulatory properties for which thalidomide is being used to treat oral and genital ulcers, and at present, it holds indication for multiple myeloma. Our objective was to analyze the efficacy and safety of thalidomide in mucocutaneous symptoms.

Methods: A systematic literature review on the efficacy and safety of thalidomide on mucocutaneous symptoms in patients with Behçet disease, Human Immunodeficiency Virus (HIV) infection, discoid chronic lupus erythematosus or angiodysplasia was performed. A broad search strategy was run at the following databases (inception to January 2010): Medline, Embase, Cochrane Library, IME, IBECS, Lilacs, Scielo, and The US National Institutes of Health Ongoing Trials Register databases. The abstracts of the ACR (2005–2009) and EULAR (2005–2009) annual scientific meetings were also searched. Additionally, we inquired manufactures of thalidomide about any published or unpublished trials, and we hand-searched the references of the included studies, and all the publications or other information provided by the manufactures. The selection criteria included: 1) randomized controlled trials (RCT), with a Jadad score ≥3, comparing thalidomide with placebo or with an active comparator—no dosage, route or frequency limits were applied; 2) patients had to be 18 or older, and present mucocutaneous symptoms and a diagnosis of: Behçet disease, discoid chronic lupus erythematosus, Human Immunodeficiency Virus (HIV) infection, prurigo or intestinal angiodysplasia; and 3) studies had to assess the efficacy of thalidomide—changes in the number, size and time needed for complete healing of lesions, and to register adverse events—teratogenicity, peripheral neuropathy, sedation, skin rashes, fatigue, constipation, neutropenia, headache, CD4+ and CD8+ lymphocytes counts, viral loads. Articles were restricted to English, Spanish, Portuguese, Italian or French. Two reviewers screened the titles and abstracts of the retrieved articles for selection criteria independently and collected the data by using ad hoc standard forms. For the grading of the quality we used Jadad score. A third researcher solved discrepancies.

Results: We screened 2,421 abstracts and evaluated 157 in detail, of which 6 RCT were included. Patients had mucocutaneous lesions; five studies reported patients with HIV and one reported patients with Behçet disease. Patients of the six included studies were mostly men, with mean age around 30 years. Thalidomide doses ranged from 100 mg/day to 300 mg/day. Meta-analysis was possible for the following outcomes and comparisons: 1) thalidomide versus placebo for the complete healing of ulcers (OR=12.1; CI 95% 4.49–32.7); 2) thalidomide versus placebo regarding adverse events: 2.a) polyneuropathy (OR=2.73; CI 95% 1.01–7.34); 2b) cutaneous rash (OR=16; CI 95% 4.75–53.9); 2.c) somnolence (OR=8.41; CI 95% 3.91–18.1).

Conclusions: Thalidomide is very effective in the treatment of mucocutaneous lesions in patients with HIV or Behçet disease, but it is likewise related to significant toxicity.

Disclosure: J. A. Martinez Lopez: None; **E. Loza:** None; **J. Maese:** None; **M. R. Rodriguez Moreno:** None; **M. P. Rosario Lozano:** None; **L. Carmona:** None.

1658

Efficacy of High Doses of Interferon-a-2a (IFN]a) in Erdheim-Chester Disease. Baptiste Hervier, Laurent Arnaud, Bertrand Wechsler, Zahir Amoura and Julien Haroche. CHU Pitié-Salpétrière, APHP, Paris France, French Reference Center for Lupus & Autoimmune Diseases

Introduction: Erdheim-Chester disease (ECD) is a rare non-langerhans form of histiocytosis, characterized by a foamy histiocyte tissue infiltration. Treatments are not standardized. Efficacy of low doses of Interferon-a-2a (IFNα) have been suggested in small series but with variation depending of the organs involved. Indeed, central nervous system (CNS) and perivascular infiltration were reported to be resistant to low doses of IFNα.

Our aim is to report our single-center experience about the use of high doses of IFNα in ECD.

Methods: Twenty patients with biopsy-proven ECD have received high doses of IFNα (IFN$\alpha \geq$ 18 MUI/week or PEG-IFN$\alpha \geq$ 180 μg/week).

IFNα efficiency was systematically evaluated both clinically and morphologically (CT-scan or MRI for vessels & CNS, cardiac MRI, bone scintigraphy or MRI. ^{18F}FDG-PET)

Results: Sixteen men & four women were included (median age at diagnosis: 56 years (29–77). The median follow-up was 18 months (6–60). Treatments were IFNα 18 millions MUI/week (n=4), IFNα 27 MUI/week (n=8), PEG-IFNα 180 μg/week (n=8).

The treatment was started because of: CNS involvement (n=5), heart involvement (n=4), association of CNS & heart involvement (n=5), severe exophtalmos (n=1) and other (n=5). High doses of IFNα were started as first line treatment (n=12) or after a low dose course of IFNα (n=8), which was insufficient.

High doses of IFNα were efficient in 17 cases: incomplete remission (n=14, 70%) & stabilization (n=3, 15%). However, two patients did not respond to this treatment (10%) and another patient could not be evaluated (early treatment interruption). For these three patients the following treatments were inefficient (deaths, n=3).

Improvement concerned CNS (60%), lung (67%), bone (64%) and heart (56%). Median time before clinical improvement was 6 months (6–24). Nevertheless, improvement of sinusal involvement (33%), vascular involvement (20%), exophthalmos (33%) and retro-peritoneal fibrosis (20%) were rare.

High doses of IFNα were well-tolerated (n=14, 70%). However, six patients displayed side effects: severe asthenia (n=3), depression (n=2), eczema (n=1) requiring an interrupted treatment course (n=2) and an early definitive interruption (n=1). One responder patient died under IFNα after 24 months of follow-up.

Conclusion: High doses of IFNα may control severe ECD (85% of the cases) and are well tolerated (70%).

Disclosure: B. Hervier: None; **L. Arnaud:** None; **B. Wechsler:** None; **Z. Amoura:** None; **J. Haroche:** None.

1659

Endothelial Anti-Inflammatory Effect of alpha2 Adrenergic Agonists. Ada Herrera[2], M. Jesús Domínguez[2], M. Teresa Arce[2], A. Diaz[2], Manuel Feria[1] and Federico Diaz[2]. [1]Medical School, Spain, [2]Rheumatology Service, Hospital Universitario de Canarias, Spain

Our group has observed that a2 adrenergic agonists are able to modulate the inflammatory response in animal models of inflammation. However, the mechanisms thought which a2 adrenergic receptors participate in the regulation of the inflammatory response have not been clarified.

Objectives: To study the mechanisms responsible for the antiinflammatory action of a2 agonists.

Methods: Surface expression of L-selectin, CD11b, ICAM-1 and VCAM-1 were assessed by flow cytometry. The a_2 agonists, xylazine and UK14304, and the a_2 antagonist, RX821002 were used in this work. The presence of the a_2 adrenergic receptor subunits: A, B and C were investigated by RT-PCT and Western blot. Neutrophil migration capability through activated endothelium was assessed in transwell assay (5μm). The dynamic interaction between neutrophils and activated endothelium was studied in a flow chamber. The endothelial intercellular junction was analyzed by the cell distribution of VE-Cadherin and CD31 by confocal microscopy. Wilcoxon signed-rank test ($p<0.05$) was used to evaluate the statistical significance.

Results: Both neutrophils and HUVEC expressed mRNA transcripts of the three subunits of a2 adrenergic receptor. However, only the presence of receptors a_2A, in PMN and a_2B, in HUVEC were detected by western blot.

Basal expression of L-selectin and CD11b, in neutrophils and VCAM-1, in HUVEC were not modified by the presence of a2 agonists. However, ICAM-1 basal expression in TNF-a-activated HUVEC showed a significative dose-dependent reduction in the presence of UK 14304. When HUVEC where activated in the presence of UK14304, the basal migration of human neutrophils through activated HUVEC in static conditions was decreased up to 40±8%. This effect was reverted by RX821002. When neutrophils were incubated with UK14304 no effect on cell migration was observed. The presence of the agonist a_2 UK 14,304 did not interfere with the ability of PMN rolling on activated vascular endothelium, but it reduced the transmigration ability of neutrophils by 60% under shear stress conditions. The endothelial intercellular surface positive for VE-Cadherin and CD31 staining was increased in a 50% by UK14.308 respect to the basal.

Conclusions: The a2 adrenergic agonists are able to modulate the inflammatory response at endothelium level. These compounds seem to increase the endothelial cell-cell interaction resulting in a reduction of the neutrophil movement across the endothelial barrier. This finding supports the endothelium as a therapeutic target for developing new anti-inflammatory agents potentially useful for inflammatory rheumatic diseases.

Disclosure: A. Herrera: None; **M. J. Domínguez:** None; **M. T. Arce:** None; **A. Diaz:** None; **M. Feria:** None; **F. Diaz:** None.

1660

Erdheim-Chester Disease: Prospective Follow-Up of a Single-Center Cohort of 48 Patients Reveals Improved Survival in Patients Treated with Interferon-alpha. Laurent Arnaud, Julien Haroche, Baptiste Hervier, Bertrand Wechsler, Nathalie Costedoat-Chalumeau, Patrice Cacoub, David Saadoun and Zahir Amoura. Department of Internal Medicine, Groupe Hospitalier Pitié-Salpêtriere, UPMC Univ Paris 6, AP-HP, 47–83 bd de l'Hôpital, Paris, France

Background: Erdheim-Chester disease (ECD) is a rare form of non-Langerhans cell histiocytosis, with poor prognosis and non-codified therapeutic management. This study was undertaken to evaluate the impact of treatment with interferon alpha on survival in ECD patients.

Methods: Forty-eight patients (36 men and 12 women; median age: 59 years; median follow-up duration: 40.8 months) with biopsy-proven ECD were included in a single-center prospective cohort study, between Nov. 1981 and Jan. 2010. Five patients were excluded because of an overlap with another form of histiocytosis. Independent predictors of survival were identified using Cox proportional hazard model.

Results: Nine patients (18.8%) died after a median follow-up of 28.1 months (13.0–155.7 months). Univariate analysis revealed no difference in survival between gender (p=0.78), patients with and without biological inflammation (p=0.64), and treatment with or without corticosteroids (p=0.54). Comparison of patients treated with (n=40) and without (n=3) interferon-alpha and/or PEGylated interferon-alpha for at least 3 months (median duration of treatment: 23.4 months [3.2–148.2 months]) revealed an almost significant improvement (p=0.059) in patients treated with interferon (5 patients were excluded from this analysis because they received interferon for ≤ 3 months). Multivariate survival analysis using Cox proportional hazard model revealed that treatment with interferon alpha and/or PEGylated interferon-alpha for at least 3 months was the sole independent predictor of survival in our cohort (Hazard Ratio, HR: 0.10, IC95%: 0.01–0.82; p=0.03).

Conclusions: Although definitive confirmation would require a randomized controlled trial, our result strongly suggests that interferon-alpha improves survival in patients with ECD.

Disclosure: L. Arnaud: None; **J. Haroche:** None; **B. Hervier:** None; **B. Wechsler:** None; **N. Costedoat-Chalumeau:** None; **P. Cacoub:** None; **D. Saadoun:** None; **Z. Amoura:** None.

1661

Expression of Type 1 Interferon Related Proteins and Plasmacytoid Dendritic Cells in the Lesional Skin of Morphea Patients. Mehran Ghoreishi[1], Cristián Vera Kellet[2] and Jan Peter Dutz[1]. [1]Department of Dermatology and Skin Science, University of British Columbia, Vancouver, BC, Canada, [2]Department of Dermatology, Pontificia Universidad Católica de Chile, Santiago, Vancouver, BC, Canada

Background: Morphea is a sclerosing condition limited to the skin and subcutaneous tissue. The co-existence of morphea with other autoimmune diseases, the elevated levels of rheumatoid factor and other auto-antibodies and the activated state of infiltrating inflammatory cells all suggest that morphea is an autoimmune disease. Type 1 interferons have been shown to promote autoimmune diseases involving the skin such as cutaneous lupus erythematosus, lichen planus and psoriasis. Type 1 interferons have recently been implicated in the pathogenesis of systemic sclerosis. The role of type 1 interferons in morphea is unknown. A type 1 interferon "signature" can be detected in tissues by the presence of interferon-α induced myxovirus A protein (MxA). Type 1 interferons are mainly produced by plasmacytoid dendritic cells (pDC), which normally do not home to the skin.

Purpose: To study the expression of type 1 interferon-induced MxA and the presence of pDCs in lesional and non-lesional skin of morphea patients.

Methods: Skin samples from 11 generalized morphea patients were collected. Paraffin embedded sections of lesional and non-lesional skin of morphea patients were stained with anti-human antibodies against MxA, CD123 and BDCA-2 and were compared with positive controls (lichen planus) and other sclerosing conditions (keloid).

Results: MxA expression was detected in keratinocytes, dermal vasculature and fibroblasts in the dermis and subcutis of morphea samples (10/11 samples). pDC can be identified by their expression of CD123 and BDCA-2. CD123 and BDCA-2 positive cells were abundant in lesions of morphea in superficial and deep dermis as well as in the subcutis (10/11). In contrast, non-lesional morphea samples (2/2) did not show detectable MxA and demonstrated few pDCs. Minimal expression of MxA was detectable in the vascular endothelium of keloid samples. There was no evidence of epidermal MxA expression in keloid.

Conclusions: To our knowledge this is the first study to show that type 1 interferons and pDCs are increased in skin lesions of morphea. This finding suggests that morphea shares the type 1 interferon dependent inflammatory pattern detected in lichenoid skin diseases such as cutaneous lupus erythematosus and lichen planus. This observation may explain the concurrence of other autoimmune diseases and the presence of auto-antibodies in morphea patients. Currently there is no useful tool to evaluate the disease activity in morphea. This study suggests that measurement of peripheral blood type 1 interferon signature, as in SLE, should be explored as a measurement of disease activity in morphea.

Disclosure: M. Ghoreishi: None; **C. Vera Kellet:** None; **J. P. Dutz:** None.

1662

Idiopathic Retroperitoneal Fibrosis: Clinical Findings in 185 Patients. Tanaz A. Kermani[1], Cynthia S. Crowson[2] and Harvinder S. Luthra[1]. [1]Mayo Clinic, Rochester, MN, [2]Mayo Clinic

Purpose: To describe the clinical manifestations, laboratory, imaging findings and treatment of 185 patients with retroperitoneal fibrosis (RF) from a single tertiary-care center.

Methods: In this retrospective study all patients with newly diagnosed RF between 1/1/1996 and 12/31/2006 were included. Diagnosis was based on compatible imaging findings. RF associated with malignancy/radiation therapy and inflammatory abdominal aortic aneurysms were excluded. Medical records were reviewed and clinical information was abstracted using standardized case report forms. Descriptive statistics were used.

Results: We identified 185 patients; 113 (61%) men, 72 (39%) women with RF, mean age at diagnosis 57.6 (±11.81) years. Diagnosis was confirmed by biopsy in 140 cases (76%). The most common presenting symptoms were back pain (37.3%) and/or abdominal pain (36.8%). At diagnosis, 33 patients (17.8%) had exposure to a medication reported as associated with RF including beta-blockers (29 patients), methysergide (2 patients), ergotamine (1 patient), methyldopa (1 patient) and pergolide (1 patient). Five patients (3%) reported asbestos exposure, and 128 patients (69%) were ever-smokers. Preceding or subsequent autoimmune diseases were present in 26 patients (15%); inflammatory bowel disease was the most common (6 patients). Eleven patients (6%) had other fibrosing conditions including mediastinal fibrosis in 3 patients.

Mean hemoglobin at diagnosis was 12.6 (±1.74) g/dL. Baseline ESR and/or CRP was elevated in 62.3% (151 patients tested). Mean creatinine (Cr) at diagnosis was 2.43 (±2.78) mg/dL. New renal insufficiency was present in 74 patients (40%); median Cr 2.3 (range 1.2–13.0) mg/dL. ANA was positive in 6/118 (5%) patients tested while rheumatoid factor was positive in 8/89 (9%) subjects tested.

Baseline imaging studies in 182 patients showed a soft tissue mass which was periaortic in 115 cases (63%), periureteric in 10 patients (6%) and periaortic and periureteric in 39 patients (21%). Hydronephrosis and renal atrophy were present in 98 patients (53%) and 15 patients (8%) respectively.

Fifteen patients (8%) were treated with surgery alone, 57 patients (31%)

with medications alone and 106 patients (57%) received medical and surgical treatment. Corticosteroids were started in 116 patients. Tamoxifen was the most commonly used medication (120 patients) followed by methotrexate (51 patients).

Follow-up was available for 151 patients (82%), and 104 (69%) had normal Cr at last visit. There were 13 deaths. Nine patients developed cancer after RF diagnosis. Median duration from diagnosis of RF to cancer was 50 (range 4–112) months.

Conclusions: Idiopathic RF is a chronic inflammatory disorder of unknown etiology. This is the largest single-center study of RF with follow-up available in 82% cases. Additionally, 70% of patients were evaluated by one of us. In contrast to prior studies, we found only a slightly increased male predominance. Also, ANA was positive in only 5% patients tested. However, 15% patients had or developed autoimmune diseases. With close observation and appropriate management, outcomes such as worsening renal dysfunction or death due to renal failure were uncommon.

Disclosure: T. A. Kermani: None; **C. S. Crowson:** None; **H. S. Luthra:** None.

1663

IL-1 Blockade for Schnitzler's Syndrome. Rona M. Smith[1], Helen J. Lachmann[2] and David R. W. Jayne[1]. [1]Addenbrooke's Hospital, Cambridge, United Kingdom, [2]UK National Amyloidosis Centre, London

Introduction: Urticarial vasculitis is a clinicopathological entity consisting of urticaria and a leucocytoclastic vasculitis on skin biopsy. It can be localised to the skin, or form part of a systemic condition, and tends to have a benign, self limiting prognosis. A few patients, however, pursue a refractory course. Schnitzler's Syndrome is a rare cause of refractory urticarial vasculitis, characterised by the presence of a monoclonal IgM component.

Methods: We have a cohort of six patients with Schnitzler's Syndrome. Detailed here are the complex courses of two patients (Patient A aged 60 and Patient B aged 35) who were diagnosed with the condition in 2009, selected to highlight the refractory nature of this condition, and the importance of making this rare diagnosis. They both presented with biopsy proven urticarial vasculitis to our clinic in 2005. Both had associated systemic symptoms, namely episodic fevers, sweats, arthralgias and significant weight loss in Patient A, and recurrent abdominal pain and distal limb parathesiae in Patient B.

Investigations: Both had marked elevations of ESR (>80mm/hr) and CRP; a persistent neutrophilia and an IgM paraprotein. Patient A had axillary and mesenteric lymphadenopathy on CT scan, but a lymph node biopsy revealed reactive cells only. Patient B had a bone marrow biopsy, which showed no evidence of lymphoproliferative disease. Both had normal PET scans, and angiograms which suggested the presence of renal and superior mesenteric artery aneurysms respectively.

Treatments: Both initially had good responses to high dose (>40mg/day) prednisolone, but relapsed on steroid taper. In light of the angiogram findings, both were treated as possible cases of polyarteritis nodosa with intravenous cyclophosphamide, but with only partial clinical effect. Multiple other immunosuppressive drugs including anti-TNF agents, calcineurin inhibitors, antimetabolites, rituximab, alemtuzumab and thalidomide were trialled over the years, but with minimal success.

Diagnosis: In view of the challenging nature of the cases, a second opinion was sought. A diagnosis of Schnitzler's syndrome was made, and therapy with anakinra (Kineret, Biovitrum AB) (an IL-1 receptor antagonist) was commenced. Both patients' clinical conditions dramatically improved within 48 hours of therapy, and their marked acute phase response completely subsided. Prednisolone doses are currently below 5mg/day—the lowest since presentation. After eight months therapy, both are tolerating anakinra well, and the transient neutropaenia that occurred in Patient B has resolved.

Conclusion: IL-1 blockade should be considered as a potential treatment for cases of refractory urticarial vasculitis, and has been shown to be particularly effective in Schnitzler's syndrome. Although extremely rare, with only about 100 reported cases in the literature, clinicians should be aware of the diagnosis of Schnitzler's Syndrome, as it responds exquisitely well to therapy, transforming patients' quality of life.

Disclosure: R. M. Smith: None; **H. J. Lachmann:** EU framework 7, 2, Novartis Pharmaceuticals Corporation, 5; **D. R. W. Jayne:** Merck Pharmaceuticals, 5, Novartis Pharmaceuticals Corporation, 2, Roche, 2, 5, UCB, Inc., 5.

1664

IL-18 Binding Protein (IL-18BP) Dramatically Improves Liver Histological Lesions in an Animal Model of Macrophage Activation Syndrome (MAS). Laura Chiossone[3], Sandra Audonnet[3], Karin Mazodier[2], Marc Dalod[3], Catherine Farnarier[1], Daniela Novick[5], Charles A. Dinarello[4], Eric Vivier[3] and Gilles Kaplanski[2]. [1]Assiatnce Publique-Hôpitaux de Marseille, Marseille, France, [2]Assistance Publique-Hôpitaux de Marseille, Marseille, France, [3]CIML, Marseille, France, [4]University of Colorado Health Science, Denver, CO, [5]Weizmann Institute of Science, Rehovot, Israel

MAS is a severe complication of various infectious, inflammatory or neoplastic diseases. Severely impaired lymphocyte cytotoxicity and large excess of inflammatory cytokines, notably IFN-g, participate in its pathogenesis. In patients with MAS, concentrations of IL-18, a strong inducer of IFN-g, are largely increased, but not those of its natural inhibitor IL-18BP, favoring a severe IL-18/IL-18BP imbalance.

Aim: We asked whether IL-18BP may be an efficient treatment in an animal model of MAS consisting in perforin-KO mice infected with murine cytomegalovirus (MCMV), which has been previously reported to be IFN-g and TNF-a-dependent.

Results: 7–12 days after infection, 100% KO mice died whereas all wild type (WT) mice survived. Injection of 10 microgram/mice/day IL-18BP starting at day 0 or day 4 post-infection did not improve KO mice survival, nor did anti-TNF-a treatment.

Liver showed very severe histological lesions in MCVM-infected KO mice which was almost completely abrogated by IL-18 BP, in a comparable way to anti-TNF-a treatment. Combination of both did not further improve the lesions.

Serum cytokine concentrations at day 6 post-infection showed very high concentrations of IFN-g (38+/−5 vs 1+/−1 ng/ml in WT) and TNF-a (13.8 +/−2 vs 0.5 ng/ml in WT) in MCMV-infected KO mice, which were 50% reduced by IL-18BP treatment (20 +/−10 ng/ml for IFN-g and 7.5+/−2 ng/ml for TNF-a, respectively). Combination of IL-18BP and anti-TNF-a treatment 100% inhibited IFN-g levels.

Conclusions: In this model of MAS which has been shown to be entirely IFN-g and TNF-a-mediated, IL-18BP appears to be as efficient as anti-TNF-a treatment in preventing liver damage through inhibition of both IFN-g and TNF-a, confirming the role of IL-18 in the pathogenesis of this disease.

Disclosure: L. Chiossone: None; **S. Audonnet:** None; **K. Mazodier:** None; **M. Dalod:** None; **C. Farnarier:** None; **D. Novick:** None; **C. A. Dinarello:** None; **E. Vivier:** None; **G. Kaplanski:** None.

1665

Is Pamidronate Useful as Very Effective Therapeutic Intervention in Midtarsal Arthropathy? Mani Nallasivan[2] and Tim Tait[1]. [1]Diana Princess of Wales Hospital Grimsby, Grimsby, Lincolnshire, United Kingdom, [2]Diana Princess of Wales Hospital, Grimsby, Northern Lincolnshire and Goole Hospital NHS Trust, Hull, Yorkshire, United Kingdom

Background: Midtarsal Arthropathy is a recognised cause of Foot pain. It usually presents as pain with or without swelling of the midfoot, extending from the ankle to the metatarso phalangeal joints. Parenteral pamidronate is used in the UK for the management of Paget's disease, tumour related hypercalcaemia, NSAID refractory AS, refractory SAPHO syndrome and in Charcot's arthropathy. Bisphosphonates are known to inhibit osteoclasts, improve bone density measurements and prevent fractures, suppress pro-inflammatory cytokines such as interleukin (IL-1), TNF-a and IL-6, and show anti-inflammatory properties in arthritis.

We have used Pamidronate for midtarsal arthropathy for the past five years and have previously reported our experience with six patients[1]. We hereby report our further experience in 20 patients, which demonstrates good clinical resolution.

Objectives: To assess the effectiveness of parenteral pamidronate in symptomatic control of midtarsal inflammatory arthropathy and also to assess improvement in imaging findings (MRI) in a few.

Methods: Retrospective case records of patients who had pamidronate infusion for midtarsal arthropathy were reviewed from 2005 until 2009. 20 patients had treatment of which 5 were male. Mean age was 64.6 years (37–79). All patients had pain in the midfoot and no history of trauma. Seven patients were having treatment for Rheumatoid arthritis but no active disease. Their Plain x-rays of the foot didn't show erosive arthropathy or fracture. These patients had isotope bone scan which showed increased uptake in the

midtarsal region. All had intravenous pamidronate infusion (60mgs) and some of them had 3–4 infusions over 2-year period.

Results: All patients reported significant improvement of pain after one infusion and became asymptomatic with five needing a second infusion. Median time interval before second infusion was 7 months. Follow up has been done for a maximum of three years.

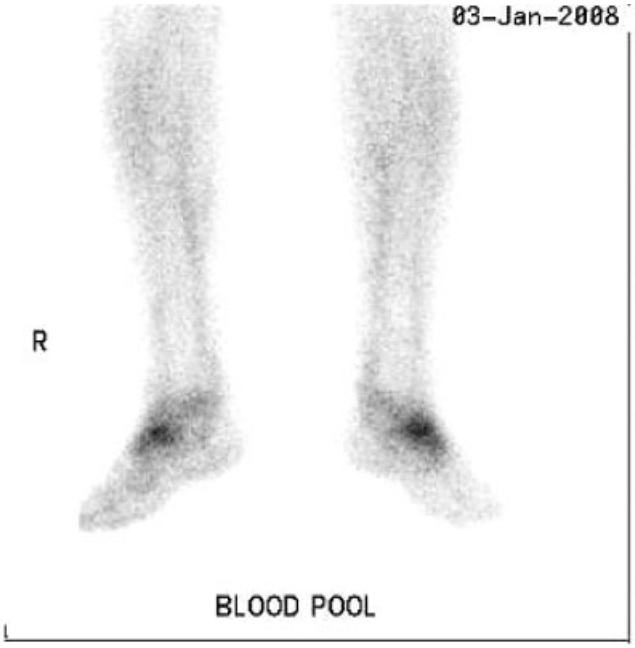

Image: Bone scan showing increased activity in midtarsal joint.

Conclusion: Pamidronate is very effective in treating midtarsal arthropathy. This warrants further study. Our five years experience further explores our understanding on the versatile benefits of this bisphosphonate.

References:

1. S. Kallankara, Tim Tait – Abstract 1631- ACR 2007 Annual Scientific Meeting. 2. A Naqvi et al. Acute Charcot arthropathy successfully treated with Pamidronate: The American Journal of the Medical Sciences: Feb 2008,Vol 335 (2), pp 145–148.

Disclosure: M. Nallasivan: None; **T. Tait:** None.

1666

Nonalcoholic Steatohepatitis as a Complication of Collagen Disease. Kae Takagi, Yasushi Kawaguchi, Yuko Ota, Akiko Tochimoto, Chikako Fukazawa, Takahisa Gono, Yasuhiro Katsumata, Masako Hara and Hisashi Yamanaka. Tokyo Women's Medical University, Tokyo, Japan

Background: Nonalcoholic fatty liver disease (NAFLD) is a silent disease, and is one of the most common causes of elevated liver enzymes. Nonalcoholic steatohepatitis (NASH) is distinguished from NAFLD by a liver biopsy revealing fatty change in the liver along with inflammation and damage. The development of NASH in collagen disease has been rarely reported. Our aims are to elucidate the frequency, clinical features, pathogenesis, and treatment of NASH associated with collagen disease.

Methods: A retrospective survey of collagen disease patients who were hospitalized and initially screened for NASH by identifying abnormalities in serum liver enzymes, and findings of severe fatty liver changes on abdominal computed tomography (CT) and ultrasound. NASH was confirmed by liver biopsy, and the clinical features of these patients before and after treatment were evaluated.

Results: Five patients were identified with NASH (3 patients with systemic lupus erythematosus and 2 patients with Weber-Christian disease). Mean age was 33.8 ± 15.6 years old. Three of five patients showed increased BMI and high HOMA-R. All patients showed the increase levels of serum aminotransferase (AST/ALT). Before diagnosis of NASH, 4 patients had been treated by small amount of corticosteroid against collagen diseases. Fatty change was revealed by CT and/or US in all patients. Three cases having ALT level higher than 150IU/l, showed more prominent fatty change in CT grading. The Liver/spleen (L/S) ratio measured by CT were observed around 0.8 higher than 0.4. Pathological examination using liver biopsy specimens showed NASH in all 5 patients. Based on Brunt's classification, pathological score of two patients were Grade 2 and Stage 2, whereas the score were 1 in other three patients.

Table 1. Clinical characteristic

	case 1	case 2	case 3	case 4	case 5
gender	F	M	F	F	F
age	29	36	21	19	62
BW	56	96	86	62	50
BMI	22.9	32.3	34.6	24.6	22.7
collagen disease	W-C	W-C	SLE	SLE	SLE
NIDDM	(+)	(+)	(−)	(−)	(−)
HL	(+)	(+)	(+)	(−)	(+)
AST (IU/l)	218	82	161	51	75
ALT (IU/l)	205	262	160	142	90
LDH (IU/l)	958	594	720	192	230
γGTP (IU/l)	344	167	100	32	157
ALP (IU/l)	308	234	159	146	332
Tchol (mg/dl)	223	256	172	175	121
HDL (mg/dl)	19	51	12	NE	37
LDL (mg/dl)	129	188	79	NE	147
TG (mg/dl)	393	104	405	220	262
Adiponectin (μg/ml)	9.17	29.4	6.5	5	11.8
Leptin (ng/dl)	11.1	20.8	24.4	14.7	19.3
Insulin (μU/ml)	1.9	72.5	175	85	14.6
BS (mg/dl)	62	181	108	120	118
HbA1C (%)	6	6.5	5.5	NE	NE
HOMA-R	0.29	29.3	46.6	25.2	4.8
TNFα (pg/ml)	37.4	1.5	4.3	3.2	5.6
CT grade	2	3	3	NE	1
CT L/S ratio	0.8	0.41	0.38	NE	
US (grade)	2	3	2	2	1
Pathology (grade)	2	1	1	1	2
(stage)	2	1	1	1	2

In order to suppress the collagen disease activity, all patients were treated by higher amount of corticosteroid (prednisolone 20–40 mg/day) with and without immunosuppressive drugs such as cyclophosphamide, ciclosporin or mizoribine. In all patients, serum AST/ALT levels were remarkably turned to be normal in parallel with improvement of collagen disease activity within six months (AST: 117.4 ± 31.2 vs.26.0 ± 3.7, $p < 0.05$; ALT: 171.8 ± 29.1 vs.48.4 ± 16.7, $p < 0.01$). Furthermore, fatty liver change determined by CT and US were diminished. The average of L/S ratio before and after treatment was changed from 0.49 ± 0.26 to 1.22 ± 0.17 with statistically significant difference ($p < 0.01$). Although HOMA-R was improved in three cases, there were no significant changes in other risk factors including body weight and BMI before and after treatment.

Conclusions: NASH is relatively rare in collagen disease patients. Corticosteroid treatment with or without immunosuppressant drugs was effective for collagen disease as well as for NASH, suggesting that autoimmune factors are involved in the development of NASH associated with collagen disease.

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1667

Prevalence of Atherosclerotic Risk Factors and the Metabolic Syndrome in Patients with Chronic Inflammatory Arthritis. Chi Chiu Mok[2], Tin Choi Ko[1], Ling Yin Ho[2], Ka Lung Yu[2], Pak To Chan[2] and Chi Hung To[2]. [1]Chinese University Hong Kong, [2]Tuen Mun Hospital

Objectives: To evaluate the prevalence of atherosclerotic risk factors and the metabolic syndrome (MetS) in patients with rheumatoid arthritis(RA), ankylosing spondylitis(AS) and psoriatic arthritis(PSA).

Patients and Methods: Consecutive patients with RA, AS or PSA who attended our out-patient arthritis clinics between July and November 2009 were recruited for a study of the prevalence of atherosclerotic risk factors and the MetS, defined according to the 2009 Joint Statements using the Asian criteria for central obesity. Participants were screened for the presence of vascular risk factors. Waist and hip circumferences, body weight, body height and blood pressure were measured; and fasting blood was taken for glucose

and lipid levels. Medications being received by patients were also reviewed. The MetS was present when ≥3 of the following components were present: (1) Increased waist circumference to ≥ 90cm in men or ≥ 80cm in women; (2) Elevated blood pressure to ≥130/85mmHg or requiring drug therapy; (3) Elevated serum triglyceride level to ≥1.7mmol/L; (4) Reduced serum high density lipoprotein (HDL)-cholesterol to ≤1.0mmol/L in men and ≤1.3mmol/L in women; and (5) Elevated fasting glucose level to ≥5.6mmol/L. The prevalence of vascular risk factors and MetS was compared among different inflammatory arthritis; and with age and gender-matched healthy controls in a 1:2 matching.

Results: 844 patients were studied (651 RA, 94 AS and 99 PSA; 72% women; age 51.7±12.6 years). The mean disease duration for patients with RA, AS and PSA was 5.1±5.4, 4.9±4.8, and 3.3±3.0 years, respectively. The prevalence of MetS was significantly higher in PSA (40%) than RA (20%) or AS (13%) ($p<0.001$). The odds ratios for the MetS compared to age and gender matched controls were 0.95 (0.75–1.19; $p=0.68$), 0.80 (0.39–1.65; $p=0.60$) and 3.27 (1.90–5.64; $p<0.001$), respectively, for RA, AS and PSA. Patients with PSA had significantly higher prevalence of impaired fasting glucose (33%; $p<0.001$), low HDL-cholesterol (34%; $p<0.001$), high triglyceride (22%; $p=0.01$) and central obesity (66%; $p=0.009$). In a logistic regression model, the odds ratio for the MetS in PSA was 2.64 (1.58–4.41) ($p<0.001$) compared to RA or AS. The adjusted odds ratios for central obesity, impaired fasting glucose, hypertriglyceridemia and low HDL-cholesterol were also significantly higher in patients with PSA. The prevalence of the MetS in all the three diseases studies was not significantly higher those patients with established (>2 years' duration) than early disease (<=2 years' duration).

Conclusions: Patients with PSA, but not RA or AS, have a significantly higher prevalence of the MetS syndrome compared to the general population. Among the three diseases studied, PSA has the highest prevalence of the MetS and is associated with highest cardiovascular risk.

Disclosure: C. C. Mok: None; **T. C. Ko:** None; **L Y. Ho:** None; **K. L. Yu:** None; **P. T. Chan:** None; **C. H. To:** None.

1668

Renal Dysfunction Is Associated with Increased Mortality in Adults with Macrophage Activation Syndrome. Bita Shakoory[3], W. Winn Chatham[3], Graciela S. Alarcon[1] and Randy Q. Cron[2]. [1]Oakland, CA, [2]Children's Hospital of Alabama, Birmingham, AL, [3]Univ of Alabama-Birmingham, Birmingham, AL

Background: Macrophage activation syndrome (MAS) remains a potentially fatal cause of multiorgan dysfunction (MOD) in adults, with an estimated mortality of 50%. This longitudinal study reports the short and long term outcomes in hospitalized adults with MAS due to various triggering factors from a single academic institution.

Methods: Patients diagnosed with MAS from April '08 to May '10 at a regional tertiary institution were identified from rheumatology consultation logs. The diagnosis was made in patients with MOD with at least one of the following: A. Tissue hemophagocytosis; B. Consensus of ≥2 physicians to treat; or C. Elevated ferritin >10,000 mg/L. Final decision for treatment was made independent of the study. The length of hospital stay (HS) and critical care (CC), the need for renal replacement therapy (RRT), vasopressor use (VP) and mechanical ventilation (MV), and death were recorded. Follow up data on survivors (chronic organ damage, readmission) were obtained from the time of discharge in 3–6 month intervals.

Results: Seventeen adults (age 17–74y), 59% non-whites (53% AA, 6% Asian), predominantly women (76%), were included. A definite predisposing disorder could not be identified in one patient. The following potential etiologies were suggested in the remaining.

Infectious: Ehrlichiosis in 3, CMV, HSV, EBV in 6.

SLE in 7, adult-onset Still disease, IgA nephropathy, Wegener disease in 3.

Hematological malignancies in 3.

Pregnancy in 2.

The average HS was 31 days (5–112d, median 28d), 76% of patients had a CC stay (mean 11.2d, median 11d). MV and VP and RRT required in 65% (n=11). Nine of the 17 patients did not survive the hospitalization (53% mortality). Follow up in survivors (Mean 13m, Median 12m, range 3–26m, last discharge March '10) showed 4 readmissions in 2 survivors (1 for delivery, 1 with 3 readmissions) with chronic organ damage in 4: stage II liver fibrosis per biopsy in 2, worsening of chronic kidney disease and RRT after discharge in 3 (<6 month in 1, permanent RRT in 2).

The need for CC, MV, or RRT occurred more frequently in those who died than in survivors. There were no differences in age, gender, ethnicity, the presence of two or more triggering factors, or the length of HS or CC stay between survivors and non-survivors (Table).

Conclusions: In adults, a diagnosis of MAS oftern results in prolonged and complicated hospital course with high mortality and should be investigated and treated in patients with early manifestations of MOD to prevent critical care interventions and associated morbidity and mortality.

The Outcomes Correlates of MAS

	Deceased (N = 9) Mean (SD)	Survived (N = 8) Student t Test	p Value	Total Mean (SD)
Age	54 (15)	38 (20)	0.3	46 (19)
LoHA	36 (31)	24 (13)	0.3	57 (24)
LoCC	11 (8)	6 (6)	0.2	8 (8)
	N (%)	N (%)	Fischer Exact Test	N (%)
Woman	7 (78)	6 (75)	1.0	13 (76)
Non-White	5 (55)	3 (38)	0.6	8 (47)
Two triggers	7 (78)	3 (38)	0.1	10 (59)
CC	9 (100)	4 (50)	<0.05	13 (76)
MV	8 (89)	3 (37)	<0.05	11 (65)
RRT	8 (89)	1 (13)	<0.005	9 (53)

MAS: macrophage activation syndrome, LoHS: length of hospital stay, LoCC: length of critical care admission, MV: mechanical ventilation, RRT: renal replacement therapy, CC: critical care

Disclosure: B. Shakoory: None; **W. W. Chatham:** None; **G. S. Alarcon:** None; **R. Q. Cron:** None.

1669

Retrospective Analysis of Relapsing Polychondritis in the US Department of Defense Population. Stephanie D. Mathew, Daniel F. Battafarano and Michael J. Morris. San Antonio Military Medical Consortium, Fort Sam Houston, TX

Purpose: Relapsing polychondritis (RPC) is a rare autoimmune disorder with an prevalence of 3.5 cases/million. RPC affects cartilaginous structures including the ear, nose, larynx, trachea, bronchi, joints, skin, heart valves and the aorta. Cardiopulmonary and vascular involvement can be life threatening. The objective of this study was to characterize the clinical features of RPC within our patient population and determine the utility of echocardiography, imaging studies and spirometry.

Methods: We performed a retrospective EMR chart review of all patients diagnosed with RPC within the Department of Defense between January 2004 and December 2009 from a beneficiary base of 9.5 million. Patients were included if they met McAdams diagnostic criteria for RPC or if they had recurrent chondritis with deformity plus vestibular dysfunction, ocular inflammation or inflammatory arthritis. Demographic information, along with disease duration, organ involvement, treatment history, imaging studies, echocardiography and pulmonary function tests (PFTs) were recorded.

Results: Thirty patients met McAdams diagnostic criteria and an additional 13 met our criteria as outlined above. Twenty-three of the patients (53%) were female; with a mean age of 51. The average age at diagnosis was 43 and disease duration of 7.1 years. Auricular chondritis was present in 38 (88%), inflammatory arthritis in 26 (60%), inflammatory eye disease in 23 (57%), pulmonary involvement in 16 (37%) sensorineural hearing loss in 16 (37%), nasal chondritis in 15 (35%) and keratoconjuntivitis in 7 (16%). Two patients had vasculitis and one presented with renal insufficiency and proteinuria. Twenty-one (49%) patients had concomitant connective tissue disease. Methotrexate was used in 18 (42%), corticosteroids in 13 (21%), NSAIDs in 10 (23%), other DMARDs in 8 (18%), biologics in 7 (16%), and dapsone in 4 (9%). Twenty (47%) required multiple medications. Thirty (70%) patients had PFTs, 18 with reviewable flow volume loops. Flow volume loop abnormalities were observed in 6 of 18 (33%); all had upper respiratory symptoms. Imaging with chest CT was performed in 27 (63%) and in 5 of 6 patients with flow volume loop abnormalities. Pulmonary CT abnormalities in 13 of the 27 patients (48%) revealed parenchymal lung disease (9), tracheal abnormalities (4) and enlargement of the great vessels (2). Echocardiography was abnormal in 12 of 25 (48%) with valvular (aortic and mitral) regurgitation or stenosis (8), aortic root dilatation (3), and pericarditis (1).

Conclusions: Our RPC patients were similar to previous studies in incidence, demographic data and organ involvement. The diagnosis of RPC was primarily based on physical examination and symptom driven diagnostic testing. There was no observable pattern for monitoring progression of

tracheobronchial tree and/or large vessel involvement. Abnormal flow volume loops are recommended with all PFTs in RPC patients to detect early laryngotracheal involvement. CT of the chest is warranted to monitor for progressive vascular and tracheobronchial tree abnormalities.

Disclosure: S. D. Mathew: None; **D. F. Battafarano:** None; **M. J. Morris:** None.

1670

Retrospective Case Series of Single Center Experience of Methotrexate and Mycophenolate Mofetil Monotherapy for Patients with Non Infectious Posterior, Intermediate and Panuveitis. Mariam Khan[1], Careen Lowder[1] and Rula Hajj-Ali[2]. [1]Cleveland Clinic Foundation, Cleveland, OH, [2]Clevelnad Clinic, Cleveland, OH

Background: Limited data is available in the literature regarding sustained clinical efficacy with the use of antimetabolites for treatment of uveitis. In addition most series have included patients with anterior inflammation which makes efficacy data appear more robust. The objective of this study was to report the sustained clinical efficacy in patients with non infectious posterior, intermediate and panuveitis.

Methods: 183 charts of patients followed in the Rheumatology and Ophthalmology Departments between 1997 and 2008 with the diagnosis of uveitis were screened. 36 patients fulfilled the inclusion criteria: a) diagnosis of non infectious posterior, intermediate or panuveitis, b) treatment with methotrexate (MTX) and/ or mycophenolate mofetil (MMF) monotherapy, c) at least six months of follow up after treatment initiation. Data extracted from the charts included demographics, detailed treatment course, disease associations and treatment response.

Initial clinical efficacy was defined as lack of inflammation at a prednisone dose of less than 10mg and without the use of antecedent (with in two months) intraocular steroid injection.

The primary outcome measure was sustained efficacy defined as lack of inflammation for at least six months following initial efficacy. Efficacy was not sustained if patients needed escalation in dose of immunosuppressive agents, intraocular steroid injections or course of oral steroids however those who were treated with brief course of topical steroids but not more than three times a year were included in this group.

Results: 30 patients received MTX, 11 received MMF (5 de novo and 5 after MTX failure). 53 % (n=19) had idiopathic disease, 17% (n=6) had ocular syndromes restricted to the eye and 30% (n=11) had systemic disease [64% (n=7) with sarcoidosis, 18 %(n=2) with multiple sclerosis, 9% (n=1) with behcet's and 9% (n=1) with crohn's disease]. 56% (n=20) had panuveitis, 42% (n=15) had posterior uveitis.One had intermediate uveitis. 5 patients treated with MMF de novo had ocular syndromes restricted to the eye, [80% (n=4) birdshot retinochoroidopathy]. Female to male ratio was 1.6:1. Mean disease duration was 7.7 years (1–20), mean age at diagnosis was 43.5 years (8–65). Average dose of MTX was 21 mg weekly (15–27.5) and of MMF was 2318 mg daily (1000–3000).

Initial and sustained clinical efficacy were higher in MMF compared to MTX (73% vs. 67 %, p =0.12) and (64 % vs. 47% p =0.16) respectively but this did not reach statistical significance. There was a trend towards significance with respect to steroid sparing effect (60% vs. 22%, p=0.069) and ability to taper antimetabolite (55% vs. 17%, p=0.06) in the MMF group compared to the MTX group respectively. Median duration of sustained clinical efficacy was significantly higher in the MMF compared to MTX group (48 vs. 20 months, p=0.002).

Conclusion: Sustained clinical efficacy in patients who received MTX was higher compared to the reported literature likely related the higher average dose of MTX used at our center. Median duration of sustained efficacy was significantly higher with MMF compared to MTX.

Disclosure: M. Khan: None; **C. Lowder:** None; **R. Hajj-Ali:** None.

1671

Rituximab Therapy Is an Effective Approach in Treatment of IgG4-Related Systemic Disease. Arezou Khosroshahi[3], Donald B. Bloch[2], Vikram Deshpande[4] and John H. Stone[1]. [1]Massachusetts General Hospital, Sudbury, MA, [2]Massachusetts General Hospital, Newton, MA, [3]Massachusetts General Hospital, Boston, MA, [4]Massachusetts General Hospital

Patients with IgG4-related systemic disease (IgG4-RSD) often have strikingly elevated serum concentrations of IgG4 and typically share certain histopathological features regardless of the affected organ(s). The histopathological features of IgG4-RSD include diffuse lymphoplasmacytic infiltration, extensive deposition of IgG4-positive plasma cells, obliterative phlebitis, and tissue fibrosis. Patients with IgG4-RSD frequently require prolonged treatment with glucocorticoids and are often unable to taper these medications. Traditional disease-modifying antirheumatic drugs (DMARDs) are generally ineffective.

Objective: We assessed the clinical and serologic responses of patients with steroid- and DMARD-refractory IgG4-RSD to B lymphocyte depletion therapy.

Methods: Eight patients with IgG4-RSD were treated with rituximab (1000 mg times two). Clinical improvement was assessed by monitoring patients' ability to taper/discontinue prednisone and DMARDs, and by measuring the serum concentrations of B lymphocytes, immunoglobulins, and IgG subclasses before and after rituximab therapy.

Results: The patients' organ involvement included the pancreas, biliary tree, aorta, salivary glands (submandibular and parotid), eyes, lacrimal glands, lymph nodes, and retroperitoneum. Five patients had elevated serum IgG4 levels at baseline, with a mean concentration of 1547 mg/dl (normal: 8–140 mg/dl). Among these patients, the serum IgG4 concentrations declined by a mean of 65% within 2 months of rituximab administration. The decline in serum IgG4 concentrations was substantially steeper than that of the autoantibody concentrations in immune-mediated conditions in which rituximab is known to be effective, such as in rheumatoid arthritis. In addition, the reduction in IgG-subclass levels was specific for IgG4.

All eight patients demonstrated striking clinical improvement within 1 month of the initiation of rituximab therapy. Tapering or discontinuation of both prednisone and DMARDs was achieved in all eight patients. Four patients had minor disease recurrences approximately six months after treatment, characterized by symptom recurrence or serum IgG4 elevations. These disease flares correlated with B cell return in the peripheral blood. All four disease flares responded to second courses of rituximab. All eight patients are now off glucocorticoids and DMARDs entirely.

Conclusion: Treatment with rituximab led to prompt clinical and serologic improvement in refractory IgG4-RSD. The swift improvement of IgG4-RSD suggests that rituximab achieves its effects in IgG4-RSD by depleting the pool of B lymphocytes that replenish short-lived IgG4-secreting plasma cells, offering insights into the mechanism of action of this treatment approach.

Disclosure: A. Khosroshahi: None; **D. B. Bloch:** None; **V. Deshpande:** None; **J. H. Stone:** None.

ACR Poster Session C
Pediatric Rheumatology - Clinical and Therapeutic Aspects: Pediatric Rheumatic Diseases II
Wednesday, November 10, 2010, 9:00 AM–6:00 PM

1672

Anti-CADM-140/MDA5 Antibody Predicts Complication of Interstitial Lung Disease in Japanese Cases of Juvenile Dermatomyositis. Ichiro Kobayashi[1], Yuka Okura[1], Yasuhiro Yamazaki[1], Shunichiro Takezaki[1], Masafumi Yamada[1], Masataka Kuwana[2] and Tadashi Ariga[1]. [1]Department of Pediatrics, Hokkaido University Graduate School of Medicine, Sapporo, Japan, [2]Keio University School of Med, Tokyo, Japan

Background: Interstitial lung disease (ILD) is a life-threatening complication of both adult dermatomyositis (DM) and juvenile dermatomyositis (JDM). We have indicated that most of ILD develops at an early stage or at the time of relapse of JDM and is rapidly or moderately progressive (Kobayashi I, et al. Rheumatology 2003). Among ILD associated with DM, rapidly progressive interstitial pneumonia preferentially develops in clinically amyopathic DM (CADM) particularly in Asian races (Sontheimer RD. Arch Dermatol. 2010). Recently, anti-CADM-140/MDA5 antibody has been identified as a disease marker for ILD associated with adult CADM. In the present study, we examined the autoantibody in JDM complicated with or without ILD.

Materials and Methods: Thirteen cases of JDM including 6 cases with ILD were involved in this study. The diagnosis of JDM was made according to the diagnostic criteria by Bohan and Peters. Sera were obtained from the patients at the time of diagnosis of JDM and stored at −20°C until use. Anti-CADM-140/MDA5 antibody was measured by enzyme-linked immunosolbent assay using purified recombinant MDA-5 as an antigen as previously described (Sato S, et al., Arthritis Rheum 2009). The antibody units

were calculated from the optical density at 450 nm results (normal range: <8.0 U).

Results: Although case 1 died of respiratory failure, the other four previously reported cases showed recovery following the commencement of cyclosporine A in combination with methylprednisolone pulse therapy and oral high-dose prednisolone, and are drug-free for at least four years without relapse of either JDM or ILD. In an additional case, ILD developed approximately two months after the diagnosis of JDM which was associated with elevation of a serum KL-6 level (2,376 U/ml). This case is now successfully treated with cyclosporine A in combination with prednisolone following methylprednisolone pulse therapy. All the cases with ILD showed clinically apparent myositis associated with elevated levels of serum muscle derived enzymes during the course. Among the seven cases without ILD, two cases lacked both clinical myopathy and elevation of muscle-derived enzymes.

Five of the six cases with ILD were positive for the anti-CADM-140/MDA5 antibody (9.5–902.3 U). Three cases with rapidly progressive ILD showed extremely high levels of the antibody (357.6–902.3 U). In two cases in which ILD developed more than 1 month after the diagnosis of JDM, the antibody was detected before the development of ILD. All of the 7 cases without ILD were negative for the antibody (1.3–3.5 U).

Conclusion: Anti-CDMA140/MDA-5 autoantibody is not only a disease marker for ILD associated with JDM but also a predictive marker for the complication regardless of the muscle weakness. Our results suggest that common or similar mechanisms are involved in the development of ILD in both adult CADM and JDM.

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1673

Characterization at Diagnosis of Children with Microscopic Polyangiitis (MPA) Defined Uniquely among Patients with ANCA-Associated Vasculitis (AAV) in a Registry for Children with Vasculitis (ARChiVe).

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Background: Descriptions of MPA are limited by the inability of definitions (e.g. Chapel Hill Consensus Conference) to uniquely define patients and exclude another related vasculitis. Classification algorithms have been used to distinguish patients with related vasculitides by applying in a hierarchical sequence, from the most specific to the least specific, diagnostic criteria for each patient in a population.

Aims: To describe interval to diagnosis, presenting features and initial treatment for children uniquely classified as having MPA in ARChiVe.

Methods: Time-of-diagnosis data on children with AAV diagnosed since 2004 by expert rheumatologists (MD-diagnosis) has been contributed to ARChiVe from 37 US/ Canadian sites. A pediatric modification of the European Medicines Agency (EMEA) for AAV and polyarteritis nodosa (PAN) classification algorithm was applied by computation to this cohort to uniquely classify patients with MPA. Descriptive data on these MPA patients were then extracted. Sensitivity and specificity of the algorithm classification of MPA were tested (MD-diagnosis reference standard). The recently validated EULAR/PRINTO/PRES pediatric Wegener's granulomatosis (WG) criteria were applied to children with MPA to determine if there was diagnostic overlap.

Results: Of the 155 patients, 18 (12%) had MPA, 113 WG, 2 Churg-Strauss syndrome, 1 PAN, and 21 were unclassifiable. For the 18 children with MPA (67% female, 56% Caucasian) the median age at diagnosis was 13 (range 3–16) y, and the median interval from disease onset to diagnosis was 23 (range 2–50) mo. Presenting features are shown in Table and included: renal 95%, constitutional 89%, pulmonary 28% and sinus-upper respiratory 17%. Anti-MPO and anti-PR3 were present in 61% and 28% of patients respectively. Necrotizing pauci-immune glomerulonephritis was reported in 20% of 15 kidney biopsies. In 14 (78%) patients corticosteroids (CS) and cyclophosphamide (6 PO, 7 IV, 1 PO+IV) were the initial treatment; plasmapheresis (n=3), rituximab (n=2), and methotrexate (n=1) were also used in these 14. The remainder (n=4) received CS alone. Sensitivity and specificity of the EMEA algorithm for MPA were 22% and 92%. No MPA patients were concurrently classified by EULAR/PRINTO/PRES as WG.

Table. Frequency of presenting clinical features in pediatric patients with microscopic polyangiitis in the ARChiVe cohort (n = 155)

Clinical feature	Affected patients, n (%)
CONSTITUTIONAL/GENERAL	58 (89)
Malaise, fatigue	14 (78)
Weight loss	9 (50)
Fever	7 (39)
RENAL	17 (95)
Elevated serum creatinine	13 (72)
Hematuria with proteinuria	11 (61)
Hematuria with red blood cell casts	6 (33)
PULMONARY	5 (28)
Shortness of breath	3 (17)
Chronic cough	3 (17)
Hemoptysis/alveolar hemorrhage	2 (11)
Respiratory failure requiring ventilation	1 (6)
EAR, NOSE, THROAT	3 (17)
Sore throat	2 (11)
Nasal stuffiness	1 (6)
ANCA SEROLOGY	
Immunofluorescence for cANCA/pANCA, positive	14 (78)
Anti-MPO positive ELISA	11 (61)
Anti-PR3 positive ELISA	5 (28)
Negative ELISA	1 (6)
ELISA not done/not available	1 (6)

Conclusion: Pediatric patients uniquely classified with MPA had predominantly renal and constitutional manifestations and a positive ANCA. A minority had upper or lower respiratory tract disease. Initial therapy varied considerably. The protracted interval from symptom onset to diagnosis suggests MPA is a poorly recognized entity in children.

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1674

Clinical and Serological Factors Associated with Lupus Serositis in Children: Results from the 1000 Canadian Faces Multiethnic Cohort. America G. Uribe[1], Jaime Guzman[1], Ross E. Petty[3], Lori B. Tucker[2], Laura Musyj[1], Earl D. Silverman[4], Gaelle Chedeville[7], Adam Huber[5], Suzanne E. Ramsey[6] and Christine A. Peschken[8]. [1]BC Children's Hospital, [2]BC Childrens Hospital, Vancouver, BC, Canada, [3]BCs Childrens Hosptial, Vancouver, BC, Canada, [4]Hosp for Sick Children, Toronto, ON, Canada, [5]IWK Health Centre, Halifax, NS, Canada, [6]IWK Health Ctr, Halifax, NS, Canada, [7]Montreal Children's Hospital, [8]Univ of Manitoba, Winnipeg, MB, Canada

Background: Studies in adult patients with systemic lupus erythematosus (SLE) report serositis prevalence of 30–60%, and more common in patients with younger age SLE onset. In childhood-onset SLE, serositis prevalence ranges from 5%-60%; positive anti-Ro,-La,-Sm and -Jo-1 antibodies are related factors. The association of ethnicity with serositis has not been explored in pediatric patients.

Aim: To determine the prevalence of serositis in a multiethnic Canadian cohort of children and adolescents with SLE, and sociodemographic, clinical and serological features associated with serositis.

Methods: Eligible patients in the 1000 Canadian Faces of Lupus cohort (a prospective multicentre observational study of incident and prevalent cases of adults and children with SLE), were those diagnosed with definite SLE at age ≤ 18 yrs (fulfilling >4 ACR criteria), regardless of disease duration. Selected baseline data included: socio-demographic information (age at diagnosis, ethnicity, gender); clinical characteristics [accrued SLE criteria, disease activity (SLEDAI, physician and patient global assessment on a 10-cm visual analogue scale) and damage (SLICC damage index)]; and serology results (ANA, anti-dsDNA, -Sm, -RNP, -La, -Ro, IgG and IgM anticardiolipin antibodies, lupus anticoagulant). Serositis was defined as the presence of pleuritis, pericarditis and/or peritonitis as per the ACR criteria or SLEDAI definitions. Factors related to serositis were examined using univariable descriptive statistics, followed by multivariable analyses.

Results: 193 children were studied (154 female). Mean (SD) age at diagnosis was 12.3 (3.3) yrs. Mean (SD) total disease duration at study entry was 2.5 (2.6) yrs. Serositis was present in 35 (18.1%) children; 18 patients had pleuritis only, 5 had pericarditis, and 12 had both. Serositis was present at diagnosis in 48.6%. Sociodemographic and clinical characteristics associated with serositis are presented in Table. In multivariable analyses, Aboriginal (OR=18.5, 95% CI 1.8–188.6) and African Canadian (OR=5.7, 95% CI 2.1–15.7) ethnicity and accrual of 5 or more ACR criteria at study recruitment (OR=12.7, 95% CI 4.0–40.9) were positively associated with serositis; conversely, mucocutaneous involvement (OR=0.1, 95% CI 0.1–0.5) and positive result for any anti-phospholipid antibody (OR=0.3, 95% CI 0.1–0.8) were negatively associated with serositis.

Variable	Serositis No (n = 158)	Serositis Yes (n = 35)	*p* value
Female, %	80.3	91.4	0.118
Age at diagnosis, years, mean (SD)	12.4	11.6	0.213
Ethnicity, %			0.002
Aboriginal	25.0	75.0	
African Canadian	52.7	47.3	
Asian	81.7	18.3	
Caucasian	87.0	13.0	
Hispanic	100.0	0.0	
Middle Eastern	75.0	25.0	
Mixed	83.3	16.7	
Mucocutaneous involvement, %	72.5	45.7	0.002
Arthritis, %	62.1	65.7	0.689
Neurologic involvement- T0, %	12.0	20.0	0.165
Renal involvement, %	38.6	40.0	0.875
Hematologic involvement, %	68.6	82.9	0.093
Fulfilled ≥ 5 ACR criteria, %	28.1	62.9	<0.001
SLEDAI score, mean (SD)	3.4 (4.4)	3.5 (3.8)	0.846
Physician global assessment, cm, mean (SD)	1.7	1.5	0.776
SLICC/ACR Damage Index, mean (SD)	0.3 (0.8)	0.4 (0.8)	0.660
Autoantibodies, positive, %			
Antinuclear	99.3	100.0	1.000
Anti-dsDNA	83.5	77.1	0.901
Anti-Sm	37.8	46.9	0.348
Any anti-phospholipid	60.0	40.6	0.080
Anti-RNP	38.1	36.1	0.853
Anti-La	16.0	30.6	0.057
Anti-Ro	33.7	41.7	0.443

Conclusion: We found a lower than expected prevalence of serositis in this multiethnic Canadian pediatric lupus cohort. Serositis was more prevalent among Aboriginal and African Canadian patients. Positive anti-phospholipid antibodies or mucocutaneous involvement were less frequent among patients with serositis.

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1675

Cogan Syndrome: A Rare but Severe Vasculitis in Pediatric Age. Ilaria Pagnini[3], Maria Elisabetta Zannin[4], Marianna Sari[2], Gabriele Simonini[1], Rolando Cimaz[6] and Francesco Zulian[5]. [1]Anna Meyer Children's Hospital, Florence, Italy, [2]Department of Medical and Surgical Specialties, Section of Otolaryngology, University of Padua, Italy, [3]Department of Pediatrics, University of Florence, Italy, [4]Department of Pediatrics, University of Padua, Italy, [5]Universita Di Padova, Padova, Italy, [6]University of Firenze, Firenze, Italy

Background: Cogan syndrome (CS) is a vasculitis characterized by systemic, ocular and vestibuloauditory symptoms. Only a few pediatric patients have been reported in literature so far and few information is available as far as disease course and outcome.

Methods and Materials: We describe three caucasian children (1M, 2F) with CS and compare them with the data of the literature. We reviewed the clinical records of patients with defined diagnosis of CS followed at two Pediatric Rheumatology Institutions and patients with pediatric-onset CS from a database search in Medline. Data collected included clinical features, ocular and ENT evaluations at onset and during the disease course, laboratory variables, treatment and outcome.

Summary of the Results: During the period 1990–2009, three patients with definite diagnosis of CS have been followed in our units and 20 more patients have been reported in 16 publications. In the whole cohort of 23 cases, the mean age at onset was 11.6 years (range 4–18) and the F:M ratio was 2:1. Half of the patients had systemic symptoms at onset such as fever (30%), or musculoskeletal pain (26%), 78% had ocular symptoms such as red eye, often with photophobia (57%), as presenting signs of interstitial keratitis (26%), episcleritis (9%) or uveitis (4%), conjunctivitis (17%), and visual loss (4%). Audiovestibular symptoms were present in 74% of the patients, most of them (65%) had sensory neural hearing loss (SNHL) and 35% vestibular dysfunction such as vertigo, vomiting or ataxia. Cardiac involvement, mainly aortic insufficiency, and skin rash were found in 22% and 13% of the patients, respectively. Treatment consisted in corticosteroids (83%), methotrexate (30%), cyclophosphamide or MMF (4%). After a mean 4 year follow-up, 35% of the patients were in complete remission with no organ damage, the remaining reported residual deafness or SNHL (35%), irreversible cardiac complications (13%), vestibular dysfunction (4%), ocular damage (4%), or chronic hepatitis (4%). Only one patient died one year after disease onset for subaracnoid hemorrhage.

Conclusions: Cogan syndrome is a rare, severe and, probably, under diagnosed vasculitis of the pediatric age. In older children with systemic symptoms, red eye, vertigo and/or hearing loss CS should be always considered in the differential diagnosis since a prompt treatment may prevent irreversible organ damage.

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1676

Decreased Vitamin D Levels in Children and Adolescents with Systemic Lupus Erythematosus. Octavio Augusto Bedin Peracchi[1], Regina Viviane Munekata[2], Maria Teresa Ramos Ascensão Terreri[2], Roseli Oselka Sacardo Sarni[2], Marise Lazaretti[2] and Maria Odete Esteves Hilario[2]. [1]Universidade Federal de São Paulo, São Paulo, Brazil, [2]Universidade Federal de São Paulo, Brazil

Background: The vitamin D deficiency has been related to the development of autoimmune diseases. There are only a few studies in the literature evaluating the nutritional status related to vitamin D in pediatric patients with rheumatic diseases.

Objectives: To evaluate the levels of 25(OH)D3 and to correlate them with disease activity, use of medications (chloroquine and glucocorticoids),

calcium and vitamin D intake, bone mineral density and parathormone (PTH) levels.

Methods: Determination of 25(OH)D3 and PTH was performed during the spring in 30 children and adolescents with Systemic Lupus Erythematosus according to the Hochberg classification criteria (1997). The patients with or without disease activity, with any clinical manifestation, in use of any medication, and with minimal disease follow-up of 6 months were compared to 30 healthy individuals age and gender matched. Controls (n= 30) were not on any medication and had no calcium metabolism impairment. Vitamin D normal levels were considered between 20–32 ng/mL. Bone mineral densitometry was also performed in the patients.

Results: We found significant different levels of 25(OH)D3 between patients and controls (mean 18.79 ng/mL and 27.18 ng/mL respectively—$p<0.001$). Fifteen (50%) patients and 6 (20%) controls had low levels of 25(OH)D3 (< 20 ng/mL). There was no association between PTH and vitamin D levels in patients and controls (mean of 35.86 pg/mL and 31.26 pg/mL respectively; $p=0.268$). Only one patient with low level of vitamin D presented with hyperparathyroidism. We found no association between disease activity when considered SLEDAI > 1 or SLEDAI > 4 and low levels of vitamin D. Eleven (37%) patients were taking vitamin D supplementation and 5 of them (17%) had low levels of vitamin D. Seven patients (23%) presented a bone mineral density under −2.0 SD and mean levels of 25(OH)D3 of 14.70 ng/mL (9.61–19.88) with no significant association between them ($p=0.456$).

Conclusion: Children and adolescents with lupus may present low serum levels of vitamin D, however with no association with disease activity, higher levels of PTH and bone mineral density alterations.

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1677

Does Atorvastatin Reduce Progression of Carotid Intimal Medial Thickening (CIMT) in Childhood SLE? Results from the Atherosclerosis Prevention in Pediatric Lupus (APPLE) Trial: A Multicenter, Randomized, Double-Blind Placebo-Controlled Study. Laura E. Schanberg[3], Christy I. Sandborg[4], Huiman X. Barnhart[3], Stacy P. Ardoin[2], Eric Yow[3], Gregory W. Evans[5], Kelly L. Mieszkalski[3], Normal T. Ilowite[2], Anne Eberhard[2], Lisa F. Imundo[1], Yukiko Kimura[2], Emily Von Scheven[2], Earl Silverman[2], Suzanne L. Bowyer[2], Lynn Punaro[2], Nora G. Singer[2], David D. Sherry[2], Deborah McCurdy[2], Marisa Klein-Gittelman[2], Carol A. Wallace[2], Richard Silver[2], Linda Wagner-Weiner[2], Gloria C. Higgins[2], Hermine I. Brunner[2], Lawrence Jung[2], Jennifer B. Soep[2], Ann Reed[2], Charles Tegler[6] and APPLE Investigators[2]. [1]Childhood Arthitis and Rheumatology Research Alliance, New York, NY, [2]Childhood Arthritis and Rheumatology Research Alliance, CARRA, [3]Duke Univ Medical Center, Durham, NC, [4]Stanford Medical Center, Stanford, CA, [5]Wake Forest Univ, [6]Wake Forest University

Background: SLE patients are at markedly elevated risk for premature cardiovascular events. Given lifelong exposure to increased atherogenic potential, children and adolescents with SLE are ideal targets for prevention. Statins reduce cardiovascular morbidity and mortality in the general population, but their efficacy in preventing atherosclerosis progression in pediatric SLE is unknown.

Methods: Children and adolescents with SLE, aged 10–21y, from 21 CARRA sites were randomized to receive atorvastatin (10–20 mg based on weight) or placebo and followed for 3 years. All subjects met 1997 ACR criteria for SLE. Exclusion criteria included nephrotic syndrome, cholesterol >350, creatinine >2.5, CPK >3X nl or liver functions >2X normal. Background therapy included hydroxychloroquine, aspirin, folate, risk factor counseling, the AHA Therapeutic Lifestyle Changes diet, and routine SLE management. The primary endpoint was rate of progression of mean common CIMT, a surrogate marker for atherosclerosis, using a standardized ultrasound protocol read by a central core. Secondary endpoints included progression of mean maximal CIMT and lipid levels. The total sample size of 220 provided 83–98% power to detect a 0.0045mm/y difference in mean-common CIMT progression rates between groups with an overall 0.05 type I error for several scenarios based on the estimated parameters for mean-mean common CIMT correlation of 0.6 between time points and SD (0.038–0.047mm), dropout (11.6–23.1%), and compliance rate (71–84%).

Results: A total of 221 subjects were randomized between 9/03–11/06 with 183 (83%) of them completing the trial. See table for baseline characteristics.

APPLE BASELINE CHARACTERISTICS (N=221)			
Age (SD)	15.7 (2.6)	CV RISK FACTORS	
% female	83%	CRP (SD)	3.6 mg/L (14)
Post-Menarchal	83%	Smoking	3%
RACE/ETHNICITY*		Diabetes	2%
Hispanic or Latino	24%	Obesity	14%
Caucasian	52%	HX HTN	34%
African American	27%	Fam HX CVD	22%
Asian	10%	Fam HX hyperlipidemia	37%
Other	19%	LIPID LEVELS	
Non-European Caucasian	65%	Total Cholesterol (SD)	155 mg/dL (38)
CLINICAL FEATURES		LDL (SD)	86 mg/dL (31)
Duration of SLE (SD)	31 mo (28.5)	HDL (SD)	46 mg/dL (13)
Positive ANA	99%	Triglycerides (SD)	114 mg/dL (66)
Positive DsDNA ab	82%	MEDICATIONS	
SLEDAI (SD)	4.8 (4.3)	Corticosteroids (HX)	82% (93%)
SLICC	No damage 73%	Cyclophosphamide (HX)	12% (38%)
Renal Biopsy	43%	Mycophenolate (HX)	24% (56%)
Class III/IV	68%	Azathioprine (HX)	14% (22%)
Creatinine (SD)	0.7 mg/dL (0.2)	ACE Inhibitor	24%

SD – standard deviation, HX – history of
*Some subjects self reported more than one category

There were 138 SAEs with 7 considered related to study drug. Rhabdomyolysis was not reported. Database was locked on 6/21/10 and the final results of primary and secondary endpoints will be presented.

Conclusions: APPLE is an RCT designed to assess the safety and efficacy of atorvastatin in preventing progression of CIMT in pediatric SLE. APPLE represents the first RCT in pediatric SLE, the first CARRA clinical trial, and the longest study of statins in a pediatric cohort. Preliminary data demonstrate successful enrollment of the target population and completion of trial within study parameters. The data quality indicates that study results will determine whether use of statins in children and adolescents with SLE decreases CIMT progression and the risk of premature atherosclerosis.

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1678

Environmental Factors Preceding Illness Onset Differ in Phenotypes of the Juvenile Idiopathic Inflammatory Myopathies. Lisa G. Rider[11], Lan Wu[12], Gulnara Mamyrova[4], David D. Sherry[13], Maria D. Perez[9], Carol A. Wallace[14], Lisa F. Imundo[6], Catherine A. Bingham[3], Lawrence S. Zemel[1], Carol B. Lindsley[8], Rafael F. Rivas-Chacon[7], Patience H. White[11], Robert Rennebohm[12], Michael Henrickson[10], Ira N. Targoff[5], Frederick W. Miller[2] and Childhood Myositis Heterogeneity Study Group[12]. [1]Connecticut Childrens Med Ctr, Hartford, CT, [2]National Institute of Environmental Health Sciences, NIH, Kennsington, MD, [3]NIEHS, NIH, Zionsville, PA, [4]NIEHS, NIH, Washington, DC, [5]NIEHS, NIH, Oklahoma City, OK, [6]NIEHS, NIH, New York, NY, [7]NIEHS, NIH, Miami, FL, [8]NIEHS, NIH, Kansas City, KS, [9]NIEHS, NIH, Houston, TX, [10]NIEHS, NIH, Cincinnati, OH, [11]NIEHS, NIH, Bethesda, MD, [12]NIEHS, NIH, [13]The Children's Hospital of Philadelphia, Philadelphia, PA, [14]University of Washington and Seattle Childerns's Hospital, Seattle, WA

Purpose: We examined whether certain environmental factors are temporally associated with the onset of juvenile idiopathic inflammatory myopathies (JIIM) and differ among age, ethnic, disease course and autoantibody phenotypes.

Method: Physicians completed questionnaires regarding documented infections, medications, immunizations, and an open-ended question about other noted exposures within six months before illness onset for 285 patients with probable or definite JIIM. Medical records were available and reviewed

for 81% of cases to confirm the exposure. Myositis autoantibodies were identified by validated immunoprecipitation methods.

Results: Sixty percent of JIIM patients had a reported exposure within six months before illness onset. Most patients (62%) had one recorded exposure, 26% had two, and 12% had 3–5 exposures. Patients older than the median age at diagnosis, those with a longer delay to diagnosis and those with anti-signal recognition particle autoantibody had a higher frequency of documented exposures (OR 3.4–31). Infections were the most common exposure and represented 44% of the total number of reported exposures, with respiratory infections being the most common (66%). Pharyngitis was the most frequent specific infection (22%) and was more frequent in older patients (OR 2.7). Noninfectious exposures included medications (18%), immunizations (11%), stressful life events (11%), unusual sun exposure (7%), and others including, chemicals, animal contact, weight training, and dietary supplement use (<5% each). Exposures varied by age at diagnosis, delay to diagnosis, race, disease course, and the presence of certain myositis autoantibodies. Children younger than the median age at diagnosis, those with ≤4 months delay to diagnosis, or with a polycyclic illness course were more likely to have an infection within six months of diagnosis (OR 1.8–4.3), whereas older children had a higher frequency of stressful life events prior to illness onset (OR 3.5). Caucasian patients and those without a myositis autoantibody had a higher frequency of infections in the six months prior to illness onset (OR 2.7 – 3.9). Older children were more likely to have two drug exposures prior to illness onset (OR 18.9), and 36% of these were potentially myopathic or photosensitizing agents.

Conclusion: While infections were the most common exposure temporally associated with the onset of JIIM, supporting prior findings, many other exposures, including non-infectious agents, were also documented within six months before disease onset. The JIIM may be related to multiple exposures, and these exposures appear to vary among illness phenotypes. This exploratory study has identified a number of environmental exposures that are potential risk factors and suggests that controlled investigations of independent populations be performed to confirm and expand upon these findings.

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High Prevalence of Inflammatory Myositis in Patients with Pediatric Systemic Lupus Erythematosus in a Southeastern US State. Jessica L. Record[3], Timothy Beukelman[2] and Randy Q. Cron[1]. [1]Children's Hospital of Alabama, Birmingham, AL, [2]University of Alabama-Birmingham, Birmingham, AL, [3]University of Alabama-Birmingham, Birmingham, AL

Background: Inflammatory myositis has traditionally been recognized as a feature in 5–11% of adult systemic lupus erythematosus (SLE) patients. The aims of this study were to determine the prevalence of myositis in a cohort of pediatric SLE patients from a single center in a southeastern US state, to compare this rate with the reported prevalence in the medical literature, and to evaluate clinical factors for possible association with myositis.

Methods: Records of 55 patients with the diagnosis of SLE who had been evaluated by the Division of Pediatric Rheumatology and satisfied at least 4 out of 11 ACR criteria for the classification of SLE were identified at an academic children's hospital in the southeastern US. Their electronic medical records were reviewed and information was collected regarding general demographics, complement levels, muscle enzymes, musculoskeletal exam, and clinical and serological manifestations. For the purpose of this study, patients were defined as having inflammatory myositis if they satisfied one of the following categories: 1) Proximal muscle weakness on physical exam with evidence of muscle edema on MRI (T2 or STIR image) of the lower extremity; 2) Proximal muscle weakness on physical exam with an elevation in one of the following muscle enzymes: CK, AST, aldolase, or LDH; or 3) Patient reported muscle weakness or muscle pain (without weakness noted on physical exam) and an elevated CK. The prevalence rate of myositis in our cohort was compared to previously reported rates using the chi-square test. Fisher's exact test and one-way ANOVA were used to determine possible associations between myositis and clinical and laboratory factors.

Results: The mean age of our cohort at the time of this study was 16.4 years. The mean age of onset of initial SLE symptoms was 13.2 years. 87.3% were female and 74.5% were African-American. Inflammatory myositis was present as a feature of SLE in 31% (n=17) with a 95% confidence interval of 19 to 45%, which is statistically different from the reported rates of 5–11% ($p<0.0001$). Myositis was shown to be positively associated with anti-ribonucleoprotein (RNP) antibodies ($p=0.009$) and anti-Smith (Sm) antibodies ($p=0.06$). Negative associations with myositis were the presence of anti-double stranded DNA antibodies ($p=0.02$) and hematological disorders ($p=0.02$).

Conclusions: In this southeastern US state, pediatric SLE myositis is present at a statistically higher rate than previously published values of adult SLE myositis. The association of myositis with anti-RNP antibodies is consistent with the medical literature. The presence of myositis can serve as a warning sign for a potential SLE flare and a marker of the effectiveness of a treatment regimen. The presence of both anti-RNP and anti-Sm antibodies further highlights the significant overlap SLE has with other autoimmune diseases such as mixed-connective tissue disease and the challenges that come with appropriately classifying and treating these overlap patients.

Disclosure: J. L. Record: None; **T. Beukelman:** None; **R. Q. Cron:** None.

1680

Infliximab for the Treatment of Intravenous Immunoglobulin Resistant Kawasaki Disease in Chinese Children. F. Q. Wu[1], X. M. Hu[2], Y. L. Zhang[2] and L. P. Yang[2]. [1]Capital Institute of Pediatrics, Beijing, China, [2]Capital Institute of Pediatrics

Objectives: Evaluate the efficacy and safety of Infliximab in patients with Kawasaki disease (KD) who were unresponsive to intravenous gamma globulin (IVIG) treatment.

Methods: The diagnosis of KD was made according to the diagnostic guidelines for Kawasaki disease (5th revised edition) of the Kawasaki Disease Committee in Japan and APP/AHA diagnostic guidelines for Kawasaki disease, published in 2004. Pediatric subjects diagnosed with KD with coronary artery lesions, and who failed treatment with IVIG, were enrolled in the study. Subjects were given a single infusion of Infliximab of 5–6mg/kg. The patients were followed up for 21 weeks. The persistence time of fever, CRP, ESR, ultrasonic cardiogram and infusion reaction were observed.

Results: A total of 12 subjects were enrolled in the study from May 2009 to Jan 2010 in Department of Rheumatology of Capital institute of Pediatrics, including seven boys and five girls. The mean age was 23.3 months and the mean duration of the symptoms was 6.6 days. Seven of the subjects were <1 year. All 12 subjects were treated with IVIG 2–3 times. Injectable dexamethasone was used in 4 subjects for fever. All subjects had taken aspirin (30mg/kg) orally before treatment with Infliximab. The Clinical and laboratory recovery times are listed in the table below. The subjects' temperature decreased within 12 hours after treatment with Infliximab. The CRP, ESR, blood cell counts and mild-to-moderate coronary artery lesions recovered within 8 weeks. No infusion reactions were observed.

Conclusion: Infliximab appears to have good efficacy and safety in the treatment of Kawasaki syndrome in patients who were unresponsive to treatment with IVIG.

Infliximab for the Treatment of Intravenous Immunoglobulin Resistant Kawasaki Disease in Chinese Children

	Patients (n)	Recover time
Clinical manifestation		
Fever	12	12–48 hours
Erythra	10	48 hours
Laboratory examination		
Increase of white cell count	12	7–10 days
Increase of platelet	12	3 months
Increase of CRP	12	7–10 days
Increase of ESR	12	7–10 days
Decrease of serum albumin	8	7 days
Increase of ALT	5	4–6 weeks
Increase of AST	5	4–6 weeks
Electrocardiogram		
T wave change	8	2 weeks
=* atrioventricular block	4	2 weeks
Echocardiography		
Left coronary artery distension	5	4–12 weeks
Left anterior descending distension	5	4–12 weeks
Circumflex coronary artery distension	2	4–12 weeks
Right coronary artery distension	1	4–12 weeks
Bilateral coronary artery distension	6	4–12 weeks
Mild coronary aneurysm	8	4–12 weeks

Recovery time of clinical manifestation and laboratory examination

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Juvenile Fibromyalgia: Responsiveness of Tools, Greatest Areas of Impairment, and Impact of an Aerobic Exercise Program. Nadia J. C. Luca[2], Brian M. Feldman[3], Larisa Tshantshapanyan[4], Lusine Abrahamyan[4], Samantha Stephens[4], Nicolette Bradley[4], Jane Schneiderman[4], Virginia Wright[1] and Shirley M. L. Tse[3]. [1]Bloorview Kids Rehab, Bloorview Research Institute, [2]Hospital for Sick Children, Toronto, ON, Canada, [3]The Hospital for Sick Children, Toronto, ON, Canada, [4]The Hospital for Sick Children

Background: Patients with juvenile fibromyalgia (FM) have generalized MSK pain, fatigue, and poor sleep, as well as high rates of school absence and functional disability.

Objectives: This study determines which areas of functioning are most impaired in children with FM, as well as the effect of an aerobic exercise program on ability to do specific activities. Also, the responsiveness of various evaluation tools in juvenile FM was evaluated.

Methods: FM patients aged 8–18 were asked to complete the FM Impact Questionnaire and Functional Status and Symptom Questionnaire (FSSQ), as well as other questionnaires, while participating in a randomized, 12-week trial of either aerobic exercise or control (qigong). Data were collected before and after the intervention. A repeated measures analysis of variance was used to compare the rates of change in ability between the groups after the exercise intervention.

Results: Thirty patients participated in the study, and 24 patients completed the program (12 in aerobic and 12 in qigong group). At baseline, a minority of patients reported difficulties with daily function (homework 11%, chores 23%) and social function (31%); whereas, on average, 56% reported difficulty with physical function. Specific activities associated with great difficulty or inability included playing sports after school (43%), running long distances (35%), and participating in gym class (25%). The most prominent symptom during physical activities was pain. Subjects also reported difficulty with waking up for school and attending overnight camp (37% and 26% respectively), mostly due to fatigue and sleep difficulties.

After the exercise intervention, subjects in both groups showed improvement in function. However, when compared with subjects in the qigong group, those in the aerobic group demonstrated a significantly greater improvement in ability to run long distances ($P=0.023$), attend school every day ($P=0.036$), and complete homework ($P=0.003$).

Greatest responsiveness, as measured by effect size, was associated with PedsQLpain2, HR QOL, C-HAQ (total score), and the FSSQ questionnaires.

Conclusions: Juvenile FM causes significant difficulties in function, mostly seen in physical activities and activities affected by poor sleep. Daily and social activities tend to be relatively spared. The most prominent symptoms experienced are pain, fatigue and sleep difficulties. Aerobic exercise was found to have greatest impact in improving physical and daily functions but, in our sample, did not affect social function. The FSSQ, as well as other evaluation tools for juvenile FM, has a strong responsiveness.

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1682

Juvenile Localized Scleroderma of the Face: A Neuro-Cutaneous Disease? Francesco Zulian[2], Mattia Parolin[3], Fabio Vittadello[3], Milena Calderone[3], Giorgia Martini[3] and Susanne Ullman[1]. [1]Bispebjerg Hospital, Copenhagen, Denmark, [2]University of Padua, Padova, Italy, [3]University of Padua

Background: Neurological involvement has been reported in few case reports of patients with juvenile localized scleroderma of the face (JLS-F). Aim of the study was to systematically investigate frequency, clinical and radiological features of CNS involvement in JLS-F.

Methods: A cohort of consecutive patients with JLS-F (including *en coup de sabre* (ECDS) and Parry Romberg syndrome (PRS)) underwent a comprehensive clinical evaluation, EEG and brain MRI. All radiographic films were analyzed by 2 neuroradiologists who were blinded to the patients' identity and clinical records. Parenchymal lesions were assessed by a standardized protocol (1) and classified by number, laterality, gray or white matter involvement and concordance with the skin lesion.

Results: 34 patients with JLS-F entered the study, F:M ratio was 1.4:1, mean age at disease onset 8,6 years. Twenty nine patients (85.3%) had linear scleroderma of the face, 5 (14.7%) presented a mixed subtype, 23 patients (67.6%) had ECDS, 11 (32.4%) PRS. CNS involvement was found 21 (61.8%) patients, 11 (32,4%) had neurological symptoms such as chronic headache (5), seizures (3), hemiparesis (1), behavioural abnormalities (1) and cranial nerve palsy (1). Ten patients (29,4) presented MRI abnormalities without symptoms. EEG was abnormal in 5 patients (14,7%), all symptomatic and/or with MRI changes. Cerebral MRI resulted abnormal in 17/34 patients (50%). Twelve patients underwent more than one brain MRI which worsened in 5 patients (41,7%), unchanged in 5 (41,7%) and persisted normal in 2 (16.6%). Eight patients had a single brain lesion, 9 a multiple pattern. In 88,2% the site of skin and neurologic lesions were concordant. White matter involvement was present in 10/17 (58,8%), lesions extended to the grey matter in 7 (41,2%).

Four group of patients have been identified: group 1 patients with neurological symptoms and organic brain lesions (mainly multiple with white and grey matter involvement) concomitant or following the onset of the scleroderma skin lesion (no.7), group 2 (no.10) patients with just organic brain lesions following the skin lesions by 1–18 years, mainly single white matter lesions concordant with the site of skin lesion, group 3 (no. 4) patients with neurological symptoms but no organic brain lesions and group 4 (no.13) patients with no neurological involvement.

Conclusion: The high prevalence of neurological involvement in JLS-F reinforces the hypothesis of a possible pathogenetic link CNS-skin in localized scleroderma and confirms the need for a careful clinical and radiological monitoring of every patient since the disease onset.

Reference:

1. Benseler S et al Primary CNS Vasculitis in Children. Arthritis Rheum 2006; 54: 1291–7

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Localized Scleroderma Therapy: When Would Be a Good Time To Stop? Thaschawee Arkachaisri[1] and Kathryn S. Torok[2]. [1]KK Women's and Children's Hosp, Singapore, Singapore, [2]Univ of Pittsburgh Med Ctr, Pittsburgh, PA

Background: Localized Scleroderma (LS) is the most common form of juvenile scleroderma. Its long-term physical and psychological impact continues to cause significant disability. Different therapy options were reported with inconsistent results. Longterm followup (FU) data after the disease is under control is unknown. Combined high dose SC methotrexate and a weaning dose of oral corticosteroids have been shown to be effective in our pediatric LS cohort.

Purpose: We report a prospective data on the longterm outcome of a single center treatment protocol in a pediatric LS cohort and propose the duration of therapy for LS.

Methods: LS patients were recruited from the Scleroderma Clinic at the Children's Hospital of Pittsburgh. Patients with active disease, defined as those with erythematous lesions, and/or new lesions, or expansion of existing lesions; were started on oral prednisone 2 mg/kg/day (max 60mg/day) and SC methotrexate (MTX) at 1 mg/kg/week. Prednisone was weaned to reach 1 mg/kg/day by the end of 6–8 weeks, and then further weaned to 0.25 mg/kg/day to complete 12 months of steroid therapy. MTX was continued for a full 24 months of SC therapy with subsequent oral therapy for 12 more months. The disease outcome parameters used to assess effectiveness of therapy were the modified LS Skin Severity Index

(mLoSSI) and the physician global assessment of disease activity (PGA). All patients were followed every 4–8 weeks with appropriate therapy adverse reaction monitoring. Flare was defined by the reoccurrence of erythematous lesions, and/or new lesions, or expansion of existing lesions. Kaplan-Meier analysis was used to analyzed recurrence rate and survival-time data.

Results: Thirty-nine patients were included (70% female, 95% Caucasians). LS Subtypes are–4 plaque morphea, 14 linear scleroderma (Li), 6 *en coup de sabre*, 3 subcutaneous morphea (SqM), 5 generalized morphea and 7 mixed LS. Median age at onset was 7.9 years (IQR 4.5–11.6). Median duration of FU was 36.9 mo(range 8.7–105.8). Clinical improvement (mLoSSI and PGA) was demonstrated at the median of 1.1 mo (IQR 0.5–1.9). No patients developed flare during therapy. During FU period, 4 patients flared(3 Li and mixed LS and 1 SqM; 3 females) after discontinued therapy after completed 36 mo and in remission. Median duration to flare was 4.7 mo (range 0.99–10.1). This gives the flare incidence 0.0034 person-months. Cumulative probability risk of recurrence is estimated from our cohort that about 25% and 50% of flare within 46 and 54 mo, respectively. Over the study period(up to 78 mo), the probability of flare does not reach 75%. There was no major complication noted.

Conclusion: The uniform treatment protocol given to all LS patients who required systemic therapy in our center enables us to assess the longterm outcome of the regimen more accurately. The therapy is effective in controlling the disease, however, after discontinuing therapy, 10% flare within 6 months. We proposed to continue the therapy longer, at least 48–54 months in order to decrease the rate of flare.

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1684

Longitudinal Study on Growth Failure and Height Deflection in Juvenile Systemic Lupus Erythematosus (JSLE): The Result of a Prospective Multicentre PRINTO Study. Marite Rygg[3], Angela Pistorio[3], Angelo Ravelli[3], Mohamad Maghnie[3], Natascia Di Iorgi[3], Erkan Demirkaya[3], Srdjan Pasic[3], Huri Ozdogan[3], Brigitte Bader-Meunier[3], Carlos Henrique M. Da Silva[3], Liora Harel[3], Maria Rosa Roldan Molina[3], Helena Canhao[3], Johannes Roth[3], Carine Wouters[3], Judith Barash[3], Rym Hajri Ben Ammar[3], Christina Dracou[3], Sylvie Gandon-Laloum[3], Alberto Martini[2] and Nicolino Ruperto[1]. [1]IRCCS G. Gaslini/Università degli Studi di Genova, Genova, Italy, [2]IRCCS G. Gaslini/Università degli Studi di Genova, [3]PRINTO

Background: Growth failure is a unique feature of JSLE, caused by long-term disease activity, side effects of drugs, and/or co-morbid conditions.

Objective: The goal of the study was to obtain longitudinal data on growth in a large-scale, multi-national cohort of patients with JSLE followed for 26 months.

Materials and Methods: This prospective, multi-centric study on JSLE was carried out in 39 countries from Northern and Southern Europe, Latin America, US and Asia between 2001 and 2004. Patients seen at the participating centers with diagnosis of JSLE, at active phase, and age younger than 18 years at enrollment were included.

Results: Data was collected from 557 patients with JSLE. There was a significant reduction in parent-adjusted height z score with time in females and males ($p<0.0001$) with a significant gender difference ($p<0.0001$), male height being most affected. Median BMI z score peaked at 6 months and was still significantly above baseline after 26 months ($p<0.01$) with no gender difference. Standardized height reduction was inversely related to age at disease onset in females, especially pronounced at onset age <8 years. Females with onset age <12 years had a median parent-adjusted height z score of -0.87 with no catch-up growth. At the end of the study, growth failure was seen in 14.7% of the females and 24.5% of the males. Height deflection (less than-0.25/year) was found in 20.7% of the females and 45.5% of the males.

Conclusions: The longitudinal effect on height is modest in JSLE females with age at onset ≥ 12 years. In spite of all our knowledge and careful treatment, females <12 years at onset and males are still at risk of experiencing a considerable height loss during the course of the disease.

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1685

Long-Term Follow Up of Hyper IgD Syndrome: A National Multicentre Study. Silvia Federici[8], Alberto Tommasini[6], Antonella Meini[7], Giuseppina Calcagno[5], Francesco Zulian[2], Rita Consolini[3], Martina Finetti[8], Luciana Breda[1], Roberta Caorsi[8], Romina Gallizzi[5], Maria Alessio[4], Alberto Martini[8] and Marco Gattorno[8]. [1]Clinica Pediatrica, Divisione Reumatologia Pediatrica, Ospedale Policlinico di Chieti, [2]Dipartimento A.I. di Pediatria, Università di Padova, [3]Dipartimento di Medicina della Procreazione e dell'Eta' Evolutiva, Università di Pisa, Italy, [4]Dipartimento di Pediatria, Università Federico II, Napoli, Italy, [5]Dipartimento di Scienze Pediatriche, AOU "G. Martino", Messina, [6]IRCCS Burlo Garofolo, Trieste, [7]Unità di Immunologia e Reumatologia Pediatrica, Spedali Civili, Brescia, [8]UO Pediatria II Istituto G. Gaslini, Genova, Italy

Purpose: Hyper-IgD syndrome (HIDS) is an autosomal recessive disease caused by mutation in the MVK gene. Aim of the study was to analyze the long term follow-up of a group of children and young adults affected by HIDS.

Patients & Methods: The first 10 exons of MVK genes were analyzed in 720 consecutive patients with periodic fever by means of denaturing high-performance liquid chromatography (DHPLC) and DNA sequencing. 40 patients carried 2 mutations of the MVK gene. Detailed clinical information were collected at the time of molecular analysis and last follow-up through a standardized questionnaire. Spontaneous disease course was classified as follows: i) resolution (no episodes in the last 6 months), ii) improvement (reduction of more then 30% of fever episodes) iii) stationarity iv) worsening (increase frequency of fever episodes or appearance of new major clinical manifestation).The Child Health Questionnaire (CHQ-PF 50) was used to assess the health related quality of life

Results: the mean age of diseaseonset was 0.7 yrs (range1 months-3 yrs). At baseline, mean duration of fever episode was 4.7 days. The clinical features associated to fever episodes were abdominal pain (97.5%), cervical lymphadenopaty (97.5%) with pain (80%), diarrhea (77.5%), erythematous pharingitis (75%), vomiting (65%) and aphtous stomatitis (57.5%). So far, data on follow-up are available for 24 patients. The mean follow-up time was 13.8 yrs (range 2.3–38.2 yrs). Steroid on demand was effective in treating fever episodes. Ten patients showed a significant spontaneous reduction of the frequency of fever episodes. In the remaining 14 patients the frequency of fever episodes was stable (7 patients) or increased (7 patients). Complete resolution was achieved after introduction of Anakinra (2 patients) and tonsillectomy (1 patient). One patients improved after Anakinra, 2 after tonsillectomy. Two patient did not respond to Etanercept. Health–related quality of life at follow-up was generally affected when compared to a cohort of healthy age-matched individuals.

Conclusions: even if a relevant percentage of HIDS patient show a spontaneous amelioration of the disease, most of them display a tendency towards a persistence of fever episodes that affect their quality of life.

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1686

Measuring Changes in Calcifications in Juvenile Dermatomyositis (JDM) Using Single Slice Computerized Tomography (CT). Maria F. Ibarra[5], Cynthia Rigsby[3], Gabrielle Morgan[2], Deli Wang[1] and Lauren M. Pachman[4]. [1]Children's Memorial Research Center's Biostatistics Core, Chicago, IL, [2]Clinical Immunology, Children's Memorial Research Center (CMRC), Chicago, IL, [3]Division of Radiology, Children's Memorial Hospital (CMH), Feinberg School of Medicine, Northwestern University, Chicago, IL, [4]Division of Rheumatology and Clinical Immunology, Children's Memorial Research Center (CMRC), Feinberg School of Medicine, Northwestern University, Chicago, IL, [5]Division of Rheumatology, Children's Memorial Hospital (CMH), Feinberg School of Medicine, Northwestern University, Chicago, IL

Objective: To determine the utility of single slice CT to measure change in the volume of calcifications in patients with JDM over time.

Methods: Children with definite/possible JDM and severe calcifications had at least two CT scans over a 2 year period. Severe calcifications were defined as a deep sheet- like deposits within intramuscular fascia, and were identified by physical examination and/or previous x rays. The limited four slice CT study focused on the area of greatest calcium burden. The area enclosing the calcification was calculated from the CT images, using a CT post processing workstation. Demographic and baseline characteristics were summarized by descriptive statistics. Generalized linear models were applied to analyze changes in the volume of calcifications and their association between clinical variables including DAS (Disease activity score) skin, DAS muscle, and the number of nailfold ERL (end row capillary loops). Data analysis used SAS 9.2.

Results: 11 children with JDM and severe calcifications were recruited. 8 patients were female; 8 were Caucasian. The average age was 13.84 years (+/− 4.9 years). The average duration of untreated disease at JDM diagnosis was 7.57 (+/− 7.2) months, and they all had active disease for an average=100 months +/− 65. The volume of calcifications changed significantly over time ($p<0.0001$). Decrease in calcification volume was significantly associated with decrease in DAS skin ($p=0.0002$) and improvement in the number of nailfold ERL ($p=0.0025$) but not with change in DAS muscle.

Conclusion: This limited CT technique provides objective measurement of the volume of calcifications over time that may be helpful as a research tool to monitor progression and regression of dystrophic deposits in JDM and other rheumatic diseases.

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Odontostomatologic Involvement in Juvenile Localized Scleroderma of the Face. Sabina Trainito[5], Troels Herlin[4], Thomas Klit Pedersen[3], Giorgia Martini, Chiara Scibetta[2], Giuseppe Fioretti, Vittorio Favero, Stefano Puggina[6], Lorenzo Favero and Francesco Zulian[1]. [1]Padova, Italy, [2]Department of Dentistry, Gnatology Unit, University of Padova, Italy, [3]Department of Orthodontics and Radiology, University of Aarhus, Denmark, [4]Department of Pediatrics, Rheumatology Unit, University of Aarhus, Denmark, [5]Department of Pediatrics, Rheumatology Unit, University of Padova, Padova, Italy, [6]Radiology Institute, University of Padova, Italy

Background: Juvenile Localized scleroderma (JLS) is the most frequent form of scleroderma in childhood. The linear facial subtype (known also as scleroderma en coup de sabre and Parry-Romberg syndrome) can lead to significant aesthetical and functional abnormalities. Despite their quite frequent clinical observation, the odontostomatologic complications are not thoroughly described in the literature and their management is challenging because of the lack of specific indicators of disease activity and progression. Aim of the study was to describe the clinical features and prevalence of the most frequent odontostomatologic abnormalities of JLS of the face and to propose clinical and radiologic criteria for the assessment and follow-up of these complications.

Methods: We performed a cross-sectional, multicenter study involving a multidisciplinary team formed by pediatric rheumatologists, orthodontists and radiologists. Selected patients with a diagnosis of JLS of the face underwent a comprehensive rheumatologic evaluation, dental examination (intraoral and gnatologic examination, orthodontic casts, photographs), conventional radiology (orthopantomography, frontal and lateral skull teleradiography) and Cone Beam Computed Tomography (CBCT). An Odonto-Maxillo-Facial score (OMF-score), based on four clinical-instrumental parameters, including facial anomalies (soft tissues and bone), dental abnormalities, asymmetry and malocclusion, was applied.

Results: 16 patients, 9 F, 7 M, aged 6.5–21.9 years, were investigated. The mean disease duration was 7.7 years (range 1.4–18.5), 62.5% had extracutaneous complications, 87.5% were in clinical remission. All patients reported at least one odontostomatologic complication. The main alterations were: overgrowth tendency of the lower third of the face (82%), malocclusion (75%), gnatologic alterations (67%), dental anomalies (63%), skeletal asymmetry (50%), bone involvement (50%), slight quantitative reduction of the soft tissues on the affected side (44%) and TMJ involvement (19%). According to the OMF-score, the odontostomatologic involvement was mild in 25% of the patients, moderate in 56% and severe in 19%. No correlation was found between degree of odontostomatologic involvement and disease duration.

Conclusions: A moderate-to-severe odontostomatologic involvement was found in the majority of the patients with JLS of the face. CBCT represents a new technique for a comprehensive assessment and monitoring of bone and soft tissues involvement. We propose a multistep clinical-radiological protocol to standardize the management of the odontostomatologic complications of JLS.

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Preliminary Criteria for Global Disease Flares in Juvenile Systemic Lupus Erythematosus (jSLE). Rina Mina[8], Michael Beresford[12], B. Anne Eberhard[13], Edward H. Giannini[3], Deborah M. Levy[15], Clarissa Pilkington[10], Marilynn G. Punaro[14], Angelo Ravelli[11], Andreas O. Reiff[2], Claudia Saad-Magalhaes[16], Laura E. Schanberg[9], Lori B. Tucker[1], Marisa S. Klein-Gitelman[4], Shannen L. Nelson[6], Jamie Eaton[5], Jun Ying[17] and Hermine I. Brunner[7]. [1]BC Childrens Hospital, Vancouver, BC, Canada, [2]Childrens Hosp LA MS60, Los Angeles, CA, [3]Childrens Hosp Med Ctr, Cincinnati, OH, [4]Childrens Mem Hosp/NW Univ, Chicago, IL, [5]Cincinnati Children's Hospital, [6]Cincinnati Children's Hospital, Cincinnati, OH, [7]Cincinnati Children's Hospital Medical Ctr, Cincinnati, OH, [8]Cincinnati Children's Med Ctr, Cincinnati, OH, [9]Duke Univ Medical Center, Durham, NC, [10]Great Ormond Street and University College London Hospitals, [11]IRCCS G Gaslini, [12]Royal Liverpool Children's Hospital, [13]Schneider Children's Hospital, New Hyde Park, NY, [14]Texas Scottish Rite Hospital for Children, Dallas, TX, [15]The Hospital for Sick Children, Toronto, ON, Canada, [16]UNESP, [17]University of Cincinnati

Background: Widely accepted valid, reliable and feasible flare criteria to assess the effects of new medications and the benefits of current treatments in jSLE are lacking.

Objectives: Develop accurate flare criteria for jSLE by employing consensus formation methodology and statistical approaches.

Methods: As part of a consensus formation process, an international group of pediatric rheumatology experts (n=138) were randomized to rate a total of 400 different patient profiles that were abstracted from prospective jSLE cohorts. jSLE flare descriptors deemed important, as per previous Delphi surveys (patient global assessment, physician global assessment, disease activity score, health status, proteinuria, anti-dsDNA antibody titer, ESR, complement C3 and C4), were considered when generating candidate flare algorithms, using various percentage changes of the flare descriptors, examination of flare criteria used in adult SLE, multinomial logistic regression, and *Classification and Regression Tree (CART).* For each candidate flare algorithm overall accuracy, sensitivity and specificity was calculated, using the consensus of the profile raters (minor flare, moderate flare, major flare, no flare) as criterion standard. An international consensus conference was held to rank the generated candidate flare algorithms following the process previously suggested by the ACR Criteria Subcommittee (consensus level 75%).

Results: A total of 2,995 expert ratings were available for analysis (survey response rate 70%). Consensus was reached that jSLE flare criteria derived by multinomial logistic regression or CART analysis are most suitable to measure jSLE flares. The highest ranked such candidate flare criteria consider absolute changes in the score of a disease activity index (SLEDAI or BILAG), the physician global assessment (PGA), spot urine protein/creatinine (P/C) ratio, and ESR when calculating a jSLE flare score. This score is then used to determine the presence of a global flare and to discriminate among categories of flare severity (minor,

moderate and major). The highest ranked preliminary jSLE flare criteria have excellent to outstanding accuracy as measured by the area under the Receiver Operating Characteristic Curve (AUC) (see Table).

Preliminary Criteria for Global Flares (All algorithms use change in variables between follow up-baseline visit)	Accuracy (AUC) Minor Flare	Moderate Flare	Major Flare
A. 0.5 × SLEDAI + 0.45 × P/C ratio + 0.5 × PGA + 0.02 × ESR	0.90	0.92	1.00
B. 0.4 × BILAG + 0.65 × P/C ratio + 0.5 × PGA + 0.02 × ESR	0.89	0.92	0.96
C. 0.4 × SLEDAI + 0.33 × P/C ratio + 0.6 × PGA	0.87	0.92	1.00
D. 0.4 × BILAG + 0.55 × P/C ratio + 0.5 × PGA	0.88	0.92	0.95
E. CART analysis (patient is categorized by highest flare level)	0.89	0.94	0.99
Major Flare: SLEDAI ≥ 10 OR PGA ≥ 6			
Moderate Flare: 7 ≤ SLEDAI ≤ 9 OR P/C ratio ≥ 2.3 OR ESR ≥ 13			
Minor Flare: 3 ≤ SLEDAI ≤ 6 OR 2 ≤ PGA < 6 OR 0.7 < P/C ratio ≤ 2.2			

Conclusions: Consensus has been reached on the preliminary criteria for global flares in jSLE. Prospective validation of these criteria is needed to assess their usefulness as outcomes for clinical trials and other research settings.

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1689

Preliminary Findings of Functional Magnetic Resonance Imaging (fMRI) Assessments of Specific Cognitive Domains in Childhood-Onset Systemic Lupus Erythematosus (cSLE) Patients and Best-Friend Controls. Blair Dina[3], Aimee Baker[4], Anna Carmela Sagcal-Gironella[4], Marisa Klein-Gitelman[3], Frank Zelko[5], Dean Beebe[1], Darren Gitelman[6], Mark DiFrancesco[2] and Hermine Brunner[4]. [1]CCHMC Division of Behavioral Medicine and Child Psychology, [2]CCHMC Neuroimaging Research Consortium, [3]Children's Memorial Hospital (CMH) Division of Rheumatology, [4]Cincinnati Children's Hospital Medical Center (CCHMC), Division of Rheumatology, [5]CMH Division of Child and Adolescent Psychiatry, [6]Northwestern University, Feinberg School of Medicine

Purpose: 1) To use fMRI to identify brain regions and associated networks that support visuoconstructional ability (VCA), working memory and attention, which are cognitive domains often affected in cSLE. 2) To characterize both behavioral and neuro-functional differences in VCA, working memory, and attention in cSLE patients and matched best-friend controls using fMRI and formal neuropsychological (NP) testing.

Methods: 36 subjects (F:M=28:8; age 10–17 years; 50% African-American, 50% Caucasian; 11% Hispanic), 18 with cSLE and 18 controls matched for age, sex, and race, performed the square completion (SC), N-Back, and continuous performance (CPT) tasks to probe VCA, working memory, and attention, respectively during fMRI. Functional data, acquired at 3 Tesla, consisted of T2*-weighted echo-planar images with TR=3s, 64×64 matrix, 256 mm FOV, and 44 axial 3 mm slices. A high resolution T1-weighted anatomic reference image was acquired for each subject. Average responses were calculated ($p<0.001$ uncorrected) for both cSLE and control groups and analyzed per anatomic regions of interest (ROI). All subjects underwent formal NP testing, measuring the same domains probed by fMRI. Correlation between ROI activations and NP measures was calculated.

Results: Activation was observed in expected brain regions for each task *(Figure 1)*. Performance of the SC task activated both dorsal ("where") and ventral ("what") visual pathways, as expected for a task measuring VCA. The attention task, CPT, produced a similar pattern plus frontal and insular activations. The N-Back task, which probes working memory, activated the dorsolateral prefrontal, parietal, insular and anterior cingulate cortices (ACC). ROI analysis revealed differences between cSLE and control groups. Controls activated more strongly for SC in the insula, ACC and dorsal visual stream. CPT resulted in greater activation for controls in the insula as well as the ventral visual pathway. The ACC activated more in the controls than in the cSLE group for the N-Back task. Group analysis resulted in deactivation in some ROI. Particularly, the hippocampus deactivated more strongly for cSLE than it did for controls when doing the NBack task. Select Z-scores attained from formal NP testing were found to correlate with ROI activation by subject in the cSLE group. A positive correlation was found between the ventral stream ROI activation for the SC task and an NP test for VCA. Activation in the same ROI for the CPT task correlated negatively with an NP test for attention.

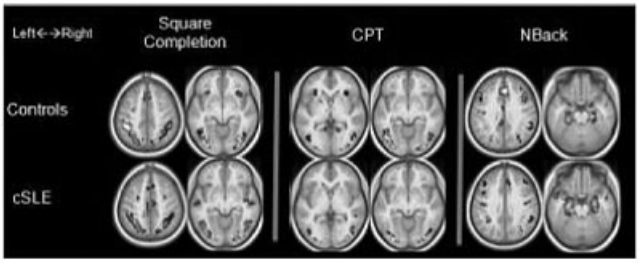

Figure 1. Group activation shown in select slices for each fMRI task. Controls are on top with corresponding cSLE patients below. Activations are in hot colors, deactivations in cool colors. For each, $p<0.0001$ uncorrected. Orientation is as indicated.

Conclusions: In this ongoing study, cSLE patients and their best-friend controls differed regarding the extent of fMRI activation in anatomic regions of interest (ROI) relevant to specific cognitive domains. Some ROIs activated per subject with correlation to performance in corresponding formal NP testing. The observed trends await confirmation as the sample size is augmented.

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Pre-Pubertal Onset Systemic Lupus Erythematosus in Girls: Clinical and Serologic Manifestations Differ from Post-Pubertal Onset SLE. Kathleen M. O'Neil[4], Lauren M. Kickingbird[7], Andrew S. Zeft[8], Hermine Brunner[2], Marilynn G. Punaro[5], Barry L. Myones[1], Suzanne C. Li[3] and Tracey Wright[6]. [1]Baylor College of Medicine, Houston, TX, [2]Cincinnati Child Hosp Med Ctr, Cincinnati, OH, [3]Hackensack University Medical Center, Short Hills, NJ, [4]OU Health Science Center, Oklahoma City, OK, [5]Texas Scottish Rite Hospital, Dallas, TX, [6]Univ of TX Southwestern, Dallas, TX, [7]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [8]University of Utah, Salt Lake City, UT

Objective: Children with pre-pubertal onset systemic lupus erythematosus (SLE) represent a small minority of children with the disease. To better understand this subset of children with lupus, and to define the role of specific hormones in SLE expression, we enrolled a cohort of girls with early onset disease in a longitudinal prospective observational study spanning the period of physiologic puberty.

Methods: The study was approved by CARRA and the institutional review boards of each participating CARRA site. Girls with 4 or more ACR diagnostic criteria of SLE between the ages of 8 and 13 years who had achieved only Tanner I or II stage of sexual development were evaluated with medical history, review of systems, physical examinations and laboratory studies every 3 months until 2 years after menarche. Clinical and laboratory manifestations of the first 28 girls enrolled were compared to 23 girls with disease onset after menarche. Abnormalities present or absent were compared as categorical variables using the chi square statistic.

Results: The two groups differed ($p<0.05$) in several clinical characteristics. The girls with pre-pubertal onset SLE had more frequent thrombocytopenia (32% vs 4%, p=0.013), anemia (57% vs 30%, p=0.05), GI complaints (46% vs 4%, p=0.0008) and depression (43% vs 4%, p=0.0017) than the girls with older onset disease. The older girls, in contrast, had more frequent morning stiffness (78% vs 43%, p=0.011), pleuritis (65% vs 18%, p=0.0006), pericarditis (39% vs 7%, p=0.006), fatigue (96% vs 39%, p=0.0003), and weight loss (39% vs 18%, p=0.01) than the girls with prepubertal SLE. In contrast, the pre-pubertal cohort had more frequent autoantibodies: anti-cardiolipin (50% vs 22%, p=0.038), dsDNA (100% vs 57%, p=0.0001), SS-A (39% vs 13%, p=0.037) and SS-B (39% vs 8%, p=0.013) compared to the teens. The occurrence of malar or discoid rash, arthritis, myositis, hematuria, fever, Raynaud phenomenon, oral/nasal ulcers, alopecia, hypertension, headache, and peripheral vasculitis did not differ between the two groups. The presence of Sm and RNP antibodies, likewise, was similar in both groups.

Conclusions: Girls with pre-pubertal onset SLE have different clinical manifestations and autoantibody profiles than girls with teen-onset SLE. In particular, the younger girls have more autoantibodies, more hematologic abnormalities, and more GI complaints; the older girls have more serositis, fatigue and morning stiffness. Further study of this large prospective cohort of children with prepubertal SLE is important to understanding the role sexual maturity and hormone changes of puberty play in SLE.

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Relative Performance of Two Validated Classification Systems for Wegener's Granulomatosis among Patients with ANCA-Associated Vasculitis (AAV) in a Registry for Children with Vasculitis: e-entry (ARChiVe). America G. Uribe[3], David A. Cabral[3], Kimberly Morishita[2], Leslie S. Abramson[38], Matthew D. Adams[6], Kevin W. Baszis[30], Susanne M. Benseler[32], Sarah S. C. Campillo[22], Peter Chira[31], B. Anne Eberhard[29], Kaleo C. Ede[26], Aimee O. Hersh[34], Gloria C. Higgins[23], Lisa F. Imundo[10], Rita S. Jerath[12], Susan Kim[8], Daniel J. Kingsbury[18], Marisa S. Klein-Gitelman[13], Suzanne C. Li[17], Daniel J. Lovell[9], Thomas G. Mason[20], Deborah K. McCurdy[19], Renee F. Modica[35], Lakshmi N. Moorthy[28], Eyal Muscal[1], Lorien A. Nassi[33], Kathleen M. O'Neil[24], Egla C. Rabinovich[15], Suzanne E. Ramsey[16], Andreas O. Reiff[7], Margalit E. Rosenkranz[11], Kenneth N. Schikler[36], Nora G. Singer[21], Anne M. Stevens[25], Mary B. Toth[5], Linda Wagner-Weiner[14], Dawn M. Wahezi[4], Amy L. Woodward[27], Andrew S. Zeft[37] and ARChiVe Investigators of CARRA. [1]Baylor College of Medicine, Houston, TX, [2]BC Children's Hospital, [3]BC Children's Hospital, Vancouver, BC, Canada, [4]Children's Hospital at Montefiore, Bronx, NY, [5]Children's Hospital Med Ctr, Akron, OH, [6]Children's Hospital of Michigan, Huntington Woods, MI, [7]Childrens Hosp LA MS60, Los Angeles, CA, [8]Childrens Hospital Boston, Boston, MA, [9]Childrens Hospital Medical Center, Cincinnati, OH, [10]Childrens Hospital of NY, New York, NY, [11]Childrens Hospital of Pittsburgh, Pittsburgh, PA, [12]Childrens Med Ctr Med Schl GA, Augusta, GA, [13]Childrens Mem Hosp/NW Univ, Chicago, IL, [14]Corner Children's Hospital, Chicago, IL, [15]Duke University Medical Center, Durham, NC, [16]IWK Health Ctr, Halifax, NS, Canada, [17]Joseph M Sanzari Children's Hospital, Short Hills, NJ, [18]Legacy Emanuel Children's Hosp, Portland, OR, [19]Mattel Children's UCLA, Los Angeles, CA, [20]Mayo Clinic Rochester, Rochester, MN, [21]MetroHealth Medical Center, Cleveland, OH, [22]Montreal Children's Hospital, Montreal, QC, Canada, [23]Nationwide Childrens Hosp, Columbus, OH, [24]OU Health Science Center, Oklahoma City, OK, [25]Pediatrics, U. of Washington, Seattle, WA, [26]Phoenix Children's Hospital, Phoenix, AZ, [27]Riley Children's Hospital, Nashville, TN, [28]Robert Wood Johnson Medical School, Metuchen, NJ, [29]Schneider Children's Hospital, New Hyde Park, NY, [30]St. Louis Children's Hospital, St Louis, MO, [31]Stanford Univ Schl of Med, Stanford, CA, [32]The Hospital for Sick Children, Toronto, ON, Canada, [33]TX Scottish Rite Hosp, Dallas, TX, [34]UCSF, San Francisco, CA, [35]University of Florida, Orlando, FL, [36]University of Louisville SOM, Louisville, KY, [37]University of Utah, Salt Lake City, UT, [38]University of Vermont, Morrisville, VT

Background: The European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society (EULAR/PRINTO/PRES) classification criteria for Wegener's Granulomatosis (WG), proposed to be more applicable to children than American College of Rheumatology (ACR) criteria, were recently validated in Ankara. The European Medicines Agency (EMEA) classification algorithm aimed to more uniquely classify related small to medium size vessel vasculitides was also recently validated in adults.

Purpose: To test the relative performance of the EULAR/PRINTO/PRES classification criteria for WG versus the ACR, applied in a cohort of children with AAV, and concurrently test the EMEA algorithm.

Methods: Data from time of diagnosis on children with diagnosed AAV by pediatric rheumatologists (MD-diagnosis) have been contributed to ARChiVe from 37 US/Canadian centers since 2004. EULAR/PRINTO/PRES and ACR criteria for WG and the EMEA algorithm were applied to all patients. Sensitivity and specificity for the EULAR/PRINTO/PRES and ACR classification criteria, and the EMEA algorithm were calculated (MD-diagnosis as reference standard). Cases where classification of a patient by EULAR/PRINTO/PRES versus ACR differed were described.

Results: MD-diagnoses for 155 patients (105 female) were: 100 WG, 25 Microscopic polyangiitis, 6 ANCA-positive pauci-immune glomerulonephritis, 3 Churg-Strauss syndrome, and 21 unclassified vasculitis. Among these patients, 87 had WG as defined by ACR, 98 by EULAR/PRINTO/PRES, and 113 by the EMEA algorithm. Respectively, the sensitivity of the ACR and EULAR/PRINTO/PRES criteria, and the EMEA algorithm for classifying WG patients in the spectrum of patients in an AAV cohort was 69%, 77%, and 90%; and specificity 67%, 62% and 60%. There were 17 patients in whom WG classification by EULAR/PRINTO/PRES versus ACR criteria differed. 14 were identified as WG by EULAR/PRINTO/PRES but not by ACR criteria: features that enabled classification were sinus involvement, ANCA positivity, subglottic-tracheal-endobronchial stenosis, or significant proteinuria. Conversely, 3 cases with WG were classified by ACR but not by EULAR/PRINTO/PRES: 2 patients had nasal-sinus involvement and granulomatous vasculitis on biopsy, and 1 patient had lung and renal involvement; all three had negative ANCA serology. Using the EMEA algorithm, 134 children could be classified as a named AAV category; 21 (14%) patients could not be classified.

Conclusion: The EULAR/PRINTO/PRES criteria are more sensitive than the ACR criteria in classifying pediatric WG. Performance of both criteria were limited when applied to a cohort that includes patients with MPA for which neither classification systems have established criteria, unlike the most sensitive EMEA classification algorithm which specifically aims to uniquely classify all patients. However, even when using the EMEA algorithm many children diagnosed with AAV remained unclassified.

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Resistance to Annexin A5 Anticoagulant Activity in Children with Rheumatic Disease Correlates with Persistent Antiphospholipid Antibodies and Thrombosis. Dawn M. Wahezi[4], Jacob H. Rand[2], Swapnil Rajpathak[3] and Norman T. Ilowite[1]. [1]Children's Hospital Montefiore, Bronx, NY, [2]Department of Pathology, Hematology Laboratories, Montefiore Medical Center, Bronx, NY, [3]Departments of Medicine, Epidemiology and Population Health, Albert Einstein College of Medicine, [4]Division of Pediatric Rheumatology, Children's Hospital at Montefiore, Bronx, NY

Background: Antiphospholipid antibody syndrome (APLS) is the most common acquired autoimmune thrombotic state in children. The underlying mechanism(s) by which aPL antibodies result in thrombosis remains poorly understood. Annexin A5, a potent anti-coagulant protein, shields anionic phospholipids on vascular endothelial cells from availability for coagulation reactions. There is a significant body of evidence to support the hypothesis that disruption of this shield by aPL antibodies plays a role in the pathogenesis of APLS in adults. In this study, we investigated the association between aPL antibodies and annexin A5 resistance in children with rheumatic diseases.

Methods: Clinical and laboratory data were collected from children with rheumatic diseases (n=90), including systemic lupus erythematosus (SLE) (n=49), juvenile idiopathic arthritis (JIA) (n=21), juvenile dermatomyositis (JDM) (n=8), primary APLS (n=6), Sjogren's syndrome (SS) (n=3), mixed connective tissue disease (MCTD) (n=1), systemic sclerosis (n=1) and systemic vasculitis (n=1). Assays for lupus anticoagulant (LA), anti-cardiolipin (aCL), anti-β2 glycoprotein I (anti-β2GPI) and anti-phosphatidyl serine (APS) antibodies were performed on all patients. Positive values were repeated 12 weeks later to confirm antibody persistence. A novel assay, the annexin A5 resistance assay (A5R), was performed measuring coagulation times in the presence and absence of annexin A5. Resistance to the anticoagulant effects of annexin A5 is expressed as a reduction in this value.

Results: Patients with persistently positive aPL antibodies had significantly lower A5R levels as compared to patients without evidence of persistent positivity (see table). Patients with an underlying diagnosis of primary APLS, SLE, SS or MCTD had significantly higher prevalence of persistently positive aPL antibodies, thrombotic events, aPL associated manifestations and low annexin as compared to the remainder of the cohort. The prevalence of reduced A5R in these patients was 49% versus 26% in the remainder of the cohort (p=0.032) with a mean A5R level of 227 vs. 246 respectively (p=0.030).

	Low A5R (%)	p value	Mean A5R	p value
Lupus Anticoagulant				
Persistent (n = 13)	69	*0.026*	191	*<0.001*
Transient (n = 8)	75	*0.041*	229	0.754
Anti-β2GPI antibodies				
Persistent (n = 10)	80	*0.008*	183	*<0.001*
Transient (n = 6)	50	0.647	226	0.679
Anti-cardiolipin antibodies				
Persistent (n = 14)	64	0.055	198	*0.001*
Transient (n = 19)	47	0.533	224	0.289
Any positive aPL				
Persistent (n = 19)	63	*0.028*	202	*<0.001*
Transient (n = 21)	48	0.489	231	0.743
Number of persistently positive aPL				
Zero (n = 71)	35	—	242	—
One (n = 7)	43	0.687	230	0.470
Two (n = 6)	67	0.127	204	*0.038*
Three (n = 6)	83	*0.020*	168	*<0.001*
Clinical correlation				
Thrombosis (n = 10)	70	*0.049*	207	*0.048*
Recurrent thrombosis (n = 3)	67	0.360	199	0.176

Conclusions: The A5R assay is the first mechanistic assay targeted at the underlying pathogenesis of APLS. This is the first report demonstrating significantly lower mean A5R levels in children with rheumatic diseases and persistent aPL antibodies. Furthermore, patients with prior history of thrombosis were shown to have reduced A5R levels as compared to patients with no history of thrombosis. We plan to expand these findings into a larger, multi-center cohort of children with SLE to determine if A5R is highly associated with thrombosis or other aPL related manifestations.

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1693

Safety and Efficiency of Rituximab in Juvenile Dermatomyositis: A Series of Eight Cases from the French AIR Registry. Brigitte Bader-Meunier[3], Helene Decaluwe[5], Pierre Quartier[3], Albert Faye[4], Vincent Guigonis[1], Anne Pagnier[2], Christine Barnerias[3], Jacques E. Gottenberg[6] and Christine Bodemer[3]. [1]Dupuytren Hospital, [2]Grenoble Hospital, [3]Necker Hospital, [4]Robert Debre Hospital, [5]Sainte Justine Hospital, [6]Strasbourg Hospitals, Strasbourg, France

Background: Juvenile dermatomyositis (JDM) is a rare vasculopathic condition of presumably autoimmune etiology. No data are available regarding the safety and efficacy of anti-CD20 treatment in patients with JDM refractory to conventional treatments except for six case reports with conflicting results.

Aim: To describe the efficacy and safety of rituximab (RTX) in JDM patients.

Methods: French multicenter retrospective study of patients with JDM diagnosed according to the criteria of Bohan and Peter treated with RTX and included in the French Autoimmunity and Rituximab (AIR) registry. Complete remission was defined by the normalization of manual muscle testing (MMT) and child myositis assessment scale (CMAS) for muscular involvement and by the disappearance of active skin lesions and abdominal pain for cutaneous and abdominal involvement.

Results: Eight patients (7 girls and 1 boy) were included. Age at diagnosis of JDM ranged from 2,5 to 10 years, and JDM duration at onset of rituximab therapy from 0,15 to 11 years. All the patients had been previously treated with immunosuppressive agents, and received rituximab because of the lack of efficiency of these treatments. The main indication for rituximab treatment was refractory muscle, skin and/or gastrointestinal involvement (6 patients) (group 1) and chronic complications consisting of severe calcinosis and severe abdominal pain associated with abdominal lipomatosis (2 patients) (group 2). The number of rituximab infusions (375–500 mg/m^2/infusion) ranged from 2 to 5. RTX was associated with corticosteroids and with immunosuppressive drugs in 8/8 and 4/8 patients respectively. The first RTX infusion had to be stopped in 1 patient (group 1) because of an infusion-related event. Clinical muscular, cutaneous and abdominal remission was achieved in 3/5 evaluable patients in group 1, including one patient with severe JDM who received plasmapheresis before and during the RTX course; MMT and CMAS returned to normal values within 3 to 12 months; normal values of serum CPK level were observed before and after RTX. In these responders steroid therapy was stopped in 1 patient 1,5 years after the first infusion of RTX, and was tapered at 10 and 15% of the baseline dosage respectively in the two others; the mean follow-up was 1,5 to 4 years, and complete remission lasted in 2 patients, while 1 patient has a relapse occurring 16 months after the start of the first course, successfully retreated with a second course of rituximab. RTX was ineffective in four patients (2 patients in each group). Calcinosis did not improve in two responders as well as in one non responder. Two patients presented localized bacterial infection of the calcinosis sites 2 and 11 months after RTX, and 1 patient died from non-related DM cause. Effective depletion of peripheral blood B cells was observed in all the patients and lasted more than 7 months in all patients except in one non responder.

Conclusion: This small series suggests that rituximab may be an effective and safe co-therapy for treating muscular and skin involvement in a subset of children with refractory JDM, but had no effect on calcinosis.

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1694

Safety and Immunogenicity of Influenza Vaccine (FluVac) in Patients with Juvenile Systemic Lupus Erythematosus (JSLE). Luciana M. de Carvalho[2], Rodrigo V. D. Silvestre[1], Wyller A. Mello[1] and Virginia P. L. Ferriani[2]. [1]Evandro Chagas Institute (WHO National Influenza Center), Ananindeua, Brazil, [2]School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil

Background: The FluVac is highly effective in general population. However there have been concerns about safety and immunogenicity of this vaccine in patients with SLE.

Objective: To evaluate safety and immunogenicity of FluVac in JSLE.

Patients and Methods: Twenty-six JSLE patients (10–18 years; mean SLEDAI score of 5.8), were immunized with trivalent split FluVac (A/Solomon Islands/3/2006, A/Brisbane/10/2007, B/Florida/2006), licensed for the 2008 Winter season in the South Hemisphere (Sanofi Pasteur SA/Butantan Institute Brazil). All but one patient were receiving prednisone (mean dose 12.2mg/day), and 17 were also receiving other drugs (methotrexate/leflunomide:4; azathioprine:12; mycophenolate mofetil:3). Influenza antibodies were measured before and 4–6 weeks after vaccination using hemagglutination inhibition (HAI) test according to standard World Health Organization procedure. Immune response (seroconversion) was defined as a 4-fold or greater rise in HAI antibodies and seroprotection rate was considered when HAI titers were at least 1:40. Local symptoms at the injection site and systemic symptoms were assessed by diary. The SLEDAI score, erythrocyte sedimentation rate (ESR), anti-dsDNA and anti-cardiolipin antibodies where evaluated before and 4–6 weeks after vaccination.

Results: All patients responded to at least 2 FluVac strains. Seroprotection rates after vaccination were 92% to A/H1N1, 73% to A/H3N2 and 100% to B-strain. Seroconversion rates were 91% to A/H1N1, 60% to A/H3N2 and 45% to B-strain. Use of medications did not interfere in seroprotection or seroconversion rates. No significant differences were found in SLEDAI score, ESR, or antibody titers against dsDNA and cardiolipin 4–6 weeks after vaccination. Local symptoms at the injection site (tenderness and/or redness) were described in 5/26 patients; 1 patient had a quickly reversible lipothymia five minutes after receiving the vaccine and 2 patients developed cough and rinorrhea without fever, one and nine days after receiving the vaccine.

Conclusion: Trivalent split influenza vaccine seems to be safe and immunogenic in patients with JSLE.

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1695

Serum Tumor Necrosis Factor alfa (TNFα) Is Associated with Disease Activity in Juvenil Systemic Lupus Erythematosus (jSLE). Mariana Postal, Karina Pereira, Karina Peliçari, Barbara Longhi, Roberto Marini, Lilian T. L. Costallat and Simone Appenzeller. State University of Campinas

Objective: To compare serum TNFα concentrations in jSLE patients, first-degree relatives and healthy volunteers. To determine clinical, laboratory and treatment features associated with TNFα in jSLE.

Methods: We included consecutive SLE patients with disease onset before the age of 16 (jSLE), first-degree relatives and age and healthy age and

sex matched controls. SLE patients were assessed for the number of non-renal and renal American College of Rheumatology (ACR) criteria ever present, disease activity [SLE Disease Activity Index (SLEDAI)], damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)] and current drug exposures. Mood disorders were determined through Becks Depression and Becks Anxiety Inventory (BDI and BAI). TNFα levels were measured by enzyme-linked immunosorbent assay using commercial kits from R&D Systems (London, UK). Analysis of variance was used to compare TNFα concentrations between groups. We assessed the effects of various demographic and clinical factors and TNFα concentrations in jSLE using univariate analyses. Multivariate analysis was performed including sex, age, SLE duration, disease activity, damage, number of non-renal and renal ACR criteria ever present, and current drug exposures.

Results: We included 50 jSLE (mean age 17.8±3.9), 45 first-degree relatives (mean age 40.2±6.3) and 49 controls (mean age 20.8±4.6). The mean level of serum TNFα was 4.6±9.6 pg/ml in jSLE, compared to 2.52 ± 2.7 pg/ml (p=0.15) in first-degree relatives and 1.8±1.9pg/ml in healthy controls (p=0.04). No difference between first-degree relatives and healthy controls was observed (p=0.13). TNFα concentrations correlated directly with SLEDAI scores (r=0.41; p=0.003), renal ACR criteria (r=0.3; p=0.05), and anxiety (r=0.34; p=0.03). No association between TNFα and SDI scores, depression, current use and dose of corticosteroids, hydroxychloroquine and immunosuppressants was observed. In adjusted analysis, TNFα levels was independently associated with SLEDAI scores (OR=3.1; 95%CI=1.6–6.5). When analyzing individual SLEDAI items, TNFα was associated with the presence of vasculitis (OR=3.9; 95%CI=1.3–4.9).

Conclusion: TNFα was significantly higher in jSLE patients when compared to healthy controls and was associated independently with disease activity in adjusted analysis. TNFα may be a useful marker for disease activity in jSLE, however longitudinal studies are necessary to determine if TNFα may predict flares in jSLE. The heterogeneity of clinical manifestations observed in SLE may be explained by different cytokine profile. Since TNFα was associated with the presence of vasculitis, anti-TNF treatment may be a treatment option for this manifestation.

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1696

Study of the Growth and Body Mass Index (BMI) of 86 Children with Familial Mediterranean Fever (FMF): Results of the French Referral Centre for Auto-Inflammatory Diseases (CeReMAI). Aurelie Klein[1], Alexia Letierce[1], Anuela Kondi[1], Veronique Hentgen[2], Isabelle Kone-Paut[1] and Severine Guillaume-Czitrom[1]. [1]Bicetre University Hospital, Le Kremlin Bicetre, France, [2]Versailles Hospital, Versailles, France

Background: Little is known on growth and BMI in FMF children.

Objective: To study the growth and BMI of FMF children, and evaluate the impact of disease severity and mutation load.

Methods: FMF children from the CeReMAI with available measures of height and weight were included. These measures were recorded at disease onset, genetic diagnosis, Colchicine start, and last visit, and Z-scores of growth and BMI matched for age and gender, calculated; Z-scores of heights were compared with the paired Wilcoxon test to Z-scores of target heights. Likewise, the BMI Z-scores were compared to the general population. Differences were analysed according to the severity of FMF evaluated with the modified Pras score and to the mutation load.

Results: 86 children were included, 49 girls and 37 boys, of whom 77 were under Colchicine therapy (90%). The median age at onset was 2.5 yrs, 4.5 yrs at genetic diagnosis and at Colchicine start, and 9.1 yrs at the last visit. Compared to the general population, target heights of FMF children were significantly lower (mean of Z=-0.24, p=0.003). Z-scores of heights at disease onset and at genetic testing were not different from the target heights. However, the Z-scores of heights at the last visit were significantly low (Z=−0.62; p<0.0001), and also lower than the Z-scores of target heights (Z=−0.62 versus Z=-0.24 p=0.014), despite Colchicine. The Z-scores of BMI were not different from those of the general population, whatever the time of evaluation. We found a significant difference between the Z-scores at the last visit and the Z-scores of target heights in children harbouring 2 mutations in the MEFV gene (n=52; p=0.002) compared to children with one mutated allele (n=34; p=0.65) and this difference was not dependent on FMF severity.

Conclusion: this series shows that height, but not BMI, is reduced in FMF after 6 yrs of evolution, despite Colchicine therapy. Our study indicates that FMF severity determined by the Pras modified score does not influence growth in FMF children. It rather suggests that FMF mutations would play a significant role in growth impairment.

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1697

The Disease Presentation and Outcome in Juvenile Behcet's Syndrome. Emire Seyahi[3], Huri Ozdogan[3], Yilmaz Ozyazgan[2], Serdal Ugurlu[3], Yesim Ozguler[1], Gulen Hatemi[3], Hasan Yazici[3] and Sebahattin Yurdakul[3]. [1]Cerrahpasa Medical Faculty, Internal Medicine Department, [2]Cerrahpasa Medical Faculty, Ophtalmology Department, [3]Cerrahpasa Medical Faculty, Rheumatology Department

Objectives: To assess clinical characteristics and outcome among patients with juvenile onset Behcet's syndrome (BS) all attending a single dedicated center.

Methods: We reviewed the charts of around 7000 patients registered between July 1977 and December 2009 at our multidisciplinary BS outpatient clinic. We surveyed patients who fulfilled the International Study Group (ISG) criteria for BS and who were 16 or younger at their initial visit. All these patients were called back within a survey period of 3 months. Demographic and clinical characteristics at initial and final visit were determined.

Results: There were 166 patients (86 boys, 80 girls). The mean age at first visit was 14.2 ± 1.9 years, the mean age at appearance of first symptom 10.9 ± 3.1 years, and the mean age at ISG fulfillment 13.1 ± 2.6 years. At the time of first visit, patients had oral ulcers (100%; 166/166), genital ulcers (68%; 113/166), pathergy positivity (63%; 104/166), papulopustular lesions (57%; 94/166), erythema nodosum (42%; 69/166), arthritis (20%; 33/166), eye disease (48%; 80/166), vascular disease (13%; 22/166) and neurological disease (8%; 13/166). The clinical manifestations at first visit such as genital ulcer, papulopustular lesions, erythema nodosum and arthritis were less frequent compared to the adult population (1). The dural sinus thrombi type of neurological involvement was the most common type of involvement (85%; 11/13). Familial history of BS was present in 41 (25%) patients. Information on the onset of puberty was available only in 94 patients. The onset was prepubertal in 39 and postpubertal in the remaining 55. While erythema nodosum was more common among those with prepubertal onset (24/39 vs 16/55), genital ulcer was more common among those with postpubertal onset (18/39 vs 44/55). A total of 13 (8%) were lost to follow-up after a single visit. Six (4%) (all males) had died. The median follow-up time in the remaining was median 10 years [4–17]. Causes of death in 6 males were pulmonary artery aneurysms (n=2), hepatic failure due to Budd-Chiari syndrome (n=1), suicide (n=2) and pneumonia (n=1). At the end of follow-up 18 patients (22.5%) had lost useful vision (bilateral: 8, unilateral: 10). The visual acuity in either eye was between 0.6–1.0 in 44 (56%) and between 0.5–0.1 in the remaining 18 (22.5%). Two patients (all males) with neurological involvement had severe neurological deficit (hemiplegia and optic atrophy. As seen adults, skin-mucosa lesions and joint involvement stopped occurring during the follow-up. Among 77 patients (50 M/27 F) in whom a final evaluation was available after a median of 9 [4–18] years, we observed that oral ulcer (90%) and papulopustular lesions (55%) were more frequent compared to genital ulcers (18%), erythema nodosum (29%) and arthritis (14%).

Conclusions: Pediatric cases made up around 0.2% of all Behçet patients. As in the adult, BS runs a severe course among the boys considering overall mortality in addition to the vascular and neurological involvement.

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1698

The Role of Montelukast in the Management of Hyperimmunoglobulinemia D with Periodic Fever Syndrome (HIDS). Donald P. Goldsmith[2], Karyl S. Barron[1], Anne Jones[1], Dawn Chapelle[1], Beverly Barham[1], Robert Lembo[1], Eric Hanson[1], Amanda Ombrello[1], Deborah Stone[1] and Daniel L. Kastner[3]. [1]National Institutes of Health, Bethesda, MD, [2]National Institutes of Health, Drexel University College of Medicine, Philadelphia, PA, [3]NIAMS, NIH, Bethesda, MD

Introduction: In 2001 Frenkel et al reported elevated urinary levels of leukotriene E_4 in 7 patients with HIDS and suggested that cysteinyl leuko-

trienes might play a role in its pathogenesis (Arch Dis Child 85:158). There is anecdotal evidence of benefits from treatment with the leukotriene receptor antagonist, montelukast.

Aim: To assess the therapeutic response of a pediatric HIDS cohort to montelukast.

Methods: This study is a retrospective chart review of 21 children with HIDS followed at the NIH Periodic Fever Program. Seventeen of 21 patients, ages 2–16 (mean 7.2y) were treated with montelukast. All were started on once daily standard doses of montelukast based on age (2–5y 4mg; 6–14y 5mg; >15y 10mg). Daily dosage was increased up to 8–12mg in 3 children; 6 patients were also treated with one additional similar dose on the first day of each febrile episode. Clinical response was assessed at each outpatient visit by the same attending physician by interview, clinical examination, and patient score cards.

Results: In 7 children there was no clinical response. In 2 the frequency of febrile episodes decreased slightly but each episode was more severe (not considered to be clinically beneficial). In 3 children, febrile episodes were judged to be less frequent and of reduced severity but montelukast was stopped because of behavioral side effects (one of these being parental fear [but not actual] of suicidal ideation). Similar improvement was noted in 4 additional children, but in all of these patients, benefit was judged to have dissipated after 6–8 months and montelukast was then stopped. Only 1 child still remains on montelukast. One child was lost to follow-up after starting montelukast.

Conclusions: Therapeutic benefit from montelukast is seen only in 7 (41%) of children and is not enduring. Significant side effects are not uncommon. In our experience montelukast is not likely to favorably alter the long term clinical course of pediatric HIDS. It seems improbable that leukotriene activation is primarily involved in the pathogenesis of HIDS but is more likely a secondary phenomenon associated with generalized immune stimulation.

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1699

The Use of Lenalidomide for Cutaneous Manifestations of SLE. Eveline Wu, Laura E. Schanberg, Heather VanMater and Egla C. Rabinovich. Duke University Medical Center, Durham, NC

Purpose: Cutaneous manifestations are common in pediatric SLE and cause significant morbidity. In the past, thalidomide has proved effective in the treatment of cutaneous disease. Its use, however, is limited by its teratogenecity and the potential for peripheral neuropathy. Lenalidomide, a thalidomide analogue, has shown promise with a more favorable side effect profile. Though their mechanism of action is not completely understood, both appear to have anti-inflammatory and immunomodulatory properties. Our objective was to evaluate the efficacy and safety of lenalidomide in the treatment of cutaneous SLE.

Methods: We performed a retrospective chart review of 5 children who received lenalidomide for treatment of cutaneous aspects of SLE. Lenalidomide dosing was 5–15 mg daily. One subject was initially taking thalidomide 100 mg daily. Patients were evaluated at drug initiation and at 6 month follow up using a standardized case report form. Statistical analysis was performed using the paired t-test. If a significant value was obtained ($P<0.05$), further statistical analysis was performed using Wilcoxon's signed rank test.

Results: All of our subjects were female and 80% were African-American. Average age at diagnosis was 12.4 years (SD +/− 3.5). Average age at time of lenalidomide or thalidomide initiation was 16.4 years (SD +/− 4.7). Subjects started the medications for treatment of skin disease, including alopecia, nasal and oral ulcers, extensive malar rash, diffuse maculo-papular eruption, discoid lesions, bullous lesions, panniculitis, and severe Raynaud's phenomenon with digital ulcerations. One patient initially received thalidomide before switching to lenalidomide 28 months later due to complaints of numbness over her anterior shin with a normal EMG. Within the first 6 months, all 5 subjects demonstrated excellent response with resolution of skin lesions. Lenalidomide maintained the remission in skin disease achieved by thalidomide in the one patient. No subject relapsed on continued therapy. Prednisone dose was decreased in all patients, from a mean of 23 mg (SD +/− 10.9) to a mean of 11 mg (SD +/− 7.4) at 6 months ($P=0.005$). ESR also decreased from a mean of 26.2 mm/hr (SD +/− 8.9) to a mean of 19.2 mm/hr (+/− 7.5) at 6 months ($P=0.015$). The results remained statistically significant with analysis using Wilcoxon's signed rank test. One patient with nephritis started IVIG during the follow up period. Others did not start a new DMARD, further supporting the positive effect of lenalidomide on prednisone dose and ESR. Both medications exhibited a favorable side effect profile. All patients had lymphopenia, but this was not statistically significant during the 6 month evaluation. One patient developed pyelonephrits.

Conclusions: Skin disease is highly prevalent among children with SLE and can be quite disfiguring. Lenalidomide is both effective and safe for the treatment of a spectrum of dermatologic conditions in pediatric SLE. Its use may allow for a reduction in prednisone dose. Prospective study of lenalidomide is needed to clarify its role in the treatment of cutaneous manifestations of SLE.

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1700

Therapeutic Approaches for the Treatment of Active Juvenile Dermatomyositis: An International Multicenter Study. Rachana Hasija[3], Angela Pistorio[3], Angelo Ravelli[3], Erkan Demirkaya[3], Raju Khubchandani[3], Dinara Guseinova[3], Clara Malattia[3], Carmen De Cunto[3], Tomas Brent Graham[3], Kathleen Haines[3], Christian Huemer[3], Yukiko Kimura[3], Harald Mangge[3], Silvana Martino[3], Carlo Minetti[3], Ellen Berit Nordal[3], Pierre Philippet[3], Manuel Salgado[3], Alberto Martini[2] and Nicolino Ruperto[1]. [1]IRCCS G. Gaslini/Università degli Studi di Genova, Genova, Italy, [2]IRCCS G. Gaslini/Università degli Studi di Genova, [3]PRINTO

Background: Recently published articles have documented a marked improvement in long-term outcome and survival of juvenile dermatomyositis (JDM) patients but little information is available on standardized evaluations of response to therapy based on current treatment options.

Objective: Our aim was to evaluate in large prospective cohort of JDM patients the response to therapy over a 24 months period, according to the PRINTO JDM response criteria.

Patients & Methods: Clinical, laboratory and therapeutic modalities were collected prospectively between 2001 and 2004 in JDM patients by PRINTO/PRCSG members from 36 countries. Patients with probable or definite JDM, age < 18 years, in an active phase of their disease, at 4 time points (baseline, 6, 12 and 24 months), were included. The validated core set variables were the global assessment by the physician and parent, muscle strength, functional ability, quality of life and disease activity tool. Patients were defined as improved if able to demonstrate at least 20% (50, 70, or 90) improvement from baseline in 3 of any 6 core set variables with no more than 1 of the remaining worsening by more than 30%, which cannot be muscle strength. Remission was defined as patients with normal muscle strength (CMAS ≥48; nv 0–52) and physician global assessment of disease activity ≤ 0.5 cm (nv 0–10) and normal CPK (≤150 U/L)

Results: The analysis data set included 275/294 (94%) patients. Patients median ages at onset and disease duration visit were 7.2 and 6 months respectively with 168 (61%) being female. The greatest improvement in clinical and laboratory measures was observed in the first 6 months of therapy and maintained thereafter. At baseline treatment options included steroids in 269 (97.8%), metotrexate (MTX) in 134 (48.7%) with 91 newly started, cyclosporine A in 44 (16%), hydroxychloroquine in 37 (13.5%), and IVIG in 38 (13.8%). Oral steroids dose at baseline and 6 months were 1 and 0.3 mg/kg/day respectively, at 24 months 91 patients (52.3%) were still on steroids at 0.21 mg/kg/day; steroids pulses were used in 100 (36.4%) at baseline. Figure reports the 20, 50, 70, 90 response and remission over time.

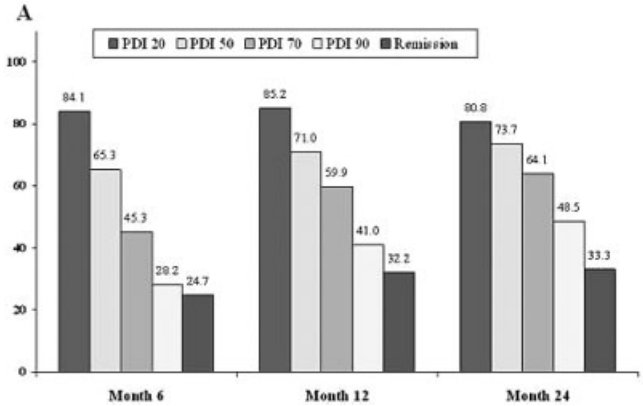

Figure 1. PRINTO JDM PDI 20, 50, 70, 90 and remission rate in 275 patients at 6, 12 and 24 months.

A substantial improvement was observed in the initial 6 months (PRINTO 20 criteria 84%) and maintained thereafter.

Conclusions: Six months of therapy lead to a significant improvement in JDM core set measures and response criteria, that was maintained up to 2 years follow-ups. These data provided standardized response to therapy data in patients with JDM treated according to the current available options.

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1701

Towards Defining Clinical Remission in Juvenile Systemic Lupus Erythematosus (jSLE). Rina Mina[5], Laura E. Schanberg[6], B. Anne Eberhard[14], Marisa S. Klein-Gitelman[3], Gloria C. Higgins[12], Karen Onel[17], Nora G. Singer[11], Kathleen M. O'Neil[13], Lori B. Tucker[1], Lisa F. Imundo[2], Emily Von Scheven[16], Shannen L. Nelson[4], Frank Dressler[10], Ruben Cuttica[7], Claudia Saad Magalhães[15], Angelo Ravelli[9], Alberto Martini[8] and Hermine I. Brunner[5]. [1]BC Childrens Hospital, Vancouver, BC, Canada, [2]Childrens Hospital of NY, New York, NY, [3]Childrens Mem Hosp/NW Univ, Chicago, IL, [4]Cincinnati Children's Hospital, Cincinnati, OH, [5]Cincinnati Children's Med Ctr, Cincinnati, OH, [6]Duke Univ Medical Center, Durham, NC, [7]Hospital General de Ninos Pedro de Elizalde, Buenos Aires, Argentina, [8]IRCCS G Gaslini, Genova, Italy, [9]IRCCS G Gaslini, [10]Medizinische Hochschule, Hannover, Germany, [11]MetroHealth Medical Center, Cleveland, OH, [12]Nationwide Childrens Hosp, Columbus, OH, [13]OU Health Science Center, Oklahoma City, OK, [14]Schneider Children's Hospital, New Hyde Park, NY, [15]UNESP, [16]Univ of Calif San Francisco, San Francisco, CA, [17]Univ of Chicago, Chicago, IL

Background: There is no established definition for global clinical remission in jSLE.

Objectives: To develop a definition of global clinical remission in jSLE and to identify candidate criteria for measuring jSLE clinical remission.

Methods: Pediatric rheumatologists from all over the world (n=137) were surveyed about issues pertaining to defining and measuring clinical remission in jSLE. Consensus for the Delphi survey was set at 70%. Survey-responses were compared to prospective clinical data from a cohort of jSLE (n=33) considered to be in clinical remission by their treating physician.

Results: Survey response rate was 65%. There was consensus that 'clinical remission' is different from 'minimal disease activity' in jSLE. There was consensus that a jSLE patient in clinical remission (a) may have some subjective symptoms (i.e. fatigue, joint pains, headaches) but should not have any objective physical signs of disease activity; (b) may have a persistently positive ANA but should not have abnormal ESR, C3 level, complete blood count and urine sediment; and thus (c) may have disease activity scores > 0. No consensus was reached as to whether remission constitutes a time point or a time period and whether medication use is important in its definition. Clinical data of jSLE patients considered to be in remission supported the survey responses (see Table).

Clinical Data from jSLE patients in Clinical Remission (n = 33)

Outcome measure	Median ± IQR	Range
SLEDAI	2 ± 3	0–6
ECLAM	1 ± 0	0–3
SLAM	2 ± 3	0–5
BILAG	1 ± 2	0–10
Physician Global Assessment	0 ± 0	0–1
Patient well being	8 ± 1	6–9
Peds QoL	90.22 ± 20.11	56.52–100
Rheum QoL	92.05 ± 10.23	59.09–100
CHQ PhS	42.76 ± 4.52	35.43–48.89
CHQ PsS	40.31 ± 5.44	31.65–48.20
SLICC-ACR DI	0 ± 0	0–3

Conclusions: Consensus has been reached on preliminary variables useful to define and measure clinical remission in jSLE. Further studies are in progress.

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1702

Towards the Development of Standardized Treatment Protocols for Proliferative Nephritis in Juvenile Systemic Lupus Erythematosus (jSLE). Rina Mina[6], Hermine Brunner[5], B. Anne Eberhard[12], Marilynn G. Punaro[14], Stacy P. Ardoin[10], Marisa S. Klein-Gitelman[4], Joyce J. Hsu[13], Lakshmi N. Moorthy[11], Linda Wagner-Weiner[8], Eyal Muscal[1], Suhas M. Radhakrishna[2], Jenny Palter[9], Laura Schanberg[7], Carol A. Wallace[16], Norman T. Ilowite[3], Emily Von Scheven[15] and for the CARRA Lupus Disease-Specific Group. [1]Baylor College of Medicine, Houston, TX, [2]Children's Hospital Los Angeles, Los Angeles, CA, [3]Children's Hospital Montefiore, Bronx, NY, [4]Childrens Mem Hosp/NW Univ, Chicago, IL, [5]Cincinnati Child Hosp Med Ctr, Cincinnati, OH, [6]Cincinnati Children's Med Ctr, Cincinnati, OH, [7]Duke Medical Center, Durham, NC, [8]La Rabida Children's Hospital, Chicago, IL, [9]Lupus Foundation, [10]Ohio State University, Columbus, OH, [11]Robert W Johnson University, Metuchen, NJ, [12]Schneider Children's Hospital, New Hyde Park, NY, [13]Stanford University, Stanford, CA, [14]Texas Scottish Rite Hospital for Children, Dallas, TX, [15]Univ of Calif San Francisco, San Francisco, CA, [16]University of Washington and Seattle Childerns's Hospital, Seattle, WA

Background: There is a paucity of clinical trials (RCTs) to help guide treatment of proliferative lupus nephritis (LN) in jSLE. Comparison of outcomes resulting from standardized treatment protocols may offer an alternative to expensive RCTs for elucidating the best therapy in this population.

Objectives: Describe current clinical practice patterns and patient-specific features that influence the management of proliferative LN in jSLE as a first step towards the development of standardized treatment protocols for LN in children.

Methods: Based on literature review, a Delphi survey pertaining to issues in LN induction and maintenance therapy was sent to 103 members of the SLE Subcommittee of the Childhood Arthritis and Rheumatology Research Alliance. Consensus was set at 80%.

Results: Survey response rate was 80%; most of the respondents had at least 6 years of clinical experience. The majority (79%) use cyclophosphamide according to the NIH protocol as induction therapy for Class IV LN. Mycophenolate mofetil (MMF) is less commonly used (17%) and rituximab and azathioprine were rarely prescribed for induction. The choice for induction agent is influenced by co-existent cerebritis and risk for non-adherence but not patient age, race or gender. MMF is the medication of choice for maintenance therapy. Although corticosteroids are almost universally utilized for LN therapy, there is a striking variability in the regimen (dose, route, and duration) employed. There was consensus that definitions of flare and response based on ACR/EULAR renal outcomes criteria are useful to guide treatment decisions. No consensus was reached about duration of induction or maintenance therapy; treatment adjustment for LN relapse; treatment-effects of nephrosis or persistent proteinuria, and strategies for prevention of medication side-effects. LN is typically monitored with C3/C4 levels, spot urine protein to creatinine ratio, anti-dsDNA antibody titers, GFR, and urine sediment while repeat kidney biopsy is not routine.

Conclusions: While there is a marked variation in practice patterns among pediatric rheumatologists in the treatment of Class IV LN in jSLE, cyclophosphamide is often the preferred induction medication, and MMF is the maintenance therapy of choice. These survey responses will help guide the development of standardized treatment protocols. Based on the experience from other chronic diseases, this will allow for comparative effectiveness studies to determine the optimal therapy for LN in children, thereby leading to improved outcomes.

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1703

Trends in Incidence and Drug Therapy of Complex Regional Pain Syndrome in Children's Hospitals across the U.S. Cara M. Hoffart[1], Pamela F. Weiss[2], Andrew J. Klink[2], D. D. Sherry[2] and Chris Feudtner[2]. [1]The Children's Hospital of Philadelphia, Philadelphia, PA, [2]The Children's Hospital of Philadelphia

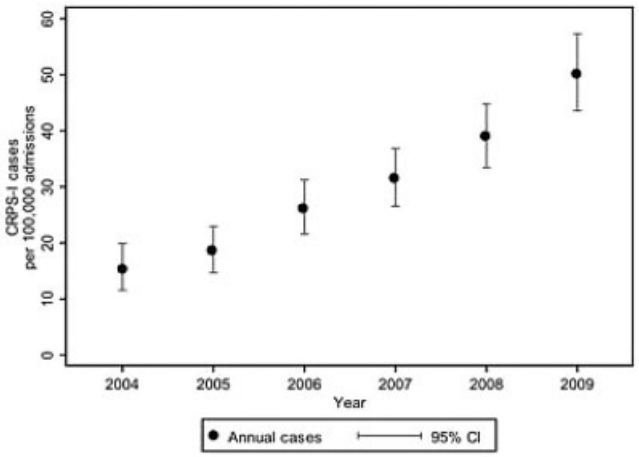
Background: The incidence of complex regional pain syndrome (CRPS) in hospitalized pediatric patients has been incompletely characterized and optimal treatment is debated.

Methods: We conducted a retrospective observational study using Pediatric Health Information Systems (PHIS), an administrative database from 40 freestanding US children's hospitals. We determined admission temporal trends, patient characteristics, and drug therapy of children with a discharge diagnosis of CRPS between 1 January 2004 and 31 December 2009.

Results: During this 6-year study, there were 848 hospitalizations for CRPS, of which 644 were an initial admission. The median age was 14 (IQR: 11, 16 years), and three-quarters of the patients were females. Seventy-five percent were white, 9% black, 2% Asian, 5% other, 9% unknown. Over time, there was a significant increase in cases of CRPS (from 18.6 cases per 100,000 admissions in 2004 to 49.2 cases per 100,000 admission in 2009; P = 0.03, by test for trend). The median length of stay for all 848 admissions was 5 days (IQR: 3, 9 days). Pharmacologic drug therapy during the initial admission included narcotics (490 patients, 78.4%), non-narcotic analgesics (410 patients, 65.6%), non-steroidal anti-inflammatory drugs (382 patients, 61.1%), psychotherapeutics (363 patients, 58.1%), sedative hypnotics (149 patients, 23.8%), and anesthetics such as ketamine (178 patients, 28.5%).

Conclusions: The number of hospitalized children with CRPS has increased significantly over the last 6 years, due to either increasing incidence of this chronic pain syndrome, improved recognition and diagnosis, a shift in diagnostic coding, or some combination of these mechanisms. Regardless, the treatments received by these patients are diverse and warrant study regarding short and long term effectiveness.

Figure: Annual hospital admissions for children with CRPS.



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1704

Update on the Juvenile Systemic Sclerosis Inception Cohort. www.juvenilescleroderma.com. Ivan Foeldvari[2], Angela Wierk[1], Claudie Len[8], Maria Martha Katsicas[4], Avcin Tadey[6], Till Kallinich[7], Isabelll Kone-Paut[9], Kirsten Minden[7], Luc Mouthon[10], Juergen Brunner[5] and Yuoef Uziel[3]. [1]Hamburger Zentrum Für Kinder- und Jugenrheumatologie, Hamburg, Germany, [2]Hamburger Zentrum Fuer Kinder- und Jugendrheumatologie, Hamburg, Germany, [3]Universitiy Childrens Hospital, Israel, [4]Universitiy Childrens Hosptial, Brazil, [5]Universitiy Childrens Hosptial, Austria, [6]University Childrens Hospital, Slovenia, [7]University Childrens Hospital, Germany, [8]University Childrens Hospital, Brazil, [9]University Childrens Hosptial, France, [10]University Hospital, France

Background: Juvenile systemic sclerosis (jSSc) is a rare autoimmune disease. Currently just retrospective data exist without a standardized assessment of the organ involvement. Our project is the first projects, where prospectively and with a standardized assessment data of early jSSc patients are collected.

Objectives: to learn about the evolvement of juvenile systemic sclerosis

Methods: Using the proposed standardized patient assessment protocol patients with early jSSc, entry into the cohort within the first 24 months of disease, are prospectively assessed. All participating centres approved the protocol over the own IRB.

Results: 42 centers from 20 countries applied to participate on the project. The assent and consent forms were translated into the local native languages. Up till now 16 patients were enrolled, the mean follow up of the patients in the cohort are 1.6 years. Thirteen of the 16 patients were female. The mean age at the onset of the non-Raynaud symptomatic were 12.4 years. Nine of the 16 have diffuse subtype, 5 of them have an overlap symptomatic. At the time of the inclusion the mean modified Rodnan Skin Score was 16.5 (range, 2 to 51). 14 were ANA positive, and 5 of them were anti-Scl 70 positive. None of them was anticentromere positive. Fourteen of the 16 have Raynaud′s, 12 of them have capillary changes and 4 of them already ulcerations. 7 of them have cardiopulmonary involvement, 4 of them have interstitial lung disease. Two of them have renal involvement. Eight of them have gastrointestinal involvement, and 5 of them oesophageal involvement. Fourteen of them have musculoskeletal involvement.

Conclusion: We present the data on the first 16 prospectively assessed patients with jSSc. The current recruitment data confirms that pediatric patients are different from the adult patients. We are only at the first phase of this project and hope to recruit up to 50 patients and follow them prospectively over the next 2 to 4 years at least.

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1705

Validation of Birmingham Vasculitis Activity Score in Childhood Vasculitis. Erkan Demirkaya[1], Seza Ozen[3], Angela Pistorio[3], Angelo Ravelli[3], Rachana Hasija[3], Raju Khubchandani[3], Salvatore Scarpato[3], Michel Fischbach[3], Nicolae Iagaru[3], Srdjan Pasic[3], Esra Baskin[3], Frank Dressler[3], Marion A. J. van Rossum[3], Julia García-Consuegra[3], Maria Teresa Apaz[3], Maka Ioseliani[3], Henryka Mazur-Zielinska[3], Alberto Martini[2], Roberta Galasso[3], Nicolino Ruperto[2] and Pavla Dolezalova[3]. [1]IRCCS G. Gaslini, Genova, Italy, [2]IRCCS G. Gaslini/Università degli Studi di Genova, [3]PRINTO

Background: Unlike for adults patients with systemic vasculitis, there are no validated tools to measure disease activity status in childhood (c-) systemic vasculitis.

Objectives: Our aim was to validate the last version of Birmingham Vasculitis Activity Score (BVAS v.3) and the Disease Extend Index (DEI) for comprehensive assessment of paediatric primary c-systemic vasculitis.

Methods: We extracted from the PRINTO database all patients who fulfilled the Henoch-Schoenlein (HSP), childhood (c) polyarteritis nodosa (c-PAN), c-Wegener (c-WG) and c-Takayasu (c-TA) EULAR/PRINTO/PRES c-vasculitis classification criteria and whose disease duration at the time of diagnosis was ≤ 3 months. Data were also available for follow-up evaluation ≥ 3 months after diagnosis. The validation of the BVAS and DEI were examined by assessing discriminant ability among the 4 vasculitis, convergent validity by Spearman correlation coefficient with physician's global assessment of disease activity (MD global), indexes of inflammation (ESR/CRP), responsiveness to change over time through the standardizes response mean (SRM); A SRM value <0.5 is considered small, ≥0.5 and <0–8 moderate, and values ≥ 0.8 represent large effect.

Results: The analysis data set included 796/1124 (71%) patients (M:F 0.96:1): there were 669 HSP, 80 c-PAN, 25 c-WG and 22 c-TA. The median age of the diagnosis was 6.99-year (6.6–11.96) and median delay for the diagnosis from the onset of signs or symptoms was 0.01 (0.003–0.027) years. In the table 1 are reported the 9 subscore of the BVAS, the total BVAS score, the DEI, the MD global and indexes of inflammation.

The BVAS was able to discriminate between the 4 c-vasculitides with total BVAS scores equal to 9 (6.0–14.0), 17.5 (11.5–24.5), 23 (19–29), 15 (11–20) in HSP, c-PAN, c-WEG and c-TA respectively.

Table 1. Discriminant ability of the BVAS total scores and the other tools:data are medians (1*-3* quartiles)

	All patients n = 796	HSP n = 669 (%)	c-PAN n = 80 (%)	c-WG n = 25 (%)	c-TA n = 22 (%)	P values*
BVAS	10 (8.0–16.0)	9 (6.0–14.0)	17.5 (11.5–24.5)	23 (19–29)	15 (11–20)	<0.001
DEI	5 (4.0–6.0)	5 (4.0–6.0)	5 (3.0–7.0)	7 (6–9)	3 (2–5)	<0.001
MD global	5 (3–7)	4 (2.5–6)	7 (7–8)	8.5 (8–9)	8 (7–8.5)	<0.001
CRP	1.38 (0.5–4.33)	1.01 (0.45–2.21)	8.14 (4.45–16.4)	9.8 (5.36–16.38)	4.63 (2.23–8.49)	<0.001
ESR	29 (14.0–51.5)	22 (12.0–36.5)	86 (53.0–115.0)	76.5 (58–107.5)	48 (40–72)	<0.001

*P values refers to ANOVA with Dunn test as a posthoc.

The cutaneous and cardiovascular sub-score are able to distinguish TA patients from the others; the ENT sub-score shows a significant ability to discriminate the c-WG patients from the others.

A strong correlation was found between the BVAS and DEI (r_s=0.80) while correlation with MD global were moderate (r_s=0.49) and poor with CRP and ESR (r_s=0.34, r_s=0.31). Responsiveness was large for BVAS total score (SRM=1.38), DEI (SRM=1.9), MD global (SRM=1.3) and ESR (SRM=0.85).

Conclusion: BVAS and DEI showed adequate discriminant ability and sensitivity to change but, poor to moderate convergent validity. Further work is needed in order to improve activity measurement in c-vasculitides.

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1706

Validation of the Newly Developed Pediatric Criteria for the Diagnosis of Familiar Mediterranean Fever in a Large Pediatric Cohort of Western European Children with Periodic Fever. Silvia Federici[7], Giuseppina Calcagno[5], Martina Finetti[7], Antonella Meini[6], Agata Vitale[5], Marco Cattalini[6], Roberta Caorsi[7], Francesco Zulian[1], Alberto Tommasini[3], Maurizia Baldi[2], Joost Frenkel[8], Isabella Ceccherini[4], Alberto Martini[7] and Marco Gattorno[7]. [1]Dipartimento A.I. di Pediatria, University of Padua, [2]Dipartmento di Genetica Umana, Ospedale Galliera, Genoa, [3]IRCCS Burlo Garofolo, Trieste, [4]Lab Genetica Molecolare Istituto G. Gaslini, Genoa, Italy, [5]Sezione di Reumatologia Pediatrica, Dipartimento di Scienze Pediatriche, AOU "G. Martino", Messina, [6]Unità di Immunologia e Reumatologia Pediatrica, Spedali Civili, Brescia, [7]UO Pediatria II Istituto G. Gaslini, Genoa, Italy, [8]Wilhelmina Children's Hospital, Utrecht, The Netherlands

Purpose: FMF belong to the group of the periodic fever and is caused by mutations in the MEFV gene. Despite the possibility of a molecular characterization the diagnosis of the disease is mainly based on clinical criteria. Several diagnostic criteria have been developed, but none of them are specific for the pediatric age. A new set of criteria for the diagnosis of FMF in children were recently proposed (Yalçinkaya et al., Rheumatology 2009; 48(4):395). Aim of the study was to verify in a pediatric cohort of Caucasian patients with periodic fever the sensitivity and specificity of the new pediatric criteria in comparison to classical adult criteria (Livneh et al A&R 1997; 40(10):1879).

Patients & Methods: Detailed clinical information on 389 pediatric patients (mean age 8,5 yrs; SD± 8,3) with periodic fever were collected. All patients were screened for mutations of *MVK*, *TNFRSF1A* and *MEFV* genes. For each patient adult FMF criteria and new pediatric FMF criteria were applied.

Results: 106 children carried mutations of MEFV gene (40 were homozygous or compound heterozygous, 66 with a single mutation), 38 patients displayed two mutations of MVK gene. Structural mutations of *TNFRSF1A* gene were found in 12 patients, whereas 18 patients displayed low-penetrance (R92Q or P46L) TNFRSF1A mutations. 215 patients were negative to all three genes. All patients (100%) carrying two mutations of MEFV gene and 49 heterozygous individuals (74%) were positive for adult FMF criteria. The same criteria were also positive in 135 (63%) of genetically negative and 71 % of individuals affected by other monogenic periodic fevers, with an overall specificity of 33.2%. Conversely, the new pediatric criteria were positive in 33/40 (82,5%) patients carrying two MEFV mutations and in 27/66 (41%) heterozygous patients, whereas its overall specificity was 76 %.Six out of the 7 patients carrying two MEVF mutations that did not satisfied the new pediatric criteria carried low penetrance mutations and generally displayed a mild phenotype.

Conclusions: Pediatric FMF criteria show an higher specificity when compared to classical adult FMF criteria.

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1707

(22–52)adrenomedullin Shifts Cytokine Balance from Th1 to Th2, Reduces IL-17A Expressions and Modulates Treg Cells in Collagen-Induced Arthritis. Marie-Dominique Ah Kioon[5], Carine Asensio[5], Korng Ea[5], Sandrine Rullé[1], Géraldine Falgarone[1], Corinne Collet[4], Jean-Marie Launay[3] and Frederic P. Liote[2]. [1]EA 4222, Paris 13 University, Bobigny, France, Metropolitan, [2]Hopital Lariboisiere, Paris, France, [3]Paris 5 University, Paris, France, Metropolitan, [4]Paris 5 University, Bobigny, France, Metropolitan, [5]UMR-S606 Inserm, Paris Diderot University, Paris, France, Metropolitan

Purpose: Rheumatoid arthritis is an inflammatory disease characterized by an increase in pro-inflammatory cytokine production due to activated Th1 and Th17 cells, and Treg dysregulation. Depending on cell types, adrenomedullin (AM) acts as a pro- or anti-inflammatory peptide in vitro. It exerts anti-inflammatory effects in vivo: AM reduces IL-1, IL-6 and TNF-α in septic mice and reduces collagen-induced arthritis (CIA) by up-regulating Treg cells. (22–52)AM, a fragment peptide which binds to AM receptors, acts also as an antagonist or agonist of ADM in vitro but its in vivo effects are unknown. Our aim was to evaluate effects of (22–52)AM on arthritis score, seric and articular cytokines expression in CIA.

Methods: CIA DBA/1 mice were treated with 1.2 μg/g (22–52)AM or saline (control) as soon as arthritis occurred. Animals were sacrificed at day 45 (D45), joints were processed for histology and protein studies and spleens for Treg expression. Expression of cytokines (ELISA) was studied in joint tissues and in sera.

Results: At D24 post-immunization, control CIA saline-treated mice started to develop arthritis as shown by arthritic score (ranging from 2 to 11 from D24–45). At sacrifice, (22–52)AM had decreased arthritic score compared to saline (5.8±2 vs 11±3, respectively; $p<0.05$). Incidence of arthritis was reduced by 25 % with (22–52)AM. Histological scores were decreased with (22–52)ADM compared to control (0.56±0.04 vs 3.78±0.26, $p<0.05$). Compared to naïve mice, saline-treated CIA mice had significantly higher serum levels of the proinflammatory cytokines TNF-α, IL-6, IL-17A). (22–52)AM completely abrogated this increase The broad systemic antiinflammatory activity of AM and (22–52)AM was accompanied by down-regulation of Th1 (TNF-α, IL-6) and Th17 (IL-17A) cytokine expression in knee extracts and up-regulation of anti-inflammatory cytokines (IL-10, IL-4). Furthermore, the number of Treg cells expressing CD4+CD25+Foxp3 was decreased in control CIA mice vs naïve mice. (22–52)AM had no effect on number of Treg cells as compared to CIA control mice but, (22–52)AM treatment significantly increased serum IL-2 level in CIA mice.

Conclusions: (22–52)AM, along with reduced clinical and histological arthritis score in CIA, dramatically decreased serum and articular pro-inflammatory cytokines and triggered a robust increase in anti-inflammatory cytokines in CIA mice. (22–52)AM did not modulate the number of CD4+CD25+Foxp3 Treg cells but, increased Treg functions, as evidenced by increased IL-2 production, a marker of Treg activity.

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1708

A New Humanized Mouse Model for Experimental Erosive Arthritis: A Possible Role of Epstein-Barr Virus (EBV) for Experimental Erosive Arthritis That Resembles Rheumatoid Arthritis (RA). Yoshikazu Kuwana[5], Masami Takei[5], Misako Yajima[3], Hirotake Inomata[6], Masaaki Shiozaki[7], Natsumi Ikumi[7], Takamasa Nozaki[7], Hidetaka Shiraiwa[7], Noboru Kitamura[7], Shigemasa Sawada[7], Hiroyuki Masuda[7], Naoki Yamamoto[3], Norio Shimizu[4], Mamoru Ito[1], Ken-ichi Imadome[2] and Shigeyoshi Fujiwara[2]. [1]Central Institute for Experimental Animals, Kawasaki, Japan, [2]Department of Infectious Diseases, National Research Institute for Child Health and Development, Tokyo, Japan, [3]Department of Microbiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, [4]Department of Virology, Division of Medical Science, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan, [5]Division of Hematology and Rheumatology, Department of Medicine, Nihon University School of Medicine, Itabashi Tokyo, Japan, [6]Division of Hematology and Rheumatology, Department of Medicine, Nihon University School of Medicine, Itabashi Tokyo, Japan, [7]Division of Hematology and Rheumatology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan

Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology characterized by destructive synovitis and systemic immunologic abnormalities. In this study, whether Epstein-Barr virus (EBV) infection could result in erosive arthritis that resembles RA in NOD/Shi-*scid*/IL-2R^{null} (NOG) mice was examined.

Methods: NOG mice, a highly immunodeficient mouse strain, in which the functional human immune system is reconstituted when they receive hematopoietic stem cell (HSC) transplants, were used. Human CD34$^+$ HSCs were obtained from cord blood using a magnetic-activated cell sorting (MACS) direct CD34 Progenitor Cell Isolation Kit. These CD34$^+$ cells (1×10^4 to 1.2×10^5 cells/mouse) were injected intravenously into 6–10-week-old, female, NOG mice. The NOG mice were inoculated intravenously through the tail vein with EBV (10^0-10^3 TD_{50}) on days 106 to 180 after stem cell transplantation. EBV DNA in peripheral blood was quantified by a real-time quantitative polymerase chain reaction (PCR) assay based on the TaqMan system (Applied Biosystems) 1 to 4 months after inoculation. One, two, six, and twelve months after being inoculated with EBV, the humanized NOG mice were sacrificed, and their joints were examined pathologically. The joint tissues were stained with hematoxylin-eosin (H-E) stain, and immunostaining and EBV in situ hybridization were performed.

Results: The joint tissues of the mice revealed pannus invading bone tissue, synovial membrane proliferation, and inflammatory tissues infiltrating the bone marrow (BM) space. Human CD4$^+$ T cells were seen proliferating to the synovium and the BM near joints. Migration of large multinuclear giant cells, thought to be osteoclasts, was also evident in the pannus site. EBV-infected cells were mainly conformed within the BM of the EBV-inoculated NOG mice, but there were few EBV-infected cells in the synovium.

Conclusions: In this study, bone erosion accompanied by pannus and synovial membrane proliferation was confirmed at the joints of EBV-inoculated NOG mice. Further, some EBV-inoculated NOG mice revealed BM erosion as a result of the inflammatory cell infiltration. The results of this study suggest that EBV-inoculated NOG mice develop erosive arthritis that resembles RA.

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1709

ASC Plays a Role in the Priming Phase of the Immune Response to Type II Collagen in Collagen-Induced Arthritis. Hideshi Yamazaki[1], Michiko Takeoka[1], Masato Kitazawa[1], Takashi Ehara[2], Naoki Itano[1], Hiroyuki Kato[2] and Shun'ichiro Taniguchi[1]. [1]Shinshu University Graduate School of Medicine, Matsumoto, Japan, [2]Shinshu University School of Medicine, Matsumoto, Japan

Background: Although rheumatoid arthritis (RA) is an autoimmune disease of unknown etiology, the role of TNF-a, IL-1β, IL-18, and IL-6 in the pathogenesis of RA has been well established. IL-1β and IL-18 are generated via cleavage of their pro-forms in the presence of the apoptosis-associated speck-like protein containing a caspase recruit domain (ASC), which is an adaptor protein that activates procaspase-1. We therefore investigated the involvement of ASC in RA progression and assessed the phase at which ASC exerts effects using ASC-deficient mice models of collagen-induced-arthritis (CIA) and collagen antibody-induced arthritis (CAIA).

Method: CIA was developed in ASC-deficient (ASC$^{-/-}$) and wild-type (ASC$^{+/+}$) mice by four back-crosses to the DBA/1J background. CAIA was induced in ASC$^{-/-}$ and ASC$^{+/+}$ mice using a mouse monoclonal anti-type II collagen five clone antibody cocktail. Histological findings and expression of pro-inflammatory cytokines in knee joints were then compared and disease severity in joint sections was graded using a scoring system. Analysis of IL-1b and IL-18 expression was also performed by immunohistochemistry.

Results: Histological examination and scoring of arthritic knee joints from ASC$^{+/+}$ and ASC$^{-/-}$ CIA mice revealed that infiltration of inflammatory cells and cartilage/bone destruction were significantly decreased in ASC$^{-/-}$ mice compared with ASC$^{+/+}$ mice. Conversely, no differences were observed between ASC-deficient mice and controls for CAIA. In CIA knee joints, IL-1β and IL-18 expression were lower in ASC$^{-/-}$ mice compared with ASC$^{+/+}$ mice, whereas these cytokines were expressed at similar levels in the knee joints of ASC$^{+/+}$ and ASC$^{-/-}$ CAIA mice.

Conclusion: We demonstrated that ASC-deficient mice were comparably susceptible to CAIA as normal mice, but were protected from disease severity in CIA. Thus, ASC is believed to be involved in early CIA development and may play a role in the priming phase of the immune response to type II collagen.

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1710

Asymmetric Arthritic Flare in the Knees of TNF-Tg Mice Is Mediated by Expansion of CD23+/CD21hi B Cells and Ipsilateral Collapse of Lymph Nodes in Series. Jie Li, Igor Kuzin, Christopher Ritchlin, Ignacio Sanz, Andrea Bottaro, Lianping Xing and Edward Schwarz. University of Rochester

Purpose: The efficacy of TNF antagonists and anti-CD20 therapy has demonstrated a critical role for TNF and B cells in the pathogenesis of rheumatoid arthritis (RA). However, the mechanism underlying arthritic flare and asymmetric arthritis in particular joints is still unknown. Previously, we used contrast-enhancement (CE) MRI and near infrared (NIR) indocyanine green (ICG) lymphatic imaging to evaluate arthritis in TNF-Tg mice, and demonstrated that arthritic progression from the ankle to the knee joint occurs following a sudden decrease in lymphatic flow from the lower limb to the adjacent popliteal lymph node (PLN). This decrease in lymphatic flow to "expanding" PLNs with high lymphatic drainage capacity (LNcap) lead to a "collapsed" PLN phenotype characterized by a marked decreases in LNcap, and translocation of CD23+/CD21hi B cells in inflamed nodes (Bin) from the follicles into the sinus space. Interestingly, this pathology is asymmetric in time to occurrence and incidence, and some TNF-Tg mice never develop bilateral knee arthritis. Since lymph from the ankle drains to PLN and lymph from knee joint drains to the iliac lymph node (ILN), we hypothesized that the correlation of PLN collapse and arthritic flare in the adjacent knee is caused by inhibited lymph drainage of the lower limb due to simultaneous collapse of ipsilateral PLN and ILN, and tested this in our murine model.

Methods: 5–7 month old TNF-Tg mice with expanding or collapsed PLNs were identified by longitudinal CE-MRI, and their knees were phenotyped for arthritic flare (defined as synovial volume $>3mm^3$). PLNs ($n>10$) and ILNs ($n>10$) were harvested from the TNF-Tg, and their WT littermate controls, for flow cytometry or immunohistochemistry (IHC) to quantify Bin and their location within the node. Lymphatic draining function of PLN and ILN were measured by NIR of ICG injected into the footpad or knee cavity, respectively.

Results: Flow cytometry of ILNs revealed a significant ($p<0.05$) 2.8-fold expansion of the Bin population from 7.2% in WT to 19.8% in TNF-Tg, which was consistent with the significant ($p<0.05$) 3.3-fold increase from 10% to 33.2% observed in WT and TNF-Tg PLN respectively. While Bin numbers were similar in both expanding and collapsed PLNs, IHC revealed that ILN ipsilateral to collapsed PLN have similar lymphoid architecture in which Bin are depleted from the follicular region, and reside in paracotical LYVE+ lymphatic sinuses. NIR-ICG imaging revealed that lymph flow to ILN ipsilateral to expanding PLNs (S-max=255) is 1.7-fold greater than that of ILN ipsilateral to collapsed PLNs (S-max=151.4).

Conclusion: Our results showed that ipsilateral ILN and PLN function in series. The decrease of lymphatic flow from the lower limb and Bin translocation from the follicles into lymphatic sinuses of draining LNs occur simultaneously. This finding supports a novel mechanism of the asymmetric arthritic flare that is triggered by Bin translocation in draining LN, which results in decreased afferent lymph flow from the inflamed joint. Future studies aimed establish this Bin "clogging" phenomena in mice and RA patients will be discussed.

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1711

CD44 Involvement in Arthritis: The Role of cd44-Splice Variants in Development of Collagen-Induced Arthritis in Mice. Celia Menckeberg[3], Marjolein van Maanen[4], Ronald van der Neut[2], Steven T. Pals[2], Margriet Vervoordeldonk[3] and Paul P. Tak[1]. [1]Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, [2]Department of Pathology, Amsterdam, The Netherlands, [3]Division of Clinical Immunology and Rheumatology, Amsterdam, The Netherlands, [4]Division of Clinical Immunoly, Amsterdam, The Netherlands

Objective: CD44 comprises a family of type I transmembrane glycoproteins with a wide tissue distribution including expression on leukocytes, fibroblasts, as well as epithelial and endothelial cells, and is capable of binding to several ligands, its preferred ligand being hyaluronic acid (HA). There have been several reports suggesting a role for CD44 and HA in rheumatoid arthritis (RA). Interestingly, it is now clear that alternative splicing and selective tissue distribution of CD44 variants confer specific functions to the CD44 molecule. Specifically, it has been shown that distinct CD44 splice variants differ in their ability to interact with extracellular matrix molecules (ECM) and with cytokines/growth factors. The role of these molecules in rheumatic diseases has been rarely studied so far, although it has for example been shown that CD44v3 is overexpressed on synovial fibroblasts, which carry an increased invasive capacity in vitro. In contrast, overexpression of CD44v8-v9 was described to correlate negatively with the invasive capacity of fibroblast-like synoviocytes. Therefore, we explored the role of CD44 splice variants in an animal model of RA by using a unique series of CD44 knock-out-knock-in mice that selectively express CD44 variants, differing in their capacity to interact with hyaluronan, chemokines/cytokines, and growth factors.

Methods: In C57BL6 mice collagen-induced arthritis (CIA) was induced at day 0 by an intradermal injection with chicken type II collagen at the base of the tail followed by the same injection on day 20. CIA was induced in wild-type (WT) mice, CD44 knock-out mice (KO), expressing none of the isoforms, and knock-out-knock-in strains CD44s/s (able to bind HA but not growth factors, chemokines), CD44v3-v10 (carrying the heparan sulphate (HS) side chains), and CD44v4-v10 mice (similar to CD44-v3-v10 but missing the HS attachment site). All mice were viable and did not show any detectable deficiencies. Mice were sacrificed on day 56 after induction of disease. Disease progression was monitored by visual clinical scoring and measurement of paw swelling. In addition, inflammation and joint destruction were examined by histology and radiology. Serum levels of anti-collagen type II antibodies were measured by enzyme-linked immunosorbent assay

Results: There was a significant decrease in the incidence and severity of arthritis in KO, CD44s/s, KO, and CD44v4-v10 mouse strains ($P<0.05$), accompanied by reduced synovial inflammation ($P< 0.05$) and bone destruction, compared to WT mice. In contrast, the CD44v3-v10 mice showed a delayed onset of disease but the clinical scores reached similar levels as those in WT. Moreover, we found a specific decrease in the collagen-specific 'Th1-associated' IgG2a response ($P<0.01$) in mice with reduced arthritis activity, but not in CD44v3-v10 mice.

Conclusion: The results suggest the involvement of the CD44 v3 region in the development and expression of arthritis.

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1712

Counter-Regulatory Role of Interferon Regulatory Factor 7 in Serum Transfer K/BxN Inflammatory Arthritis. Susan E. Sweeney[1] and Trevor B. Kimbler[2]. [1]University of California San Diego, La Jolla, CA, [2]University of California San Diego

Purpose: Innate immune response pathways play a role in synovial activation and cell recruitment into the rheumatoid joint. Viral-stress inducible proteins such as type I interferon (IFNα and IFNβ), IP-10, and RANTES are produced through the activation of NF-κB, MAP kinases, and IFN-regulatory factors (IRF) as a result of innate sensor recognition of dsRNA. The IRF family not only regulates the IFN response, but also cell differentiation, cell cycle, and apoptosis. This study examines the effect of genetic deficiency of IRF7 in regulation of the type I IFN response in murine synoviocytes, macrophages, and a passive K/BxN serum transfer model of arthritis.

Methods: Fibroblast-like synoviocytes (FLS) and peritoneal macrophages isolated from IRF7$-/-$ mice were stimulated overnight with poly (I-C) followed by Q-PCR to evaluate gene expression. Passive K/BxN serum transfer arthritis was induced in IRF7$-/-$ mice and additional groups were treated with IFNβ or poly (I-C). Clinical arthritis scores were measured and synovial tissue Q-PCR was performed. Mouse serum was analyzed for IFNβ, IL-10, and IL-1RA by ELISA.

Results: Poly (I-C) stimulation of murine IRF7$-/-$ FLS resulted in increased induction of pro-inflammatory gene expression of RANTES (5.2-fold, $p<0.01$), MIP1α (1.8-fold, $p<0.05$), and MMP-3 (2.7-fold, $p<0.05$) compared with C57BL/6 wild type FLS. In contrast, IRF7$-/-$ macrophages stimulated with poly (I-C) showed significantly less induction of inflammatory cytokine gene expression, including IFNβ, IP-10, MIP1α and IL-6 (8.8-fold, $p<0.01$; 11.2-fold, $p<0.01$; 5.3-fold, $p<0.05$; 21.7-fold, $p<0.005$ respectively). In the K/BxN passive in vivo model, arthritis severity in IRF7$-/-$ mice was significantly increased (day 12 score 8.8 vs. 3.9; $p<0.01$) compared with wild type K/BxN. Gene expression of IFNβ, RANTES, MIP1α, and IL-6 was decreased in IRF7$-/-$ synovial tissue compared with K/BxN control synovium (3.9-fold, $p<0.05$; 2.2-fold, $p<0.05$; 2.4-fold, $p<0.04$; 1.7-fold, $p<0.05$ respectively). The serum IFNβ level in IRF7$-/-$ mice was also significantly decreased compared with control K/BxN serum (2.8-fold, $p<0.04$). IRF7$-/-$ mice injected with IFNβ had a decrease in paw score (ΔPaw score = 1.8) similar to wild type mice (ΔPaw score = 2.9), suggesting that the increased arthritis might be partially due to decreased IFNβ. Poly (I-C) treatment diminished arthritis severity (17% change, $p<0.05$) in IRF7$-/-$ mice and increased serum IFNβ levels (1.6-fold, $p<0.05$).

Conclusion: These data suggest that IRF7 contributes to regulation of the type I IFN response and cytokine production in cell-specific manner in macrophages (pro-inflammatory) and synovioctyes (anti-inflammatory). IRF7 plays an anti-inflammatory role in passive transfer K/BxN arthritis possibly through regulation of IFNβ. IRF7 also partially contributes to poly (I-C)-mediated inhibition of arthritis in this model. Our data suggest that TLR agonists that induce IRF7 might represent a novel therapeutic approach in the treatment of inflammatory arthritis.

Disclosure: S. E. Sweeney: None; **T. B. Kimbler:** None.

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Dectin-1 and NOD2 Mediate Zymosan-Induced Arthritis in Mice. Holly L. Rosenzweig[1], Jenna S. Clowers[4], Gabriel Nunez[3], James T. Rosenbaum[2] and Michael P. Davey[5]. [1]Oregon Health & Science University/VA Medical Ctr, Portland, OR, [2]Oregon Health Science Univ, Portland, OR, [3]University of Michigan Medical School, Ann Arbor, MI, [4]VA Medical Ctr, [5]VA Medical Ctr/Oregon Health & Science University, Portland, OR

Purpose: Rheumatoid arthritis (RA) remains a disease of unknown etiology. Genetics, the environment and specific features of diarthroidial joints are presumed to play contributory roles. Receptors of the innate immune system within diarthroidial joints may contribute to arthritis by detecting components of infectious agents, a hypothesis often implicated in the etiology of RA. We sought to elucidate the role of innate immune receptors within the Toll-like receptor (TLR), NOD-like receptor (NLR) and C-type lectin receptor (CLR) families in the well-established murine model of zymosan-induced arthritis (ZIA).

Methods: Arthritis was elicited by intra-articular injections of zymosan or fungal cell wall components: curdlan, laminarin and mannan. The extent of disease within the joint was assessed by NIR-fluorescence imaging and histology. The contribution of individual immune receptors or a signaling molecule (CR3, TLR2, MyD88, Dectin-1, Dectin-2, NOD1, or NOD2) was assessed using knock-out mice or blocking antibodies. For fungal infection, mice were infected with *Candida albicans* and the presence of fungi and joint inflammation were assessed by PAS/green staining and NIR-imaging.

Results: Systemic fungal infection caused mild arthritis in mice that coincided with the presence of fungi within the joint. As previously demonstrated, intra-articular injection of zymosan triggered arthritis in mice at 3 days following injection. This response was dependent on Dectin-1, a member of the CLR family. Dectin-2 also contributed to ZIA, but to a lesser extent than Dectin-1. However, deficiency in TLR2, MyD88 or CR3 did not significantly alter ZIA. Injection of curdlan, laminarin or mannan (the individual components of zymosan) showed that curdlan alone was the arthritogenic component of zymosan and the effect was dependent on Dectin-1. Somewhat surprisingly, we found that ZIA was dependent on NOD2 as NOD2 KO mice were resistant to disease. In contrast to NOD2, we found that NOD1 deficiency did not alter arthritis.

Conclusion: The present study elucidates the receptors involved in mediating ZIA. Together, Dectin-1 and NOD2 are essential receptors of the innate immune system in the arthritogenic effects of zymosan. This is the first association of NOD2 with innate immune responses to fungal components and points to a regulatory role for NOD2 in the normal physiology of diathroidial joints. Given that mutations in NOD2 cause of an inherited form of arthritis (Blau syndrome), our findings further implicate NOD2 as an important protein within diarthroidial joints contributing to inflammatory arthritis.

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Dendritic Cell-Based Immunotherapy Combined with Low-Dose Methotrexate Is Effective in the Treatment of Advanced Collagen-Induced Arthritis in Mice. Mi-Sun Kang[4], Jung-Wook Lee[4], Hyun-Soo Lee[4], Chan-Bum Choi[1], Hye-Soon Lee[3], Sang-Cheol Bae[2] and Yong-Soo Bae[5]. [1]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Republic of Korea, [2]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Korea, Republic of, Korea [3]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, [4]Research Institute for DC Immunotherapy, CreaGene Inc., [5]Research Institute for DC Immunotherapy, CreaGene Inc., Department of Biological Science, Sungkyunkwan University

Objectives: We have previously demonstrated that semi-mature dendritic cells (smDC)-based immunotherapy was effective in the treatment of early stage collagen-induced arthritis (CIA). This work was initiated to determine the efficacy of combination therapy with smDC and methotrexate (MTX) in advanced stage of CIA mice.

Methods: CIA mice in arthritis score 2–3 (5–6 weeks after primary CII inoculation) were treated with MTX and collagen-loaded smDCs (CII-smDC) in three consecutive therapeutic cycles. Each therapeutic cycle was completed by administration of MTX three times on days 2, 4 and 6, followed by administration of CII-smDC on day 7. Footpad thickness and the disease severity of each mouse were measured once or twice a week for 90 days after completion of three therapeutic cycles. Foxp3-positive regulatory T cell (Treg) populations, Th1/Th2 immune response, and cytokine profiles were assessed in the spleen and lymph nodes.

Results: Combination therapy with low-dose (0.5mg/kg) MTX and CII-smDC was more effective than high or low dose MTX alone or combination of high dose MTX and CII-smDC in inhibiting disease progression. Treatment with CII-smDC alone also showed comparable effect. $CD4^+Foxp3^+$ Treg populations were markedly increased in mice treated with the combination therapy compared to mice treated with CII-smDC alone as well as other treatments. IL-10 secretion also increased in proportion to the level of induced Treg. The combination therapy reduced the secretion of interferon gamma (IFN-γ), but did not affect or slightly increased the IL-4 secretion in the mixed lymphocyte reaction with spleen or lymph node T cells. Treg induced by combination therapy were effective in inhibiting CII-specific T cell proliferation. However, total CD4+ T cell populations were not significantly changed by the combination therapy.

Conclusion: Combination therapy with low-dose MTX and smDC, or smDC alone, was efficacious in the treatment of advanced arthritis mice by inducing antigen-specific Treg population, rather than changing Th1/Th2 immune deviation, followed by blocking autoreactive T cell proliferation, resulting in disease control.

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Histone Deacetylase Inhibitor (HDAi) Ameliorates Chronic Arthritis in SKG Mice by Altering Conventional Dendritic Cells (cDCs) Phenotype into Tolerogenic DCs. Kenta Misaki[2], Akio Morinobu[2], Jun Saegusa[2], Yoshiaki Miyamoto[2], Shinpei Kasagi[2] and Shunichi Kumagai[1]. [1]Clinical Immunology and Pathology, Kobe University, Kobe, Japan, [2]Clinical Immunology and Pathology, Kobe University, Japan

Background & Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory polyarthritis, leading to joint destruction. CDCs contribute to pathogenesis of RA by triggering the immune responses. HDAi plays a significant role of controlling gene transcription, and has been reported to regulate immune responses. Here we examined the therapeutic effects of HDAi (Trichostatin A: TSA) on the RA model mice and cDCs.

Methods: SKG mice were injected with Zymosan A (ZyA) to induce chronic arthritis. DMSO or TSA was daily administrated to SKG mice. Cell surface molecules and cytokine production in splenic cDCs, clinical arthritis scores, histological arthritis scores were evaluated in each group. The effects of TSA on bone marrow cells-derived cDCs treated with ZyA (BMcDCs-ZyA) were assessed by flow cytometry, ELISA, real-time PCR (RT-PCR) and the allo-mixed lymphocyte reaction (allo-MLR) *in vitro*.

Results: Clinical arthritis scores and histological arthritis scores in SKG mice treated with TSA were significantly lower than those with DMSO. CD80 and CD86 expression of splenic cDCs in TSA group were notably down-regulated compared to those in DMSO group. IL-17A production in CD4 positive splenocytes was also decreased in TSA group. *In vitro*, IL-12p70, IL-12p40, IL-6 secretions and CD80, CD40 levels of BMcDC-ZyA were reduced in BMcDC-ZyA with TSA by flow cytometry and ELISA, respectively. Indoleamine 2,3-dioxygenase (IDO) expression in BMcDC-ZyA with TSA was much higher than those in BM-cDC-ZyA determined by RT-PCR. Pretreatment of BMcDCs with ZyA+TSA resulted in significantly reduced naïve CD4 positive T cell proliferation compared to that with BMcDCs-ZyA in allo-MLR.

Conclusions: TSA has notable anti-arthritis effects on SKG mice by modulating functions of cDCs. TSA alters DC function into tolerogenic DC, such as decreased expression of co-stimulatory molecules and pro-inflammatory cytokines, increased IDO expression, and reduced T cell proliferation. This is the first report that HDAi ameliorates the disease activity of SKG mice.

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IDO Expressed CD11c+CD11b+ Dendritic Cells Enhance the Differentiation of Ag Inducible CD4+CD25+ Regulatory T Cells in Induction of Oral Tolerance under the Inflammatory State. Min Jung Park[2], Yong-Geun Jung[2], Su-Jin Moon[2], Ji-Min Kim[2], Seung-Ki Kwok[2], Ji-Hyeon Ju[2], Kyung-Su Park[2], Hyun Sil Park[2], Mi-La Cho[2], Sung-Hwan Park[2] and Ho-Youn Kim[1]. [1]Kang Nam St Marys Hospital, Seoul, Korea, Republic of, [2]Kang Nam St Marys Hospital

Repeated oral administration of an antigen is known to induce immunological hypo-responsiveness to that specific antigen, which is called oral tolerance. The mechanism of oral tolerance is believed to involve regulatory T cells (Tregs), tolerogenic dendritic cells (DCs) and several immune-regulatory molecules. Indoleamine 2,3-dioxygenase (IDO) which is expressed by DCs suppress T cell responses by catabolizing tryptophan and generating Tregs. In this experiment, we tried to identify which DC subsets in spleen express IDO and are involved in the generation of CD4+CD25+ Tregs during oral tolerance induction in murine collagen-induced arthritis (CIA) model.

We separated CD11c+ CD11b+ DCs from CIA mice after repeated oral administration of type II collagen (CII). The splenic CD11c+CD11b+ DCs produced IL-10 and TGF-β which are preferentially involved in the oral tolerance induction. In addition, splenic CD11c+CD11b+ DCs from CII fed mice expressed higher level of IDO than those from PBS fed CIA mice did. We compared the CII oral tolerance-induced IDO expression by and Treg inducing effect of CD11b+ DCs from CII-immunized CIA mice with those from un-immunized control mice. IDO expression in CD11b+ DCs as well as the proportion of Foxp3+ T cells in spleen and Peyer's Patch was significantly higher in CII-fed CIA mice (infalmmatory state) than in CII-fed non-immunized mice. Our data suggest that the immunoregulatory effect of CD11b+ DCs is more prominent in CII fed CIA(inflammation) condition. CD11c+CD11b+DCs from tolerized mice suppressed CII-specific T cell response and down-regulated proinflammatory cytokine production in an IDO-dependent manner. Notably, IDO-expressing $CD11c^+CD11b+$ DCs converted CD4+CD25-T cell into CD4+CD25+ Foxp3+ regulatory T cells with regulatory property.

Our results demonstrated that after repeated CII administration the specialized, tolerogenic DC subset, such as CD11b+ DCs can induce the peripheral differentiation of Tregs, prominently in inflammatory condition. Our data suggest that IDO-expressing CD11c+CD11b+ DCs play a crucial role in oral tolerance through an IDO-dependent pathway in inflammatory state and may be a candidate cell population for therapeutic modality in the treatment of autoimmune arthritis.

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Immunisation with Citrullinated Human and Porphyromonas Gingivalis Enolase Induces Rapid Onset Arthritis in HLA DR4 Transgenic Mice. Andrew J. Kinloch[2], William Brintnell[5], David Yue[5], Lillian Barra[5], Natalia Wegner[1], Karin Lundberg[1], David A. Bell[3], Ewa Cairns[4] and Patrick J. Venables[1]. [1]Imperial College London, [2]Imperial College London, London, United Kingdom, [3]SJHC, London, ON, Canada, [4]Univ Western Ontario, London, ON, Canada, [5]University of Western Ontario

Background: Antibodies to citrullinated (cit) proteins/peptides are specific for RA, and predict more severe disease. Well-documented specific cit protein antigens include cit-fibrinogen and, more recently, cit-a-enolase. HLA DR4 alleles are genetic risk factors for antibodies to both antigens, with a preferential link with antibodies to an immunodominant peptide (CEP-1) of cit-a-enolase (Mahdi et al, Nature Genetics, 2009). The CEP-1 sequence is conserved in the enolase orthologue of *Porphyromonas gingivalis*, a bacterium which also expresses an active deiminase, which can citrullinate both a-enolase and fibrinogen. This suggests that antigens generated by this bacterium could breach immunological tolerance. Hill et al. (J Exp Med, 2008) demonstrated that mice expressing the human *0401* gene (DR4-IE transgenic mice) immunised with cit-fibrinogen developed chronic arthritis after 40 days and that this arthritis was dependent on the *0401* transgene. Given that the link with *0401* is particularly strong for anti-CEP-1 in human disease, the purpose of this study was to examine the arthritogenicity of cit-enolase in the same DR4-IE transgenic mouse model.

Methods: Recombinant human and *P gingivalis* enolase were citrullinated *in vitro* with rabbit PAD2 and used to immunise DR4-IE mice and control mice (MHC class II knockout and C57BL/6). Arthritis was quantified by measuring ankle swelling in the hind paws. The joints were examined by histopathology. Serum IgG reactivity with enolase and cit- enolase was assayed by Western blotting and ELISA. IgG antibodies to CEP1 and the arginine-bearing control (REP1) were measured by ELISA.

Results: All DR4-IE mice immunised with cit-enolase, both from human and *P gingivalis*, developed significant ankle swelling (mean 0.98 +/− 0.05 mm) in both hind paws, which peaked at day 20 whereas none of the other groups developed arthritis (swelling < 0.2 mm) $p < 0.0001$ (Student's *t*-Test). Pathology of arthritic joints showed synovial hyperplasia, but a relative paucity of leukocyte infiltration. IgG antibodies reacting with both cit- and non-cit-enolase, and also CEP1 and REP1 were detectable in all groups apart from the relatively immunodeficient MHC class II knockout group.

Conclusions: Both human and *P gingivalis* cit-enolase induce arthritis in DR4-IE mice. The arthritis was restricted to the group with the *0401* transgene, whereas the antibody response to both cit and non-cit antigens was not MHC-dependent. These data support recent epidemiologic evidence in humans that cit-enolase is an antigen of etiologic importance in RA in the context of DR4 risk alleles, and provides a novel model for investigating an etiologic role for *P gingivalis* in RA.

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JNK1 Deficiency Limits Macrophage Mediated Antigen Induced Arthritis. Monica Guma[1], Gary S. Firestein[2], Michael Karin and Mary Corr[2]. [1]UCSD, [2]UCSD School of Medicine, La Jolla, CA

Objective: To elucidate the non-redundant roles of JNK1 and JNK2 in antigen-induced arthritis.

Methods: Mice that were genetically disrupted in Jnk1 or Jnk2 were primed with mBSA in complete Freund's adjuvant and then given an intraarticular challenge with mBSA in the knee on day 21. Bone marrow chimeras were generated and similarly treated. Joints were harvested and prepared for histological assessment. T cell responses were verified by proliferation response and relative immunoglobulin responses were measured by ELISA. Cytokine mRNA expression levels were measured by Q-PCR. Peritoneal macrophages and neutrophils were elicited by thioglycollate. Macrophage migration was tested in vitro. The peptide inhibitor D-JNKi was injected daily starting four days after intraarticular mBSA injection in wild type (WT) mice and inflammation was histologically scored.

Results: JNK1-deficient but not JNK2-deficient mice, had a marked reduction in inflammatory infiltration and bone erosion. This effect was restricted to hematopoetic cells, but B and T cell responses were preserved in mBSA injected mice. JNK1-deficient macrophages produced cytokines and chemokines comparably to WT counterparts. However, macrophage migration was impaired in vivo and in vitro. Targeting JNK with the peptide inhibitor D-JNKi dramatically reduced inflammation and joint destruction in WT mice.

Conclusions: Antigen-induced arthritis is dependent on JNK1, but not JNK2. JNK1 is a promising molecular target for reducing autoimmune inflammation as its inhibition impairs macrophage migration.

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Loss of Integrin alpha2beta1 Suppresses Joint Inflammation and Cartilage Destruction in Mouse Models of Rheumatoid Arthritis. Marvin A. Peters[4], Doreen Wendholt[6], Simon Strietholt[6], Svetlana Frank[6], Adelheid Korb[5], Leo A. B. Joosten[2], Wim B. Van Den Berg[8], George Kollias[7], Elena Neumann[3], Beate Eckes[1], Ulf Muller-Ladner[9] and Thomas Pap[10]. [1]Department of Dermatology, University of Cologne, [2]Department of General Internal Medicine, Radboud University Nijmegen Medical Centre, [3]Department of Internal Medicine and Rheumatology, Justus-Liebig-University Giessen, Kerckhoff Clinic, Bad Nauheim, Germany, [4]Department of Internal Medicine and Rheumatology, Justus-Liebig-University Giessen, Kerckhoff Clinic; Institute of Experimental Musculoskeletal Medicine, University of Muenster, Bad Nauheim, Germany, [5]Department of Internal Medicine D, University of Muenster, [6]Institute of Experimental Musculoskeletal Medicine, University of Muenster, Muenster, Germany, [7]Institute of Immunology, Biomedical Sciences Research Center, [8]Radboud Univ Nijmegen Med Cntr, Nijmegen, The Netherlands, [9]Univ.Giessen/Kerckhoff-Clinic, Bad Nauheim, Germany, [10]University Hospital Münster, Münster, Germany

Background: Integrins are the main receptors for cell-matrix interactions, and integrin signaling is critical for a variety of cellular functions such as adhesion, cell spreading and inflammatory responses. Alpha2beta1 integrin acts as major receptor for type I collagen on a number of different cells, including inflammatory cells and fibroblasts. Although alpha2-deficient mice appear normal apart from mild platelet dysfunction, it was shown that alpha2 contributes to the induction and activation of MMPs in tissue remodeling. Based on the hypothesis that under stress conditions such as chronic inflammation alpha2beta1 integrin may be involved in the activation of synovial cells, we investigated its role in inflammatory arthritis.

Methods: The role of alpha2 was examined in two different murine models of arthritis, (i) alpha2-deficiency during antigen-induced arthritis (AIA), and (ii) alpha2-deficient mice crossed with arthritic human TNFalpha transgenic (hTNFtg) mice. Clinical signs of arthritis, weight and histological scores of synovitis and cartilage destruction were investigated using standard clinical evaluation and histomorphometric analysis. In addition, we analyzed MMP expression in tissue sections, serum and fibroblast-like synociocytes (FLS) from all genotypes and analyzed changes in proliferation and ERK phosphorylation. The role of the alpha2 subunit in the attachment of FLS to healthy and IL-1 damaged articular cartilage was analyzed using an established *in vitro* assay.

Results: At day 5 after AIA induction, alpha2(−/−) mice showed a decrease of joint inflammation (−57%) and proteoglycan loss (−54%) compared to wildtype mice. In addition, MMP3 levels were significantly lower in tissue sections of alpha2(−/−) mice. In hTNFtg mice, the loss of alpha2 integrin resulted in improved clinical signs and symptoms. hTNFtg/alpha2(−/−) mice had less paw swelling (1.80 vs. 2.38), increased grip strength (−1.71 vs. −2.42) and a less pronounced weight loss compared with hTNFtg mice. The histological analysis revealed that alpha2(−/−) mice had a decreased cartilage erosion (−48,5%) and significantly reduced attachment of FLS to cartilage (−55,5%). MMP-3 expression was reduced in the serum and in FLS of alpha2(−/−) mice. Additionally, the proliferation of alpha2(−/−) FLS was decreased *in vitro* and we demonstrated that this is mediated through ERK signaling pathways. Futhermore, attachment of alpha2-deficient FLS was reduced, particularly after induction of proteoglycan loss in IL-1 treated articular cartilage *in vitro*.

Conclusions: The results support the hypothesis that alpha2 deficiency is an important factor in inflammatory cartilage destruction by interfering with fibroblast attachment and proliferation as well as by modulating MMP expression.

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1720

Lung Inflammation and Pulmonary Function Alterations in Collagen-Induced Arthritis and in the Absence of Interferon-gamma Signaling. Evelien Schurgers[1], Freya Mertens[2], Jeroen Vanoirbeek[3], Tania Mitera[2], Stéphanie Put[2], Benoit Nemery[3] and Patrick Matthys[2]. [1]Laboratory of Immunobiology, Rega Institute, Katholieke Universiteit Leuven, Leuven, Belgium, [2]Laboratory of Immunobiology, Rega Institute, Katholieke Universiteit Leuven, Leuven, Belgium, [3]Research Unit of Lung Toxicology (Laboratory of Pneumology), Katholieke Universiteit Leuven, Leuven, Belgium

Background: Rheumatoid arthritis (RA), a systemic inflammatory disease affecting the joints, is regularly associated with extra-articular symptoms. Lung complications are one of these manifestations and have a profound impact on patient well-being and survival. There are no reports on pulmonary complications in collagen-induced arthritis (CIA), a widely used animal model for RA. We investigated potential lung inflammation and changes in pulmonary functions during CIA, using both wild type and interferon-gamma (IFN-γ) receptor knock-out (IFN-γR KO) mice, which develop a more severe form of arthritis.

Methods: CIA was induced in mice by a subcutaneous injection of collagen type II in Freund's adjuvant. At various time points after induction, cytokine and chemokine expression in the lungs and in synovial tissues were analysed by qPCR. Cell influx in the airways and inflammation in lung tissue were determined by broncheoalveolar lavage (BAL) and histology, respectively. To analyse the impact of arthritis on lung physiology, lung function measurements were assessed via the invasive forced oscillation technique of the flexiVent system. Resistance and elastance of the whole lung and more specific, the large airways and the alveoli were measured.

Results: Upon induction of CIA, the onset of arthritic symptoms was accompanied by induction of interleukin-1β (IL-1β) and the neutrophil chemokine Granulocyte Chemotactic Protein 2 (GCP-2) in the synovial tissues of both wild type and IFN-γR KO mice. In the lungs of wild type mice, IL-1β levels became detectable at day 10, before the onset of arthritis. In arthritic IFN-γR KO mice, lungs expressed GCP-2 and other chemokines such as KC and Monocyte Chemotactic Protein 1 (MCP-1). BAL fluid of arthritic wild type and IFN-γR KO mice contained elevated numbers of cells as compared to their respective naïve counterparts. The increase in cell numbers was caused by influx of macrophages and lymphocytes. BAL fluid of immunized IFN-γR KO mice showed an additional influx of neutrophils. On histological examination, lungs of arthritic IFN-γR KO mice demonstrated a perivascular lymphocytic infiltration into the lung tissue which was absent in arthritic wild type mice and in naïve animals. When lung function measurements were performed, tissue elasticity (H) and resistance (Rn) of the lungs were significantly elevated in arthritic IFN-γR KO mice as compared to naïve mice. No such effects could be observed in wild type mice.

Conclusions: Lung manifestations, as evident from expression of pro-inflammatory cytokines and chemokines in lung tissue and from cell influx in BAL, were detectable in both wild type and IFN-γR KO mice after induction of CIA. Perivascular infiltration into the lung tissue was exclusively present in arthritic IFN-γR KO mice and these changes negatively influenced the function of the lungs since these mice presented with a more rigid lung tissue. These results demonstrate that pulmonary manifestations do exist in CIA, and become more manifest upon deletion of one single gene (in this case IFN-γ). Therefore, CIA may prove a useful animal model to study the association between inflammation in the joints and in the lungs, as seen in RA patients.

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1721

Macrophage Migration Inhibitory Factor Plays an Important Role in Inflammatory Arthritis. Mohammad A. Amin[2], Jeffrey H. Ruth[2], Bradley J. Rabquer[2], Phillip L. Campbell[2], Solhee Lee[2], John R. David[1] and Alisa E. Koch[3]. [1]Harvard School of Public Health, [2]University of Michigan, [3]VA Medical Service and University of Michigan Medical School, Ann Arbor, MI

Purpose: Macrophage migration inhibitory factor (MIF) is a proinflammatory cytokine which plays an important role in chronic inflammatory diseases such as rheumatoid arthritis (RA). We have previously shown that MIF mediates angiogenesis via phosphatidylinositol 3 kinase (PI3K) and mitogen activated protein kinase, and upregulates the expression of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 in monocytes via Src, PI3K, and NFκB. In this study, we examined the contribution of MIF to experimental inflammatory arthritis using K/BxN serum induced arthritis by employing MIF null and wild type (wt) mice.

Methods: We induced serum transfer K/BxN arthritis in MIF null and wt mice to examine the role of MIF in mouse inflammatory arthritis. We injected 150 μl of pooled K/BxN serum on days 0 and 2. Mice were scored clinically and ankle circumference was measured with a caliper before the induction of arthritis and then every day by an observer blinded to the experimental groups. We used enzyme linked immunosorbent (ELISA) assays to determine cytokine levels in arthritic MIF null ankle homogenates compared to wt mouse ankle homogenates. We also performed immunohistochemistry (IHC) to determine the inflammatory response in MIF null and wt mouse ankle sections. To further elucidate the contribution of MIF in an animal model of arthritis, we subjected MIF null and wt mice to sublethal total body irradiation. We performed bone marrow transfer experiments. In these experiments, irradiated MIF null mice received wt bone marrow cells (10^6 cells in 100 μl of PBS) and vice versa. After 12 weeks of bone marrow transplant, we induced K/BxN arthritis in these mice and collected ankles.

Results: MIF null mice had significantly less arthritis, showing a significant decrease in ankle circumference and articular index compared to wt mice. Mouse ankles were harvested on day 9 (day of maximal arthritis). Some of ankles were snap frozen for homogenization and cytokine analysis, while others were frozen in OCT for histology. While there was no difference in interleukin-1β in mouse ankle joint homogenates, monocyte chemoattractant protein-1 (MCP-1/CCL2) was significantly decreased in MIF null mouse arthritic ankle homogenates compared to wt mouse arthritic ankles. This decrease was ~ 2 fold, suggesting an important role of MIF in the regulation of MCP-1/CCL2). IHC of MIF null ankle sections revealed reduced inflammation compared to wt mice. There was a marked decrease in MCP-1/CCL2 levels in irradiated wt mice injected with bone marrow harvested from MIF null mice compared to irradiated MIF null mice which received wt bone marrow, further confirming the significance of MIF in inflammatory arthritis.

Conclusions: These data suggest an important role for MIF in induction of MCP-1/CCL2 in mouse inflammatory arthritis. MIF may be a potential therapeutic target for the treatment of chronic inflammatory diseases like RA.

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1722

Matrix Components Influence the Aggressive Behavior of Rheumatoid Arthritis Synovial Fibroblasts. Stephanie Lefevre[2], Birgit Zimmermann[3], Matthias Geyer[3], Angela Lehr[5], Henning Stürz[4], Jürgen Steinmeyer[1], Stefan Rehart[5], Ulf Müller-Ladner[3] and Elena Neumann[3]. [1]Dept Experimental Orthopedics, Justus-Liebig-University Giessen, [2]Dept Internal Medicine and Rheumatology, Justus-Liebig University Giessen, Bad Nauheim, Germany, [3]Dept Internal Medicine and Rheumatology, Justus-Liebig University Giessen, [4]Dept Orthopedics and Orthopedic Surgery, Justus-Liebig-University Giessen, [5]Dept Orthopedics and Trauma Surgery, Markus-Hospital, Frankfurt

Background: Central mediators in joint destruction in rheumatoid arthritis (RA) are activated synovial fibroblasts (SFs). They adhere to and invade into human cartilage but the molecular details of this disease-specific behavior are known only to a limited extent. As we could show the migratory potential of RASFs in the SCID mouse model of RA, in the present study we addressed the role of extracellular matrix (ECM) regarding RASF adhesion and migration.

Methods: Chemotactic effects of finely ground cartilage were analyzed *in vitro*. After (membrane-) coating with Matrigel, growth factor-reduced Matrigel or collagen type II and adding RASFs, adhesion (after 30min) and transmigration (after 16h) of RASFs were analyzed. Isolated RASFs or whole synovial RA tissue were coimplanted with healthy human cartilage (ipsilateral; I) subcutaneously into SCID mice. Cartilage without RASFs was inserted contralaterally (Co). To analyze potential effects of the ECM, bovine or murine cartilage or cartilage without vital chondrocytes was implanted. ECM components were analyzed *in vivo* by coating the carrier matrices in various combinations (either the ipsilateral or the contralateral carrier matrix or both) with the following factors: Matrigel, fibronectin, aggrecan, growth factor-reduced Matrigel, collagen type II, PuraMatrix Peptide Hydrogel. Histological analyses of implants followed after 60 days.

Results: RASFs invaded the coimplanted cartilage directly and migrated to and invaded into the cartilage inserted contralaterally independent of the species background and the source of RASFs (isolated or whole RA synovium). Cartilage inserted into carrier matrices coated with growth factor-reduced Matrigel showed a reduced invasion (invasion score I (non-coated carrier-matrix): 1.7±0.5, Co (coated carrier matrix): 0.2±0.3; I (coated carrier matrix): 0.9±0.6, Co (non-coated carrier matrix): 2.0±0) compared to cartilage in uncoated matrices (control; I: 2.1±0.6; Co: 1.5±0.4). A concentration-dependent increase of the chemotactic effect of finely ground cartilage regarding RASF migration was demonstrated *in vitro*. Transmigration and adhesion of RASFs were decreased *in vivo* after coating with growth factor-reduced Matrigel compared to coating with Matrigel or collagen type II (up to 86fold or 49fold resp.).

Conclusion: The ECM as well as matrix associated components such as growth factors influence RASF migration from the ipsilaterally to the contralaterally implanted cartilage. Accordingly, adhesion of RASFs to growth factor-reduced Matrigel was decreased compared to other coatings. In contrast, chondrocyte vitality and species background of the cartilage appear

not to be crucial for RASF migration. Taken together, matrix components play a central role in RASF migration, transmigration, adhesion to cartilage and following joint destruction.

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1723

Monocytes Are Required for Progression but Not for Initiation of Arthritis in Mouse Model of Autoantibody-Mediated Arthritis. Alexander Misharin[1], Evan Weber[1] and Harris R. Perlman[2]. [1]Division of Rheumatology, Northwestern University, Chicago, IL, [2]Northwestern University, Chicago, IL

Background: Monocytes and macrophages play essential role in pathogenesis of rheumatoid arthritis. However their role in initiation vs. perpetuation of inflammatory arthritis in rodent models is unclear. K/BxN serum-transfer model is a commonly used model for studying the effector phase of arthritis in mice. Role of the neuthrophils and mast cells in this model has been studied in details and it is now clear that these cells are essential for initiation of arthritis. Thought there are no doubts that monocytes and macrophages play very important role arthritis, it is less well studied. Previous studies have shown that mice depleted of macrophages by clodronate liposome treatment are completely resistant to K/BxN serum-induced arthritis and that reconstitution of these mice with macrophages from naïve animals reverses this resistance. However effect of clodronate is long-term and irreversible and it does not allow assessing role of monocytes and macrophages in different steps of effector phase of arthritis. Therefore we decided to take advantage of a conditional ablation system mediated by diphtheria toxin (DT) receptor (human hbEGF) expressed under CD11b promoter to study the effects of monocytes and macrophages depletion on the course of serum transfer arthritis.

Methods: Bone marrow from transgenic mice (C57Bl/6) expressing DTR under CD11b promoter was transferred into irradiated hosts. Six weeks after reconstitution all mice received injection of K/BxN serum and the severity of arthritis was assessed by measuring ankle width and clinical score for each limb on day 0, 2, 4, 7, 9, 11 and 14. Additionally mice were divided into three groups: arthritis only or control group – did not receive DT treatment; initial monocytes depletion—received DT on days −1 and 0; and continuous monocytes depletion—received DT on days −1, 0 and every 48 hours till the end of experiment (days 2, 4, 6, 8, 10 and 12). To assess the effects of DT peripheral blood was obtained on day −6, day 0 and day 14 and analyzed by flow cytometry.

Results: Single injection of DT did not affect T and B cells populations, but induced profound decrease of monocytes in peripheral blood (from 10.7% to 1.4% and from 13.2% to 1% for initially and continuously depleted mice, respectively). At the end of study levels of monocytes in mice that received only two injections of DT returned to baseline values and did not differ from control group (11.0% and 15.7%, correspondingly), while in mice that received continuous treatment with DT levels were significantly lower (3.87%). There was no decrease in neutrophils in DT-treated mice. All mice developed arthritis initially, however only mice continuously treated with DT failed to display progression of arthritits.

Conclusions: Continuous depletion of monocytes and macrophages prevents further progression of arthritis but not of initiation of K/BxN serum transfer arthritis. Taken together with recent findings about role of neutrophils in the effector phase of inflammatory arthritis, our work suggest that monocytes are necessary for its progression and bone damage while neutrophils are required for initiation of arthritis.

Disclosure: A. Misharin: None; **E. Weber:** None; **H. R. Perlman:** None.

1724

Overexpression of RORγt Attenuated Collagen Induced Arthritis (CIA). Zhaojin Yao[2], Yuya Kondo[2], Masahiro Tahara[2], Satoru Takahashi[1], Isao Matsumoto[2] and Takayuki Sumida[3]. [1]Department of Anatomy and Embryology, Biomolecular, and Integrated Medical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, [2]Division of Clinical Immunology, Major of Advanced Biochemical Applications, Graduate School of Comprehensive Human Science, University of Tsukuba, Ibaraki, Japan, [3]Univ of Tsukuba/Inst Clin Med, Tsukuba City, Japan

Background: IL-17 producing CD4+ T cells such as Th17 cells play a crucial role in the generation of collagen induced arthritis (CIA). However, it is unclear how Th17 specific master regulator RORγt contributes to the development of arthritis. The purpose of the present study is to determine the role of RORγt overexpression on T cells in the generation of subpopulation with CIA.

Methods:

1) RORγt transgenic (RORγt Tg) mice were generated in C57BL/6 (B6) mice background under the promoter of CD2 gene. RORγt Tg and B6 mice were immunized with type II collagen (CII) emulsified with complete Freud's adjuvant (CFA).

2) Cells in draining lymph nodes were harvested on day 10 after immunization of CII and they were analyzed for the proportion and number of T cell subsets by flow cytometry.

3) After these cells were cultured in vitro with CII for 72 h, the expression of RORgt and Foxp3 in CD4+ cells was analyzed by intracellular staining method.

4) Cytokine production (IL-17, IFN-γ, IL-21, IL-6, and IL-4) by CD4+ T cells was analyzed by intracellular cytokine staining method, and levels in supernatants were measured by enzyme-linked immunosorbent assay (ELISA).

5) CII specific IgG antibodies (Abs) in sera on day 56 after immunization were measured by ELISA.

Results:

1) The incidence and severity of arthritis was significantly suppressed in RORγt Tg mice.

2) The number of total T cells in the draining lymph node after immunizations was not significantly different between RORγt Tg mice and B6 mice.

3) The RORγt expression in CD4+ T cells in RORgt mice was increased compared to B6 mice. Whereas, foxp3 expression was not changed.

4) Flow cytometry analyses shows that the number of IL-17 producing cells increased in RORγt Tg mice. ELISA assay also revealed the increase of IL-17 in supernatants.

5) CII specific IgG Abs production was significantly suppressed in RORγt Tg mice.

Conclusion: Overexpression of RORγt in T cells suppresses the development of autoimmune arthritis, in spite of the induction of antigen-specific Th17 responses. Low level of antigen specific IgG Abs production might be one of the factors for reduction of CIA in RORγt Tg mice.

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1725

Paradoxical Decrease in Collagen Induced Arthritis Severity in Gadd45β Deficient Mice. Yubin Luo[2], David L. Boyle[1] and Gary S. Firestein[1]. [1]UCSD School of Medicine, La Jolla, CA, [2]UCSD School of Medicine

Purpose: Growth arrest and DNA damage inducible 45b (Gadd45β) is involved in stress responses, cell cycle regulation, and oncogenesis. The mechanism of action for many functions relates to the ability of Gadd45β to block c-Jun amino terminal kinase (JNK) activity by binding to its upstream kinase MKK7. Gadd45β−/− mice have increase JNK activation and greater disease severity in models of innate immunity (passive K/BxN arthritis) and adaptive immunity (experimental allergic encephalomyelitis). We examined the role of Gadd45β in collagen-induced arthritis, which is a more complex model that includes an initial adaptive immune response to an autoantigen followed by an immune complex mediated effector phase.

Methods: CIA was induced in wild type DBA/1 (WT) and Gadd45β−/− DBA/1 mice by immunizing with type II collagen in complete Freund's adjuvant. Arthritis severity was assessed by clinical arthritis scores (maximum score=16) and histological evaluation of synovitis, bone erosion, extra-articular inflammation and proteoglycan damage (max score=16). Serum anti-collagen antibodies were measured by ELISA. Cytokine and matrix metalloproteinase (MMP) expression in joint and spleen extracts was determined by quantitative PCR. Phospho-JNK (P-JNK) in the joints was measured by Western blot analysis.

Results: The initiation onset and peak arthritis severity were similar in Gadd45β−/− and WT mice (Day 34 WT=13±1; Gadd45β−/−=12±2; P>0.5) Unexpectedly, the resolution phase was accelerated in Gadd45β−/− mice (Day 55 clinical scores: WT=11±1; Gadd45β−/−=6±1; P=0.03). Histology scores and joint damage were also significantly lower in the Gadd45β−/− mice (Day 55 WT=9±1; Gadd45β−/−=5±2; P=0.04).

However, serum anti-collagen antibody levels were similar in the two groups. Consistent with histologic evidence of joint damage, MMP3 and MMP13 expression was 4-fold higher in WT mice compared with Gadd45β−/− mice (P=0.01). Despite higher synovial MMP expression P-JNK levels in Gadd45β−/− and WT were similar (P>0.1). mRNA levels for synovial IL-1, IL-6, and TNF were similar in WT and Gadd45β−/− mice. Spleen qPCR demonstrated 2-fold higher levels of IFNγ and IL-10 mRNA in Gadd45β−/− compared with WT (P<0.05).

Conclusions: Gadd45β deficiency is usually associated with increase JNK activation and disease severity in murine inflammation models. Surprisingly, Gadd45β−/− mice had normal onset and peak severity of CIA but had accelerated resolution of arthritis. Adaptive immune responses were normal, as judged by autoantibody production. These data suggest that Gadd45β plays a complex role in immune responses. Enhanced resolution of arthritis could be due to altered cytokine balance in central lymphoid organs, such as increased IL-10 production.

Disclosure: Y. Luo: None; **D. L. Boyle:** None; **G. S. Firestein:** None.

1726

Protection from Collagen-Induced Arthritis in a CX3CR1-Deficient Mouse Strain. Grainne Murphy[1], Arun Kumar[2], Fergus Shanahan[1], Sinead Harney[1], Michael Molloy[1] and Noel Caplice[2]. [1]Cork University Hospital, Cork, Ireland, [2]University College Cork, Cork, Ireland

Background: Fractalkine(FKN), is up-regulated in RA and has been implicated in the immunological dysfunction associated with this disease. FKN interacts specifically with its receptor, CX3CR1 and lacks the redundancy characteristic of many other chemokine partnerships. The role of the FKN-CX3CR1 interaction in the initiation of RA is however unknown.

Objective: To compare the incidence and severity of collagen-induced arthritis(CIA) in a CX3CR1 homozygote deficient transgenic mouse strain with that of wild-type and competent heterozygote mice.

Methods: We used a transgenic mouse model, on a C57/B6 background, where one or both copies of the CX3CR1 gene were replaced by enhanced Green Fluorescent Protein (eGFP), generating the homozygote functionally deficient or competent heterozygote state. The incorporated GFP construct facilitated the direct tracking of peripheral and bone marrow (BM) derived CX3CR1+ cells. CIA was induced in homozygotes (11), heterozygotes (9) and wild-type mice (9) using 2 intra-dermal injections of a 1:1 ratio of chick collagen and Freunds adjuvant (5mg/ml Mycobacterium TB). Circulating and bone marrow derived CX3CR1+ cells were analysed by flow cytometry. Following sacrifice, joints were analysed by H&E and immunohistochemistry to characterize the inflammatory infiltrate. Serum was collected on Day 40 for analysis of the IgG2a and IgG2b anti-collagen antibody responses.

Results: Homozygote mice had a significantly delayed onset of a very mild clinical phenotype in 18% compared with 77% in both the heterozygote and wild-type strains (p<0.001). Histologically, homozygotes had significantly milder synovial hyperplasia (p.0.01) with no evidence of bone or cartilage destruction. Analysis of the inflammatory infiltrate in the heterozygote and wild-type strains demonstrated a significant accumulation of F4/80+ macrophages, 95% of which co-expressed CX3CR1. BM and peripheral CX3CR1+ cells were expanded in both the hetero- and homozygotes. Moreover although strains were comparable in IgG2a responses, IgG2b was significantly higher in hetero- than homo-zygotes, an isoform thought to be of pathologic significance in the C57/B6 strain

Conclusion: Despite the lack of clinical disease in homozygote CX3CR1 deficient mice, peripheral CX3CR1+ cells were similarly mobilized compared to heterozygotes. This implies that while the expansion of this leukocyte population is FKN independent, the FKN-CX3CR1 interaction is crucial for the trafficking of inflammatory cells into synovium, thus initiating CIA. These findings demonstrate that monocytes are central to the initiation of CIA and that the FKN-CX3CR1 interaction is critical in their egress from PB to ST.

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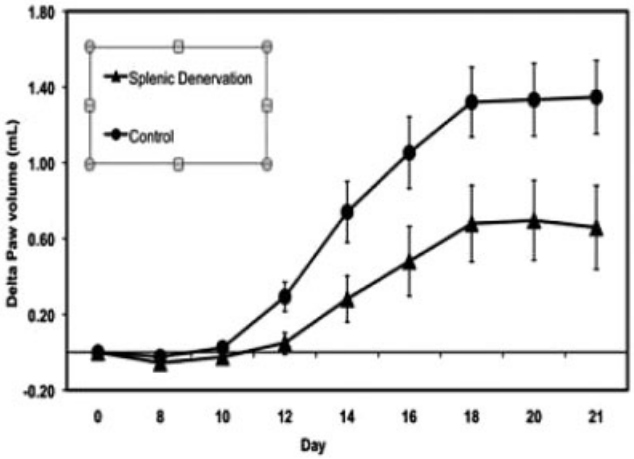
1727

Role of the Central Nervous System (CNS) in Peripheral Inflammation: Sympathetic Innervation of the Spleen Regulates Inflammatory Arthritis. David L. Boyle[1], Meghan Edgar[2], Linda Sorkin[2] and Gary S. Firestein[1]. [1]UCSD School of Medicine, La Jolla, CA, [2]UCSD School of Medicine

Purpose: The CNS has been identified as a key regulator of peripheral inflammatory and immune responses, especially spinal reflexes and the vagus nerve. However, the sympathetic nervous system can also modulate inflammation in animal models of arthritis, with counter-balancing pro-inflammatory and anti-inflammatory effects at different times during the course of the model. The mechanism of sympathetic influence on immune regulation in arthritis is unknown. Because the spleen is a secondary lymphoid organ exclusively innervated by sympathetic fibers, we explored the role of splenic denervation on adjuvant arthritis in the rat.

Methods: Surgical splenic denervation of male Lewis rats was performed by dual transection and removal of the intervening segment of the splenic nerve and confirmed by norepinephrine assay of the spleen. Adjuvant arthritis was induced by injecting 1mg complete complete Freund's adjuvant at the base of the tail. Arthritis severity was measured by hind-limb plethysmometry. Hind-limb radiographs were scored on a 0–6 point scale. Splenic mRNA expression was determined by QPCR and expressed as relative expression units (REU).

Results: Splenic denervation (SD) decreased paw swelling by 48% compared with controls (C) (SD 0.65±0.2ml versus C 1.34±0.1ml; p<0.0001). Radiographic analysis showed that SD significantly decreased bone destruction (SD 1.1±0.4; C 2.20±0.2; p<0.03).



Splenic norepinephrine levels in C animals were 3.1±0.4ng/mg tissue at baseline (day 0) and trended to higher levels in active arthritis (day 12, 4.8±1.1ng/mg), and decreased to below baseline levels at the end of the model (day 21, 0.9±0.1ng/mg; p<0.0001 compared to baseline). Denervation reduced splenic norepinephrine to 0.48±0.34 ng/mg at all time points. TNF expression in arthritic animals was also reduced in denervated spleens (0.258±0.03 REU in SD vs 0.48±0.12 REU in SH; p<0.02). IL-1, GRO/CINQ1, IFNγ, IL-2 and TGF-β were not affected. Spleen mass was indistinguishable between SD and C groups in the presence or absence of arthritis, although spleen mass was doubled in arthritic animals compared with non-arthritic.

Conclusion: The sympathetic nervous system regulates the immune response in acute and chronic inflammation. Surprisingly, sympathetic innervation of the spleen is a key mechanism for neuro-regulation of inflammatory arthritis and is required for full expression of synovitis and matrix destruction. The mechanisms might include direct effects of neurotransmitters on immune cells via β adrenergic receptors, such as macrophages, with reduced splenic TNF production.

Disclosure: D. L. Boyle: None; **M. Edgar:** None; **L. Sorkin:** None; **G. S. Firestein:** None.

1728

SapC-DOPS Agents in Imaging Arthritis. Sherry Thornton[1], Malinda Pinkerton[2], Monica DeLay[2], Tristan Bourdeau[2], Rachel Mason[2], Zhengtao Chu[2], Matthew Flick[2] and Xiaoyang Qi[1]. [1]Cincinnati Children's Research Foundation, Cincinnati, OH, [2]Cincinnati Children's Research Foundation

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects about 1% of the population worldwide. The devastating endpoint of RA pathology is the destruction of cartilage and bone ultimately leading to loss of joint function. Early detection and intervention of disease represents the best hope for successful treatment and preservation of joint

mobility and function. To date, reliable and non-invasive techniques that accurately measure arthritis onset and progression are largely lacking. Here we investigate a novel method of disease assessment that has the advantages of being (i) non-invasive, (ii) highly sensitive, and (iii) both qualitative and quantitative. We recently developed an agent, composed of the membrane-associated lysosomal protein Saponin C incorporated into 1,2-Dioleoyl-sn-Glycero-3-Phospho-L-Serine lipid nanovesicles (SapC-DOPS). SapC-DOPS has a high affinity for phosphatidylserine (PS)-rich domains on cellular surfaces, and fuses with PS-rich membranes on target cells. SapC-DOPS is tracked by labeling with a CellVue Maroon fluorophore (CVM). Since PS is normally present only on the inner leaflet of plasma membranes but is "flipped" to the outer leaflet upon cell damage, we hypothesized that the SapC-DOPS-CVM could be used to detect local tissue damage in inflammatory arthritis. To test this concept, two animal models of arthritis, K/BxN and collagen-induced arthritis (CIA) were utilized. Both of these models exhibit histological changes similar to RA including mononuclear cell infiltration, pannus development, fibrin deposition, and cartilage and bone erosion. SapC-DOPS-CVM was administered to arthritic and non-arthritic mice and detected by in vivo optical imaging (IVIS®). Our data indicate localization of SapC-DOPS-CVM to arthritic paws with 100% penetrance in both animal models; however, SapC-DOPS-CVM was not observed in non-arthritic paws. Flow cytometry analyses of total cells harvested from paws demonstrate that SapC-DOPS-CVM localized to approximately 20% of the joint cells from arthritic mice while less than 2% of cells from non-arthritic paws were CVM-positive. Preliminary studies indicated that in K/BxN arthritis, SapC-DOPS localized primarily to CD11b+ cells that are CD11c- and CD8-, with additional studies being performed to further characterize the cell types that are targeted by SapC-DOPS in each arthritis model. Results from the current studies provide support for the use of SapC-DOPS-CVM in imaging arthritis onset and progression in live subjects. Furthermore, this imaging strategy provides a novel method for tracking cells involved in inflammatory processes during arthritis.

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1729

Systemic, Lentiviral Gene Delivery of the Stress Protein BiP (Binding Immunoglobulin Protein) Improves Clinical, Histological and Immunological Parameters of Collagen-Induced Arthritis Via Suppression of IL-17. Adrian M. Shields[2], Paul H. Wooley[3], Rana Alyahya[2], Gabriel S. Panayi[1], Stephen J. Thompson[2] and Valerie M. Corrigall[2]. [1]King's College London, London, United Kingdom, [2]King's College London, [3]Via Christi Reg Medical Ctr, Wichita, KS

Introduction: Rheumatoid arthritis is an autoimmune disease principally manifesting as an autoimmune polyarthritis in the small diarthrodial joints. It is also characterised by multiple systemic sequelae.

Gene therapy offers a novel therapeutic approach to multisystem inflammatory diseases by permitting highly specific and disease-response, temporal and spatial expression of therapeutic genes.

The endoplasmic reticulum (ER) stress protein BiP (Binding immunoglobulin Protein) has demonstrated profound anti-inflammatory activity in human myeloid lineage cells and impressive therapeutic efficacy in multiple animal models of inflammatory arthritis. This study investigated the therapeutic potential of lentiviral gene therapy using BiP in the murine collagen-induced arthritis (CIA) model.

Methods: The murine BiP gene was manipulated to facilitate efficient protein secretion from transduced cells and cloned into a 3rd generation, self-inactivating HIV-1 lentiviral vector backbone containing the CMV immediate-early promoter and the WPRE stabilisation element (Lenti-BiP). An equivalent vector containing the GFP gene was produced as a control (Lenti-GFP). CIA was established in DBA/1 mice and lentiviral vectors were administered intraperitoneally at arthritis onset. Clinical, histological and immunological parameters of disease were studied.

Results: 2×10^{-7} infectious viral particles encoding the murine BiP gene significantly suppressed clinical disease scores compared to Lenti-GFP treated animals when delivered at disease onset (Fig. 1) (day 55: Lenti-GFP - 8.6±0.6 vs. Lenti BiP – 5.1±0.7, p=0.001).

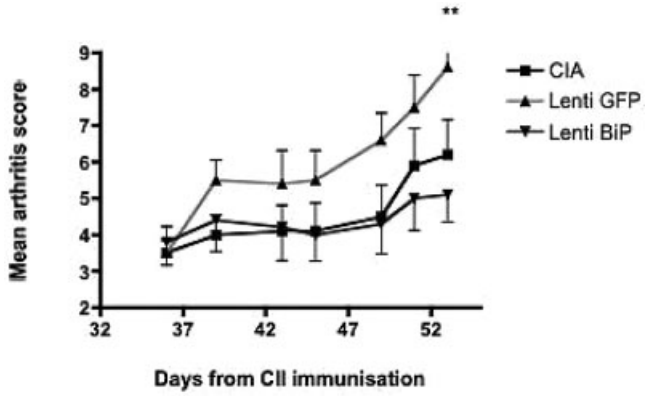

Figure 1. Lenti-BiP modulates collagen induced arthritis.

Lower doses of Lenti-BiP ($1\times10\hat{7}$) also suppressed clinical and histological manifestations of disease, but not signficantly. The mechanism of Lenti-BiP mediated disease suppression depends on the inhibition of IL-17. The splenocytes of Lenti-BiP treated animals produced significantly less IL-17 in response to collagen-II restimulation compared to Lenti-GFP treated animals (Lenti-GFP - 3819±1502pg/ml vs. Lenti-BiP – 2087±722pg/ml, $p<0.05$). Furthermore, Lenti-BiP treatment facilitated the development of regulatory cells; in admixing experiments, splenocytes from Lenti-BiP treated animals significantly suppressed IL-17 production from CII primed responder cells compared to Lenti-GFP treated animals (Lenti-GFP - 6119±689pg/ml vs. Lenti BiP – 2697±444pg/ml, $p<0.05$). This was associated with significantly greater IL-10 secretion in co-cultures containing Lenti-BiP treated cells (Lenti-GFP – 519±18pg/ml vs. Lenti BiP – 662±49pg/ml, $p<0.05$)

Conclusion: Lentiviral delivery of the murine BiP gene modulates clinical, histological and immunological parameters of CIA. Further experiments are underway to examine the mechanism of Lenti-BiP mediated suppression and to target anti-inflammatory gene expression using stress-responsive promoters.

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1730

Targets of Innate and Adaptive Immunity in a Humanized Arthritis Model: Research Value of the RA Synovium SCID Mouse Model. Marije I. Koenders[3], Shahla Abdollahi-Roodsaz[4], Renoud J. Marijnissen[4], Franco E. Di Padova[2], John Dulos[1], Annemieke M. H. Boots[1] and Wim B. van den Berg[4]. [1]MSD, Oss, The Netherlands, [2]Novartis Pharma AG, Switzerland, [3]Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, [4]Radboud University Nijmegen Medical Centre, The Netherlands

Target discovery and drug development is a very time consuming and expensive process, which is partly due to the fact that preclinical findings from animal models cannot always be translated to the clinical situation. To provide an intermediate step between classical arthritis models and clinical trials, the RA synovium SCID mouse model could be a valuable tool during preclinical research. In this study, the validity of this humanized mouse model was investigated.

SCID.CB17 mice were engrafted with two standardized pieces of human RA synovial tissue subcutaneously on the back, and subsequently the therapeutic effect of various biologicals on these grafts was assessed. After an engraftment period of seven days, mice were systemically treated with anti-TNF (Abalimumab), anti-IL-1, CTLA4-Ig (Abatacept), anti-CD20 (Rituximab), or isotype control antibodies at an excess dose of 10 mg/kg. In addition, this RA SCID model was used to study two new potential therapeutic targets, using the TLR4 antagonist B. quintana LPS, and anti-hIL-17A antibodies. As readout, serum levels of human cytokines and chemokines were analyzed by Luminex, and the synovial grafts were isolated for histological analysis.

Anti-TNF treatment significantly reduced serum levels of IL-6 and IL-8, and histological analysis demonstrated that this coincided with a clear reduction in the inflammation scores of the grafts and suppressed expression of TNF and IL-1 in the synovium as demonstrated by immunohistochemistry. In contrast, anti-IL-1 therapy did not show any effect. Since Adalimumab also

shows great efficacy in the clinics, anti-TNF antibodies were used as positive control throughout our further SCID studies.

The potential of the RA SCID model for T and B cell-related therapies was investigated using CTLA4-Ig and anti-CD20 respectively. Abatacept treatment was not effective in this RA SCID model, despite pre-screening of the synovial tissue for the presence of CD3+ T cells and the B7 molecules CD80/86 that provide costimulatory signals for T cell activation. In contrast, anti-CD20 treatment did reduce serum cytokines and histological scores, suggesting that this model is more sensitive to B cell than T cell-related therapies.

Our recent studies in IL-1Ra-deficient mice and collagen-induced arthritis suggested an important role for TLR4 in recognition of both exogenous and endogenous ligands that contribute to the pathological process during arthritis. Also for anti-IL-17 treatment great therapeutic potential was observed in mice, but additional proof was needed in more translational models. While our TLR4 inhibitor showed therapeutic effects comparable to anti-TNF treatment, IL-17 blocking seemed to be selectively effective in cases where high numbers of CD3+ T cells were present in the synovium.

In conclusion, the human RA synovium SCID mouse model seems a powerful tool in preclinical research. Using this model, further evidence was obtained that TLR4 and IL-17 might indeed be interesting therapeutic targets in RA. Further characterization of the RA patients' individual synovial profile is of great importance to achieve tailor-made therapy.

Disclosure: M. I. Koenders: None; **S. Abdollahi-Roodsaz:** None; **R. J. Marijnissen:** None; **F. E. Di Padova:** Novartis Pharmaceuticals Corporation, 3; **J. Dulos:** MSD, 3; **A. M. H. Boots:** MSD, 3; **W. B. van den Berg:** None.

1731

The Role for TIM-2 in Collagen-Induced Arthritis. Toshio Kawamoto[2], Hisaya Akiba[1], Yoshiyuki Abe[2], Shinji Morimoto[2], Ken Yamaji[2], Naoto Tamura[2] and Yoshinari Takasaki[2]. [1]Department of Immunology, Juntendo University School of Medicine, [2]Department of Rheumatology, Juntendo University School of Medicine

Introduction: T cell Ig and mucin domain-2 (TIM-2) has been shown to regulate CD4 T cell activation. TIM-2-deficient mice developed more severe airway inflammation under Th2-polarizing condition.Thus, it seems likely that TIM-2 is a negative regulator of Th2 immune responses. However, the immunological function of TIM-2 under Th1-polarizing condition is still unclear. This study therefore examined the contribution of TIM-2 to the development of collage typeII (CII)-induced arthritis (CIA), which is a Th1-polarized disease model, by administering a newly generated anti-TIM-2 mAb.

Methods: In this study, we investigated the effects of anti-TIM-2 monoclonal antibodies in a collagen-induced arthritis (CIA), which is a mouse model of rheumatoid arthritis, to determine whether TIM-2 contributes to the development of pathogenic Th1 or Th17 cells and joint inflammation. A murine model of CIA can be induced by injection of CII emulsified with adjuvant in genetically susceptible DBA/1 mice. Mice were examined daily for the onset of CIA. The swelling of four paws was graded from 0 to 4,each paw was graded, and the four scores were totaled so that the maximal score per mouse was 16. Draining lymph node cells were isolated and pooled, and cultured in the presence or absence of indicated dose of denatured bovine CII. All cultures were pulsed with 3H-thymidine for the last 6h of a 72h or 96h culture and harvested. To determine the production of cytokines, cell-free supernatants were collected at 72h or 120h and assayed for INF-γ or IL-17 were measured by ELISA. Serums were collected and titers of anti-CII IgG Abs were measured by ELISA.

Results: Administration of anti-TIM-2 mAbs in early phase, but not late phase, significantly exacerbated the development of CIA. Although anti-TIM-2 mAbs treatment did not affect the development of Th1 or Th17 cells in the draining lymph node, the serum levels of anti-type II collagen Abs were significantly increased in the anti-TIM-2 mice. TIM-2 expression was found on splenic B cells and further up-regulated by anti-IgM, anti-CD40, and IL-4 stimulation. In contrast, CD4 T cells did not express TIM-2 even when stimulated with both anti-CD30 and anti-CD28 mAbs. Intrestingly, anti-TIM-2 mAbs enhanced proliferation and Ig production of activated B cells in vitro.

Conclusions: These results suggest that the exacerbation of CIA by anti-TIM-2 mAbs is caused by enhancement of B cell activation and Ab production.

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1732

The TNF-Ligand APRIL Can Control CIA by Regulating Antibody-Production and Stimulating Anti-Inflammatory IL-10 Producing B Cells. Leticia Fernandez[5], Cecilia Rocha[5], Carla Carvalho-Pinto[6], Jan Paul Medema[2], Bernard G. Combe[3], Dominique Baeten[1], Jacques Morel[4] and Michael Hahne[5]. [1]Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, [2]Academic Medical Center, University of Amsterdam, [3]Hopital Lapeyronie, Montpellier, France, [4]Hopital Lapeyronie, [5]Institut de Génétique Moléculaire de Montpellier, [6]Universidade Federal Fluminense/UFF, Niteroi

Background: TNF family members are frequently implicated in inflammation and autoimmunity. Increased levels of the TNF-ligand APRIL (A Proliferation Inducing Ligand) were found in synovial fluid and serum of patients with inflammatory arthritis pointing to a pro-inflammatory role of APRIL. APRIL can bind to BCMA and TACI, two receptors of the TNF family, which can also bind the B cell activating factor (BAFF). In the collagen-induced arthritis (CIA), administration of TACI-Ig was found to prevent disease progression and to lower disease scores, compared with controls. As TACI binds both APRIL and BAFF, it remained to be determined, whether this effect was due to the capacity of TACI to block just one or both ligands.

Methods: CIA was induced in APRIL-transgenic (Tg) DBA/1 mice and littermates. Severity of disease was scored for each paw using a scale 0–4. In addition, mice were analyzed for histological signs of arthritis. Anti-collagen antibody titers were determined by ELISA. Lymphocyte populations in draining lymph nodes, spleen and peritoneum were analyzed by FACS. In another experimental setting mice were exposed to the collagen antibodies induced arthritis (CAIA). In addition, we employed the contact hypersensitivity model (CHS). For this, APRIL Tg and control mice were sensitized and challenged at the ear with oxazolone. Ear swelling and histological alterations were monitored.

Results: APRIL Tg (n=14) mice displayed in contrast to littermates (n=16) a lower disease score (maximal score at day 38 after first immunization: 4.9+/−0.9 versus 1.0+/−0.5), a lower incidence of arthritis ($p<0.01$), and also produced less collagen specific antibodies ($p<0.001$, at day 41 after first immunization). Joints of littermates had higher IgG levels. One of the main effector mechanisms of anti-collagen antibodies in arthritis is the activiation of mast cells by immune-complexes. Indeed we detected decreased number of degranulating, thus activated, mast cells in the joints of Tg mice. To confirm that the decreased IgG levels developed in the CIA model in APRIL Tg mice are directly linked to the less severe disease development, we employed the model of CAIA. In fact, disease development in CAIA was similar in APRIL Tg and control mice. In addition, we detected a significantly increased IL-10 production of peritoneal B cells in APRIL Tg mice in the CIA model (n=8 for each group, $p<0.05$). Evidence is accumulating that IL-10 producing B cells can regulate autoimmune diseases including arthritis. The regulatory role of APRIL by modulating activity of mast cells and IL-10-producing B was confirmed in the CHS model.

Conclusion: Our results show that APRIL can control inflammation in two disease models, i.e. arthritis and CHS. This suggests a therapeutic potential of APRIL agonists to down-regulate inflammatory diseases such as rheumatoid arthritis.

Disclosure: L. Fernandez: None; **C. Rocha:** None; **C. Carvalho-Pinto:** None; **J. P. Medema:** None; **B. G. Combe:** None; **D. Baeten:** None; **J. Morel:** None; **M. Hahne:** None.

1733

Towards Personalized Arthritis Gene Therapy: Screening of Computationally-Designed Promoters in an In Vivo Mouse Model and in Human Synovial Fibroblasts. Fons A. J. van de Loo, Eline Vermeij, Onno J. Arntz, Miranda B. Bennink, Jeroen Geurts and Wim B. van den Berg. Department of Rheumatology, Radboud University Nijmegen Medial Centre, Nijmegen, The Netherlands

Introduction: Chronic synovial inflammation is a hallmark of the autoimmune disease rheumatoid arthritis (RA). The synovial membrane is regarded as the primary target tissue for local gene therapeutic treatment of arthritic joints. RA is a truly heterogeneous disease, which is supported by gene expression analyses of RA tissues that have revealed molecularly distinct inflammatory subtypes. Therefore, personalized gene therapy using

disease inducible promoters might be a good approach to fine-tune supply of biologicals in an offer-meets-demand fashion, increasing safety and efficacy.

Methods: Previously, we developed a computational approach for selecting suitable promoters from endogenous genes differentially regulated in the inflamed synovium of collagen-induced arthritis mice. Based on this approach, we constructed lentiviral luciferase reporters containing proximal promoter regions that were predicted to be predominantly regulated by the transcription factors NFκB (*Cxcl1, Cxcl5, Il1β*), AP-1 (*Mmp3, Mmp13, Timp1*) or C/EBPβ (*Saa3, Chi3l1, Has1*).

Results: Next, we investigated kinetics and strength of these promoters as compared to a strong constitutive promoter (*PGK*) in experimental arthritis with two relapsing flares of inflammation. Surprisingly, only *Saa3* and *Cxcl1* were strongly upregulated (10–50 fold) during the first challenge, while a second challenge induced strong luciferase expression for all constructs (10–200 fold). The *Saa3* promoter activity showed a clear correlation with joint edema as measured by ^{99m}Tc uptake. Interestingly, in the absence of a second flare the *Cxcl1* promoter activity still increased whereas the *Saa3* promoter activity returned to basal levels. Promoter analysis suggested that hypoxia-response elements in the *Cxcl1* promoter are likely causative for this difference in expression profile with *Saa3*. Finally, we characterized the response of computationally-defined promoters in RA synovial tissue of varying inflammatory subtypes. *Saa3, Cxcl1, Cxcl5* and *Il1β* promoters could be induced by stimulation of RA synovial fibroblasts with pro-inflammatory stimuli. Uniquely, relative *Saa3* promoter responses to cytokines and a TLR4 agonist were significantly higher in fibroblasts with an inflammatory genetic imprint both as a group as in individual samples. Relative *Cxcl1* promoter responses did not discriminate between inflammatory synovial fibroblast subtypes.

Conclusion: These data demonstrate that computational design of promoters is of great value for the development of disease-regulated gene therapy, Towards personalized arthritis gene therapy, the *Saa3* promoter appears an excellent candidate for sensing the extent of joint inflammation and responding differentially in human arthritic synovium according to their inflammatory phenotype.

Disclosure: F. A. J. van de Loo: None; **E. Vermeij:** None; **O. J. Arntz:** None; **M. B. Bennink:** None; **J. Geurts:** None; **W. B. van den Berg:** None.

ACR Poster Session C
Rheumatoid Arthritis - Clinical Aspects: Classification, Biomarkers, Predictors of Response, Disease Activity, Severity III
Wednesday, November 10, 2010, 9:00 AM–6:00 PM

1734

A Longitudinal Trivariate Model of Disease Activity Score, Physical Function and Radiographic Damage: Results from SONORA Study. Maggie Chen[1], Xiuying Li[1], Pooneh Akhavan[2] and Claire Bombardier[3]. [1]University Health Network, [2]University of Toronto, University Health Network, [3]University of Toronto, University Health Network, Mount Sinai Hospital, Toronto, ON, Canada

Purpose: Rheumatoid arthritis (RA) affects approximately 1% of adults in North America. Active disease leads to radiographic damage and poor physical function. The purpose of this study is to demonstrate the use of a novel longitudinal trivariate model to identify simultaneously common significant predictors for three important outcomes in RA: Disease Activity Score (DAS); physical function measured with the Health Assessment Questionnaire (HAQ) and radiographic damage (Sharp Score).

Method: 994 Patients diagnosed as having new onset RA (symptoms ≥3 but ≤12 months) by a board-certified rheumatologist were recruited from 98 rheumatology practices. Clinical, laboratory, X-ray and health questionnaire data were collected by the enrolling rheumatologist at baseline, year 1 and year 2. A trivariate longitudinal model of DAS28, HAQ and sharp score was constructed and estimated using pooled cross sections for two years period, adjusting the significant predictors from the univariate analysis at the same time allowing for the latent individual-level effect. Different covariance structures were tested for the assumptions among these three outcomes in the model.

Results: The mean age of patients was 53 years (SD, 14.8), with 72% female and 90% Caucasian. The mean RA symptom duration was 170 days (180). The DAS28, HAQ and Sharp score were 4.4(1.32), 1(0.73) and 5.01 (7.28) at baseline, 3.4(1.38), 0.82(0.71) and 6.19(8.73) at year 1, 3.2(1.34), 0.77(0.72) and 6.39(9.25) at year 2, respectively. Partial correlation adjusting for time point showed that DAS, HAQ and Sharp score are significantly correlated (all p-values <0.001). The longitudinal trivariate model showed that only higher baseline DAS, HAQ or Sharp Score value ($P<0.0001$), higher 28 swollen joint count ($P<0.0001$), longer disease duration ($P=0.002$) and lower house hold income ($P=0.015$) were significant predictors for these three combined outcomes.

Conclusion: This innovative method identified the significant common predictors for three outcomes which related to the different aspects of RA patients. This method can help us better understand the longitudinally complex relationship between different aspects from a broader view of the disease. These identified factors can help rheumatologists to identify the patients who are at greater risk of worsen disease, physical function and radiographic damage and make treatment decisions for RA patients at the early stage.

Disclosure: M. Chen: None; **X. Li:** None; **P. Akhavan:** None; **C. Bombardier:** None.

1735

A Randomized Controlled Trial of Rheumatologist Education Impacting on Systematic Measurements and Treatment Decisions in Rheumatoid Arthritis (RA): Results of the Metrix Study. Janet E. Pope[3], J. Carter Thorne[2], Alfred A. Cividino[1] and Kurt Lucas. [1]McMaster University, Hamilton, ON, Canada, [2]Southlake Regional Health Care, Newmarket, ON, Canada, [3]St Joseph Health Care London, London, ON, Canada

Objective: The Metrix study was an investigator initiated pilot study where consenting rheumatologists in Ontario were randomized either to an IRB approved, accredited educational intervention over 6 months or no intervention and involved 2000 RA patient-encounters to determine if an intervention could result in behavioral change.

Methods: Twenty rheumatologists participated (all of whom who did a prospective chart audit of 50 consecutive RA patients at the beginning and again 50 consecutive RA patients at end of 6 months) and 10 rheumatologists were randomized to intervention. Only the intervention group was aware of the results of their practice audit including the frequency of measurements they were performing and outcomes of their patients compared to the others in both the intervention and control groups (comparative data of their practice to others). Interventions were monthly web-based conferences on the value of systematic assessments in RA and barriers to care with recent evidence based information, journal club, surveys and improvements on forms used in daily practice to collect data.

Results: 1000 serial RA charts were audited at 0 and another at 6 months with no between groups differences in patient characteristics (mean disease of 10 years and 77% women, 74% RF positive and mean DAS 3.7); 68% on current Mtx, 14% on steroids and 27% on biologics. At 6 months, there were significantly different within and between groups changes in how often many variables were measured and changes in treatment. The intervention group collected more patient global assessments (53% pre vs 66% post intervention and MD globals 51% vs 60%; $p<0.05$) and HAQs collected went from 37% to 42%; whereas control group had no change in outcomes collected. For the intervention group there was a 32% increase in calculable composite scores (such as DAS, CDAI, SDAI) ($p<0.05$) and no change in the control group. There was more targeting to a low disease state. For those with SDAI between 3.3 and 11, the % receiving a change in Rx (injection, or change in DMARD) was 66% in intervention and 36% in control group ($p<0.05$); similarly in DAS between 2.4 and 3.6; 57% of intervention and 38% of control group made changes to treatment ($p<0.05$). Table shows within and between groups differences.

Table. Between and Within Groups Differences for Intervention and Control Groups: Changes in Practice (Performing Measurements and Making Treatment Changes)

	Intervention	Control
Swollen Joint Count	Pre 96%	Pre 94%
	Post 98%	Post 93%
Tender Joint Count	Pre 80%	Pre 93%
	Post 79%	Post 92%
CRP	Pre 69%	Pre 69%
	Post 74%	Post 73%
HAQ	Pre 37%	Pre 42%
	Post 42%	Post 44%
Patient global frequency	Pre 53% $p < 0.05$	Pre 66% $p < 0.05$
	Post 62% (within group)	Post 59% (within group) (frequency decreased)
MD global frequency	Pre 50% $p < 0.01$	Pre 71% $p = 0.17$
	Post 60% (within group)	Post 66% (within group)
CDAI > 2.8 but <10 receiving joint injection or DMARD change	44%	33% $p = 0.44$*
SDAI > 3.3 but <11 receiving joint injection or DMARD change	56%	26% $p < 0.01$*
DAS28 > 2.4 but <3.6 receiving joint injection or DMARD change	57%	38% $p < 0.01$*

*Between groups differences

Conclusions: Despite a good baseline systematic assessment and many patients in a low disease state, there was improvement in the intervention group that surpassed the control group in both the frequency of performing assessments and the number of treatment changes when patients were not in remission. This is the first RCT of RA rheumatologist education where a result of a change in behavior has been linked directly to an intervention (comparative practice and education) as the control group did not change behavior. Small group learning with feedback from practice audits is an inexpensive way to improve outcomes in RA.

Disclosure: J. E. Pope: Abbott Laboratories, 2; **J. C. Thorne:** Abbott Laboratories, 2; **A. A. Cividino:** Abbott Laboratories, 2; **K. Lucas:** Abbott Laboratories, 2.

1736

A Simple Fatigue Severity Scale Predicts Poor Health Outcomes, Frailty and Death in the Long-Term Follow-Up of Patients with Rheumatoid Arthritis. Gisela Westhoff and Angela Zink. German Rheumatism Research Centre Berlin, Berlin, Germany

Background: Rheumatoid arthritis (RA) patients highlighted fatigue as permeating every sphere of life. The EULAR/ACR task force recommended that fatigue should be implemented in an RA outcome measure core set. We investigated the association between baseline fatigue severity and 8-year outcomes in an early RA inception cohort.

Methods: Data from 1,057 RA patients with a disease duration <24 months at inclusion were used. Self reports of functional capacity, pain, global health (GH) and fatigue, measured by 11-point numerical rating scales (NRS 0–10), were collected for up to 8 years. Reasons for drop out were investigated thoroughly. Clinical and self-reported baseline parameters were compared between patients who attained the 8th year in favorable GH (0–6) and those who did so with unfavorable outcomes, i.e. they attained the 8th year in poor GH (7–10), had stopped participation without specifying reasons, had dropped out due to frailty or had died. Multivariate logistic regression analyses were performed to identify baseline predictors of adverse outcomes.

Results: At inclusion, 42.6% of the patients reported no or mild fatigue, 36.2% reported moderate fatigue and 21.2% reported severe fatigue. At 8 years, 12.7% of the patients had died, 7.0% had terminated participation due to frailty, 6.2% had withdrawn without specifying reasons, 3.2% were lost to follow-up and 13.2% reported poor GH (7–10). Three baseline parameters were significantly associated with unfavorable outcomes in the multivariate analyses. Besides higher age and substantial functional limitations, severe fatigue almost doubled the risk for adverse outcomes (adjusted OR 1.82; 95% CI 1.21–2.75). Furthermore, severe fatigue at inclusion was the only parameter predicting each individual type of drop-out, i.e. drop-out without specifying reasons (OR 2.8; CI 1.4–5.3), drop-out due to frailty (OR 2.3; CI 1.2–4.5) or death (OR 2.3; CI 1.3–4.2). Acute phase reactants, DAS28, erosiveness, rheumatoid factor and pain were not predictive of unfavorable outcomes.

Conclusions: Severe fatigue in early RA is indicative of poor long-term outcomes; it outranges all other baseline parameters taken into consideration. Therefore, fatigue should be implemented in an RA outcome measure core set, and, equally important, high attention should be paid to RA patients suffering from substantial fatigue.

Disclosure: G. Westhoff: None; **A. Zink:** None.

1737

Age, Sex, RF Antibodies, Baseline HAQ and DAS28 Score—But Not the Type of Initial Treatment—Are Predictive of Clinical Remission at 1 Year in Early Inflammatory Arthritis. Bindee Kuriya[9], Boulos Haraoui[4], Gilles Boire[2], Carol A. Hitchon[7], Janet E. Pope[6], J. Carter Thorne[5], Diane S. Ferland[3], Ed C. Keystone[8] and Vivian P. Bykerk[1]. [1]Brigham and Women's Hospital, Toronto, ON, Canada, [2]CHUS-Sherbrooke University, Sherbrooke, QC, Canada, [3]Hospital Maisonneuve Rosemount, LaSalle, QC, Canada, [4]Institut de Rhumatologie, Montreal, QC, Canada, [5]Southlake Regional Health Care, Newmarket, ON, Canada, [6]St Joseph Health Care London, London, ON, Canada, [7]University of Manitoba, Winnipeg, MB, Canada, [8]University of Toronto, Toronto, ON, Canada, [9]University of Toronto, Brookline, MA

Background: Aggressive DMARD therapy is more effective when given early in the disease course and the goal of treatment is remission. Factors associated with remission have been inconsistently reported in studies of early inflammatory arthritis (EIA). In Canada, access to biologics is reserved for those who have failed ≥ 2 DMARDs. Identifying those who will achieve remission can facilitate decisions to prevent over/under-treatment with limited resources. Our aim was to identify baseline and early treatment predictors of DAS28 remission at 1 year.

Methods: As of November 2009, 893 subjects were recruited to the Canadian ArThritis CoHort (CATCH). Patients are >16 years old, have symptoms between 6 weeks–12 months, have ≥ 2 swollen joints or 1 swollen MCP or PIP joint and ≥1 of: positive RF, anti-CCP, morning stiffness, response to NSAID or painful MTP squeeze test. Patients are assessed every 3 months and therapy is adjusted to minimize disease activity. Baseline demographic and clinical characteristics were analyzed via logistic regression.

Results: 363 subjects had ≥ 1 year of follow-up. Over this time, 288 (79%) patients met criteria for RA and 75 (21%) remained undifferentiated or fulfilled other diagnoses. Overall, 147 (41%) achieved DAS28 remission at 1 year. In univariate analyses, patients who experienced remission were younger, male, had lower HAQ scores, lower ESR and lower disease activity at baseline. Physical examination findings and radiographic erosions did not discriminate between the two groups. The presence of RF antibodies was less frequent among those who experienced remission but anti-CCP antibodies did not differ. The use of DMARDs early in the disease course was variable; methotrexate monotherapy was used less, while combination DMARD therapy was used more frequently in patients achieving remission. No patients were commenced on biologics during the first 3 months. After adjusting for significant univariate predictors ($p<0.10$), the multivariate model revealed 5 factors to be associated with remission: age, sex, RF, HAQ score and DAS28 score (Table, $p<0.05$).

Conclusion: Clinical remission was achievable in 41% of EIA patients. Predictors that favorably impacted this response included younger age, male sex, absent RF, low HAQ, and low disease activity at baseline. While sustained treatment with DMARDs has favorable long-term outcomes, DMARD use during the first 3 months alone or in combination did not accurately predict remission at 1 year.

Table. Multivariate analysis of baseline predictors for DAS28 remission at 1 year.

Characteristic	OR (95% CI)	*p*-value
Age*, years	0.98 (0.9–1.01)	0.03
Female sex	0.44 (0.25–0.78)	0.01
RF positive	0.78 (0.47–0.99)	0.04
HAQ score*	0.66 (0.44–0.98)	0.04
DAS28 score	0.06 (0.44–0.98)	0.03
ESR*, mm/hr	0.99 (0.98–1.01)	0.77
MTX monotherapy	0.59 (0.29–1.21)	0.15
Combination DMARD therapy	1.52 (0.84–2.75)	0.16

*Treated as continuous variables

Disclosure: B. Kuriya: Amgen Inc., 2, Pfizer Inc, 2; **B. Haraoui:** Amgen Inc., 2, Pfizer Inc, 2; **G. Boire:** Amgen Inc., 2, Pfizer Inc, 2; **C. A. Hitchon:** Amgen Inc., 2, Pfizer Inc, 2; **J. E. Pope:** Amgen Inc., 2, Pfizer Inc, 2; **J. C. Thorne:** Amgen Inc., 2, Pfizer Inc, 2; **D. S. Ferland:** Amgen Inc., 2, Pfizer Inc, 2; **E. C. Keystone:** Amgen Inc., 2, Pfizer Inc, 2; **V. P. Bykerk:** Amgen Inc., 2, Pfizer Inc, 2.

1738

Algorithm Using Genome-Wide SNP Analysis for Prediction of Progression of Joint Destruction in RA Patients from Multiple Medical Cohorts. Tsukasa Matsubara[4], Satoru Koyano[7], Yoshitada Sakai[1], Keiko Funahashi[7], Takafumi Hagiwara[5], Takako Miura[4], Kosuke Okuda[4], Akira Sagawa[8], Takeo Sakurai[2], Hiroaki Matsuno[6], Tomomaro Izumihara[3] and Eisuke Shono[9]. [1]Himeji Dokkyo University, Himeji, Japan, [2]Inoue Hospital, Takasaki, Japan, [3]Izumihara Rheumatic and Medical Clinic, Kagoshima, Japan, [4]Matsubara Mayflower Hospital, Kato, Japan, [5]Matsubara Mayflower Hospital, Kato, Japan, [6]Matsuno Clinic for Rheumatic Diseases, Toyama, Japan, [7]Research Institute of Joint Diseases, Kobe, Japan, [8]Sagawa Akira Rheumatology Clinic, Sapporo, Japan, [9]Shono Rheumatology Clinic, Fukuoka, Japan

Purpose: Although not yet fully possible, ideally, the prediction of progression of joint destruction would be pivotal in establishing a strategy of treatment for individual RA patient since patients with rapidly progressing joint destruction need tight initial control. We have developed an SNP algorithm with the aim of enabling the prediction of progression of joint destruction with genome-wide SNP analysis by using multiple medical cohorts.

Patients and Methods: One-hundred and twenty-seven RA patients whose disease duration was within 5 years were enrolled in this study from 6 hospitals in different regions of Japan. All patients were treated with biologics after the failure of DMARDs therapy. RA joint destruction was estimated by Sharp score. Forty-five patients had a Sharp score of >100 (severe joint destruction), 30 had a score of 100-50 (intermediate joint destruction) and 52 had a score of <50 (mild joint destruction). Genome-wide SNP genotyping was performed by Illumina HumanHap300K chip. Case-control analyses between 278,347 SNPs and joint destruction (severe vs. mild) were examined by Fisher's exact tests. We selected 10 SNPs associated with joint destruction ($p < 0.0001$). We then scored relationship between each SNP and progress of joint destruction, the estimated total score of 10 SNPs (estimated scoring in each SNP was as follows: homo allele in the majority in severe joint destruction group: +1 point, hetero allele: 0 point, and homo allele in the majority of mild joint destruction group: −1 point), and examined relationships between the severe and mild group, and the total score.

Results: Accuracy ((true positive+true negative)/total), specificity (true negative/(false positive+true negative)) and sensitivity (true positive/(true positive+false negative)) of the algorithm for distinguishing the severe destruction group from the mild destruction group ranged from 92–97%. It is therefore suggested that the SNP algorithm may enable the prediction of rapidly progressing severe joint destruction.

Conclusion: This highly accurate algorithm using SNP analysis may be useful in initially distinguishing severe joint destruction, and, in this way, may contribute to establishing a strategy of treatment for individual RA patients.

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An Algorithm Using Genome-Wide SNP Analysis for Prediction of Interstitial Pneumonia in RA Patients. Takeshi Nakamura[3], Satoru Koyano[5], Keiko Funahashi[5], Takafumi Hagiwara[3], Takako Miura[3], Kosuke Okuda[3], Akira Sagawa[6], Takeo Sakurai[1], Hiroaki Matsuno[4], Tomomaro Izumihara[2], Eisuke Shono[7] and Tsukasa Matsubara[3]. [1]Inoue Hospital, Takasaki, Japan, [2]Izumihara Rheumatic and Medical Clinic, Kagoshima, Japan, [3]Matsubara Mayflower Hospital, Kato, Japan, [4]Matsuno Clinic for Rheumatic Diseases, Toyama, Japan, [5]Research Institute of Joint Diseases, Kobe, Japan, [6]Sagawa Akira Rheumatology Clinic, Sapporo, Japan, [7]Shono Rheumatology Clinic, Fukuoka, Japan

Purpose: Interstitial pneumonia (IP) is a serious complication for collagen diseases such as RA and is strongly associated with the prognosis of the disease. The presence of IP also limits the selection of medication. There is, however, no method for prediction of the risk of occurrence of IP. We established an algorithm based on genome-wide SNP analysis for prediction of IP (usual interstitial pneumonia: UIP; non-specific interstitial pneumonia: NSIP) in RA patients.

Patients and Methods: The first population sample included 215 RA patients, the second included 115 patients: a total of 330 patients from 6 hospitals in different regions of Japan. Classification of IP was determined by three doctors (one physician and two radiologists) according to UIP and NSIP criteria. The first population included 14 UIP (average disease duration: 9.8 years), 27 NSIP (average disease duration: 11.7 years) and 174 non-IP (average disease duration: 10.7 years) patients, and the second included 10 UIP (average disease duration: 10.5 years), 16 NSIP (average disease duration: 11.5 years) and 89 non-IP (average disease duration: 11.0 years) patients. Genome-wide SNP genotyping was performed by HumanHap300K chip. Case-control analyses between 285,548 SNPs and classification of IP were examined by Fisher's exact tests. We selected 10 SNPs associated with IP, UIP, or NSIP, which were common in analyses of both the first and second population ($p < 0.02$). We then scored the relationship between each SNP and classification of IP, the estimated total score of 10 SNPs (estimated scoring in each SNP was as follows: homo allele in the majority in IP: +1 point, hetero allele: 0 point, and homo allele in the majority of non-IP: −1 point), and examined the relationships between IP and non-IP, and the total score.

Results: Accuracy ((true positive+true negative)/total), specificity (true negative/(false positive+true negative)) and sensitivity (true positive/(true positive+false negative)) of the algorithm for UIP ranged from 86–91%. For NSIP, accuracy, specificity and sensitivity of the algorithm ranged from 87–93%. It is therefore suggested that the SNP algorithm can distinguish IP (UIP and NSIP) in individual RA patients.

Conclusion: This highly accurate algorithm using SNP analysis may be useful for the prediction of UIP and NSIP in individual patients, and, in this way, can contribute to establishing a strategy of treatment such as the selection of medication and prevention of IP in treated patients.

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1740

Anti-Citrullinated Protein Antibodies Are Detected in a Significant Proportion of Patients with Anti-CCP-Negative, Early RA: Implications for Improved RA Diagnosis and Guided Therapy. Reuven Bromberg[3], Jeremy Sokolove[2], Piyanka Chandra[3], Aarat Patel[8], Stacy Cofield[7], Theresa McVie[5], S. Louis Bridges[4], Larry W. Moreland[6] and William Robinson[1]. [1]Stanford Univ School of Med, Stanford, CA, [2]Stanford University, Mountain View, CA, [3]Stanford University, [4]Univ of Alabama-Birmingham, Birmingham, AL, [5]Univ of Alabama-Birmingham, [6]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [7]University of Alabama-Birmingham, [8]University of Pittsburgh, Pittsburgh, PA

Purpose: The presence of anti-cyclic citrullinated peptide (CCP) antibodies, as detected by the anti-CCP2 test, is highly specific for the diagnosis of rheumatoid arthritis (RA). However, anti-citrullinated protein antibodies (ACPAs)—only some of which recognize CCP—collectively target many different antigens, and the anti-CCP2 test may therefore fail to detect the entire population of patients with anti-citrulline reactivity. We profiled ACPA reactivity in a cohort of patients with early RA by using a novel multiplex autoantigen array and compared our array results with those obtained using the commercial anti-CCP2 ELISA.

Methods: We performed multiplex autoantibody profiling using the Bio-Plex System to evaluate the presence of 16 ACPA specificities in serum from untreated patients with early RA who were enrolled in the Treatment of Early Aggressive RA (TEAR) trial and in serum from 80 non-RA controls. Bead arrays were used to profile antibodies targeting citrullinated epitopes derived from fibrinogen, vimentin, histone 2B, clusterin, biglycan and other candidate synovial antigens. Values that were 3 SD above the median value in controls were considered positive. Diagnostic sensitivity and specificity, as well as negative and positive predictive values, were calculated for seropositivity for 2, 3, or 4 different ACPAs, and the results were compared to those obtained with the commercial anti-CCP2 ELISA.

Results: Of 360 patients with early RA, 270 (75%) were positive for anti-CCP antibodies. Of the 90 anti-CCP-negative patients, 30 (33.3.1%), 16 (17.8%), and 11 (1.22%) had 2, 3, or 4 ACPAs, respectively. Diagnostic sensitivity of anti-CCP2 was 75%, whereas sensitivity of >/= 2, 3, or 4 ACPAs was 81.1%, 73.9%, and 67.2%, respectively. Diagnostic specificity was maintained even when the presence of only a small number of ACPAs was used for diagnosis: specificity was 91.3%, 97.6%, and 97.6% when using a threshold of 2, 3, or 4 ACPAs, respectively. Combining detection of ACPAs and anti-CCP improved diagnostic sensitivity over that achieved with anti-CCP alone with minimal decrease in diagnostic specificity.

Conclusion: We demonstrate the presence of >/=2 ACPA in 33.3% of patients designated seronegative by the commercial anti-CCP2 ELISA. Given that anti-CCP positivity has been shown to be a marker of more aggressive disease and potentially an indication for the need for earlier and more

aggressive intervention, our data suggest that an additional subpopulation may benefit from the use of a broader panel of ACPA biomarkers in the diagnosis and treatment of RA. Profiling of other ACPAs in addition to those detected by the current anti-CCP assay could yield greater sensitivity in the diagnosis of RA.

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1741

Anti-Cyclic Citrullinated Peptide Antibodies: Beyond Rheumatoid Arthritis. Dolors Grados, Melania Martinez-Morillo, Susana Holgado, Sonia Mínguez, Anna Moltó, Beatriz Tejera, Lourdes Mateo, Xavier Tena, Anna Marín, Iñaki Salvador, Eva Martínez-Caceres, Estíbaliz Ruiz and Alejandro Olivé. Hospital Universitari Germans Trias i Pujol

Background: The determination of anti-cyclic citrullinated peptide antibodies has diagnostic and prognostic value in rheumatoid arthritis, with a sensitivity similar to that of the rheumatoid factor and of greater specificity.

Objectives: To describe the clinical characteristics of a cohort of patients with positive anti-cyclic citrullinated peptide antibodies.

Methods: The retrospective study was done at the university hospital with a reference population of 700,000 between 2007 and 2009. We reviewed the medical records of patients with anti-cyclic citrullinated peptide antibodies (citrullinated vimentin peptides) greater than or equal to 20 U/ml excluding those cases without clinical information. Technique used: ELISA anti-CMV (Orgentec, Freiburg, Germany).

Results: We carried out 1222 determinations, of which 418 (34%) were positive. We analyzed 320 patients: 103 men (32%) and 217 women (68%). In 234 cases (73%) patients had an associated rheumatic disease.

Table 1.

	20–50 U/ml	51–100 U/ml	101–500 U/ml	>500 U/ml	Total
Rheumatoid arthritis	21	19	36	51	127
Elderly-onset arthritis	5	3	5	2	15
Non-titrated arthritis	18	4	2	1	25
Connective and vasculitis	30	2	2	2	36
Stills disease	1	2	1	0	4
Palindromic rheumatism	1	3	1	2	7
Miscellaneous	15	3	1	1	20

64.5% of patients with rheumatoid arthritis, who had values above 100 U/ml, where seropositive and erosive forms. In the cases of vasculitis and connective tissue disease the values were between 20 and 50 U/ml. They were above 50 U/ml only in six patients: 3 with SLE and 3 with Sjogren syndrome. The distribution in Still's disease, palindromic rheumatism and elderly-onset arthritis was similar for all values. 72% of the non-filiated arthritis had values between 20 and 50 U/ml. In the miscellaneous group (psoriatic arthritis, microcrystalline arthritis, polymyalgia rheumatica, sarcoidosis, arthritis associated with inflammatory bowel disease and postinfectious arthritis), 75% had values less than 50 U/ml. The value of 100 U/ml was only exceeded in a case of polymyalgia rheumatica and a case of chondrocalcinosis.

In 86 cases (27%) the patients did not have any associated rheumatic disease.

Table 2.

	20–50 U/ml	51–100 U/ml	101–500 U/ml	>500 U/ml	Total
Endocrinology and nephropathy	16	2	2	0	20
Lung disease	9	0	2	0	11
Hematology and infections	18	4	2	0	24
Miscellaneous	28	3	0	0	31

Fifteen patients (17%), two of whom were smokers, had values above 50 U/ml. In six cases the values were greater than 100: 2 with nephropathy, 2 with lung disease (pulmonary hypertension and idiopathic pulmonary fibrosis), 1 with autoimmune hemolytic anemia and 1 case of drepanocytosis.

Conclusion: Although anti-cyclic citrullinated peptide antibodies are highly specific for rheumatoid arthritis, they have also been described in other rheumatic diseases. Values above 100 U/ml usually relate to rheumatoid arthritis. Values between 20–50 U/ml without articular simptoms, must be considered negative, so this determination must be valued only in the context of rheumatic disease.

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Assessment of Nontraditional Prognostic Markers in Patients with Rheumatoid Arthritis. Bozena Targonska-Stepniak and Maria Majdan. Department of Rheumatology and Connective Tissue Diseases, Medical University of Lublin, Lublin, Poland

Background: Rheumatoid arthritis (RA) is associated with patients' shortened life expectancy. Premature deaths are mostly due to accelerated cardiovascular disease (CVD) which cannot only be explained by the presence of traditional CV risk factors. The search for early markers of poor prognosis seems to be crucial. N-terminal pro-BNP (NT-proBNP) concentrations are increased in CVD and predict the risk of CV events. Renal involvement worsens both the course of RA and CVD. Cystatin C (Cys-C) is used as an endogenous, precise marker for glomerular filtration rate. Carotid intima-media thickness (cIMT) assessed by ultrasound reflects early stages of atherosclerosis and is a strong predictor of CV events.

The purpose of the study was to assess the value of chosen prognostic markers in patients with RA in association with markers of disease activity.

Methods: The study population consisted of 140 RA patients (111 women and 29 men); with the mean (SD): age 50.3 (10.9) years and disease duration 120.6 (89.8) months. Disease Activity Score in 28 joints (DAS28) was calculated as a primary outcome measure. High disease activity (DAS28≥5.1) was observed in 42 patients (30%), erosive form of RA in 117 (83.6%). Plasma NT-proBNP concentration was assessed in patients and 20 healthy controls with chemiluminescent immunometric method. Serum Cys-C concentration was assessed with quantitative enhanced immunonephelometry method (normal range 0.53– 0.95 mg/l). cIMT was measured in patients and 31 healthy controls using high-resolution B-mode ultrasonography.

Results: The mean (SD) concentration of NT-proBNP was significantly higher in RA patients than in controls [120.1 (212.3) pg/ml vs 30.8 (30.6) pg/ml ($p< 0.0001$)], as well as cIMT [0.75 (0.17) mm vs 0.59 (0.12) mm] ($p< 0.0001$)]. The mean (SD) serum Cys-C concentration was 0.78 (0.3) mg/l (range 0.42–3.37).

The three markers correlated positively with each other (NT-proBNP and cIMT: $R=0.29$; $p=0.0005$; NT-proBNP and Cys-C: $R=0.34$; $p=0.00003$; Cys-C and cIMT: $R=0.44$; $p=0.00001$). There were significant associations with metabolic variables: between cIMT and cholesterol (total and LDL), atherogenic index, glucose, body mass index; between Cys-C concentration and triglycerides, atherogenic index.

The value of cIMT, Cys-C, NT-proBNP correlated positively with the patients' age and inflammatory markers (ESR, fibrinogen). Both NT-proBNP and Cys-C were also significantly associated with markers of RA: immunological (ACPA) and functional (HAQ). Only Cys-C concentration showed significant correlation with markers of disease activity (DAS28, CRP, morning stiffness, VAS patient's global assessment of disease activity).

Conclusions: The values of Cys-C, NT-proBNP and cIMT in RA patients were associated with the age and metabolic parameters, but also with markers of the disease activity. These nontraditional prognostic markers may be helpful in early diagnosis of complications associated with the course of RA.

Disclosure: B. Targonska-Stepniak: None; **M. Majdan:** None.

1743

Baseline ADAMTS5 Expression Could Sort the Prediction of Response to Infliximab or Adalimumab in Patients with Rheumatoid Arthritis. Kensei Tsuzaka[1], Yuka Itami[2], Naoshi Shinozaki[2] and Tetsuo Morishita[2]. [1]Tokyo Dental College Ichikawa General Hospital, Ichikawa, Chiba, Japan, [2]Tokyo Dental College Ichikawa General Hospital, Ichikawa, Chiba, JAPAN

Objective: We have reported a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5) as a candidate marker for predicting the efficacy of infliximab (IFX) in RA patients in the last ACR meeting. In this paper, we investigate ADAMTS5 as a predicting marker for the

adalimumab (ADA) treatment in RA to certify the sorting of ADA or IFX by baseline ADAMTS5 expression.

Methods: Forty-eight and one hundred active RA patients were treated with ADA and IFX, respectively. Peripheral blood samples were collected at baseline and ADAMTS5 mRNA was quantified using real-time PCR.

Results: Baseline ADAMTS5 mRNA levels ($\times$ 10-4) in the ADA good responder (GR) (3.54 $\pm$ 2.18) were significantly ($p=0.003$) higher than that in the ADA moderate and non-responder (NGR) (2.02 $\pm$ 1.23) at 12 weeks' ADA treatment. The DAS28 at 12 weeks' ADA treatment was significantly lower in the baseline High-ADAMTS5 ($\geq 4.90 \times$ 10-4) groups than in the Low-ADAMTS5 groups, respectively (Fig.1). We observed high positive predictive value (PPV) of the baseline High-ADAMTS5 ($\geq 4.90 \times$ 10-4) for predicting ADA GR and ADA remission (DAS28<2.6 at 12 weeks) as shown in Table 1.

On the other hand, baseline ADAMTS5 mRNA level ($\times$ 10-4) in the IFX GR (1.82 $\pm$ 1.31) was significantly ($p=0.004$) lower than that in the IFX NGR (2.78 $\pm$ 1.77) at 14 weeks' IFX treatment. The DAS28 at 14 weeks' IFX treatment was significantly lower in the baseline Low-ADAMTS5 ($<1.12 \times 10^{-4}$) group than in the High-ADAMTS5 group (Fig. 1). We observed high positive predictive value (PPV) of the baseline Low-ADAMTS5 ($<1.12 \times 10^{-4}$) for predicting IFX GR and IFX remission (DAS28<2.6 at 14 weeks) as shown in Table 1.

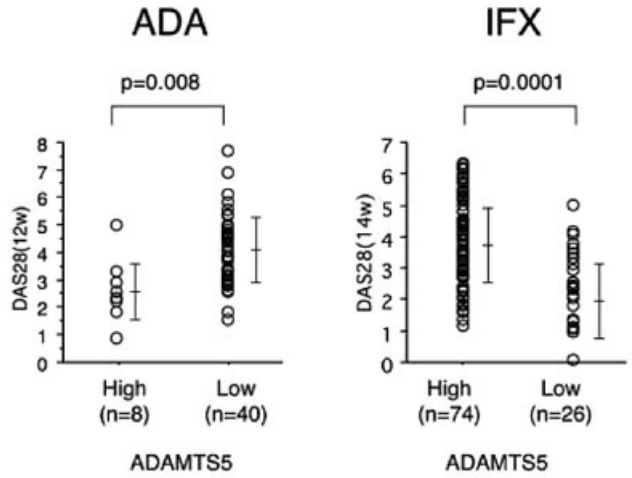

Fig. 1.

Table 1. Prediction of response to adalimumab or infliximab using ADAMTS5

	Prediction by High-ADAMTS5[b]		Low-ADAMTS5[c]	
	ADA GR	ADA Remission	IFX GR	IFX Remission
PPV (%)	75.1	61.5	70.4	62.5
NPV (%)	66.7	78.4	68.5	90.1

ADA: Adalimumab, IFX: infliximab, GR: good responder
High-ADAMTS5[b]: ADAMTS5 $\geq 4.90 \times 10^{-4}$
Low-ADAMTS5[c]: ADAMTS5 $< 1.12 \times 10^{-4}$
PPV: Positive prediction value, NPV: negative prediction value

Conclusion: Baseline Low-ADAMTS5 mRNA level ($< 1.12 \times 10^{-4}$) could predict good response to IFX while High-ADAMTS5 ($\geq 4.90 \times 10^{-4}$) could predict respectable reaction to ADA, suggesting ADAMTS5 could sort the prediction of response to these two anti-TNFα biologics.

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Classification of Rheumatoid Arthritis—Comparison of the 1987 ACR and 2010 ACR/EULAR Criteria. M. P. M. van der Linden, R. Knevel, T. W. J. Huizinga and A. H. M. van der Helm-van Mil. Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands

Objective: New criteria to classify RA have been derived in order to increase the specificity and sensitivity for early RA compared to the 1987 criteria. This study evaluated differences in classification between the 1987 ACR criteria and 2010 ACR/EULAR criteria and determined the test characteristics of the 2010 ACR/EULAR criteria.

Methods: 2258 early arthritis patients included in the Leiden Early Arthritis Clinic cohort between 1993 and February 2009 were studied. Fulfilment of the 1987 and 2010 criteria for RA was determined at baseline. Also the diagnosis at the 1 year visit was assessed. The sensitivity and specificity of the 2010 criteria were determined using three outcome measures: initiation of metrotrexate therapy or any DMARD therapy during the first year of followup and having persistent arthritis over 5 years. Persistent arthritis was defined as the absence of remission, which was defined by the absence of arthritis for at least one year after the cessation of eventual DMARD-therapy.

Results: At first presentation, 1090 patients fulfilled the 2010 criteria and 726 patients fulfilled the 1987 criteria for RA. 85 of the 726 patients (12%) that fulfilled the 1987 criteria did not fulfill the 2010 criteria at the same time point.

		2010 ACR/EULAR Classification Criteria		
		RA at baseline	no RA at baseline	*Total*
1987 ACR classification Criteria	RA at baseline	641	85	*726*
	no RA at baseline	449	1083	*1532*
	Total	*1090*	*1168*	*2258*

68% of the patients that fulfilled the 1987-criteria during the first year of the disease but not at baseline did fulfill the 2010 criteria at baseline. This indicates that the 2010 criteria indeed classify RA in an earlier stage of the disease. The sensitivity and the specificity were 0.90 and 0.56 with initiation of methrotrexate therapy as outcome and 0.83 and 0.74 respectively with use of any DMARD as outcome. When taking arthritis persistency over 5 years as outcome, the sensitivity and specificity were 0.70 and 0.63.

	2010 ACR/EULAR Classification Criteria		
Outcome Measure	Sensitivity	Specificity	AUC
MTX-use	0.90	0.56	0.73
DMARD-use	0.83	0.74	0.78
Persistency over 5 years	0.70	0.63	0.66

Conclusion: Compared to the 1987 criteria, the 2010 criteria classify more patients with RA and in an earlier phase of RA. The discriminative ability of the 2010 criteria is reasonable.

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Clinical Utility and Validity of Self Assessed Joint Involvement in Rheumatoid Arthritis (RA) Patients with Low Active Disease. Helga Radner[4], Tanja Alexandra Stamm[3], Johannes Grisar[2], Josef S. Smolen[1] and Daniel Aletaha[3]. [1]Krankenhaus Lainz, Vienna, Austria, [2]Medical Universitiy Vienna, [3]Medical University of Vienna, Vienna, Austria, [4]Medical Universty Vienna, Vienna, Austria

Background: Joint swelling and tenderness are essential clinical manifestations of RA disease activity. Especially in patients in low disease activity states without significant joint involvement regular performance routine visit are usually less frequent. In these patients, self assessment of joints, and potentially, the use of a purely patient derived disease activity score might be an acceptable alternative. As a first step, we evaluated the validity of patient self assessed joint counts and a composite disease activity scores calculated from patient derived scores.

Methods: 212 patients with established RA were instructed to perform self-assessment of joints regarding swelling and tenderness on the 28 joint count (SJC28, TJC28) before an independent routine assessment by a trained evaluator. A randomly chosen subgroup of patients (n=79) received short training of joint assessment by a physician.

Based on patient derived joint counts a composite index of disease activity was calculated (patient clinical disease activity index CDAIp = TJC28 patient + SJC28 patient + patient global assessment (PGA) in cm) and correlated with the standard CDAI (CDAIe) via Spearman Correlation. Furthermore we calculated the concordance of CDAI states and differences in swollen and tender joint counts between the two different assessors using Wilcoxon test. Subsequently patients were divided into their level of disease activity defined by CDAIe and agreement was analyzed in the 4 subgroups.

Last, differences of agreement for trained and untrained subgroups were calculated separately to investigate the effect of training.

Table 1. Wilcoxon test comparing patient and evaluator derived swollen and tender joint counts (SJC28p, TJC28p; SJC28e, TJC28e) as well as the clinical disease activity index calculated by patient derived values (CDAIp) compared to the standard one (CDAIe) in the total cohort and subgroups defined by CDAI

Wilcoxon Test	TOTAL	REM	LDA	MDA	HAD
SJC28p>SJC28e	76	7	39	21	9
SJC28p<SJC28e	75	4	39	25	7
ties	61	26	26	7	2
TJC28p>TJC28e	86	10	45	26	5
TJC28p<TJC28e	45	3	22	12	8
ties	81	24	37	15	5
CDAIp>CDAIe	36	7	22	7	0
CDAIp<CDAIe	47	0	23	15	9
ties	129	30	59	31	9
total	212	37	104	53	18

Results: We found a significant correlation ($p<0.01$) of patient and assessor derived SJC28 ($r=0.42$), TJC28 ($r=0.71$) and CDAI ($r=0.79$). Wilcoxon test showed good accordance of CDAI level between CDAIp and CDAIe (ties=129 of 212) and slightly lower agreement of SJC28 (ties= 61) and TJC28 (ties=81). In different subgroups of CDAI-level we found a high concordance of patient and evaluator derived values using Wilcoxon test (see table) and significant ($p<0.01$) correlation of CDAI in all subgroups of disease activity except HDA (REM $r=0.61$; LDA $r=0.50$; MDA $r=0.38$; HDA $r=0.36$ $p=0.13$).

Comparing trained and untrained patients we found no significant differences between these two subgroups regarding Spearman correlation of CDAIp and CDAIs (trained $r=0.74$; untrained $r=0.83$) or Wilcoxon test (ties CDAI level trained =48 of 79, untrained =81 of 133).

Conclusion: Patients self assessment of joints show good correlation with those performed by specialists, regardless of training. To improve effective follow-up, especially in patients with REM or LDA, a purely patient derived disease activity index seems valid and might be a helpful tool in daily clinical practice.

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1746

Comparing the Validity of the EuroQol-5D, Short Form-6D and the Well-Being Preference-Based Scores Using the Mean Short Form-36 Health Dimension Scores in Patients with Rheumatoid Arthritis and in Healthy Controls.

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Background: Over the years, the interest of the preference-based generic instruments, used to measure the health-related quality of life in a general population or in rheumatoid arthritis (RA) patients, have been increased. However, the several instruments have several discrepancies in terms of utility of results.

Objective: To compare the validity of the EuroQol-5D (EQ-5D), Short Form-6D (SF-6D) and the well-being preference-based scores (RS) using the mean Short Form-36 health dimension scores in patients with rheumatoid arthritis and in healthy controls.

Methods: A cross-sectional study was carried out among 511 patients with RA (384 women, 127 men) who were attending at Rheumatology Department. Each patient was asked to complete EQ-5D, SF-6D and the RS questionnaires. The SF-6D was derived from the Short-Form 36 health dimension (SF-36) questionnaire. SF-6D utility scores were calculated using the eight mean SF-36 scores by algorithms developed from the UK general population. Agreement between the utility instruments was assessed by comparing their score distributions, medians, interquartile range (IQR), intraclass correlation coefficients (ICCs) and a Bland-Altman plot. Interrelationship of the EQ-5D, SF-6D and RS with Disease Activity Score, 28 joint (DAS28), radiographic damage score (by Sharp v van der Heijde score method), disease duration and socio-demographic factors (age, gender and educational level) were also assessed.

Results: Baseline scores from all measures were not normally distributed (Kolmogorov–Smirnov test, all $p < 0.001$). The median baseline values have different locations in their respective scoring ranges: the median EQ-5D score was located in the top quarter and the median SF-6D and RS scores in the middle part. Median (IQR) EQ-5D utility score was 0.43 (0.34–0.55), the median (IQR) SF-6D utility score was 0.56 (I0.52–0.64) and the median (IQR) RS utility score was 0.50 (0.42–0.60). All measures were able to discriminate between patients and controls ($p < 0.001$). Agreement among measures was poor, with an ICC that range from 0.45 to 0.51. The Bland-Altman plot showed proportional error, and wide limits of agreement. Instrument correlated equally with disease activity and demographic characteristics. The SF-6D showed smaller average differences in utility between patients with better and worse disease compared with the EQ-5D and the RS. Damage score showed weak correlation with HRQL measures.

Conclusions: Although EQ-5D, SF-6D and the RS exhibited satisfactory psychometric properties for use among patients with RA, the EQ-5D and SF-6D appeared to be quite different. The low agreement and the differences in median values and scoring range show that the EQ-5D and SF-6D yield incomparable scores in patients with RA Moreover, measures of damage were weakly correlated with these instruments, suggesting that HRQL is an important complementary source of information about patients with RA. Further research is required to fully understand the respective roles of the above mentioned instruments and to examine their implications for estimates the impact of health care interventions in RA.

Disclosure: F. Salaffi: UCB, Inc., 2; **M. Carotti:** UCB, Inc., 2; **S. Gasparini:** UCB, Inc., 2; **A. Ciapetti:** UCB, Inc., 2; **W. Grassi:** UCB, Inc., 2.

1747

Computer Assisted Patient Reported (PR) Versus Physician Generated (PG) Joint Count (JC) and DAS28 Scores for Rheumatoid Arthritis (RA) Patients.

Norman B. Gaylis[2], Jeffrey Scott[3], Sue North[3], Marty True[3], Guss Savloff[1] and Barry V. Fortner[3]. [1]Arthritis & Rheumatic Disease Specialties, [2]Arthritis & Rheumatic Disease Specialties, Aventura, FL, [3]P4 Healthcare

Background: JCs and the DAS scores are established clinical indicators of disease severity, treatment response, and outcome measurement for RA. The purpose of this study was to evaluate the similarity and difference between JCs and corresponding DAS scores generated by computer assisted patient self-report or through clinical interview.

Methods: An electronic homunculus was created allowing RA patients to rate the severity of tenderness (TEN) and swelling (SW) for indicated joints through touch screen computer tablets. PG JCs were generated through normal clinical interview. A clinician interface allowed the same JC information to be recorded electronically by medical staff. JCs were combined with erythrocyte sedimentation rates (ESR) to calculate DAS28 scores using PR and PG data respectively using accepted scoring methodology. The clinician was not formally blinded to the PR scores and the order of completion was determined by clinical circumstance. The analysis design is an anonymous, retrospective, within subject correlational design testing the convergent validity PR JCs and PR DAS28 scores with corresponding PG scores. The primary hypothesis was that the PR JCs and DAS28 scores would be similar to and not different from PG JCs and DAS28 scores.

Results: At the time of this report, 51 RA patients (M[SD] age = 59.3 [11.2]; 86% female) had available PR and PG JCs and DAS28 scores on the same day. PR and PG SWJCs were significantly correlated ($R = 0.52$, $p < .001$) and were not significantly different (M[SD] PRSWJC = 3.2 [6.0], M[SD] PGJC = 4.5 [5.1], paired samples t-test, $t(df) = 1.1$ (48), $p > .1$). PR and PG TENJCs were significantly correlated ($R = 0.56$, $p < .001$) and trended toward being higher when PG (M[SD] PRJC = 2.8 [5.2], M[SD] PGJC = 4.4 [6.7], paired samples t-test, $t(df) = 1.9$ (48), p.07). PRDAS28 scores PGDAS28 scores were significantly correlated ($R = 0.75$, $p < .001$) and not significantly different (M[SD] PRDAS28 = 3.6 [1.6], M[SD] PGDAS28 = 3.7 [1.8], paired samples t-test, $t(df) = 0.8$ (50), $p < 0.4$). As shown in the table, PRTENJC, PRSWJC, and PRDAS28 scores were significantly correlated with RAPID3, RAPID4, and PGDAS28. An exploratory principal components factor analysis was performed on PRTENJC, PRSWJC, PGTENJC, PGSWJC, RAPID4, and ESR. Two components were extracted (Eigenvalues >1) accounting for > 73% of the variance. Component 1 (Symptomatology) was characterized by PRTENJC, PRSWJC, PGTENJC, PGSWJC, and RAPID4. Component 2 (Inflammation) was characterized by ESR PRTENJC, PRSWJC, and PGSWJC.

Conclusions: This study suggests that a computer assisted PR JCs are valid and may be used to produce DAS28 scores comparable to PGDAS28 scores. Initial evaluation suggests the PRJCs are related to both RA symptomatology and inflammation. Future evaluations will also compare PR JCs

and DAS scores to other available RA measures, such as radiologic indices, and will examine test-retest reliability. The primary study limitations are that PR and PG JCs were blinded and the post hoc nature of the hypothesis.

Disclosure: N. B. Gaylis: P4 Healthcare, 5; **J. Scott:** P4 Healthcare, 3; **S. North:** P4 Healthcare, 3; **M. True:** P4 Healthcare, 3; **G. Savloff:** None; **B. V. Fortner:** P4 Healthcare, 3.

1748

Concurrent Depressive or Anxiety Disorders Significantly Worsen the Health-Related Quality of Life of Patients with Rheumatoid Arthritis. Eugenia Y. C. Lok[1], Chi Chiu Mok[2], Fuk Chi Cheung[1] and Chi Wai Cheng[1]. [1]Castle Peak Hospital, [2]Tuen Mun Hospital

Objectives: To study the effects of depressive or anxiety disorders on the health-related quality of life (HRQOL) of patients with rheumatoid arthritis (RA).

Methods: Consecutive Chinese patients who fulfilled the ACR criteria for RA were recruited from an out-patient rheumatology clinic. Written consent was obtained from these patients who were interviewed by a psychiatrist for the presence of depressive and anxiety disorders using the Chinese-bilingual Structured Clinical Interview for DSM-IV Axis I disorders, Patient research version (CB-SCID-I/P). HRQOL was measured by the validated Chinese version of the MOS 36-item Short Form Health Survey (SF-36) questionnaire. Socio-demographic and clinical data (age, gender, duration of RA, disease activity scores (DAS28), family income, education level) at the time of interview were also collected.

Results: Between July 2007 and June 2008, 200 patients with RA were studied (79% women, mean age 51.4±10.5 years; median RA duration 4.0 years [IQR 2.0–9.0]). 47 (23.5%) patients were diagnosed to have a current psychiatric disorder (depressive disorders 14.5%, anxiety disorders 13.0%). There were no statistically differences in the age, sex distribution, education level, marital status, disease activity scores and duration of RA in patients who had either depressive or anxiety disorders compared to those without any psychiatric disorders (univariate analysis). However, RA patients with either depressive ($p=0.002$) or anxiety disorders ($p=0.02$) had significantly lower family income than those without psychiatric disorders. The mean scores (out of 100) of the eight subscales of SF-36 of RA patients with depressive disorders were 34.8±21.7 (physical functioning), 11.2±22.7 (role physical), 26.4±16.9 (bodily pain), 17.8±15.0 (general health), 22.1±17.5 (vitality), 34.6±24.5 (social functioning), 3.4±18.6 (role emotional) and 34.5±16.4 (mental health), respectively. The mean scores of the eight subscales of SF-36 of RA patients with anxiety disorders were 45.2±16.2 (physical functioning), 11.5±25.7 (role physical), 34.0±15.9 (bodily pain), 23.6±12.5 (general health), 27.9±14.8 (vitality), 50.2±27.4 (social functioning), 11.5±26.6 (role emotional) and 45.7±15.4 (mental health), respectively. The scores of each of the eight subscales of SF-36 of patients with either depressive or anxiety disorders were significantly lower than those of RA patients who did not have any psychiatric disorders ($p<0.001$ in both cases). In linear regression models, both depressive disorders and anxiety disorders were independently and inversely associated with the total SF-36 scores after adjustment for socioeconomic and demographic variables ($P<0.001$ in both models). A lower family income was another independent factor for lower SF-36 scores.

Conclusion: The presence of concomitant depressive or anxiety disorders in patients with rheumatoid arthritis is associated with a significant worsening of the HRQOL, which is independent of demographic and socioeconomic factors.

Disclosure: E. Y. C. Lok: None; **C. C. Mok:** None; **F. C. Cheung:** None; **C. W. Cheng:** None.

1749

Construct Validity and Reliability of the Quick Disability of the Arm, Shoulder and Hand Questionnaire in Rheumatoid Arthritis Based on IORRA Cohort Study. Asami Tokita[1], Takuji Iwamoto[2], Ryo Hiroshima[2], Yu Sakuma[2], Koichiro Yano[2], Kosei Kawakami[2], Katsunori Ikari[2], Atsuo Taniguchi[2], Hisashi Yamanaka[2] and Shigeki Momohara[2]. [1]Institute of Rheumatology, Tokyo Women's Medical University, Kawada-cho, Shinjuku-ku, Tokyo, Japan, [2]Institute of Rheumatology, Tokyo Women's Medical University, Japan

Background: The Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire and the QuickDASH, which is a shorter version, are used for clinical research involving upper extremity musculoskeletal disorders. The purpose of this study is to test the reliability and validity of the Japanese Society for Surgery of the Hand Version of the QuickDASH in patients with rheumatoid arthritis (RA).

Methods: For the validation, we examined the correlation between DASH and Quick DASH was examined in RA patients who have the upper extremity disorders. The correlation between DASH, QuickDASH and Cooney's wrist score were also examined in patients with wrist disorders. Reliability was tested by a test-retest method for an average of 9.9 days interval in other patients. Moreover, the correlation between QuickDASH and Japan Health Assessment Questionnaire (J-HAQ), Visual analog scale (VAS), Disease Activity Score (DAS28) were investigated on 5,191 patients who participated in the Japanese RA cohort project (Institute of Rheumatology RA cohort: IORRA). Validity was tested using a Pearson correlation analysis.

Results: The QuickDASH was calculated for 85 out of 94 patients (90.4%). The mean of QuickDASH score was 36.25 (0–89). DASH and QuickDASH showed extremely high correlation ($r=0.97$).

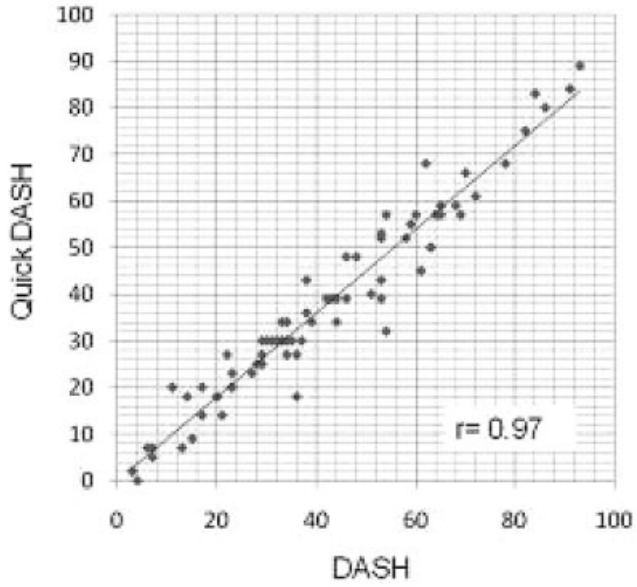

Fig. 1. DASH—Quick DASH.

The Cooney's wrist score correlated strongly with the DASH ($r=-0.79$) and the QuickDASH ($r=-0.7$). Reliability of the DASH and QuickDASH was excellent. The intraclass correlation of DASH was 0.96, and QuickDASH was 0.95. In the IORRA cohort study, the QuickDASH could be calculated for 4,946 out of 5,192 patients (95.3%). The mean of QuickDASH score was 19.9 (0–97.7). The QuickDASH and J-HAQ also showed high correlation ($r = 0.88$).

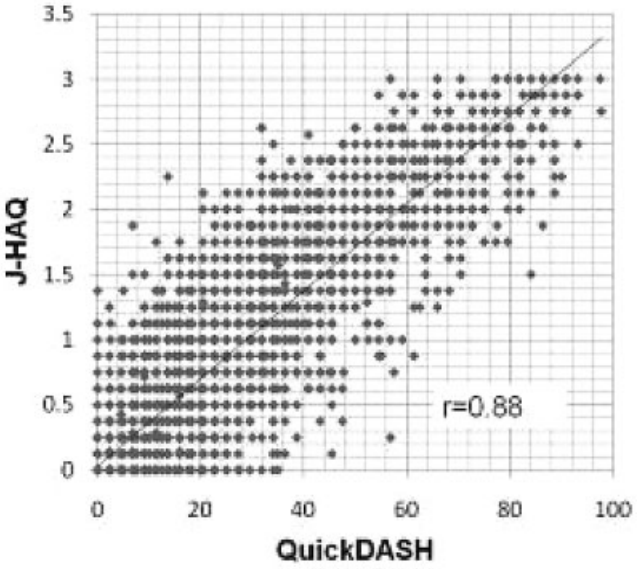

Fig. 2. QuickDASH—J-HAQ.

The clinical scores had relatively low correlations with the QuickDASH (VAS, r=0.63; DAS28, r=0.53).

Conclusions: The QuickDASH is a valid and reliable instrument for measuring the functional status of RA patients, and it is useful for large cohort study because of its high response rate.

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Contribution of the Rheumatoid Arthritis Impact of Disease (RAID) on Disease Activity in Rheumatoid Arthritis (RA). Till Uhlig[1], Turid Heiberg[3], Cathrine Austad[2] and Tore K. Kvien[1]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]Oslo University Hospital, Oslo, Norway

Purpose: The RAID score is a new patient reported outcome developed through a EULAR task force (1). The OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials) group recently put on its research agenda a need to explore how RAID relates to disease activity in RA. Currently, patient global assessment of disease activity (PatGlob) is the patient reported variable included in DAS28.

Objectives: To provide data on validity of RAID and contribution to assessment of disease activity in a large data set from a population based RA registry 2009 (ORAR).

Methods: In a population based RA registry in Oslo, Norway, 868 patients aged 20–79 years (mean (SD) age 59.9 (12.3) years, disease duration 13.0 (10.8) years, 77.1% females, 57.0 % RF+ or CCP+) responded in 2009 to a mailed questionnaire (response rate 60.6%). RAID score (0–10) is calculated from seven domains, perceived by patients to be particularly important: pain, functional disability, fatigue, sleep problems, emotional and physical well-being, coping. The Rheumatoid Arthritis Disease Activity Index (0–10) was used to assess disease activity. Other patient reported outcomes separately assessed included pain, fatigue and PatGlob on 100 mm visual analogue scales, modified HAQ, SF-36 with physical (PCS) and mental component summary (MCS) (low scores=poor health), and SF-6D derived utility.

Pearson correlation coefficients are reported between RAID and measures of disease activity. We further used linear regression analysis to calculate the explained variance of RAID and of PatGlob for disease activity in RA.

Results: RAID was mean 3.35 (SD 2.16), disease activity (RAID) was 3.20 (SD 1.71) and both were strongly correlated (r=0.82). RAID was also highly or substantially correlated to other core measures of disease activity: pain (r=0.81), patients global (r=0.84), for physical function HAQ (r=0.67) and PCS (r=0.72), and also to fatigue (r=0.68), mental health (MCS) (r=0.52) and SF-6D derived utility (r=0.78).

RAID explained 67% of the variance in disease activity, PatGlob explained 71%, and both together explained 77%.

Conclusion: RAID was highly and substantially related to core measures and to an index (RADAI) of disease activity. PatGlob explained only slightly more than RAID of the variation in disease activity. These results support that RAID as a global composite of disease is closely related to disease activity in RA.

References:

1. Gossec L et al. Elaboration of the preliminary Rheumatoid Arthritis Impact of Disease (RAID) score: a EULAR initiative. ARD 2009:68:1680–5.

Disclosure: T. Uhlig: None; **T. Heiberg:** None; **C. Austad:** None; **T. K. Kvien:** None.

1751

CXCL2 as a Potential Biomarker of Disease Activity in Rheumatoid Arthritis. Kichul Shin[2], Ji Ah Park[3], Jun Wan Kim[3], Hong Hee Kim[1], Eun Bong Lee[3] and Yeong Wook Song[3]. [1]Department of Cell and Developmental Biology, BK21 and DRI, Seoul National University School of Dentistry, Seoul, Korea, [2]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea, Republic of, [3]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea

Background: The diverse role of chemokines in rheumatoid arthritis (RA) includes enhancement of leukocyte migration, angiogenesis, and osteoclastogenesis in the synovium. CXCL2 is a chemokine produced by activated macrophages and acts as a mediator for chemotaxis of neutrophils, regulation of transmigration and extravascular tissue accumulation of leukocytes. We recently demonstrated that CXCL2 contributes in osteoclastogenesis and bone erosion *in vivo*. We investigated the relationship between serum CXCL2 concentration and clinical and radiological parameters in RA patients.

Methods: Eighty one RA patients who visited the rheumatology outpatient clinic participated in this study. All patients fulfilled the 1987 ACR classification criteria for RA. Serum CXCL2, CRP levels and blood ESR were measured. Clinical parameters including DAS28, visual analog scale (VAS) of physician's and patient's global assessment, pain, fatigue, and health assessment questionnaire (HAQ) score as well as simple erosion narrowing score (SENS) were evaluated at the time point obtaining the samples. In additional 19 patients treated with infliximab, sera at pre- and post-treatment (5 infusions) were obtained.

Results: Demographic data of 81 RA patients (female ratio 79 %) included mean age of 51 years, mean disease duration of 9.7 years, and DAS28(ESR) of 4.8 ± 1.8 (mean ± standard deviation). The serum level of CXCL2 in RA patients and healthy controls were 963.3 ± 42.1 vs. 505.0 ± 40.7 pg/ml (p= 0.002) respectively. Among the clinical parameters, a positive correlation was shown between DAS28(ESR) and CXCL2 levels (r= 0.235, p= 0.035). ESR and CRP levels also showed positive correlation with CXCL2 (r= 0.310, p= 0.005 and r= 0.540, p< 0.001, respectively). SENS did not correlate with CXCL2 levels. Serum CXCL2 levels tended to decrease compared with baseline in 19 RA patients after receiving 5 infusions of infliximab (p= 0.055).

Conclusion: Serum CXCL2 levels correlated well with DAS28(ESR), and ESR, CRP levels in RA patients. CXCL2 may be a potential biomarker of disease activity of RA.

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1752

Development by the STPR Group of the Flare Instument, a New Tool To Identify Flare in Rheumatoid Arthritis (RA) in Clinical Practice. Jean-Marie Berthelot[4], Michel De Bandt[2], Jacques Morel[1], Arnaud Constantin[3], Philippe Gaudin[3], Xavier Le Loët[3], Jean-Francis Maillefert[3], Olivier Meyer, Thao Pham, Alain Saraux, Elisabeth Solau-Gervais, Daniel Wendling, Elisabeth Spitz, Bruno Fautrel and Francis Guillemin. [1]Montpellier, France, [2]Aulnay Sous Bois, France, [3]France, [4]Rheumatology Unit CHU Nantes, Nantes, France

Introduction: Rheumatoid arthritis (RA) patients may have stable disease activity at two determinations but flares may occur between two scheduled evaluations, not captured by any activity score. There is no measure for such flares in RA patients, although they could impact on radiographic and functional outcome.

Objectives: To explore the concept of flare (transient or lasting exacerbation of disease activity) in clinical practice in RA, from both patient's and rheumatologist's perspectives, and to develop a self-administered questionnaire enabling the prospective or retrospective detection of flare(s) in the timeframe between two medical visits.

Methods: To capture the patient perspective, 105 established RA patients from 12 rheumatology centres were proposed to participate in an individual, semi-structured interview scheduled to record their feeling about flare. Content analysis was used to identify verbatim and derive candidate items. The most representative and frequently reported items were selected. To explore the physician perspective, 13 RA-experienced physicians from the STPR (Strategy of Treatment in Patients with Rheumatoid arthritis) panel, participated to a Delphi exercise. They were asked to list the signs or symptoms best reflecting RA flare(s) from their point of view. The items listed were reduced in a 5-round Delphi process in which all items cited by at least 75% were definitively selected and those cited by less than 25% of the respondents were excluded.

Results: In the patient perspective, 10 items were selected: swollen joints, fatigue, unbearable pain, pain-killer intake, night awakening, being restricted to inaction, need for help, wish to be alone, drop in mood, irritability. They were integrated in a self-administered questionnaire presenting items with Likert scale-type response frame. In the physician perspective, 9 items were identified: morning stiffness, night awakening, joint swelling, raise in ESR or CRP, worsening of nightly or morning pain, deterioration in arthritis, increase in corticosteroid intake, increase in pain-killer intake, feeling of a flare. They

were presented with discrete answers. Four dimensions were common to physicians and patients: joint swelling, pain, sleep disturbance, increase in pain killer intakes.

Conclusion: The study enabled the identification of 15 different items and will allow the construction of a self-administered questionnaire potentially able to detect flares between two medical evaluations in clinical practice, regardless any disease activity index.

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Development of a Multi-Biomarker Test for Rheumatoid Arthritis (RA) Disease Activity (Vectra™ DA). Marije F. Bakker[8], Yijing Shen[3], Johannes W. J. Bijlsma[7], Johannes W. G. Jacobs[8], Floris P. J. G. Lafeber[8], Guy Cavet[3], Michael Centola[4], Doug Haney[3], Lyndal K. Hesterberg[3], David Chernoff[3], John Carulli[1], Nancy A. Shadick[2], Michael E. Weinblatt[2], Max I. Hamburger[6], Roy M. Fleischmann[5], Jeffrey R. Curtis[9] and Ed C. Keystone[10]. [1]Biogen Idec, [2]Brigham & Womens Hospital, Boston, MA, [3]Crescendo Bioscience, Inc., [4]Oklahoma Med Research Foundation, Oklahoma City, OK, [5]Rheumatology Associates, Dallas, TX, [6]Rheumatology Associates of LI, Dix Hills, NY, [7]University Medical Ctr Utrecht, Utrecht, The Netherlands, [8]University Medical Ctr Utrecht, [9]University of Alabama-Birmingham, Birmingham, AL, [10]University of Toronto, Toronto, ON, Canada

Background: Increasing emphasis on tight control in RA management relies on efficient, quantitative monitoring of disease activity. Given the heterogeneous biology of RA, we sought to develop a quantitative, objective, multi-protein test of RA disease activity. To develop this test, we used a stepwise approach, starting with a broad survey of RA biology, to reach a final set of biomarkers and algorithm to combine them into a single, easy-to-interpret score.

Methods: 25 serum protein biomarkers were previously selected from 137 candidates based on their relationship with disease activity in prior studies: SAA, IL-6, TNF-RI, VEGF-A, PYD, MMP-1, ICAM-1, calprotectin, YKL-40, MMP-3, EGF, IL-1RA, VCAM-1, leptin, resistin, CRP, IL-8, ApoAI, ApoCIII, CCL22, IL-1B, IL-6R, IL-18, keratan and ICTP. Biomarker assays were systematically optimized for analytical performance. Biomarkers were analyzed in 512 serum samples from Index For Rheumatoid arthritis Measurement (InFoRM), a multi-center observational study of North American RA patients, and 167 from the Brigham and Women's Rheumatoid Arthritis Sequential Study (BRASS). Algorithms combining multiple biomarkers were trained to derive a single clinical disease activity measure with scores between 1 and 100; models were developed using ordinary least squares, Lasso and Elastic Net regression, and Curds and Whey, as well as combinations of these approaches. Performance was evaluated by Pearson correlation (r) and area under the ROC curve (AUROC), a measure of classification performance, comparing to the DAS28CRP. Evaluation used cross-validation within the training dataset to guard against over-fitting. A final algorithm was developed and assessed in an independent cohort, i.e. patients from the CAMERA tight control study (testing dataset), to determine performance.

Results: Concentrations of the 25 biomarkers were cross-sectionally measured in 512 patient samples from InFoRM. Associations between concentrations and multiple measures of disease activity were used to prioritize 15 top biomarkers which were subsequently measured in 167 BRASS patient samples. The combined set of 679 patients was diverse in geographic location, ethnicity, age, and RA disease activity. Multiple algorithms were developed; the algorithm with the best performance included 12 biomarkers and used an algorithm similar to the DAS calculation, with different subsets of the biomarkers used to estimate SJC28, TJC28 and patient global. The 12-biomarker algorithm (DA Test) was assessed in the CAMERA cohort, an independent test set, where it achieved r of 0.73 with DAS28CRP and AUROC of 0.87. The DA Test score decreased significantly between the baseline and 6 month study visits, reflecting patients' clinical response to therapy. The DA Test was advanced into independent validation in other cohorts.

Conclusion: An objective test (DA Test) integrating multiple serum biomarkers representing diverse RA pathophysiology has been derived and tested; it can quantify RA disease activity. Once validated in an independent cohort to confirm its performance and additional value, this test has the potential to enhance clinical assessment of RA patients.

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Evaluation of Patients with Rheumatoid Arthritis in Clinical Remission with 12 Joints Ultrasonography. Preliminary Results. José M. Senabre[1], José C. Rosas[2], Carlos Santos-Ramírez[2], Gregorio Santos-Soler[2], Xavier Barber[3], Nuria Llahí[2], Catalina Cano[2] and Rosa Riestra[2]. [1]Hospital Marina Baixa, Villajoyosa, Alicante, Spain, [2]Hospital Marina Baixa, [3]University Miguel Hernández

Objective: To assess wether gray scale and power Doppler (PD) ultrasound of 12 joints can detect disease activity in rheumatoid arthritis (RA) patients classified as clinical remission by DAS28-ESR and / or DAS28-CRP <2.6.

Material and Methods: We included prospectively RA patients in clinical remission (DAS28-ESR and / or DAS28-CRP <2.6) from the Rheumatology Clinic of the Hospital Marina Baixa and within 30 days of clinical evaluation a gray scale and PD ultrasound scan (Esaote, MyLab25 Gold) was performed, by the same rheumatologist who was unaware of the clinical data. We evaluated the presence of joint effusion and PD signal: elbows (anterior and posterior), wrists, 2nd and 3rd MCPs joints (dorsal and palmar aspects), knees (suprapatelar, medial and lateral recesses) and ankle (anterior). The effusion was scored from 0 to 3 points (OMERACT) and the patients were classified into 2 groups (> or <10 points) under the joint global summation.

Results: We analyzed 33 consecutive RA patients in clinical remission, 73 % were women and the mean age was 60 ± 16 years. The average time course of RA was 88 ± 80 months (median 60). PD signal was detected in any joint in 52% of patients. Some degree of joint effusion was detected in 88% of patients. 22% of patients were in group A with effusion > 10 points and 78% in group B with effusion < 10 points. The mean time since diagnose of AR was 81 in group B vs 114 months in the group A. Presence of erosions was 27% in group B vs 57% in group A. No significance was detected in the statistical analysis.

	DOPPLER SIGNAL					
	ABSENCE			PRESENCE		
	Mean	Standard deviation	Median	Mean	Standard deviation	Median
Time in remission (months)	21	21	11	19	25	9
RA Diagnose (months)	81	71	56	94	89	60
DAS28-ESR	1,25	0,45	1,00	1,59	0,507	2,000
DAS28-CRP	1,13	0,35	1,00	1,18	0,39	1,00
Age (years)	54,81	16,1	50,00	64,59	13,72	67,0

Conclusions: 1—Ultrasonographic inflammatory activity (presence of PD) was detected in 52% of RA patients (in clinical remission). 2—22% of patients were in group A with effusion > 10 points. 3—In this group a greater percentage of erosions was detected (57% vs 27%).

Disclosure: J. M. Senabre: None; **J. C. Rosas:** None; **C. Santos-Ramírez:** None; **G. Santos-Soler:** None; **X. Barber:** None; **N. Llahí:** None; **C. Cano:** None; **R. Riestra:** None.

1755

Feasibility of Online Registration of Physical Functioning by RA Patients in the Out Patient Clinic. Rosanne Koevoets[3], N. A. de Glas[3], I. Speyer[1], A. A. Schouffour[3], T. W. J. Huizinga[3], Thea P. M. Vliet Vlieland[2] and Cornelia F. Allaart[2]. [1]Bronovo Hospital, The Hague, [2]Leiden University Medical Centre, Leiden, The Netherlands, [3]Leiden University Medical Centre, Leiden, The Netherlands

Background: Monitoring functional ability is important to assess efficacy of treatment in rheumatoid arthritis (RA), however implementation of routine assessment of functional ability in daily practice remains difficult.

Purpose: To assess the feasibility of and patients' opinion about autonomic online health assessment questionnaire (HAQ) registrations by RA patients in our out patient clinic

Methods: RA patients visiting the out patient department were given an oral instruction and asked to fill in a computerized HAQ in METEOR, a free web based program designed for monitoring both functional ability and disease activity. The time needed to fill in the HAQ and any problems arising were registered. Next, patients answered questions on computer access, the usefulness of the HAQ and the METEOR program. Answers were filled in on a 5 point Likert scale with a high score representing a positive answer and a low score a negative one.

Results: Of 111 consecutive patients, 92 agreed to participate, and 78 patients completed the whole evaluation, while 14 patients stopped early because of time constraints. Seventy-seven percent of the participants were female, and the average age was 58.4 years (range 25–78). Mean (SD) disease duration was 10.4 (8.7) years and mean (SD) HAQ score at the time of assessment was 1.01 (0.72). Of all participants, 84% had personal computer access and 73% reported frequent (daily or weekly) computer use. The mean time patients needed to fill in their own HAQ was 6 minutes, which 99% of patients reported as reasonable or good. Patients felt they had not needed much assistance when filling in the HAQ, although the investigator had noted that some assistance (mainly concerning technical computer problems) was needed in 78% of all patients. Average scores on questionnaire items are presented in table 1. Ninety-five percent of patients said they would be willing to fill in the computerized HAQ at the next visit and 83% was prepared to come to the hospital earlier to fill in the HAQ there, 73% of patients would like the option of filling in the HAQ at home. Twenty percent of patients felt there were missing subjects in the HAQ, in particular work-related activities, social activities and sports, as well as registration of fatigue and psychological problems. Ninety-four percent reported that the subjects included in the HAQ were all relevant. According to patients discussing problems in daily functioning is important, however it is not always part of the out patients visit to the rheumatologist (table1).

Table 1. Results of patients survey questions.

	Mean	Sd
1. What was your opinion about filling in the HAQ on the computer? (1=very difficult 5=very easy)	4.5	1.1
2. Would you be capable of filling in the HAQ independently the next visit? (1=definitely not 5=definitely)	4.2	1.3
3. Did you appreciate filling in the HAQ on the computer in the waiting room? (1=no, not at all 5=yes, very much)	4.0	1.2
4. How important is it discuss about problems in daily functioning with you rheumatologist? (1=not important at all 5=very important)	4.0	1.1
5. How often are problems in daily functioning discussed with the rheumatologist? (1=never 5=always)	3.5	1.3
6. Do the questions in the HAQ give an accurate representation of your abilities and limitations in daily functioning? (1=not at all 5=very much)	3.9	1.2

Conclusion: Independent computerized registration of physical functioning by RA patients in the out patient clinic is feasible and is appreciated by patients. Filling in the HAQ using the METEOR tool before seeing the rheumatologist may stimulate to discuss functional (dis)ability during the consultation, which patients find important, but is not always done.

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1756

Identification of a Novel Marker of Radiological Damage in RA. A. Kleszcz, M. Teare, D. Moore, J. Worthington, A. Barton and G. Wilson. The University of Sheffield

Introduction: Recent genome-wide meta-analysis association studies have identified 10 new risk loci for rheumatoid arthritis: *CD2 and CD58, PRDM1, PTPRC, TAGAP, FCGR2A, CD28, C5orf30, RBPJ, CCR6, and PXK*. The aim of this study was to determine whether RA risk variants were also associated with disease severity as assessed by modified Larsen scores in patients with established rheumatoid arthritis.

Methods: Modified Larsen scores of radiographic damage were determined in a cross-sectional population of patients with established rheumatoid arthritis (n=946). Rheumatoid factor and anti-cyclic citrullinated antibody levels were assayed using nephelometry and ELISA respectively. The Kruskal-Wallis nonparametric test was used to compare median Larsen scores for each genotype, followed by Nonparametric Trend Test.

Results: Of the 10 risk loci, an allele-dose association with increased radiological damage was found for rs26232 ($P = 0.001$) in C5orf5, with the common genotype CC having the highest median modified Larsen score. Stratification by antibody status suggests that the association is strongest for in RF and anti-CCP positive RA ($P = 0.005$), however the number of antibody negative patients was relatively small.

Conclusions: The data indicates that rs26232 is strongly associated with severity of radiological joint damage in patients with rheumatoid arthritis. The SNP rs26232 is located at chromosome 5q21 within the intron of the predicted gene C5orf30 where no obvious biological candidate gene has been found. Similar to DRB1 and TNFAIP3 alleles, this marker is associated with both risk and severity of RA.

Disclosure: A. Kleszcz: None; **M. Teare:** None; **D. Moore:** None; **J. Worthington:** None; **A. Barton:** None; **G. Wilson:** None.

1757

Improvement of Serological Rheumatoid Arthritis Diagnostics by Autoantibody Profiling. Karsten Conrad[2], Dirk Roggenbuck[1] and Kirsten Lüthke[3]. [1]Generic Assays GmbH, Dahlewitz, Germany, Germany, [2]Institute of Immunology, Medical Faculty of the Technical University of Dresden, Germany, [3]Rheumatological Practice, Dresden, Germany, Germany

Appropriate treatment at a sufficiently early stage can have a favourable effect on progression and serious clinical complications of rheumatoid arthritis (RA). CCP antibodies are used as specific markers for RA but are detectable in less than 80%. Therefore, a multiparametric analysis of RA-associated autoantibodies (RA-AAB) may increase the diagnostic sensitivity.

Sera of 349 patients with definite rheumatoid arthritis (RA) and 535 patients with various diseases other than RA were tested for rheumatoid factors (IgM and IgA-RF) and antibodies to RA33 (HUMAN GmbH, Germany), CCP (GA Generic Assays GmbH, Germany), mutated citrullinated vimentin (MCV) (ORGENTEC Diagnostika GmbH, Germany), and citrullinated protein (CPA) (HUMAN GmbH, Germany). The diagnostic sensitivity and specificity as well as the receiver operating characteristics were analyzed for these autoantibodies. The cut-off values were determined, at which the diagnostic specificity reaches >98% (optimized cut-off). 76.8% of RA patients were positive for CCP antibodies. In 22 of the CCP antibody negative RA patients, at least one of the other RA-AAB could be found at the optimized cut-off. Hence, the diagnostic sensitivity for RA can be increased to 83.7% by parallel or sequential determination of RA-AAB without loss of diagnostic specificity.

In conclusion, the serological diagnosis of RA can be improved by varying cut-off values to increase diagnostic specificity of certain RA-AAB and by determination of RA-AAB profiles to increase diagnostic sensitivity. A further improvement depends on the discovery of novel RA-AAB with high specificity and high predictive values as well as on methodological aspects (e.g., multiplex analyses).

Disclosure: K. Conrad: None; **D. Roggenbuck:** Generic Assays GmbH, 2; **K. Lüthke:** None.

1758

In Patients with Rheumatoid Arthritis Who Are in a Low Disease Activity State or Remission, Does Lack of Fatigue Relate to Better Function and Damage Scores. George A. Wells[2], Tracy Li[1] and Maarten Boers[3]. [1]Bristol-Myers Squibb, Princeton, NJ, [2]Univ of Ottawa Faculty of Med, Ottawa, ON, Canada, [3]VU University Medical Center, Amsterdam, The Netherlands

Purpose: With current treatment options for patients with rheumatoid arthritis (RA), low disease activity (LDA) and remission are reasonable treatment goals. Most criteria for LDA and remission are based on physician-reported measures and traditional patient-reported outcomes (PRO). The Outcome Measures in Rheumatology (OMERACT) initiative has recently recommended fatigue be assessed in all clinical trials. The importance of fatigue in relation to response and disease activity criteria on function and damage scores needs to be evaluated. To evaluate the added affect of fatigue on function and radiography in patients with RA meeting response, LDA and remission criteria.

Methods: The active RA patients under study were from a 12-month,

randomized, double-blind, placebo controlled trial (AIM trial) comparing abatacept (n=433) to placebo (n=219) on a background of MTX. Assessments at 12 months included: function (HAQ), radiography (erosions, joint space narrowing, total), fatigue (100mm visual analog scale) and core set measures used to derive response (ACR20, ACR50, ACR70), LDA (DAS28<3.2, SDAI≤11, CDAI≤10) and remission (DAS28<2.6, SDAI≤3.3, CDAI≤2.8) criteria at 6 months. The following patient groups are of interest at 1 year: criteria not met (NC) and criteria met (C); and within the latter, those with high (>10; C-hiF) and low fatigue levels (≤10; C-loF). These 4 groups will be compared on their function and radiography.

Results: The results for function (HAQ) are given in the table. Except for SDAI remission criteria, the HAQ is significantly lower in the patients that met the criteria and fatigue was low (≤10) compared to patients that met the criteria and fatigue was high (>10). For NC vs C and for NC vs C-loF, p<0.0001 for all criteria. For radiography, there was no significant difference between low and high fatigue for patients meeting the criteria.

Table. HAQ-functional progression (mean ± SD)

Criteria	Criteria Not Met (NC)	Criteria Met (C)	Criteria Met + Fatigue > 10 (C-hiF)	Criteria Met + Fatigue ?10 (C-loF)	p-value C-loF vs C-hiF
ACR 20	1.50 ± 0.65 (n=154)	0.90 ± 0.66 (n=412)	1.05 ± 0.63 (n=307)	0.43 ± 0.45 (n=101)	<0.0001
ACR 50	1.36 ± 0.64 (n=315)	0.69 ± 0.59 (n=251)	0.86 ± 0.60 (n=165)	0.36 ± 0.38 (n=86)	<0.0001
ACR 70	1.23 ± 0.67 (n=429)	0.54 ± 0.52 (n=137)	0.74 ± 0.56 (n=70)	0.32 ± 0.37 (n=67)	<0.0001
DAS28 <2.6	1.14 ± 0.68 (n=496)	0.47 ± 0.49 (n=58)	0.65 ± 0.48 (n=28)	0.29 ± 0.44 (n=30)	0.0043
DAS28 <3.2	1.17 ± 0.68 (n=467)	0.53 ± 0.52 (n=87)	0.76 ± 0.54 (n=44)	0.29 ± 0.39 (n=43)	<0.0001
CDAI ?2.8	1.12 ± 0.68 (n=522)	0.38 ± 0.50 (n=44)	0.57 ± 0.60 (n=14)	0.28 ± 0.43 (n=30)	<0.0001
CDAI ?10	1.24 ± 0.67 (n=388)	0.68 ± 0.61 (n=178)	0.90 ± 0.62 (n=106)	0.36 ± 0.41 (n=72)	<0.0001
SDAI ?3.3	1.11 ± 0.68 (n=530)	0.38 ± 0.54 (n=36)	0.61 ± 0.64 (n=11)	0.27 ± 0.46 (n=25)	0.0756
SDAI ?11	1.23 ± 0.66 (n=392)	0.68 ± 0.62 (n=172)	0.90 ± 0.64 (n=103)	0.36 ± 0.41 (n=71)	<0.0001

Conclusions: For patients meeting various response and remission criteria, there is a significantly better function among patients with low fatigue, but no effect on radiography. As it relates to function, fatigue is an important factor to be considered in clinical practice and treatment evaluati

Disclosure: G. A. Wells: Bristol-Myers Squibb, 2; **T. Li:** Bristol-Myers Squibb, 1, 3; **M. Boers:** None.

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Is Exclusion of Joints of the Feet in a Disease Activity Index like DAS28 a Clinical Problem When Assessing the Individual RA Patient? M. F. Bakker[2], J. W. G. Jacobs[2], P. M. J. Welsing[1], F. P. J. G. Lafeber[2] and J. W. J. Bijlsma[2]. [1]Rheumatology & Clinical Immunology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands, [2]Rheumatology & Clinical Immunology, University Medical Center Utrecht, The Netherlands

Background: The disease activity of RA patients is often assessed with the DAS28, in clinical trials as well as in daily practice. However, the DAS28 has not been validated for use in individual patients and joints of feet are not included. The aim of this investigation was to study whether this last drawback could be a clinical problem.

Methods: Patients within the CAMERA trial were divided into 3 'damage progression' groups according to local radiographic progression rates: 1) primarily progression of the feet, 2) similar progression of hands and feet, and 3) primarily hand progression. This was done for radiographic progression within the first 2 years, between 2 and 5 years and from 0 until 5 years. Time-averaged DAS28, its individual components (TJC, SJC, ESR, and VAS-GH), and tender and swollen joints of feet were compared between the 3 groups within the first 2 time periods. The longitudinal relation of DAS28 with radiographic damage (total SHS score) over the 5 year period was investigated within the 3 'damage progression' groups with RF-status, baseline joint damage as well as the SJC and TJC of the feet as covariates using longitudinal regression analysis (mixed model analysis).

Results: After 2 and 5 years of treatment, respectively 145 (55%) and 66 (33%) patients had no radiographic progression, 30 (11%) and 33 (16%) primarily feet progression, 60 (23%) and 69 (35%) similar progression and 30 (11%) and 32 (16%) primarily hand progression. Over the first two years the primarily feet and hand progression groups (group 1 and 3) had a similar mean (SD) DAS28: 4.0 (1.0) vs. 3.9 (0.9), respectively. However, compared to the primarily hand group, the primarily feet group had more tender and swollen joints of the feet: 3.4 (2.2) vs. 1.5 (1.3), p<.001 and 2.8 (1.9) vs. 1.1 (1.2), p<.001, respectively. This statistically significant difference was not present in the 2 until 5 year period. In both time periods, the 'similar progression' group (group 2) had lower disease activity scores and involvement of the feet in between those of groups 1 and 3.

On group level there was a longitudinal relation between the DAS28 and radiographic progression. The 'damage progression' groups modified the relation between the DAS28 and radiographic progression, with the 'primarily foot progressors' (group 3) showing more (change in) radiographic progression with the same (change in the) DAS28 as compared to the other groups (interaction term DAS28*primarily foot progressors: β=1.2, 95%CI: 0.6–1.9, p<.001). In other words, in the 'primarily foot progressors' the disease activity when assessed by the DAS28 seems to be underestimated. In the primarily foot progressors the joint counts for the feet were also longitudinally related to radiographic progression.

Conclusions: In a subgroup of RA patients the DAS28 underestimates the total joints involved (especially during the first 2 years of the disease) and the expected joint damage. This could particularly be a problem in tight control, using the DAS28 remission or low disease activity definition. For follow-up of individual patients, assessment of all for RA relevant joints seems indicated.

References:

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1760

Level of Agreement of 1987 ACR and 2010 ACR/EULAR Classification Criteria: An Analysis Based on the ESPOIR Cohort Data. Bruno Fautrel[3], Nathalie Rincheval[4], Bernard G. Combe[1], Maxime Dougados[2] and ESPOIR Scientific Committee. [1]Hopital Lapeyronie, Montpellier, France, [2]Hospital Cochin, Paris, France, [3]Pitie Salpetriere Hospital, Paris, France, [4]UIRC Montpellier

New rheumatoid arthritis (RA) classification criteria have been developed conjointly by the ACR and EULAR in 2010 to replace the 1987 ACR ones. However, information is lacking to determine in what extent the "old" and "new" sets identify similar patients as having RA.

Objective: To assess the agreement between 1987 ACR and 2010 ACR/EULAR criteria and the source of potential disagreement of the 2 sets, based on the ESPOIR cohort data.

Patients and Methods: 813 patients with early arthritis (EA) were included into the cohort between 2002 and 2005 and followed every 6 months during the first 2 years. Inclusion criteria were: 18 to 70 years old; more than 2 swollen joints for more than 6 weeks and less than 6 months; with suspected RA diagnosis.

The agreement between the 2 criteria sets was based on Kappa coefficient calculation.

Results: Data on 811 patients were available with main characteristics as follows: female 77%; mean age 48 ±13 years; mean HAQ 1.0 ± 0.7; swollen joint count 7.2 ±5; tender joint count 8.4 ±7; DAS28 5.2 ±1.5; ESR 29 ±25 mm/1 hr; CRP 22 ±34 mg/L, IgM RF+ 47 %, anti-CCP+ 39 %; structural damage on X-ray 22 %. 579 (71.4%) patients met the 1987 ACR criteria and 641 (79.0 %) met the 2010 ACR/EULAR ones at baseline. 168 patients were discordant, 115 only satisfying the 2010 criteria and 53 only the 1987 ones. The concordance between the 2 sets was fair with a Kappa coefficient of 0.45 [95% CI: 0.38; 0.52]. Main sources of disagreement are indicated in the table below.

Patients meeting:	Both sets (n=526)	Only 2010 set (n=115)	Only 1987 set (n=53)
Tender joints, mean ± sd	10.4 ± 7.2	7.2 ± 6.2	3.8 ± 2.7
4 to 10 involved small joints, n(%)	91 (17.3)	31 (27.0)	38 (71.7)
≥ 10 involved joints, n (%)	421 (80.0)	61 (53.1)	1 (1.9)
Swollen joints, mean ± sd	9.1 ± 5.5	3.9 ± 3.2	5.2 ± 2.6
≥3 synovitis, n (%)	503 (95.6)	52 (45.2)	51 (96.2)
Symmetrical arthritis, n (%)	486 (92.4)	42 (36.5)	52 (98.1)
Morning stiffness ≥60 min, n (%)	497 (94.5)	74 (64.4)	53 (100)
RF +, n (%)	309 (58.7)	58 (50.4)	3 (5.7)
ACPA +, n (%)	274 (52.1)	39 (33.9)	2 (3.8)
RA diagnosis certainty at inclusion on a 0–10 VAS	7.9 ± 1.8	5.0 ± 2.4	6.2 ± 2.1
RA diagnosis certainty at 2 years on a 0–10 VAS	8.1 ± 2.7	6.3 ± 3.6	6.4 ± 3.5

The concordance of the 2010 set with the 1987 ACR criteria at 2 years was also tested since 1987 criteria perform better at that time point (Saraux et al. Arthritis Rheum 2001;44:2485). Kappa coefficient remained fair: 0.42 [95% CI: 0.33; 0.51].

Conclusion: 2010 criteria identify more patients than 1987 criteria as having RA. However, the 2010 set failed to identify as RA patients with symmetrical sero-negative arthritis with limited joint involvement.

Disclosure: B. Fautrel: None; **N. Rincheval:** None; **B. G. Combe:** None; **M. Dougados:** None; **ESPOIR Scientific Committee:** None.

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Levels of Soluble CD163 Is Associated with Disease Activity and Radiographic Progression in Early Rheumatoid Arthritis. Stinne R. Greisen[6], Malene Hvid[4], Kristian Stengaard-Pedersen[1], Merete L. Hetland[2], Kim Hørslev-Petersen[7], Holger J. Møller[3] and Bent Deleuran[5]. [1]Arhus University Hospital, Aarhus, Denmark, [2]Copenhagen Univ Hosp Hvidovre, Hvidovre, Denmark, [3]Department of Clinical Biochemistry, Aarhus University Hospital, Denmark, [4]Institute of Medical Microbiology and Immunology, University of Aarhus and Department of Dermato-venerology Aarhus University Hospital, Denmark, [5]Institute of Medical Microbiology and Immunology, University of Aarhus, and Aarhus University Hospital, Denmark, [6]Institute of Medical Microbiology and Immunology, University of Aarhus, Denmark, [7]King Christian X Hospital for Rheumatic Disease, University of Southern Denmark

Background: The macrophage is the predominant cell type in the cartilage-panus junction, and is strongly associated with joint destruction in rheumatoid arthritis (RA). Resident macrophages exclusively express the scavenger receptor CD163, which is also present in plasma and joint fluid in a soluble form (sCD163).

Objective: The aim was to investigate the degree of macrophage activity by the presence of solouble and cell surface CD163. Soluble CD163 was investigated for its association with core parameters for disease activity including radiographic progression in early RA, and cell surface CD163 was examined for its co-expression with the known monocyte/macrophage marker CD14.

Methods: In a longitudinal sample set of early RA patients (n=34) we measured plasma levels of sCD163 at baseline and after 9 months of treatment, and correlation levels with disease activity in 28 joints (DAS28), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and total Sharp score (TSS). In a transverse sample set of chronic (>8 years of disease) RA patients (n=24) we measured paired plasma and joint fluid levels of sCD163 by ELISA. We also examined the cellular expression of CD163 and CD14 by flow cytometry. Statistical correlations were assessed by Spearman's rho, and data are expressed as median with IQR in parenthesis.

Results: In early RA, patients had significantly higher plasma levels of sCD163 (1.69 mg/L (1.42–2.10)) at baseline, than after 9 months of treatment (1.28 mg/L (0.963–1.66) p=0.001). Plasma levels of sCD163 at baseline were strongly correlated with sCD163 at 9 months, (r2=0.672, p=0.00001). At baseline sCD163 correlated with DAS28, CRP and ESR. Interestingly sCD163 at 9 months, but not at baseline, was associated with radiographic progression (TSS) between year 2 and 3 (r2=0.468, p =0.02). Chronic RA patients had higher plasma levels of sCD163 than early RA patients (3.05 mg/L (1.84–6.04)), p<0.001). The levels in joint fluid were even higher (8.32 mg/L (6.04–10.65)) and correlated with sCD163 in plasma (r2=0.4, p=0.05).

Cell surface CD163 was almost exclusively detected on synovial macrophages, compared with cells in peripheral blood (p=0.02), and all CD163+ cells co-expressed CD14.

Conclusion: Plasma levels of sCD163 are associated with core parameters for disease activity and radiographic progression, and decreases significantly after 9 months of effective treatment. The observation that sCD163 in the synovial fluid correlates with plasma levels, and that CD163 is highly expressed by synovial macrophages, supports that resident macrophages are important for the joint destruction in early RA, and that plasma sCD163 reflects the macrophages population within the inflamed joint. This supports the role of sCD163 as a biomarker of disease activity and joint destruction.

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Liver Injury in Patients with Rheumatic Diseases and Inflammatory Syndrome: A Case-Control Prospective Analysis Using Biomarkers (FibroTest, ActiTest and SteatoTest). Cécile Gaujoux-Viala[2], Mathilde Benhamou[2], Mona Munteanu[1], Yen Ngo[1], Djamila Messous[1], Françoise Imbert-Bismut[1], Vlad Ratziu[1], Pierre Bourgeois[2], Thierry Poynard[1], Bruno Fautrel[2] and SAFE-T DILI-GHPS Study Group. [1]Paris 6–Pierre et Marie Curie University; Hepatology, Pitié-Salpêtrière Hospital, Paris, France, [2]Paris 6– Pierre et Marie Curie University; Rheumatology, Pitié-Salpêtrière Hospital, Paris, France

Background: Several drugs used in chronic rheumatic diseases (RHU) can induce liver damage. Few studies on consecutive cohorts are available because of the limitations of liver biopsy.

The aim was 1) to use validated biomarkers to evaluate the presence of fibrosis (Fibrotest), necroinflammatory activity (Actitest), and steatosis (Steatotest) and associated risk factors among RHU subjects hospitalized in a rheumatology department 2) to evaluate the impact of inflammatory syndrom estimated by C-reactive protein (CRP) on FibroTest parameters.

Methods: 211 prospective RHU were compared to 211 healthy controls without known liver disease (CTR), matched for age, gender, self-declared alcohol intake (SDA) and body mass index. Standard thresholds were: Fibrotest<0.27 for no/minimal fibrosis (METAVIR F0) and Fibrotest>0.48 for advanced fibrosis (AF, METAVIR>F2); Actitest<0.29 for no/minimal activity (METAVIR A0); Steatotest<0.38 for no steatosis.

Results: Among RHU (36.4% male, age 48 years, median [range] CRP 4g/L[4–72]), 96 had rheumatoid arthritis (RA), 57 ankylosing spondylitis (AS), 14 psoriatic arthritis (PsA) and 50 other diagnoses; 36.5% were treated with methotrexate (MTX), 22.7% with corticosteroids, 22.8% with non-steroid anti-inflammatory, 8.1% with infliximab (IFX), 29.4% with paracetamol. Median [range] number of treatments per subject was 3[0–11]. The mean (SE) SDA in PsA compared with others was 12g/d (7.7) vs. 5g/d (0.7) (p=0.02).

The prevalence of presumed lesions in RHU versus CTR in overall population and according to etiology was presented in the table.

	RHU	CTR	p
Fibrosis %	10.9	7.2	0.17
- RA	7.3	5.2	NS
- AS	8.8	5.3	NS
- PsA	21.4	7.1	NS
AF	2.4	0.1	0.025
Activity %	10.4	4.3	0.015
		OR=2.61 [1.17–5.82]	
- RA	11.5	3.1	0.026
		OR=4.012 [1.082–14.88]	
- AS	8.8	1.8	0.09
- PsA	21.4	14.3	NS
Steatosis%	38.5	30.2	0.048
		OR=1.44 [0.95–2.17]	
- RA	41.2	33.7	NS
- AS	30.2	34	NS
- PsA	64.3	28.6	0.058

Steatosis was more prevalent in patients treated with MTX or IFX than in CTR (40.3% vs 29.9%, p<0.0001; 52.9%vs17.6%, p=0.031 respectively). The prevalence of other lesions was not different according to treatment regimen.

CRP was not correlated [Spearman correlation coefficient (SCC)] with alpha2-macroglobulin (SCC= 0.01, p=0.89) and was correlated only with haptoglobin (SCC= 0.71, p<0.0001) without impact on FibroTest results (SCC=−0.07, p=0.36).

Conclusions: Compared with CTR, RHU had a higher prevalence of necroinflammatory activity and steatosis presumed with biomarkers. The subjects with RA had greater presumed activity, and subjects with PsA more frequent steatosis. The presumed steatosis was associated with treatments with MTX and IFX. Haptoglobin and not alpha2macroglobulin was correlated with inflammatory syndrom without impact on final FibroTest results.

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New 2010 ACR-EULAR Rheumatoid Arthritis Classification Criteria Are Highly Sensitive in Patients with Early Rheumatoid Arthritis. Sarang Chitale[2], Nicola J. Goodson[2], David W. Sharpley[2], Robert N. Thompson[1], Robert J. Moots[2] and Cristina Estrach[2]. [1]Academic Rheumatology Department, University Hospital Aintree, Liverpool, Merseyside, United Kingdom, [2]Academic Rheumatology Department, University of Liverpool, Liverpool, Merseyside, United Kingdom

Background: Rheumatoid Arthritis (RA) requires early recognition & treatment with disease modifying anti-rheumatic drugs (DMARD) to prevent erosive damage and long-term disability. Many patients with early RA (eRA) do not satisfy the 1987 ACR classification criteria [1] at initial presentation. Other revised criteria have been proposed to improve the identification of such patients [2].

ACR and EULAR have jointly formulated new RA classification criteria, to facilitate early recognition of patients likely to have persistent and progressive disease and require DMARD therapy [3].

Aims: To explore whether a cohort of patients with symptom duration ≥12 months, diagnosed with eRA (based on the opinion of the rheumatologist) and started on DMARDS, met ACR-EULAR criteria at the initial assessment.

And to compare the percentage of patients diagnosed with RA at baseline by using 4 sets of criteria [1–3].

Methods: Baseline data on patients with eRA attending between May 2006 and March 2010 were examined & included symptom duration, joint involvement (small & large), symmetry, early morning stiffness in minutes, swollen and tender joint counts out of 44 joints, radiographic changes, anti-CCP & rheumatoid factor (RF) status and titre and ESR & CRP at initial presentation. All patients had at least 1 clinically swollen joint at baseline.

1987 ACR criteria, ACR tree criteria [1], anti-CCP revised criteria and the new ACR-EULAR 2010 RA classification criteria were applied. A score of ≥6 out of 10 by the ACR-EULAR criteria equals definite RA. Analysis was repeated for patients presenting with very early RA (veRA: defined as symptom duration ≤3 months).

Results: 208 patients with eRA were identified, with mean age 58.7 years (SD 15.7 years) and median symptom duration of 16 weeks, IQR [9.5, 28 weeks]. 130 (62.5 %) were female, 123 (59%) tested positive for both RF & anti-CCP and 28 (13%) had radiographic erosive disease at baseline. 91 (44%) presented with veRA.

171 (82%) with eRA & 74 (81%) with veRA had definite RA by the ACR-EULAR RA classification criteria. Proportion of eRA & veRA patients satisfying each of the four sets of RA classification criteria at their initial rheumatology assessment is shown in Table 1.

Table 1. Number of eRA & veRA patients satisfying RA criteria at baseline rheumatology assessment

	eRA patients n=208		veRA patients n=91	
	n	%	n	%
ACR 1987 criteria	121	58	48	53
ACR Tree format	142	68	61	67
Anti-CCP revised criteria (CCP-6)	166	80	68	74
ACR-EULAR Definite RA (≥6 points)	171	82	74	81

Conclusion: This study demonstrates that the ACR-EULAR criteria are more sensitive for identifying RA at the initial rheumatology assessment than the other RA and eRA classification criteria in this EAC cohort.

This difference was most marked in those patients presenting with veRA, with the highest sensitivity for ACR-EULAR criteria. Applying these criteria in the EAC setting should facilitate more rapid initiation of DMARD therapy and has the potential to improve long-term outcomes for RA patients.

References:

1. Arnett FC et. al. Arthritis & Rheum 1988;31(3):31–4.
2. Liao KP, et al. Ann Rheum Dis 2008; 67: 155–1.
3. Aletaha et. al ACR-EULAR 2010 classification criteria. Submitted for publication

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Novel Multiplex Technology for Diagnostic Characterization of Rheumatoid Arthritis. Piyanka E. Chandra[4], Jeremy Sokolove[3], Berthold G. Hipp[1], Heike Eberl[1], Ursula Klause[1] and William Robinson[2]. [1]Roche Diagnostics, [2]Stanford Univ School of Med, Stanford, CA, [3]Stanford University, Mountain View, CA, [4]Stanford University

Purpose: To develop a clinical-grade, automated, multiplex system for the diagnosis and molecular stratification of rheumatoid arthritis (RA).

Methods: We profiled autoantibodies, cytokines, and bone-turnover products in sera from 120 patients with a diagnosis of RA of <6 months' duration, as well as in sera from 27 patients with ankylosing spondylitis, 28 patients with psoriatic arthritis, and 25 healthy individuals. We used a bead-based commercial assay to measure cytokine levels, and developed an array-based assay using a novel multiplex technology research platform (Immunological Multi-Parameter Chip Technology) to evaluate autoantibody reactivities and bone-turnover markers. Positive values were defined as 2 standard deviations above that of healthy controls. Data were analyzed by Significance Analysis of Microarrays and hierarchical clustering software. Prediction rules were generated

Results: We developed a highly reproducible, automated, multiplex biomarker assay that can reliably distinguish between RA patients and healthy individuals or patients with other inflammatory arthritides. Multiplex measurement of a subset of the differentiating biomarkers provided high sensitivity and specificity for the diagnostic discrimination of RA. Identification of distinct biomarker signatures enabled molecular stratification of early-stage RA into clinically relevant subtypes.

Conclusions: The multiplex biomarker assay described herein has the potential to diagnose RA with greater sensitivity and specificity than do current clinical tests. Its ability to stratify RA patients in an automated and reproducible manner paves the way for the development of assays that can guide RA therapy.

Table 1. Performance characteristics of multiplex-assay autoantibody profiles in the diagnosis of rheumatoid arthritis.

Biomarker panel	PPV	NPV	Sensitivity	Specificity
1+ markers	79.5%	92.6%	96.7%	62.5%
2+ markers	91.8%	89.7%	93.3%	87.5%
3+ markers	95.3%	79.8%	84.2%	93.8%
4+ markers	95.9%	61.1%	59.2%	96.3%

Biomarker panel includes: Histone 2B/e (1–20), Vimentin (58–77) (Cit 64, 69, 71), FibrinogenA (616–635) (Cit 621, 627, 630), COMP (453–472), Profilaggrin (293–310) {Cit 301, 305}, RF-IgA.

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Patient Questionnaire Scores for Physical Function and Pain Are More Likely Than Erythrocyte Sedimentation Rate (ESR) To Document a Quantitative Abnormality in New Patients with Rheumatoid Arthritis (RA). Theodore Pincus[1] and Christopher J. Swearingen[2]. [1]New York University Hospital for Joint Disease, Hastings-on-Hudson, NY, [2]University of Arkansas for Medical Sciences, Little Rock, AR

Purpose: To analyze the capacity of 3 quantitative measures—erythrocyte sedimentation rate (ESR), physical function on a multidimensional health assessment questionnaire (MDHAQ-FN) and pain (PAIN) on a 0–10 visual analog scale (VAS)—to document an abnormality at presentation of 413 new patients with RA seen between 1982 and 2006, by comparing the proportions with normal versus abnormal results.

Methods: All new patients seen at a weekly academic rheumatology clinic complete an MDHAQ with scores for MDHAQ-FN and PAIN. Patients with RA also had assessment of ESR. Complete data for ESR, MDHAQ-FN and PAIN scores were available for 413 new patients with RA seen between 1982 and 2006. Abnormal values were ESR ≥28 mm/h (clinical trial inclusion criterion), MDHAQ-FN >2 on a 0–10 scale (>0.6 on a 0–3 scale), and PAIN >2 on a 0–10 VAS. The proportions of patients with abnormal and normal values at presentation were compared, using descriptive statistics.

Results: Of the 413 patients, 192 (46%) had normal ESR <28 mm/h (54% had ESR ≥28), 122 (30%) had normal MDHAQ-FN scores ≤2 (70% had MDHAQ-FN >2), and 44 (11%) had normal PAIN scores ≤2 (89% had PAIN >2). Patients with ESR <28 were more likely to have MDHAQ-FN or

PAIN score ≤2. Nonetheless, among the 192 patients with a normal ESR of <28, 112 (58%) had an abnormal MDHAQ-FN score of >2, and 161 (84%) had an abnormal PAIN score of >2. A normal score for MDHAQ-FN, PAIN, and ESR was seen in only 26 patients, 14% of those with ESR <28, and 6% of all patients.

	Number (%) normal*	Number (%) abnormal*	Number (%) of normal ESR with abnormal MDHAQ scores**
ESR (< vs ≥28 mm/h)	192 (46%)	221 (54%)	NA
MDHAQ-FN (≤2 vs >2)	122 (30%)	291 (70%)	112 (58%)
PAIN (≤2 vs >2)	44 (11%)	369 (89%)	161 (84%)

*Percentage of all 413 patients. **Percentage of 192 patients with ESR <28 mm/h.

Conclusion: Among new patients with RA, 54% had an abnormal ESR, while 94% had at least one of 3 abnormal measures: ESR, MDHAQ-FN or PAIN. Patient self-report questionnaire scores for physical function and pain are more likely than ESR to document an abnormality in patients with RA at presentation. An abnormal quantitative baseline measure is desirable to assess changes over time. Scores for physical function and pain can be collected easily in the infrastructure of usual clinical care to improve quality and document quantitatively responses to therapies.

Disclosure: T. Pincus: None; **C. J. Swearingen:** None.

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Preliminary Rheumatoid Arthritis (RA) Flare Assessment for Randomized Clinical Trials (RCTs): An Outcome Measures in Rheumatology (OMERACT) Data-Driven, Patient-Centered, and Consensus-Based Initiative. Clifton O. Bingham[3], Ernest Choy[4], Rieke Alten[6], Maarten Boers[11], Peter Brooks[9], Vivian Bykerk[1], Robin Christensen[5], Dan Furst[8], Sarah Hewlett[10], Amye Leong[2], James May, Christof Pohl[6], Tessa Sanderson[10], Vibeke Strand[7] and Thasia Woodworth. [1]Brigham and Women's, [2]Healthy Motivation, [3]Johns Hopkins University, Baltimore, MD, [4]King's College, [5]Parker Institute: Musculoskeletal Statistics Unit Copenhagen University Hospital, [6]Schlosspark Klinik University Charite, [7]Stanford University, [8]UCLA, [9]University of Queensland, [10]University of the West of England, [11]Vu University Medical Center

Background: There is no established definition of flare in RA, a potentially disabling disease feature that can impair function, confidence, and productivity. Patients (pts) use "flare" to describe episodes of disease worsening, but the magnitude, quality and duration of symptoms leading to a change of therapy have not been studied. Our objective was to establish a framework for the assessment of RA flare in RCTs which could serve to develop new efficacy parameters and/or facilitate tapering strategies and tight disease control.

Methods: An international multidisciplinary group of health care providers (HCPs), outcomes researchers, and pts established that RA flare would be anchored by worsening or return of disease activity of sufficient duration and intensity to result in (re)initiation or/and change of therapy. Qualitative research in RA pts utilizing detailed thematic analysis identified potential relevant domains. Additional candidate domains were obtained from literature search, face-to-face meetings, teleconferences, and stakeholder survey. Parallel HCP and pt research partner Delphi exercises identified and ranked potential domains as essential, important, or not important. To evaluate measurement properties of these items, standardized response means (SRMs) were derived from LOS and RCT databases. At the OMERACT 10 conference approximately 120 HCPs and pt experts participated in data review, in depth discussions, and consensus voting regarding domains to detect and measure flare. In consensus voting analysis, "don't know" responses were imputed conservatively as "no", and descriptive statistics used for reporting.

Results: HCPs and researchers (>100) and 78 pts identified >20 potential domains and participated in online Delphi exercises prior to OMERACT10 with strong agreement regarding importance of pain, function, patient global assessment (PtGA), swollen joints (SJC) and tender joints (TJC) (core domains). Analyses of LOS and RCT showed that instruments assessing most potential domains are available and moderately sensitive to change. There was >90% agreement that the above core domains and investigator global assessment (MDGA) should be included in a preliminary flare core set. Respondents also identified fatigue (80%), stiffness (70%), and laboratory features (eg ESR/CRP, 66%) as domains of potential importance. 75% affirmed the importance of symptom persistence, and 74% that pt self report of flare should be measured. Other important areas included systemic features (60%), participation (57%), and self-management (58%).

Conclusions: Developing a common set of items to prospectively capture RA flare in RCTs is needed. Qualitative research and stakeholder consensus identified the existing RA core set of SJC, TJC, pain, function, PtGA, MDGA, and acute phase response to define RA flare. In addition, fatigue and stiffness were identified as requisite domains and systemic features, participation, and self-management as desirable to include. A preliminary flare assessment tool will be incorporated in upcoming RCTs and LOS for refinement and validation. Ongoing data analysis and a third Delphi will inform a final consensus based definition.

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Preliminary Validation for the Short Version of the Valued Life Activities Questionnaire (S-VLA). Afton L. Hassett[5], Diane C. Radvanski[3], Anagha Nadkarni[1], Steven Buyske[2], Sam A. Schiff[3], Moti L. Tiku[3] and Patricia P. Katz[4]. [1]Bristol-Myers Squibb Co, Princeton, NJ, [2]Rutgers University, New Brunswick, NJ, [3]UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, [4]University of California, San Francisco, CA, [5]University of Michigan Medical School, Ann Arbor, MI

Background: Individuals with rheumatoid arthritis (RA) often experience a decreased ability to participate in valued life activities, such as working, traveling, gardening and attending social events. Many will make accommodations in order to continue participating in these activities. Such accommodations may be associated with the progression of disability in RA. To assess this important domain, including the need for accommodations, a short form of the Valued Life Activities Questionnaire (VLA) was developed and its initial reliability and validity demonstrated using item response analysis[1]. The short form of the VLA (S-VLA) is a 14-item self-report questionnaire with scores that range from 0 to 4, with higher scores indicating greater disability. A large validation trial is currently underway to evaluate the psychometric properties of the S-VLA for patients with RA. The results from the first 100 participants are reported here.

Methods: In the S-VLA validation trial, patients meeting ACR criteria for RA completed a series of questionnaires, including the S-VLA, Rheumatoid Arthritis Disease Activity Index (RADAI), Health Assessment Questionnaire-Disability (HAQ-D), Short Form-36 (SF-36) Health Survey, Satisfaction with Activities and Well-being Scale (SAWS) and the Activity Participation Questionnaire (APaQ). Data from the first 100 patients were analyzed using Cronbach's alpha for internal consistency reliability. Test–retest reliability was also calculated for a randomly selected subset of patients. Next, item statistics were calculated to assess the correlations between individual items and the total score on the S-VLA, while also correcting for overlap and scale reliability. Lastly, correlations between the S-VLA and the other measures were used to evaluate convergent and discriminant validity.

Results: 100 of 150 patients have been enrolled. Mean (standard deviation) age was 55.01 (14.8) years, duration of RA was 12.5 (10.0) years and 71.0% were female. Test–retest reliability was 0.92 based on the responses of a random subset of 25 patients. Cronbach's alpha for the S-VLA was 0.93, and none of the 14 items were associated with improved alpha coefficients when omitted. All items were strongly correlated with the S-VLA total score. Item-total correlations ranged from 0.59 to 0.79. As anticipated, the total score for the S-VLA was highly positively correlated with patient-reported disease activity (RADAI [$r=0.71$; $p\leq0.001$], the HAQ-D [$r=0.77$; $p\leq0.001$], SAWS total score [$r=0.77$; $p\leq0.001$], SAWS satisfaction with abilities subscale [$r=0.77$; $p\leq0.001$] and APaQ days with activity limitations [$r=0.61$; $p\leq0.001$]). As hypothesized, the S-VLA was significantly inversely correlated with SF-36 Physical Component Summary score ($r=-0.76$; $p\leq0.001$) and the SF-36 subscales: Physical Functioning ($r=-0.75$; $p\leq0.001$), Role Physical ($r=-0.68$; $p\leq0.001$) and Social Functioning ($r=-0.71$; $p\leq0.001$).

Conclusions: The S-VLA is a new instrument for the measurement of valued life activities in RA. Data from the initial cohort of 100 patients from the larger validation trial lend support to its reliability and validity.

Reference:
[1]Katz P, et al. *Arthritis Rheum* 2009;**60:**S421

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Presence and Predictors of Poor Functional Outcomes in US Hispanics with Rheumatoid Arthritis (RA). George A. Karpouzas[4], Soha Dolatabadi[1], Rosalinda C. Moran[3], Perry Nicassio[5] and Michael H. Weisman[2]. [1]Cedars Sinai, Los Angeles, CA, [2]Cedars-Sinai Medical Center, Los Angeles, CA, [3]Harbor UCLA, Carson, CA, [4]Harbor-UCLA, Long Beach, CA, [5]UCLA

Background: Functional outcomes of Hispanics (H) with RA in the US have been under-reported and their predictors remain largely unknown. Prior works suggest worse function, pain, and global assessment scores in H despite a seemingly appropriate control of disease measures. We address self-reported outcomes, their relationships and determinants in a recently established cohort of H with RA from a single center in the US.

Methods: We describe the first 193 of 349 H fullfiling 1987 ACR criteria for RA and with regular follow-up. Demographic, serologic (RF, a-cyclic citrullinated peptide Ab-ACPA), radiographic parameters and treatments were recorded. Irreversible articular damage (IAD: ankylosis, sublaxation, arthrodesis, prosthesis) and joint replacement surgeries (JRS) were tracked. Patients (pts) were evaluated quarterly and Disease Activity Score (DAS2–v-ESR), disability (HAQ-DI), pt-reported pain by visual analogue scale (pain-VAS: 0–3), and depression scores (PHQ-9 scales) were collected. Exploratory linear regressions with forward selection were performed followed by hierarchical multivariate regression to identify independent predictors of disability as reported by HAQ-DI. Data was analyzed with STATA 10.

Results: Median (IQR) DAS28 was 3.28 (2.5–4.1) and low disease activity (DAS28≤3.2-LDAS) was present in 46%. RF was seen in 93% and ACPA in 85%. Overall, 51% had HAQ-DI≥1.5 and 67% ≥1. In the LDAS group in particular, 42% had HAQ-DI≥1.5 and 58% had DI≥1. Generally, 36% of pts had PHQ-9≥10, consistent with clinical depression. Pain-VAS, JRS, disease activity, depression, age and IAD were univariate determinants of disability (table). RF or ACPA status, erosions, biologics and number of DMARDs did not predict disability. In a multivariate model, pain-VAS was the most robust predictor of disability (standardized regression coefficient =0.4), followed by DAS28 (0.22), JR (0.21), depression (0.17) and age (0.12).

Conclusion: The majority of H report poor functional outcomes and high level of disability despite well controlled disease by physician standards. Pt-reported pain is the cardinal independent predictor of this disability, followed by disease activity, JR, and depression. The directionality for these relationships is being explored with a focus on future intervention.

Table. Determinants of disability

			univariate		multivariate
categorical	**b**	**SE**	***p***	**R^2**	***p***
Female	0.42	0.18	*0.02*	0.03	
Prednisone	0.3	0.12	*0.01*	0.03	
IAD	0.48	0.11	*3.5E-05*	0.09	
JR	0.88	0.16	*2.8E-07*	0.13	0.007
Fibromyalgia	0.43	0.17	*0.01*	0.04	
continuous					
Age	0.02	0.005	*2E-05*	0.09	0.06
duration	0.017	0.006	*0.008*	0.04	
DAS28-3v	0.2	0.04	*5.8E-06*	0.1	0.007
ESR	0.005	0.003	*0.04*	0.02	
CRP	0.09	0.04	*0.03*	0.03	
Pain-VAS	0.57	0.07	*0*	0.32	<0.001
PHQ-9	0.05	0.01	2.1E-06	0.17	0.03

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Progression Patterns of Radiographic Damage: Results from SONORA Study. Maggie Chen[1], Xiuying Li[1], Pooneh Akhavan[2] and Claire Bombardier[3]. [1]University Health Network, [2]University of Toronto, University Health Network, [3]University of Toronto, University Health Network, Mount Sinai Hospital, Toronto, ON, Canada

Purpose: Identifying progression patterns and its characteristics for radiographic damage is important to understand early rheumatoid arthritis (RA). Data from the SONORA (study of new-onset rheumatoid arthritis) was analyzed to explore patterns of radiographic progression in early RA patients.

Methods: A total of 529 patients diagnosed as early RA (symptoms ≥3 and ≤12 months) and with hand radiographs at baseline, year 1 and 2 were included in this study. The radiographs were scored according to original Sharp method (range 0 to 280) in random order per patient. Radiographic progression was defined by a change of at least 3.5 in total Sharp score within a year. Four patterns of radiographic progression were identified; never progressed, progressed at year 1 only, progressed at year 2 only and progressed at both year 1 and year 2. Demographic and clinical characteristics were compared across these four patterns using ANOVA for continuous outcomes and Chi-square test for categorical outcomes.

Results: Among these four patterns, 86% subjects never had radiographic progression, 3.4% progressed in the first year only, 7.6% progressed in the second year only and 2.6% progressed in both year 1 and year 2 (table 1). There were significant differences ($p < 0.05$) between the patients in the four patterns of progression, for, sharp score, CRP, anti-CCP and RF positive. Subjects who had no radiographic progression in two years were those who are younger, had less swollen joint counts, lower DAS score, lower sharp score, lower CRP, anti-CCP negative and RF negative at baseline.

Table 1.

	No progression N=457	Progression at year 2 only N=18	Progression at year 1 only N=40	Progression at year 1 and 2 N=14	P-value
Age	52 (13.79)	60 (14.45)	53 (14.15)	57 (18.33)	0.05
Baseline swollen joint count	4.89 (6.09)	2.61 (3.32)	6.75 (7.40)	8.29 (6.66)	0.02
Baseline tender joint count	4.88 (6.38)	3.89 (5.32)	5.90 (7.17)	6.35 (6.50)	0.55
Baseline DAS	3.85 (1.34)	3.64 (1.14)	4.17 (1.18)	4.63 (1.06)	0.03
Baseline HAQ	1.38 (0.74)	0.83 (0.66)	1.46 (0.83)	1.36 (0.47)	0.06
Baseline Sharp score	4.06 (5.57)	9.33 (11.17)	8.28 (8.47)	14.0 (19.97)	<0.0001
Baseline CRP	2.70 (3.17)	4.3 (3.69)	3.91 (3.94)	4.36 (3.70)	0.009
Disease duration (days)	160 (123)	124 (82)	146 (93)	148 (82)	0.55
Anti-CCP positive	49.72%	61.54%	80.77%	81.82%	0.0003
Male	23.41%	11.11%	32.50%	21.43%	0.57
Rheumatoid factor positive	58.72%	66.67%	70%	78.57%	0.04
Ever smoking	57.74%	41.18%	58.82%	50%	0.57

Conclusion: The majority of the early RA subjects in routine practice do not have radiographic progression within the first two years of the disease. Very few subjects continuously progressed within 2-year period. Baseline sharp score is the best indicator of whether the subject will progress or not followed by anti-CCP positive, CRP and swollen joint count. These identified indicators can help clinicians to identify the subjects who are at high risk of continuous radiographic progression.

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Quantification of Periarticular Osteopenia in Rheumatoid Arthritis. Inhye E. Ahn[3], Ji Hyeon Ju[1], Kwi Young Kang[2], Seung-Ki Kwok[1], Kyung-su Park[1], Sung-Hwan Park[1] and Ho-Youn Kim[1]. [1]Department of Internal Medicine, Division of Rheumatology, Catholic University of Korea, Seoul, Korea, Republic of, [2]Department of Internal Medicine, Division of Rheumatology, Chungbuk University, Cheongju, Korea, Republic of, [3]Department of Internal Medicine, The Methodist Hospital, Houston, TX

Objectives: By quantifying localized hand bone mineral density (BMD), we aimed to validate a new diagnostic method for evaluating the periarticular bone damage in rheumatoid arthritis (RA).

Methods: The study enrolled 195 patients with polyarthritis and was conducted in three steps.

Table 1. Clinical and demographic features of patients and controls.

	RA	Non-RA	P^a
N (total=195)	*45*	*150*	
Sex (female/male)	40/5	113/37	0.881
Age (years), mean (SD)	47.98 (16.36)	48.24 (15.69)	<0.05
BMI (kg/m^2)	22.06 (3.93)	23.94 (3.28)	0.262
L-spine T-score	−1.22 (1.23)	−0.80 (1.39)	0.415
L-spine Z-score	−0.23 (0.93)	0.02 (1.23)	0.099
Medications			
Corticosteroids	86.67%	28.67%	
Duration of corticosteroids treatment (years)	4.36 (5.42)	3.48 (3.79)	
Biphosphonate	28.89%	17.33%	
Calcium and/or Vitamin D supplements	60.00%	42.67%	
Morbidities & Comorbidities			
Ostearthritis	3	59	
Crystal-induced arthropathy (eg. Gout)	0	4	
Systemic Lupus Erythematosus	1	14	
Sjogren's disease	0	10	
Dermatomyositis/Polymyositis	1	6	
Ankylosing Spondylitis	1	39	
Behcet's disease	0	9	
Others		2 Systemic sclerosis 1 Raymonds disease 1 Stills disease 5 Unspecified	

Abbreviations: SD: standard deviation. BMI: body mass index
[a] Mann-Whitney rank sum test for unpaired differences p under 0.05 was considered statistically significant.

First, inter-observer agreement of periarticular osteopenia in the conventional hand x-ray was evaluated. Second, BMDs of periarticular and non-periarticular regions were quantified by digital x-ray radiogrammetry (DXR). BMD ratios were calculated out of eight designated areas on proximal phalanges and compared between RA (n=45) versus non-RA (n=149) groups. Third, medical records of RA patients were retrospectively reviewed to identify clinical conditions predisposing to the loss of juxta-articular bone minerals.

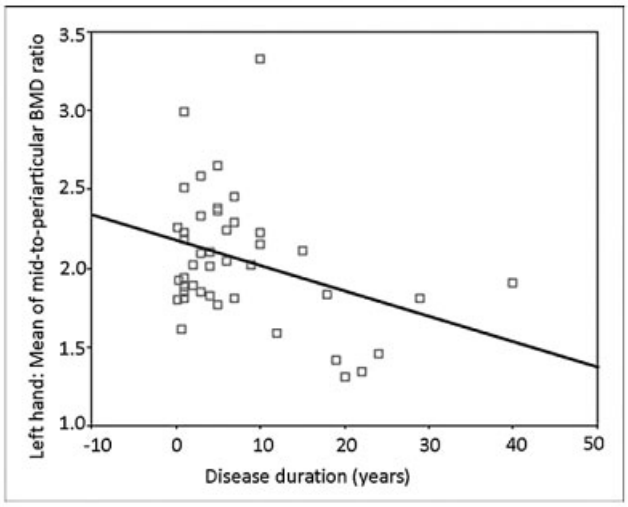
Results: The interpretation of periarticular osteopenia on x-ray reached a moderate degree of inter-observer agreement among four physicians (kappa 0.47, $p<0.001$). On DXR-assisted BMD quantification, we designed three types of mathematical formulae; the ratio of non-periarticular to periarticular BMD, the mean of ratios, and the ratio of sums.

Table 2. Periarticular osteopenia in RA versus non-RA patients

	Non-RA	Total RA		RA<10Y		RA≥10Y	
	mean (SD)	mean (SD)	*p*	mean (SD)	*p*	mean (SD)	*p*
N (total=195)	*150*	*45*		*31*		*12*	
Digits of left hand							
Index: L1′/L1	1.85 (0.27)	1.98 (0.47)*	0.018	2.10 (0.24)*	<0.01	1.65 (0.44)*	0.028
Middle: L2′/L2	1.90 (0.33)	1.97 (0.38)	0.249	2.07 (0.35)*	0.012	1.72 (0.37)	0.079
Ring: L3′/L3	2.03 (0.35)	2.17 (0.58)*	0.041	2.25 (0.48)*	<0.01	2.03 (0.78)	0.949
Small: L4′/L4	1.91 (0.37)	2.06 (0.58)*	0.031	2.07 (0.40)	0.058	2.09 (0.92)	0.144
Digits of right hand							
Index: R1′/R1	1.84 (0.31)	1.93 (0.50)	0.119	2.04 (0.46)*	<0.01	1.66 (0.53)	0.099
Middle: R2′/R2	1.85 (0.30)	1.96 (0.44)	0.051	2.05 (0.40)*	<0.01	1.64 (0.37)*	0.034
Ring: R3′/R3	2.00 (0.33)	2.08 (0.40)	0.227	2.19 (0.31)*	<0.01	1.87 (0.48)	0.187
Small: R4′/R4	1.94 (0.36)	2.04 (0.52)	0.221	2.04 (0.49)	0.200	2.08 (0.64)	0.233
Formulae							
Left: mean of mid-to-peri BMD ratio	1.92 (0.25)	2.05 (0.40)*	0.012	2.12 (0.31)*	<0.01	1.87 (0.56)	0.589
Right: mean of mid-to-peri BMD ratio	1.91 (0.26)	2.01 (0.35)	0.085	2.08 (0.28)*	<0.01	1.81 (0.44)	0.267
Both: mean of mid-to-peri BMD ratio	1.91 (0.24)	2.03 (0.35)*	0.015	2.10 (0.26)*	<0.01	1.84 (0.47)	0.379
Left: sum of mid BMD/sum of peri BMD	1.90 (0.25)	2.01 (0.38)*	0.033	2.09 (0.30)*	<0.01	1.79 (0.48)	0.182
Right: sum of mid BMD/sum of peri BMD	1.89 (0.26)	1.97 (0.35)	0.088	2.05 (0.29)*	<0.01	1.76 (0.43)	0.132
Both: sum of mid BMD/sum of peri BMD	1.89 (0.24)	1.98 (0.34)	0.058	2.06 (0.26)*	<0.01	1.77 (0.43)	0.107

[a]Independent t-test to compare means of non-RA patients versus one of the three groups; all RA patients, RA under 10 years, RA for and over 10 years.
An asterisk (*) indicates a statistically significant difference with p value under 0.05 when compared to the non-RA group. Other unlabled values were not significant. Values are the mean (SD) in g/cm^2.

These values were significantly higher in patients with RA for less than 10 years than in non-RA group ($p<0.05$). RA for 10 years or longer blunted the BMD ratios, and the disease duration was inversely correlated to the ratio (correlation coefficient −0.35).



Cut-off values were within 2.10–2.15 (sensitivity 36.67–80.64%, specificity 52.17–86.42%). In bivariate analysis, body mass index, the duration of steroids and c-telopeptide showed correlation with BMD ratios ($p<0.05$).

Conclusion: In DXR-assisted localized quantification and proportional calculation, periarticular osteopenia is a distinctive feature of RA under 10 years of duration.

Clinical Trial Registration Number: KC09OISI0258

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1771

Radiological Progression in Very Early Rheumatoid Arthritis, Results of the DREAM Remission Induction Cohort. Marloes Vermeer[3], Ina H. Kuper[3], Monique Hoekstra[1], Hein J. Bernelot Moens[4], Piet L. C. M. van Riel[2] and Mart A. F. J. van de Laar[3]. [1]Isala Klinieken, Zwolle, The Netherlands, [2]Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, [3]University of Twente and Medisch Spectrum Twente, Enschede, The Netherlands, [4]Ziekenhuisgroep Twente, Almelo/Hengelo, The Netherlands

Background: Previous studies suggest that disease activity at baseline and even stronger disease activity over time are related to radiological progression in rheumatoid arthritis (RA) (1, 2). This emphasizes the importance of controlling inflammatory activity and inducing remission rapidly. The objective of this study was to assess the relationship between disease activity and radiographic progression after 1 year in a remission induction cohort of patients with very early RA.

Methods: Data of the Dutch Rheumatoid Arthritis Monitoring (DREAM) remission induction cohort were used. Inclusion criteria were: a clinical diagnosis of RA, age ≥ 18 years, duration of symptoms ≤ 1 year and no previous treatment with DMARDs and/or prednisolone. DMARD medication was adjusted based on 4–8 weekly DAS28 measurements, aiming at remission (DAS28 < 2.6). The treatment protocol started with methotrexate (MTX), addition of sulfasalazine in case of inefficacy, followed by MTX + anti-TNF. Radiographs of hands and feet were obtained at baseline, after 6 and 12 months and evaluated in chronological order by two observers (consensus score) according to the Sharp-van der Heijde Score (SHS). An increase in SHS ≥ 5 U/year was regarded as clinically relevant radiological progression (3). Primary outcome was the association of the area under the curve (AUC) of the DAS28 (0, 3, 6, 9 and 12 months) and radiological progression after one year. This was analyzed in a logistic regression model with correction for confounders, in case of missing values the principle of last observation carried forward was applied. Secondary outcome was the percentage of patients without radiological progression after one year.

Results: One year radiological data were available for 143 patients. After one year, observed DAS28 levels were: 61.5% (88/143) remission (DAS28 < 2.6), 16.1% (23/143) low (2.6 ≥ DAS28 ≤ 3.2), 19.6% (28/143) moderate (3.2 < DAS28 ≤ 5.1) and 2.8% (4/143) high (DAS28 > 5.1). Median (IQR) SHS was 5.0 (2.0–10.0) and median (IQR) progression of SHS was 2.0 (1.0–5.0). Hundred of the 143 patients did not show radiological progression (69.9%). In the remission group, there were more patients without radiological progression than in the group with active disease (DAS28 > 3.2): 72.7%

(64/88) vs. 59.4% (19/32). The majority of patients achieved remission on conventional DMARD therapy. A higher AUC of DAS28 over the first year was associated with radiological progression (p=0.054, corrected for baseline SHS).

Conclusion: In very early RA, disease activity over time is associated with radiological progression. In this very early RA cohort, radiological progression was limited. Patients in remission showed less radiological progression than patients with persistent disease activity.

References:

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2. Welsing et al. Arthritis Rheum. 2004;50(7):208–93.
3. Bruynesteyn et al. J Rheumatol. 2001;28(4):904–10.

Disclosure: M. Vermeer: None; **I. H. Kuper:** None; **M. Hoekstra:** None; **H. J. Bernelot Moens:** None; **P. L. C. M. van Riel:** None; **M. A. F. J. van de Laar:** None.

1772

Retinal Vascular Caliber Is Altered in Patients with Rheumatoid Arthritis: A Biomarker of Disease Activity and Cardiovascular Risk? Sharon Van Doornum[3], Gemma Strickland[2], Ryo Kawasaki[3], Jing Xie[3], Lauren Hodgson[3], Ian Wicks[1] and Tien Wong[3]. [1]Royal Melbourne Hospital, Melbourne, Australia, [2]Royal Melbourne Hospital, [3]University of Melbourne

Introduction: Examination of the retinal vasculature is a novel method for assessing cardiovascular (CV) risk. Changes in retinal vascular caliber (narrowing of arteriolar caliber and/or widening of venular caliber) have been independently associated with CV risk factors and also with an increased risk of CV events. Retinal venular dilatation has also been associated with elevated biomarkers of inflammation.

Methods: 51 RA patients and 51 age and gender matched population controls had retinal photographs taken according to a standardized protocol. The digital images of all subjects were analysed by a single trained assessor using a validated computer program. The caliber of arterioles and venules were summarised as central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) respectively. Disease activity in RA patients was classified according to the 28 joint Disease Activity Score (DAS).

Results: Demographic characteristics and mean CRVE and CRAE of the RA patients and controls are shown in

Table 1. Demographic and clinical details and retinal vascular caliber measurements in RA and control patients

	RA (n=51)	Controls (n=51)	p value
Female	34 (67)	34 (67)	NS
Age (years)	59.5 ± 12.5	59.5 ± 12.5	NS
Systolic blood pressure (mmHg)	131 ± 19	132 ± 22	NS
Diastolic blood pressure (mmHg)	77 ± 11	69 ± 11	0.002
Diabetes mellitus	5 (9.8)	6 (11.8)	NS
Smoking status			
Current smoker	7 (13.7)	2 (3.9)	NS
Ex-smoker	8 (15.7)	14 (27.4)	NS
Never smoker	36 (70.6)	35 (68.6)	NS
Body mass index	29.7 ± 5.6	29.2 ± 5.3	NS
Total cholesterol (mmol/l)	5.2 ± 1.2	5.3 ± 1.1	NS
HDL cholesterol (mmol/l)	1.6 ± 0.	1.3 ± 0.4	0.012
LDL cholesterol (mmol/l)	2.9 ± 0.9	3.3 ± 0.9	NS
Triglycerides (mmol/l)	1.4 ± 0.6	1.5 ± 0.8	NS
RA disease duration in years (median (range))	9.4 (0.3–55)	N/A	
DAS (median (range))	3.4 (1.2–7.9)	N/A	
No. of DMARDs (median (range))	2 (0–4)	N/A	
Central retinal arteriolar equivalent (μm)	152.3 ± 15.3	143.7 ± 13.9	0.004
Central retinal venular equivalent (μm)	235.9 ± 24.6	211.6 ± 21.0	<0.00001

Data are n (%) or mean±SD unless otherwise indicated. HDL high density lipoprotein, LDL low density lipoprotein, DAS disease activity score, DMARD disease modifying anti-rheumatic drug

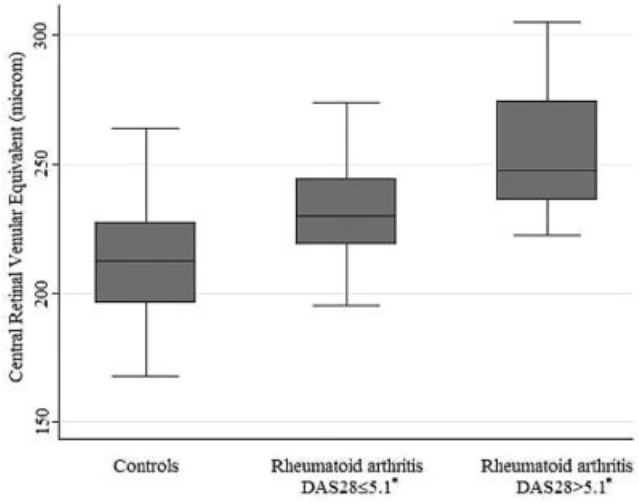
Table 2 shows the relative difference in CRAE and CRVE between RA patients and controls in an unadjusted comparison and after adjustment for relevant clinical variables. In the unadjusted analysis both CRAE and CRVE were significantly wider in the RA group compared with controls. After adjustment for all relevant variables the CRVE remained significantly larger in the RA patients (mean CRVE 20.3 mm greater in RA vs controls, 95% CI 10.4–30.3) whereas CRAE was not different between the groups.

Table 2. Difference in CRAE and CRVE in RA patients as compared with matched Controls

	Unadjusted analysis (mean, 95% CI)	Adjusted analysis* (mean, 95% CI)
CRAE in RA relative to controls, μm	8.6 (2.8–14.4)	2.4 (−4.3–9.1)
CRVE in RA relative to controls, μm	24.3 (15.2–33.2)	20.3 (10.4–30.3)

CRAE central retinal arteriolar equivalent CRVE central retinal venular equivalent
*Adjusted for age, gender, body mass index, systolic and diastolic blood pressure, lipid levels, diabetes status, smoking status and companion vessel calibre.

We also investigated the relationship between CRVE and inflammation. Figure 1 compares CRVE in controls and in the RA patients grouped according to disease activity. CRVE in the RA patients with high disease activity was greater than the controls and remaining RA patients, and this difference remained significant after adjusting for potential confounders.



RA rheumatoid arthritis; DAS28 28 Joint Disease Activity Score
*DAS28≤5.1 = moderate or lower disease activity; DAS28>5.1 = high disease activity

Figure 1. Central retinal venular equivalent in controls and RA patients.

Conclusion: To our knowledge this is the first report of retinal vascular caliber measurement in patients with RA. We have demonstrated increased CRVE in RA patients and a relationship between RA disease activity and CRVE. Longitudinal studies correlating CRVE with subsequent CV events will be required to further evaluate this relationship and to examine the predictive role of CRVE measurement in this patient group.

Disclosure: S. Van Doornum: None; **G. Strickland:** None; **R. Kawasaki:** None; **J. Xie:** None; **L. Hodgson:** None; **I. Wicks:** None; **T. Wong:** None.

1773

Serum Undercarboxylated Osteocalcin Levels in Patients with Rheumatoid Arthritis. Kuninobu Wakabayashi, Kumiko Otsuka, Michihito Sato, Ryo Takahashi, Tsuyoshi Odai, Takeo Isozaki, Nobuyuki Yajima, Yusuke Miwa and Tsuyoshi Kasama. Division of Rheumatology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

Purpose: Elevated serum levels of undercarboxylated osteocalcin (ucOC) is indicative of vitamin K (VK) deficiency in bone and increased risk of osteoporotic fracture. We assessed serum ucOC levels in patients with rheumatoid arthritis (RA).

Methods: Serum ucOC levels were measured in 100 RA patients, and the relationships between ucOC levels and age, sex, C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR) and prednisolone (PSL) dosage, with or without bisphosphonate (BP), were assessed. Patients whose usOC levels were above a cut-off value of 4.5 ng/ml were treated with menatetrenone (vitamin K_2), and ucOC levels before and after the treatment were compared. Serum ucOC levels were measured using an electrochemiluminescence immunoassay (ECLIA).

Results: Serum ucOC levels were elevated in 37 of the RA patients tested, and the ucOC-positivity rate was higher among female patients than among male patients ($p<0.05$). We observed a significant negative correlation between serum ucOC levels and PSL dosage ($p<0.001$).

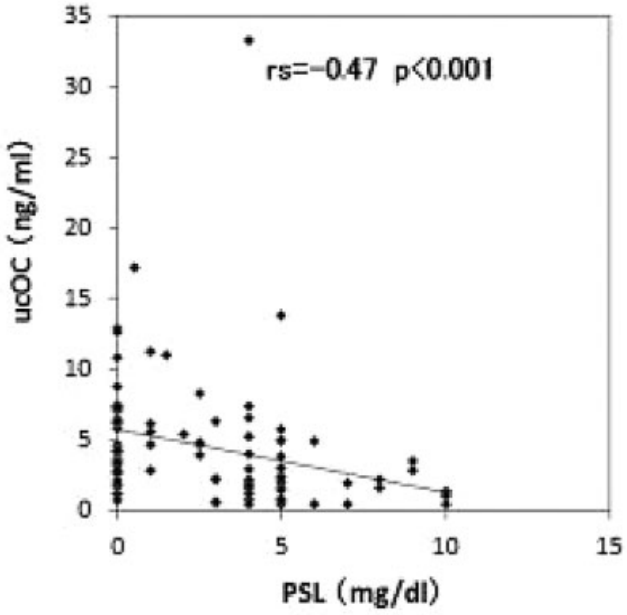


Figure 1.

Thus ucOC levels were significantly lower in RA patients treated with PSL 5–10 mg/day than in patients treated with PSL <5 mg/day ($p<0.01$) or in untreated patients ($p<0.001$).

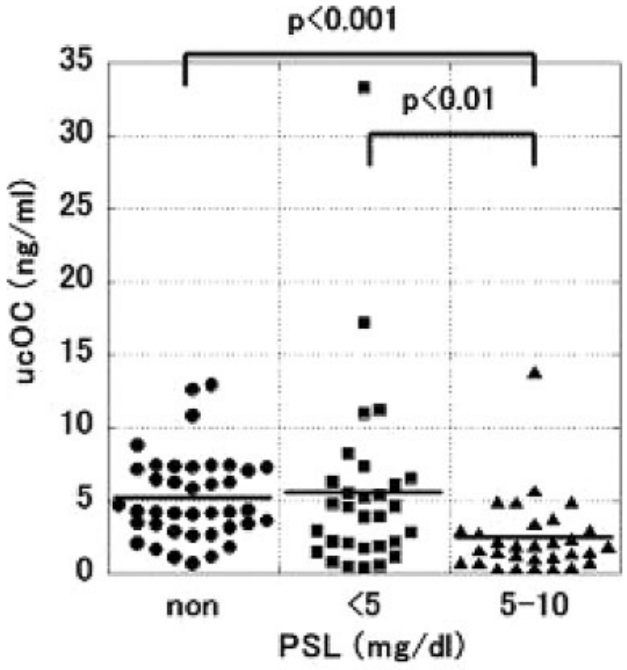


Figure 2.

Moreover, those also receiving BP showed lower ucOC levels than those not receiving BP ($p<0.02$). Twenty-four patients with high ucOC levels were treated with menatetrenone (vitamin K_2), which significantly reduced ucOC levels after 3 months of treatment ($p<0.001$). There was no correlation between serum ucOC levels and age, CRP or ESR.

Conclusion: PSL is known to inhibit bone formation and osteocalcin production. We suggest that levels of vitamin K, which is necessary for γ-carboxylation of the glutamate residues in osteocalcin, are reduced in RA patients treated with PSL >5 mg/day. In RA patients treated with PSL <5 mg/day and whose serum ucOC levels are above a cut-off value of 4.5 ng/ml, menatetrenone (vitamin K_2) treatment is effective against osteoporosis.

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1774

The 2010 ACR/EULAR Criteria for Rheumatoid Arthritis Perform Well in Prediction of Clinical RA Diagnosis at 6 Months in Very Early Arthritis Patients: Longitudinal Data from the NOR-VEAC Cohort.

Maria D. Mjaavatten[3], Desiree M. Van Der Heijde[8], Till Uhlig[5], Anne J. Haugen[1], Halvor Nygaard[6], Olav Bjørneboe[9], Nils G. Arvidson[7], Hans C. Gulseth[2] and Tore K. Kvien[4]. [1]Østfold Hospital, Moss, Norway, [2]Betanien Hospital, Skien, Norway, [3]Diakonhjemmet Hospital, Oslo, Norway, [4]Diakonhjemmet Hospital, Oslo, Norway, [5]Diakonhjemmet Hospital, Oslo, Norway, [6]Hospital for Rheumatic Diseases, Lillehammer, Norway, [7]Innlandet Hospital, Kongsvinger, Norway, [8]Leiden University Medical Center, Meerssen, The Netherlands, [9]Martina Hansen's Hospital, Sandvika, Norway

Background: The new ACR/EULAR criteria for rheumatoid arthritis (RA) were designed to predict risk of RA development at an early stage. The algorithm yields a score from 0–10 points where a patient needs >= 6 points to be classified as RA. The criteria need validation in cohorts of early arthritis patients.

Methods: Patients in the Norwegian Very Early Arthritis Clinic (NOR-VEAC) (swelling in>=1 joint with duration <=16 weeks, 18–75 years) were followed for 6 months and assessed for development of RA (clinical diagnosis). Only patients that did not contribute with data to Phase 1 of the criteria development were included to minimize overfitting of data. Sensitivity, specificity and likelihood ratios (LR) for different cut-offs were calculated and overall discriminatory ability was assessed with a receiver operating characteristics (ROC) curve.

Results: 298 patients (50 % females, median age 46.6 years, median duration of joint swelling 39 days, anti-CCP/IgM rheumatoid factor positives 18.5 %/14.2 %) were included in the analyses. After 6 months, 72 (24.2 %) patients had RA by the judgement of a rheumatologist (seropositive RA 45 (62.5 %)). Median (range) ACR/EULAR score at inclusion in RA/non-RA patients was 7(3–10)/3(0–9). Area under the ROC curve (95% CI) was 0.93 (0.90–0.96). The proposed cut-off of 6 points for RA classification showed a good combination of sensitivity, specificity and LRs (table). All seropositive RA patients had a score >=6, while 19/27 (70.4 %) seronegative clinical RA patients fulfilled the new criteria.

Conclusion: The new ACR/EULAR RA classification criteria performed well for prediction of clinical RA diagnosis in a cohort of very early arthritis patients. This validation supports the use of these criteria in clinical practice.

Table. Sensitivity, specificity and likelihood ratios for clinical RA diagnosis for different cut-offs for the 2010 ACR/EULAR RA criteria.

Cut-off (points)	Sensitivity (%)	Specificity (%)	LR+	LR−
3	100	36.3	1.57	0.00
4	98.6	58.8	2.39	0.02
5	91.7	76.5	3.90	0.11
6	88.9	83.2	5.29	0.13
7	63.9	93.4	9.68	0.39
8	47.2	99.4	78.67	0.53

LR+: positive likelihood ratio; LR-:negative likelihood ratio.

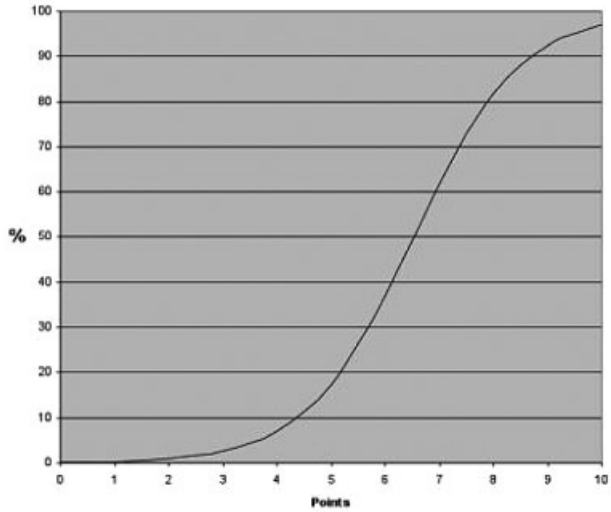

Figure. Predicted probability of RA development for increasing number of points in the algorithm.

Disclosure: M. D. Mjaavatten: None; **D. M. Van Der Heijde:** None; **T. Uhlig:** None; **A. J. Haugen:** None; **H. Nygaard:** None; **O. Bjørneboe:** None; **N. G. Arvidson:** None; **H. C. Gulseth:** None; **T. K. Kvien:** None.

1775

The ACR/EULAR 2010 Criteria as Well as Other Predictive Algorithms for Rheumatoid Arthritis Show Good Diagnostic Performance. Celina Alves[2], Jolanda Luime[1], Jendé van Zeben[4], Margriet Huisman[4], Angelique Weel[3], Pieternella Barendregt[3] and Johanna Hazes[1]. [1]Erasmus MC, [2]Erasmus MC, Rotterdam, The Netherlands, [3]Maasstad Ziekenhuis, [4]Sint Franciscus Gasthuis

Background: The ACR/EULAR devised new diagnostic criteria to improve early diagnosis of rheumatoid arthritis. The criteria were developed as a diagnostic algorithm for persistent and/or erosive disease, what was previously considered to be rheumatoid arthritis. Several other diagnostic algorithms already exist [1,2].

Objectives: To evaluate the diagnostic performance of the ACR/EULAR 2010 criteria, van der Helm algorithm [1] and Visser algorithm [2] to identify persistent arthritis at 1 year using different patient sets and 2 outcomes.

Methods: Eligible patients in the Rotterdam Early Arthritis CoHort presented with inflammatory arthritis or ≥ 2 inflammatory tender joints and symptom duration less than 12 months. Diagnostic algorithms were tested on discrimination using ROC-curves and calibration by calibration plots. Robustness was tested using different (sub) sets of patients: (i) all patients (n=736) (ii) classified and unclassified arthritis (n=532), and (iii) undifferentiated arthritis (n=301). Two outcomes evaluated were: (a) persistence, defined as arthritis or the need for DMARDs and (b) the 1987 ACR criteria for rheumatoid arthritis.

Results: Patients (n=736) had mean age 51 yr (sd 14), median ESR 15 (0–121), RF+ 21%, Anti-CCP+ 20%, median SJC 2 (0–44), median TJC 6 (0–38), erosions 5% at baseline. Table 1 shows discrimination performance for each algorithm per patient set (i;ii;iii) and for outcome (a) and (b). The algorithms had comparable performance on discrimination and calibration, with better performance the ACR/EULAR 2010 and van der Helm algorithm on discrimination. The ACR/EULAR 2010 criteria and van der Helm algorithm performed best in sample (i). Figure 1 shows ROC-curves and calibration plots for the algorithms in patient set (i).

References:

[1] van der Helm-van Mil AH et al A&R 2007

[2] Visser H Et al A&R. 2002

Table 1. AUCs (95% CI) for all algorithms in 3 patient subsets with either the outcome persistent arthritis or the *1987 ACR criteria* (in italic).

	ACR/EULAR 2010	Van der Helm	Visser
(i)	0.83 (0.79–0.86)	0.81 (0.77–0.85)	0.74 (0.69–0.78)
(ii)	0.78 (0.73–0.83)	0.76 (0.71–0.82)	0.79 (0.74–0.84)
(iii)	0.73 (0.66–0.80)	0.74 (0.66–0.82)	0.73 (0.65–0.80)
(i)	*0.83 (0.79–0.87)*	*0.83 (0.79–0.87)*	*0.78 (0.73–0.83)*
(ii)	*0.77 (0.72–0.82)*	*0.77 (0.71–0.82)*	*0.76 (0.70–0.82)*
(iii)	*0.61 (0.51–0.70)*	*0.60 (0.50–0.71)*	*0.59 (0.50–0.69)*

(i) all patients; (ii) (un-) and classified arthritis; (iii) undifferentiated arthritis

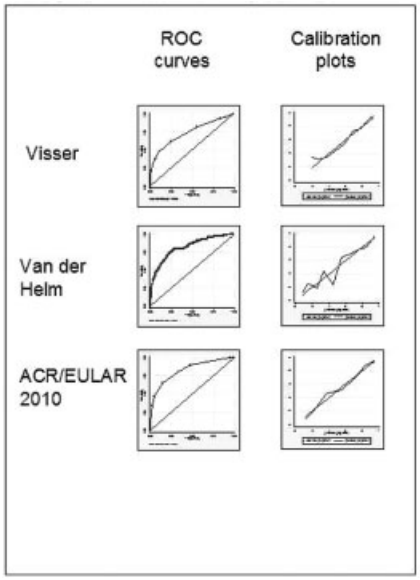

Figure 1. ROC-curves and calibration plots for patient set (i) and outcome persistence.

Conclusion: The algorithms had comparable performance. However, on discrimination the ACR/EULAR and the van der Helm algorithm performed best in the full patient set. The well performing algorithms enable use in different settings (e.g. primary and specialized care) and suggests that any of these models will improve early diagnosis of patients at risk for rheumatoid arthritis.

Disclosure: C. Alves: None; **J. Luime:** None; **J. van Zeben:** None; **M. Huisman:** None; **A. Weel:** None; **P. Barendregt:** None; **J. Hazes:** None.

1776

The Diagnostic Performance of the ACR/EULAR 2010 Criteria If One of Its Parameters Is Not Available. Results from the Rotterdam Early Arthritis CoHort (REACH). Celina Alves[2], Jolanda Luime[1], Jendé van Zeben[4], Margriet Huisman[4], Angelique Weel[3], Pieternella Barendregt[3] and Johanna Hazes[1]. [1]Erasmus MC, [2]Erasmus MC, Rotterdam, The Netherlands, [3]Maasstad Ziekenhuis, [4]Sint Franciscus Gasthuis

Background: Recently, criteria were developed for the diagnosis of RA to improve early diagnosis of RA, devised as a predictive algorithm for persistent and/or erosive arthritis. They contain 4 domains: joints, serology, acute phase reactants (APR) and duration. However, in daily clinical practice components may not be available due to various reasons. Therefore we set out to evaluate the diagnostic value of the ACR/EULAR criteria if one of its parameters is not available.

Methods: Eligible patients for REACH presented with synovitis or ≥ 2 tender joints and symptom duration less than 12 months. The outcome used was persistent disease, defined as synovitis or the need for DMARDs at 1 year. Statistical analysis was done using ROC-curves for discriminative power and sensitivity and specificity when using the proposed cut off of 6 or higher. Data were analysed for the full model and 9 models with a missing or modified parameter: (i) use of swollen joint count (SJC) instead of SJC and tender joint count (TJC) for joints, (ii) missing RF, (iii) anti-CCP, (iv) ESR or (v) CRP and (vi, vii, viii, ix) serology low or high values were replaced by a binary result attaching 2 or 3 points if the biomarker was present.

Results: Patients (n=736) had mean age 51 yr (sd 14), median ESR 15 (0–121), RF+ 21%, Anti-CCP+ 20%, median SJC 1 (0–38), median TJC 6 (0–42), erosions 5% at baseline. Complete information was not obtained for 36 patients. Figure 1 shows the ROC-curves for the full criteria set and all modified criteria sets. The model with only SJC provided the best AUC was 0.82 (95%CI 0.79–0.85) while the lack of anti-CCP provided the poorest model (AUC 0.71 (95%CI 0.68–0.75)). Table 1 shows sensitivity and specificity for the full set and all modified sets. All models performed well in identifying the non-diseased (specificity), but moderate performance was shown for identifying those who were ill (sensitivity).

Conclusion: The ACR/EULAR 2010 criteria are robust against missing values shown by a consistent diagnostic performance. However, the model with all 4 variables available but only swollen joints taken into account performed better than the original criteria including tender joints.

Table 1. AUC (95% CI), sensitivity and specificity. Sensitivity and specificity were calculated for the proposed cut-off of 6 or higher. (n=700)

	AUC, 95% CI	Sensitivity	Specificity
(0) ACR/EULAR 2010 criteria	0.73 (0.70–0.77)	0.53	0.80
(i) ACR/EULAR 2010 criteria with only SJC	0.82 (0.79–0.85)	0.37	0.97
(ii) ACR/EULAR 2010 criteria; RF missing	0.73 (0.70–0.77)	0.49	0.81
(iii) ACR/EULAR 2010 criteria: Anti-CCP missing	0.71 (0.68–0.75)	0.49	0.80
(iv) ACR/EULAR 2010 criteria: ESR missing	0.73 (0.70–0.77)	0.52	0.80
(v) ACR/EULAR 2010 criteria: CRP missing	0.73 (0.69–0.77)	0.51	0.80
(vi) ACR/EULAR 2010 criteria: no value for RF, RF pos (2 points)	0.73 (0.70–0.77)	0.52	0.81
(vii) ACR/EULAR 2010 criteria: no value for anti-CCP, anti-CCP pos (2 points)	0.73 (0.69–0.76)	0.52	0.80
(viii) ACR/EULAR 2010 criteria: no value for RF, RF pos (3 points)	0.73 (0.69–0.77)	0.53	0.79
(ix) ACR/EULAR 2010 criteria: no value for anti-CCP, anti-CCP pos (3 points)	0.73 (0.70–0.77)	0.53	0.79

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The Performance of the Hospital Anxiety and Depression Scale for Screening of Depressive and Anxiety Disorders in Patients with Rheumatoid Arthritis (RA). Eugenia Y. C. Lok[1], Chi Chiu Mok[2], Fuk Chi Cheung[1] and Chi Wai Cheng[1]. [1]Castle Peak Hospital, [2]Tuen Mun Hospital

Objectives: To evaluate the performance of the Hospital Anxiety and Depression Scale (HADS) for screening of depressive and anxiety disorders in patients with rheumatoid arthritis.

Methods: 200 consecutive Chinese patients who fulfilled the ACR criteria for RA were recruited from an out-patient rheumatology clinic. Written consent was obtained from these patients who were then interviewed by a psychiatrist for the presence of depressive disorders and anxiety disorders using the Chinese-bilingual Structured Clinical Interview for DSM-IV Axis I disorders, Patient research version (CB-SCID-I/P). Patients were invited to complete a validated Chinese version of the HADS questionnaire (depression sub-score 0–21; anxiety sub-score 0–21) before the psychiatric interview. Socio-demographic and clinical data such as age, gender, duration of RA, disease activity scores (DAS28), pain, income and education level at the time of interview were also collected. The sensitivity and specificity of the cut-off scores of the HADS depression and anxiety subscale for the clinical diagnosis of depressive or anxiety disorders was evaluated by the receiver operating curve (ROC) analysis.

Results: Between July 2007 and June 2008, 200 patients with RA were studied (79% women, mean age 51.4±10.5 years; median RA duration 4.0 years [IQR 2.0–9.0]). 47 (23.5%) patients were diagnosed to have a current psychiatric disorder (depressive disorders 14.5%, anxiety disorders 13%). Major depressive disorder was the commonest current mood disorder whereas generalized anxiety disorder was the most common current anxiety disorder. The mean depression sub-score of HADS in RA patients who were diagnosed to have depressive disorders was 13.1±3.1, which was significantly higher than that in patients without depressive disorders (5.7±3.5; $p<0.001$). On the other hand, the mean anxiety sub-score of the HADS in patients with anxiety disorders was also significantly higher than those without anxiety disorders (11.2±3.4 vs 5.4±3.9; $p<0.001$). Using ROC analysis, the optimal cut-off score of the HADS depression subscale was 10 for the presence of depressive disorders, yielding a sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 90%, 85%, 50% and 98%, respectively (area under the ROC: 93%). The optimal cut-off score of the anxiety subscale of HADS was 8 for the presence of anxiety disorders, with a sensitivity of 89%, specificity of 74%, PPV of 34% and NPV of 98% (area under the ROC: 87%).

Conclusion: As a screening tool, the HADS perform better for depressive disorders than anxiety disorders in patients with RA. A cut-off of 10 points in the HADS depression subscale yields a good sensitivity and specificity for picking up depressive disorders.

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The Role of Objective Measures vs. Patient Reported Outcomes (PROs) as a Reflection of Flares in Patients with RA: Results from the Brigham RA Sequential Study (BRASS). Vivian Bykerk[1], Daniel Hal Solomon[5], Clifton O. Bingham[6], Michelle Frits[3], Christine Iannaccone[4], Michael E. Weinblatt[5] and Nancy A. Shadick[5]. [1]Brigham & Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital, Jamaica Plain, MA, [3]Brigham and Women's Hospital, Boston, MA, [4]Brigham and Women's Hospital, MA, [5]Brigham and Womens Hospital, Boston, MA, [6]Johns Hopkins University, Baltimore, MD

Background: Worsening of disease activity or RA flare can be severe enough to warrant a change of therapy. Little is known about how frequently flares occur in RA or which measures best reflect a flare of RA.

Objective: To describe the frequency of self-reported flares in a population of patients with RA and determine which variables best relate to patients' recall of flare in the prior 6 months.

Methods: Data were collected in a prospective, observational, single- academic center cohort of RA patients treated according to preference of their rheumatologist. Patients were questioned every 6 months if they'd had a flare of their disease, what the duration was and how they'd treated it. Variables analyzed included patient reported outcomes, composite indices of disease activity and laboratory measures. Univariate logistic regression analyses using generalized estimating equations (GEE) were performed to determine possible predictors of flare. Disease measures with a $p \leq 0.10$ were included in a multiple logistic regression model using GEE. Additional multiple logistic regression models were performed, with patient reported measures and with objective measures.

Results: Of 1095 RA patients, 567 with ≥ 3 yrs follow-up reporting on flares were included for this analysis. Baseline characteristics included mean age: 57 ±13 yrs; 85% female, 93% Caucasian, mean disease duration14 years. 75% reported flares at baseline, 59% at 6 months and 55 % reported flares every 6-months thereafter. 30% reported flares lasting > 2 weeks, 27% lasting 1–2 weeks & 43% lasting ≤ 3 days. Variables significantly associated with current flare in the multivariate analysis overall, were pain, physician global, tender joint count (TJC), and age (figure 1). The TJC dropped out in the model containing just objective measures (figure 1). For predicting a flare within the next 6 months, pain, emotional distress, physician global, AM stiffness, and age were statistically significant (figure 2). Patient reported treatment during a flare included increases or changes in: prednisone by 35%, DMARDs by 32%, NSAIDs by 27%, biologics by 6%, narcotics by 5%, other pain meds by 13%.

Current flare analyses indicates variables that are associated with a recent flare as reported by the patient. (Odds Ratios from GEE)

Variables significantly associated with a current flare (Multivariate Regression)
All Measures:

Variable	Odds Ratio	Lower 95% CI	Upper 95% CI	P value
Age	0.9833	0.9711	0.9957	0.0084
CRP	1.0024	0.9925	1.0124	0.6361
Emotional Distress FSM15	0.9935	0.9831	1.004	0.225
Gender	0.9742	0.599	1.5844	0.9161
Patient Global (MDHAQ scale)	1.0054	0.9952	1.0158	0.2999
Pain (MDHAQ Pain Scale)	1.023	1.0141	1.0319	<.0001
Sleep	1.0054	0.9952	1.0158	0.2999
Tender Joint Count (0–28)	0.9638	0.9295	0.9993	0.0454
Physician Global	1.0268	1.016	1.0376	<.0001
AM Stiffness	1.2255	0.8078	1.8591	0.3389
Swollen Joint count (0–28)	0.9946	0.9598	1.0307	0.7666
Patient Reported Measures:				
Variable	**Odds Ratio**	**Lower 95% CI**	**Upper 95% CI**	**P value**
Age	0.9835	0.9719	0.9952	0.0059
Emotional Distress FSM15	0.9941	0.9842	1.004	0.2426
Gender	1.0101	0.6155	1.6576	0.9683
Patient Global (MDHAQ scale)	1.0066	0.9972	1.0161	0.1675
Pain	1.0271	1.0186	1.0357	<.0001
Sleep	1.0066	0.9972	1.0161	0.1675
AM Stiffness	1.3846	0.9138	2.0981	0.1249
Objective Measures:				
Variable	**Odds Ratio**	**Lower 95% CI**	**Upper 95% CI**	**P value**
Age	0.9799	0.9704	0.9896	<.0001
CRP	1.0053	0.9993	1.0114	0.085
Gender	1.0395	0.7203	1.5001	0.836
Tender Joint Count (0–28)	0.9857	0.9626	1.0093	0.2336
Physician Global	1.0377	1.0303	1.045	<.0001
Swollen Joint Count (0–28)	0.9936	0.9706	1.0173	0.5949

Future flare analyses: variables predicting which patients who will experience a flare in the next 6 months (Odds Ratios from GEE)

Predicting Flare in Next 6 Months (Multivariate Regression)
All Measures:

Variable	Odds Ratio	Lower 95% CI	Upper 95% CI	P value
Age	0.9889	0.977	1.001	0.0716
CRP	0.9964	0.9877	1.0053	0.4298
Emotional Distress FSM15	0.9879	0.9787	0.9973	0.0119
Patient Global (MDHAQ Scale)	0.9951	0.9863	1.0039	0.2733
Pain (MDHAQ Pain Scale)	1.0131	1.0046	1.0218	0.0026
Tender Joint Count (0–28)	0.974	0.9434	1.0056	0.1061
Physician Global	1.0137	1.0041	1.0234	0.0052
AM Stiffness	1.3999	1.0241	1.9138	0.0349
Swollen Joint count (0–28)	1.0065	0.9749	1.0392	0.6889
Patient Reported Measures:				
Variable	**Odds Ratio**	**Lower 95% CI**	**Lower 95% CI**	**P value**
Age	0.9873	0.9758	0.999	0.0339
Emotional Distress FSM15	0.9896	0.9807	0.9987	0.0246
Patient Global (MDHAQ scale)	0.9968	0.9885	1.0051	0.4453
Pain	1.014	1.006	1.022	0.0006
AM Stiffness	1.5421	1.134	2.0971	0.0058
Objective Measures:				
Variable	**Odds Ratio**	**Lower 95% CI**	**Lower 95% CI**	**P value**
Age	0.9856	0.9758	0.9954	0.0041
CRP	1.0051	0.9985	1.0117	0.1297
Tender Joint Count (0–28)	0.9946	0.9738	1.0158	0.6158
Physician Global	1.0198	1.013	1.0267	<.0001
Swollen Joint count (28)	0.9964	0.9749	1.0183	0.7426

Conclusions: Patient self reported flares are frequent in RA; 50% last ≥ 1 week. Patient pain VAS, physician global and TJC best reflect flare in patients with RA. When considering PROs, only pain independently reflects flare at baseline.

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Total MRI Inflammatory Score Correlates with Disease Activity Measures after Aggressive Treatment of Rheumatoid Arthritis. Veena K. Ranganath[3], David A. Elashoff[4], Paul Maranian[4], Kambiz Motamedi[4], Espen Haavardsholm[2], Fiona M. McQueen[5], Theresa McVie[7], Stacey S. Cofield[7], Larry W. Moreland[6], Weiling Chen[4] and Harold E. Paulus[1]. [1]Encino, CA, [2]Diakonhjemmet Hospital, [3]UCLA, Los Angeles, CA, [4]UCLA, [5]Univ of Auckland Sch of Med, Auckland, New Zealand, [6]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [7]University of Birmingham

Purpose: MRI is a sensitive imaging modality to investigate "inflammation" in rheumatoid arthritis (RA) joints. Tenosynovitis, synovitis, and bone edema independently correlate with disease activity measures in RA and suggest radiographic progression. The purpose of this study was to evaluate the relationship of clinical disease activity measures with two composite total MRI inflammatory score measures and their components, after 2 or more years of aggressive treatment of RA.

Methods: MRI with gadolinium contrast (1.5 Tesla) of the dominant wrist was obtained in 118 early (RA duration 4.1 ± 10.8 months) seropositive or erosive RA patients after completing the TEAR 2-year controlled clinical trial comparing various combinations of MTX, etanercept, HCQ, and SSZ. Clinical disease activity measures were recorded every 12 weeks during the trial and at the time of MRI. MRIs were scored for tenosynovitis (T: range 0–30), synovitis (S: 0–9), and bone marrow edema (BME: 0–42) using published RA MRI(RAMRIS) and tenosynovitis scoring methods. One method of calculating the total MRI inflammatory score was by: T+ S + BME. Another method produced a weighted measure, by taking the actual values of T, S, and BME and dividing by the range for each component. These values were then added together to give the weighted total MRI inflammatory score.

Results: After 2 years of aggressive RA treatment, the patients' average age was approximately 51 years. The mean DAS28 and clinical disease activity index (CDAI) fit into the mild disease activity categories, 2.9 and 9.2 respectively. More clinical core set measures correlated significantly with the weighted and unweighted total MRI inflammatory score than with the individual components of the scores (T, S, and BME), and the Rho values were also higher. T correlated significantly with only the physician global and swollen joint count. S correlated with CDAI, physician global, patient global, ESR, pain, stiffness, and arthritis severity. BME correlated with age, CDAI, physician global, stiffness, and swollen joint count. No single correlation coefficient was greater than >0.4. Weighting the MRI inflammatory score components did not improve the correlations.

Conclusions: The total composite MRI inflammatory score was shown to correlate better than the individual components of the MRI scores, with residual disease activity as assessed by standard core set measures and patient self-reported pain and stiffness.

Table 1. Descriptive statistics of Clinical Measures and correlation coefficients with MRI Inflammatory Scores

Clinical Variable, [mean (SD)]	N	mean	SD	Tenosynovitis *(7.1 (3.2))*	*Synovitis** *(3.7 (1.5))*	Edema** *(3.5 (5.3))*	Inflammatory Score* *(14.3 (7.8))*	Inflammatory Score *(weighted)**
age, yrs [50.5(13)]	118	50.53	12.99	<.01	0.03	0.23*	0.07	0.05
RA duration, yrs [0.3(0.9)]	118	0.34	0.89	0.02	0.02	<.01	0.01	0.01
DAS28 [2.9(1.4)]	115	2.94	1.37	0.15	0.18	0.06	0.23*	0.23*
CDAI, [9.2(11.1)]	115	9.23	11.12	0.18	0.20*	0.20*	0.27*	0.26*
Ptrys Global VAS, [1.5(1.8)]	117	1.54	1.81	0.24*	0.31*	0.24*	0.40*	0.39*
ESR, [19.9[20.2]]	115	19.92	20.23	0.13	0.20*	−0.01	0.33*	0.28*
Pt Global VAS, [2(2.3)]	113	2	2.25	0.08	0.20*	0.16	0.22*	0.22*
Pain VAS [2.5(2.6)]	113	2.48	2.56	0.09	0.20*	0.16	0.22*	0.22*
Fatigue VAS, [3.0(2.6)]	113	2.96	2.64	−0.07	0.09	0.08	0.09	0.08
Stiffness VAS, [2.4(2.5)]	113	2.4	2.47	0.12	0.34*	0.24*	0.34*	0.36*
Arthritis VAS, [2.4(2.4)]	113	2.41	2.38	0.08	0.19*	0.17	0.20*	0.21*
HAQ-DI, [0.6(0.6)]	115	0.61	0.63	0.11	0.18	0.12	0.20*	0.21*
TJC, [2.9(4.8)]	117	2.91	4.77	0.14	0.11	0.11	0.17	0.16
SJC, [2.8(4.4)]	117	2.78	4.37	0.18*	0.16	0.20*	0.25*	0.23*

*Pearson correlations, **Spearman correlations, *p < 0.05, Phys=Physician, Pt=Patient

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Towards a Data-Driven Evaluation of the 2010 ACR/EULAR Criteria for Rheumatoid Arthritis: Is It Sensible To Look at Levels of Rheumatoid Factor? M. P. M. van der Linden[4], M. R. Batstra[1], L. E. Bakker-Jonges[1], J. Detert[2], H. Bastian[2], H. U. Scherer[2], G. R. Burmester[2], M. D. Mjaavatten[3], T. K. Kvien[3], R. E. M. Toes[4], T. W. J. Huizinga[4] and A. H. M. van der Helm-van Mil[4]. [1]Department of Medical Laboratories, Reinier de Graaf Group, Delft, The Netherlands, on Behalf of SKML-HIM (WGHAS), [2]Department of Rheumatology and Clinical Immunology, Charité University Medicine Berlin, Berlin, Germany, [3]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [4]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands

Objective: The classification criteria for Rheumatoid Arthritis (RA) have been recently updated. The diagnosis of RA requires achieving ≥6 points; anti-citrullinated protein/peptides antibodies (ACPA) or Rheumatoid Factor (RF) presence yields 2 points and high levels 3 points. High RF level has an increased specificity for RA compared to RF-positivity, however the same holds for ACPA-positivity. This study evaluated the prognostic performance of high RF levels compared to the presence of ACPA (as determined by anti-CCP antibodies) for the development of RA. The predictive ability for the severity of RA was also assessed.

Methods: Three independent cohorts with a total of 972 undifferentiated arthritis patients were studied for RA-development (according to the 1987 ACR criteria) and arthritis persistency. Positive and negative predictive values (PPV, NPV) and likelihood ratios (LR) were compared for different levels of RF with the presence of anti-CCP antibodies. A similar comparison was made in 686 RA-patients for the rate of joint destruction during 7 years of follow-up and achievement of sustained DMARD-free remission. The variation in RF levels obtained by different measurement methods in the same RF-positive sera was explored.

Results: Presence of anti-CCP had a better balance between LR+/LR- and PPV/NPV than high RF levels for RA-development. The additive value of anti-CCP assessment after high level RF-testing was higher than vice versa. High level RF was less strongly associated with RA severity than anti-CCP antibodies. The RF level obtained by different methods in the same patients' sera varied considerably.

Conclusion: Level determination of RF is subject to large variation; high level RF has limited additive prognostic value compared to anti-CCP-positivity.

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Ultrasound Evaluation Reveals the Reason for High Interrater Variability in Joints of the 66/68 Joint Count. Matthias Nikolaus Witt[2], Monika Ronneberger[1], Amelie Schnez[3], Ruediger Laubender[4], Matthias Engelbrecht[1], Arthur Kavanaugh[6], Hendrik Schulze-Koops[5] and Mathias Grunke[3]. [1]Department of Internal Medicine 3, University of Erlangen-Nuremberg, Erlangen, Germany, [2]Division of Rheumatology, Ludwig-Maximilians-University, Munich, Germany, [3]Division of Rheumatology, Ludwig-Maximilians-University, Munich, Germany, [4]Institute of Medical Informatics, Biometry and Epidemiology (IBE), Ludwig-Maximilians-University, Munich, Germany, [5]Ludwig-Maximilians-University, Munich, Germany, [6]University of California-San Diego, La Jolla, CA

Background: In patients with rheumatoid arthritis, joint counts are the key outcome parameter in clinical trials as well as in daily clinical practice. It has been shown, however, that there is a huge variability between different assessors of the same patient. In a previous paper we have shown, that this can be reduced by a standardised training of the EULAR examination technique. We have also shown, however, that the effect of standardisation is worse for the 66/68 than for the 28 joint count.

Objectives: To evaluate the reason for the higher interrater disagreement in the assessment of the 68/66 in contrast to the 28 joint count. Is it the greater difficulty in assessing the joints of the lower extremity and can this be ruled out by ultrasonography?

Methods: Participants of joint examination seminars evaluated a given RA patient before and after they were made familiar with the EULAR examination technique. Joints were rated positive or negative for tenderness and swelling without graduation. The amount of tender and swollen joints as well as the variability between the examiners (groups of 4–6 trainees per patient) before and after the training were compared. For every single joint, the degree of agreement was calculated using the Fleiss-Kappa test. In a subgroup of 40 patients, the clinical results were compared to an independent ultrasound examination of the MTP joints.

Results: 340 health professionals participating in standardised joint assessment trainings were evaluated. 256 were instructed in the 68/66, 84 in the 28 joint count. For both joint counts, the disagreement between different examiners was higher for the dimension of joint swelling than for tenderness. After the training of the EULAR examination technique, there was a significant reduction of interrater variability, which was more pronounced in the 28 than in the 68/66 joint count. Comparisons between manual and ultrasound assessment revealed, that concerning the dimension of swelling manual examination has a very low sensitivity and high variability in the joints of the feet.

Conclusion: Standardisation of the joint examination technique significantly reduces variability. The relatively better performance of the 28 joint count is partly due to the higher number of examined joints in the 68/66 joint count. Another reason is, that the joints of the feet, although they are more often rated negative by manual than by ultrasound evaluation, tend to imply a higher disagreement between different assessors.

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Validation of a Multi-Biomarker Test for Rheumatoid Arthritis (RA) Disease Activity (Vectra™ DA) in a Multi-Cohort Study. Jeffrey R. Curtis[9], Doug Haney[3], Annette H. M. van der Helm[5], Yijing Shen[3], Rachel Knevel[5], Guy Cavet[3], Linda Dirven[5], Cornelia F. Allaart[4], Thomas W. J. Huizinga[5], Michael Centola[6], Lyndal K. Hesterberg[3], David Chernoff[3], John Carulli[1], Nancy A. Shadick[2], Michael E. Weinblatt[2], Max I. Hamburger[8], Roy M. Fleischmann[7] and Ed C. Keystone[10]. [1]Biogen Idec, [2]Brigham & Womens Hospital, Boston, MA, [3]Crescendo Bioscience, Inc., [4]Leiden Univ Med Ctr, Leiden, The Netherlands, [5]Leiden Univ Med Ctr, [6]Oklahoma Med Research Foundation, Oklahoma City, OK, [7]Rheumatology Associates, Dallas, TX, [8]Rheumatology Associates of LI, Dix Hills, NY, [9]University of Alabama-Birmingham, Birmingham, AL, [10]University of Toronto, Toronto, ON, Canada

Background: Regular measurement of disease activity enables more effective management of rheumatoid arthritis (RA). DAS28CRP is a validated tool for assessment of disease activity, but it requires enumeration of tender and swollen joints, which are subject to significant inter- and intra-assessor variability, and is not routinely performed by all physicians. A test based on serum protein biomarkers involved in RA pathophysiology has the potential to provide quantitative, objective and reproducible information that has not previously been available to clinicians. A 12-biomarker test of RA Disease Activity (DA Test) has recently been developed in a series of clinical studies. Here we show in a prospectively-designed study that the biomarker-based DA Test validly quantifies RA disease activity as compared to the DAS28CRP.

Methods: 230 RF+ and/or anti-CCP+ patients were selected from participants in the Index for Rheumatoid Arthritis Measurement (InFoRM), Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS), and Leiden Early Arthritis Clinic studies. To ensure test validity across a wide range of disease activity, patients representing all levels of disease activity were selected. The concentrations of 12 serum biomarkers (IL-6, EGF, VEGF-A, Leptin, SAA, CRP, VCAM-1, MMP-1, MMP-3, Resistin, YKL-40, and TNF-RI) were measured and combined in a pre-specified algorithm to generate DA Test scores ranging from 1–100. The DA Test score was calculated from an equation similar to that for DAS28CRP where scores for TJC28, SJC28, and Patient Global were individually modeled using serum biomarkers. To calculate area under the ROC curve (AUROC), a DAS28CRP cutoff of 2.67[i] was used to assign cases to low vs moderate/high disease activity. A separate, longitudinal analysis of patients from the InFoRM study with significant changes in DAS28CRP was undertaken to understand whether changes in DA Test score were associated with changes in DAS28CRP.

Results: The AUROC for DA relative to the DAS28CRP cutpoint of 2.67 was 0.77 (CI: 0.70 – 0.83; $p < 0.001$); the correlation between DA and DAS28CRP was 0.56 (CI: 0.46 – 0.64; $p < 0.001$). Decomposition of the DA Test into a non-CRP DA Test score and a CRP term demonstrated that the non-CRP DA Test score was an independent predictor of DAS28CRP ($p < 0.001$) in multivariate analysis (after controlling for CRP). In longitudinal analysis, there was a significant association between change in DA Test score and change in DAS28CRP ($p<0.01$). Exploratory analysis suggests the DA Test may more accurately detect low disease activity than CRP (Fig. 1).

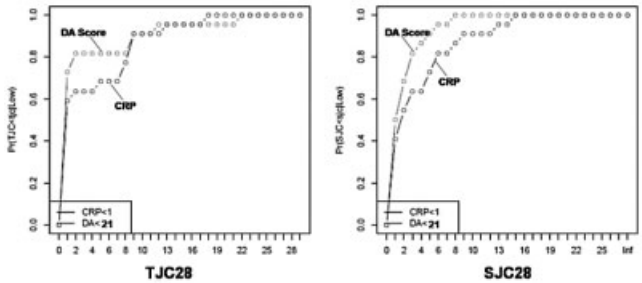

Fig. 1. Proportion of patients with joint counts below a threshold for those with low CRP or DA test score.

Conclusion: The DA Test has been validated as a quantitative, objective, biomarker-based test of RA disease activity. It could be used to optimize clinical care and provide an objective measure of treatment response in observational analyses or randomized trials.

[i] Inoue et al. *Ann Rheum Dis.* 2007; 66:407–409

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Validation of New Classification Criteria for Rheumatoid Arthritis in Japanese Population. Hisanori Shimizu[1], Hiromichi Tamaki[3], Eishi Uechi[3], Mitsumasa Kishimoto[2], Ken-ichi Yamaguchi[3] and Masato Okada[1]. [1]St. Luke's International Hospital, Tokyo, Japan, [2]St. Luke's International Hospital, Chuo-ku, Tokyo, Japan, [3]St. Luke's International Hospital

Background: The Classification Criteria of Rheumatoid Arthritis has been revised by ACR/EULAR joint committee in 2009. The new criteria is aimed to establish the diagnosis earlier to initiate appropriate disease modifying anti-rheumatic drugs without delay in the current era when complete remission before joint damage becomes a realistic goal with the advance of medical treatment.

Objectives: We performed retrospective validation of the new criteria in patients with undifferentiated arthritis who were later diagnosed as rheumatoid arthritis based on 1987 ACR classification criteria.

Methods: We reviewed electronic medical records of all the patients who were referred to St. Luke's International Hospital-Tokyo from October 2007 to November 2009 as undifferentiated arthritis before institution of any diseases modifying anti-rheumatic drugs (DMARDs). We applied the new ACR/EULAR criteria for all the patients to determine in which points they could be diagnosed as rheumatoid arthritis if the new criteria was utilized instead. We also compare patients who had delayed diagnoses based on the old criteria to patients whose time of the diagnoses did not differ, to analyze the clinical characteristics and also prognosis of the joints.

Results: There were two hundreds six patients who were referred to our institution without definitive diagnoses of rheumatoid arthritis over the period. We excluded all the patients who had been prescribed any DMARD for any purpose in other institution. There were eighteen patients without definitive diagnoses at the time of chart review and none of them was classified as rheumatoid arthritis even with the new criteria.

For the rest of fifty eight patients who were later diagnosed as definitive rheumatoid arthritis based on 1987 ACR classification criteria, we applied the new ACR/EULAR criteria. The average age was 54.0, and 50 of them were female and 8 were male. Rheumatoid factor were positive in 39 (67%), and anti-CCP antibody (second generation) was significantly elevated in 46 patients (79%). Bone erosions were already detectable in 11 patients at their first visits. In seventeen patients (group 1), the definitive diagnoses could be established significantly earlier with the new criteria and the average difference was 63.1 days. In forty one patients (groups 2), the diagnoses was not delayed even with the old criteria. Overall, the durations of days from the first visits to diagnoses were 36.2 days and 17.7 days with the old and new criteria, respectively. Biologics were eventually prescribed in two of seventeen patients (group 1) and eight of forty one patients (group 2).

Conclusion: The new ACR/EULAR Classification Criteria was effective to establish the diagnoses of rheumatoid arthritis significantly earlier in substantial percentage of patients, who eventually require intensive medical treatment such as biologics.

Table 1. Baseline characteristics of patients who were diagnosed as definitive rheumatoid arthritis based on 1987 ACR classification criteria (n=58)

Age	**54.0**
Female, n. (%)	50 (86)
No. of joint involvement*	
- Total joints	7.3
- Small joints	5.1
DAS-CRP (ESR)*	4.22 (4.90)
RF positive, no. (%)	39 (67)
Anti-CCP positive, no. (%)	46 (79)
Duration of synovitis (≥6 weeks), no. (%)	55 (95)
Bone erosions, no. (%)	11 (19)
No. of days from the first visit to the diagnosis	36.0
Treatment	
- DMARDs alone, no.(%)	30 (52)
- MTX, no. (%)	23 (40)
- Biologics, no (%)	10 (17)

*Evaluated at the diagnosis of RA based on new criteria

Disclosure: H. Shimizu: None; **H. Tamaki:** None; **E. Uechi:** None; **M. Kishimoto:** None; **K.-i. Yamaguchi:** None; **M. Okada:** None.

1784

Validity of Clinical Associations of Biomarkers in Translational Research Studies: The Case of Systemic Autoimmune Diseases. Maria Tektonidou[2] and Michael Ward[1]. [1]National Institute of Arthritis and Musculoskeletal and Skin Diseases, [2]National University of Athens

Objective: Validity of biomarkers may be impacted if studies do not include certain features in their design. We evaluated if translational research studies of potential biomarkers incorporated design features important for valid clinical associations.

Methods: We searched 10 journals for translational studies in 6 systemic autoimmune diseases published in 2004–2009. We included studies that reported associations between laboratory markers and the presence of disease, measures of disease activity, or prognosis. We examined the following design features: age-, sex- and race-matching; control for effects of treatment on expression of the biomarker; inclusion of both patients with early and late disease, or both active and inactive disease; longitudinal or cross-sectional design; and use of validated activity and damage measures.

Results: Among 170 articles, 156 articles examined potential biomarkers for diagnosis, 37 for disease activity assessment and 9 for prognosis; 67 were studies of rheumatoid arthritis (RA), 48 of systemic lupus erythematosus, and 41 of other diseases. Gene expression profiles were the most commonly examined potential biomarkers (N =51). Less than one-half of studies incorporated study design features important for valid clinical associations. Only 47.4% of studies of biomarkers for diagnosis had groups that were age-matched, 45.5% were sex-matched, and 35.3% controlled for treatment. Studies that examined biomarkers in histological samples and studies of RA were less likely to include important design features.

Conclusion: Less than one-half of translational studies of potential biomarkers incorporated design features needed for valid interpretation of clinical associations. Attention to these features could reduce false-positive and false-negative associations.

Disclosure: M. Tektonidou: None; **M. Ward:** None.

1785

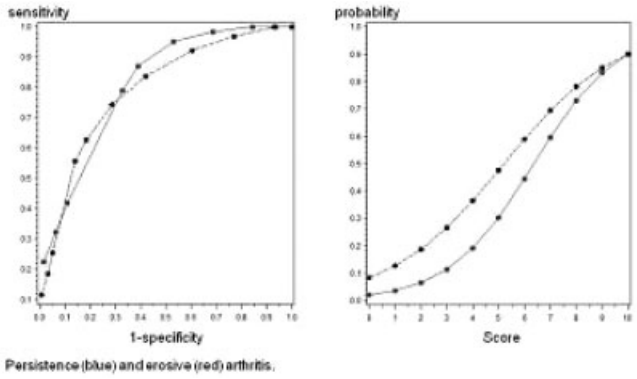
Validity of the Revised ACR/EULAR Classification Criteria for Rheumatoid Arthritis: Predicting Persistent Arthritis and Joint Erosions after 2 Years in Patients with Early Undifferentiated Arthritis. Jaap Fransen[3], Mieke Hazes[2] and Henk Visser[1]. [1]Alysis Hospital, Arnhem, The Netherlands, [2]Erasmus Medical Centre, Rotterdam, The Netherlands, [3]Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Background: The revised ACR/EULAR criteria for the classification of RA were developed to enable a more timely diagnosis. With the criteria the probability of developing persistent inflammatory or erosive arthritis that is considered to be 'RA' is calculated. However, the revised criteria were not validated against these two outcomes.

Objective: To study the revised ACR/EULAR criteria for the ability to correctly predict persistent arthritis and joint erosions after 2 years in patients with early undifferentiated arthritis.

Methods: Data were used from an existing cohort of patients with early arthritis (N=566) [1]. Patients with undifferentiated arthritis were included for the current analysis if at baseline they had: synovitis in at least 1 joint (N=561/566), arthritis not explained by another diagnosis (N=396/561), no joint erosions on X-ray (N=322/396), completed 2 year follow-up (N=286/322). Patients had been clinically assessed at baseline, including joint involvement, RF and ACPA, symptom duration, ESR and CRP. Scoring for joint involvement was slightly modified because small joint swelling was registered in Ritchie units. The 'risk' score (0–10) of the revised classification criteria was applied to the baseline data, persistent arthritis and joint erosions on X-ray at year 2 were the outcomes.

Results: At year 2, 45% (129/286) had persistent arthritis and 48% (62/129) of them had erosions. At baseline, the median (P25-P75) number of swollen joints was 2 (1–4), 23% were RF positive and 18% ACPA positive, median symptom duration was 13 weeks, median (P25-P75) ESR was 26 (13–44). Height of the 'risk' score (0–10) was significantly associated with persistent arthritis, OR (95%CI) 1.6 (1.4–1.8), and erosions, OR (95%CI) 1.8 (1.5–2.3), with areas under the ROC curve of.79 and.81, respectively. Patients with a 'risk' score of ≥6 at baseline had a.74 probability to develop persistent arthritis at year 2 and given persistence there was a.68 probability to develop erosions. The proposed cut point for 'definite RA' may be held at ≥6, while ≥3 may be an appropriate cut point for 'probable RA'. The diagnostic criteria of Visser et al. [1] performed slightly better, the list version of the 1987 ACR classification criteria was outperformed by both the other criteria.



Graph. Discrimination and calibration.

Conclusion: The revised ACR/EULAR classification criteria for RA are valid to predict future persistent arthritis and joint erosions in patients with early undifferentiated arthritis.

References:

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Disclosure: J. Fransen: None; **M. Hazes:** None; **H. Visser:** None.

1786

Vitamin D Levels Do Not Correlate with Disease Activity, Erosions, or Inflammatory Markers in Patients with Active Rheumatoid Arthritis. Joshua Baker[2], Daniel G. Baker[1], Gary Toedter, Justine Shults and Mary B. Leonard. [1]Centocor Inc, Malvern, PA, [2]University of Pennsylvania, Philadelphia, PA

Introduction: Evidence supports vitamin D deficiency as a potential risk factor for autoimmune disease. Small studies have yielded controversial data with regard to an association between vitamin D and disease activity measures among patients with RA.

Methods: Vitamin D levels were performed at baseline on 500 randomly selected patients with rheumatoid arthritis from the golimumab RCT. Participants met ACR criteria for the diagnosis, had active disease, and were naïve to both methotrexate and to other biologic therapies. Spearman correlations and multivariable linear regression were performed to assess associations between vitamin D levels and demographic and disease activity measures.

Results: 83% of patients had vitamin D levels <30 ng/mL, while 48% had levels <20 ng/mL. Vitamin D level did not correlate with the DAS28 score, ESR, CRP, or erosion score at baseline (Table 1). Vitamin D levels correlated with age ($p=0.005$), sex ($p=0.009$), BMI ($p=0.02$), HAQ scores ($p=0.02$), and patient reported health ($p=0.03$) (Table 1). The 6 black patients also had significantly lower vitamin D levels ($p=0.03$). Disease activity was similar across quartiles of vitamin D in a multivariable linear regression model. Age was the most important confounder of the non-significant trend between vitamin D and disease activity in the unadjusted model (Table 2). Disease activity was significantly decreased in the 22 patients with a vitamin D level >40 ng/mL. Age, race, BMI, and disease duration alone helped significantly to predict vitamin D levels in a predictive regression model.

Conclusions: Vitamin D levels do not correlate cross-sectionally with disease activity measures, erosion scores, or inflammatory markers in a large sample of patients with RA. Overall, vitamin D correlated with HAQ scores and patient reported health, but these were not independent predictors of vitamin D level in a predictive model including age, race, and BMI. Limitations include unknown geographic area and a study population that was selected for high disease activity. Overall, these data do not support a contribution of vitamin D in the activity of rheumatoid arthritis.

Table 1.

Variable	Spearman's Rho	P value
Das28 Score (with ESR)	−0.08	0.09
ESR	−0.04	0.4
CRP	−0.01	0.8
Tender Joint Count	−0.03	0.5
Swollen Joint Count	−0.03	0.6
Erosion Score	−0.002	0.97
HAQ Score	−0.10	0.02
Patient Reported Health (VAS)	−0.10	0.03
Patient Reported Pain (VAS)	−0.08	0.07
Age	−0.17	0.0001
BMI	−0.11	0.02

Table 2.

Variable	Coeff. (Δ DAS28)	P value	95% CI
Unadjusted			
Vitamin D 20–30	0.18	0.24	(−0.12–0.48)
Vitamin D 15–20	0.22	0.21	(−0.12–0.55)
Vitamin D <15	0.27	0.096	(−0.046–0.59)
Adjusted*			
Vitamin D 20–30	0.087	0.55	(−0.20–0.37)
Vitamin D 15–20	0.088	0.59	(−0.23–0.41)
Vitamin D <15	0.091	0.55	(−0.21–0.39)

*Adjusted for age, race, sex, BMI, disease duration, elevated HAQ score, and winter month.

Disclosure: J. Baker: None; **D. G. Baker:** None; **G. Toedter:** None; **J. Shults:** None; **M. B. Leonard:** None.

1787

Work Disability in Early Rheumatoid Arthritis: Prognostic Factors after Two Years of Follow-Up. Fausto Salaffi[1], Gianfranco Ferraccioli[3], Marina Carotti[2], Alessandro Ciapetti[1], Stefania Gasparini[1] and Walter Grassi[1]. [1]Department of Molecular Pathology and Innovative Therapies, Division of Rheumatology, University of Ancona (Politecnica delle Marche), Italy, [2]Department of Radiology, University of Ancona (Politecnica delle Marche), Italy, [3]School of Medicine, Catholic University of the Sacred Heart, Rome, Italy

Objective: Premature work disability in rheumatoid arthritis (RA) patients is a serious problem that needs to be addressed. The aims of the study was to explore the prevalence of work disability (WD) and to identify socio-demographic and disease-related factors that can predict future WD in patients with early RA over a 2-year period.

Methods: Two hundred and eleven working-age patients with early (<1 year) RA were evaluated every 3 months for a period of 2 years. At baseline Health Assessment Questionnaires (HAQ) were administered to each patient and socio-demographic data (age, gender, status of living, educational level), the presence of anti-cyclic citrullinated peptide (anti-CCP) antibodies and/or rheumatoid factor and comorbidities were recorded. The current occupations were categorized into four groups: predominantly mental demands, a combination of physical and mental effort, light physical demand and heavy physical demands. Radiological damage was evaluated by using the Sharp/van der Heijde score–SHS). The cumulative inflammatory burden was estimated by the evaluation of time-integrated values (area under the curve - AUC) of Disease Activity Score–28 joints (DAS28). The association between risk factors and WD was assessed using multiple logistic regression analysis (with Wald statistic as measures of WD risk).

Results: Among the 211 patients work disability rates were 2,8% and 8.1% at 12 months and after 24 months, respectively. Time-integrated values of DAS28 (Wald test = 10.82; $p<0.001$) and the work status (Wald test = 6.72; $p<0.01$) were identified as independent predictors variables of increased risk for new WD in the final logistic regression model. The strength of association of the model were Cox and Snell R^2 0.240 and Nagelkerke R^2 0.558. In the stratified analyses, the use of an anti-Tumor Necrosis Factor (TNF) drug revealed to protect against work disability among subjects with shorter disease duration.

Conclusions: Work demands and disease activity significantly and independently contributes to WD. Since WD frequently occurs within the first 2 years of disease adequate therapeutic interventions are advisable to start early in the course of RA.

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Disclosure: F. Salaffi: None; **G. Ferraccioli:** None; **M. Carotti:** None; **A. Ciapetti:** None; **S. Gasparini:** None; **W. Grassi:** None.

ACR Poster Session C
Rheumatoid Arthritis Treatment - Small Molecules, Biologics and Gene Therapy: Biologic DMARDs III
Wednesday, November 10, 2010, 9:00 AM–6:00 PM

1788

A Study To Evaluate the Effectiveness and Safety of the Interleukin-6 (IL-6) Receptor Antagonist Tocilizumab (TCZ) after 4 and 24 Weeks in Patients with Active Rheumatoid Arthritis (RA)—Final Effectiveness Results of the TAMARA Study. Eugen Feist[1], Andrea Rubbert-Roth[2], Jürgen Braun[6], Jörg Kaufmann[4], Herbert L. Kellner[7], Reiner Kurthen[3], Jürgen Wollenhaupt[5] and Gerd R. Burmester[1]. [1]Campus Charité Mitte, Med. Klinik Abt. Rheumatologie u. Klin. Immunologie, Berlin, Germany, [2]Klinik I für Innere Medizin, Uniklinik Cologne, Cologne, Germany, [3]Praxis für Innere Medizin und Rheumatologie, Aachen, Germany, [4]Praxis für Innere Medizin und Rheumatologie, Ludwigsfelde, Germany, [5]Rheumatologikum Hamburg, Schön-Klinik Hamburg-Eilbeck, Hamburg, Germany, [6]Rheumazentrum Ruhrgebiet, St. Josefs-Krankenhaus, Herne, Germany, [7]Schwerpunktpraxis fuer Rheumatologie und Gastroenterologie, Munich, Germany

TAMARA was a multi-center, open-label, single-arm (TCZ 8 mg/kg iv q4w), Phase IIIb study over 24 weeks (wks) to confirm the effectiveness and safety of TCZ in a treatment setting close to real-life medical care in Germany. Pts. with moderate/severe RA in spite of treatment with conventional (c)DMARDs and/or Biologics were enrolled at 70 sites; inclusion criteria included baseline DAS28 >3.2, ESR ≥28mm/h or CRP ≥1mg/dL, and previous treatment with at least 1 cDMARD continued during the study. Primary endpoint was the proportion of pts. achieving DAS28 "low disease" (LDAS, ≤3.2) at Wk24. Secondary effectiveness variables included ACR responses, CDAI, SDAI, inflammatory markers, and patient-reported outcomes such as HAQ-DI and FACIT-F (fatigue). Additional analyses considered several subgroups, e.g. based on rheumatoid factor (RF) at Baseline (RF^+ vs. RF^-), inadequate response (IR) to previous antirheumatics (TNFα-IR vs. cDMARD-IR), or Baseline DAS28 (>4.1-≤5.1 vs. >5.1).

Results: 286 pts. (ITT; median age: 55 yrs., 75.5% women, Baseline DAS28: 6.0±1.0) received TCZ; 239 pts. (71.6%) completed the 24wk treatment. 119 pts. (41.6%) had previously received TNFα-blockers; 163 (57.0%) cDMARDs only. 81 pts. (28.3%) were considered RF^- and 184 pts. (64.3%) RF^+. 47 pts. (16.4%) showed a Baseline DAS28 4.1-≤5.1 whilst 217 pts. (75.9%) had DAS28 >5.1.

At Wk24, 57% of the ITT pts. (95%-CI: [51.0; 62.8]) had achieved LDAS, ACR20/50/70 response rates were 65.0%/50.7%/33.9%. "Good" and "moderate" EULAR response was seen in 54.9% and 20.3% of pts., respectively. A clinically significant DAS28 reduction from Baseline (by ≥1.2) was seen in 74.5% of pts.; 47.6% achieved DAS remission (<2.6). The mean course of continuous effectiveness variables is provided in Table 1 (relevant improvements were seen as early as Wk4).

Table 1. Results (continuous data) of the Week 24 effectiveness analyses (ITT, LOCF)

	Baseline mean ± SD (N obs.)	Week 24/Early withdrawal mean ± SD (N obs.)	Mean Change mean ± SD (N obs.)
Single variables			
SJC (n)	9.6 ± 5.4 (286)	2.6 ± 3.7 (286)	−7.0 ± 5.5 (286)
TJC (n)	12.6 ± 6.8 (286)	4.3 ± 6.1 (286)	−8.3 ± 6.6 (286)
VAS-Disease Activity (mm)	62.2 ± 20.2 (286)	26.3 ± 25.4 (286)	−35.9 ± 30.2 (286)
ESR (mm/h)	37.4 ± 22.1 (274)	7.1 ± 9.5 (286)	−30.3 ± 21.7 (274)
CRP (mg/L)	23.1 ± 30.7 (274)	3.0 ± 7.7 (286)	−20.1 ± 29.9 (274)
Composite measures			
DAS28	6.0 ± 1.0 (274)	2.6 ± 1.5 (286)	−3.4 ± 1.4 (274)
CDAI	34.7 ± 12.5 (284)	11.3 ± 11.5 (285)	−23.5 ± 13.3 (284)
SDAI	37.2 ± 13.1 (272)	11.6 ± 11.5 (285)	−25.9 ± 13.7 (272)
Patient-reported outcome (PRO) measures			
HAQ-DI	1.48 ± 0.65 (285)	1.00 ± 0.75 (286)	−0.48 ± 0.60 (285)
FACIT-F (fatigue)	28.8 ± 11.2 (283)	37.4 ± 12.2 (286)	8.6 ± 11.1 (283)

N obs.=number of observations, SD=standard deviation.

The proportions of subgroup pts. achieving LDAS or DAS remission at Wk 24 are summarized in Table 2.

Table 2. LDAS and DAS28 remission in several subgroups at Week 24

Baseline Characteristics	N (=100.0%)	LDAS n (%)	DAS28-Remission n (%)
Rheumatoid factor			
Positive	184	105 (57.1)	85 (46.2)
Negative	81	48 (59.3)	41 (50.6)
Previous RA treatment			
Conventional DMARD-IR	163	103 (63.2)	87 (53.4)
TNFα-IR	119	60 (50.4)	49 (41.2)
Baseline DAS28			
4.1 < DAS28 ≤5.1	47	34 (72.3)	27 (57.4)
DAS28 >5.1	217	115 (53.0)	95 (43.8)

Conclusions: In a clinical setting close to usual care the treatment with TCZ led to rapid and sustained improvement of RA symptoms, thereby indicating the therapeutic benefits of TCZ. This improvement was consistently observed in all applied outcome measures independent of the measure characteristics. Subgroup analyses showed numerically better outcomes (i.e., difference by >10.0 percentage points in both LDAS and DAS remission when compared with the complementary group) in cDMARD-IR vs. TNFα-IR pts. or pts. with baseline DAS28 4.1-≤5.1 vs. >5.1, whereas no such differences were seen between RF^+ vs. RF^- pts., thereby suggesting that RF seemed not to relevantly predict the outcome at Wk 24.

Disclosure: E. Feist: Roche, 2, 5, 6; **A. Rubbert-Roth:** Roche, 5, 8; **J. Braun:** None; **J. Kaufmann:** None; **H. L. Kellner:** None; **R. Kurthen:** None; **J. Wollenhaupt:** Chugai, 5, 8, Roche, 5, 8; **G. R. Burmester:** Roche, 2, 5, 8.

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Age at Onset and Comorbidities Correlate with the Health Assessment Questionnaire and Clinical Disease Activity Index (CDAI) Responses to Etanercept in Rheumatoid Arthritis Patients.

Man R. Shim[6], Harold E. Paulus[1], Sandeep Chaudhari[3], JingYaun Feng[2], David A. Elashoff[4] and Veena K. Ranganath[5]. [1]Encino, CA, [2]Amgen, [3]Kforce Clinical Research/Amgen, [4]UCLA, [5]UCLA School of Med Rehab 32–59, Los Angeles, CA, [6]UCLA/ VA Greater Los Angeles Healthcare System, Los Angeles, CA

Objective: To investigate the influence of age of onset of rheumatoid arthritis (RA) and comorbidities on the health assessment questionnaire and clinical disease activity index (CDAI) responses in patients with active RA after 6 months of treatment with etanercept (ETN).

Methods: A cohort of 1,960 RA patients enrolled in the RA Disease-Modifying Anti-Rheumatic Drug (DMARD) Intervention and Utilization Study (RADIUS) 2 met the following inclusion criteria: initiated ETN, continued therapy for at least 6 months, and were not in remission at baseline (CDAI ≤ 2.8). Seventeen patient-reported comorbidities were recorded at baseline, and patients were classified by five quintiles of age of onset, <32, 32–41, 42–48, 49–55, and >55 years. Changes in HAQ and CDAI scores over 6 months were analyzed across the age categories using ANOVA. Linear and logistic regression models were constructed to evaluate the independent association between age of onset and number of comorbidities with change in HAQ/CDAI scores or achieving low disease activity (CDAI<10) after accounting for other covariates.

Results: Seventy-seven percent of patients were female, average age was 44 yrs, mean disease duration was 8.6yrs and average CDAI was 35.6. Baseline tender joint count and CDAI were statistically different across the age quintiles (Bsl CDAI grp1 33.9, grp2 35.5, grp3 35.4, grp4 37.2, grp5 36.3), however not clinically different. HAQ, patient global, physician global, swollen joint count and pain visual analogue scales (VAS) were similar across the age groups at baseline. Improvement in HAQ and CDAI scores after at least 6 months of treatment was not clinically different across the age groups, although both were statistically different across age. The results of the multiple linear regression model demonstrated that younger age at onset, higher baseline HAQ/CDAI score, positive rheumatoid factor, shorter disease duration, male gender, and fewer comorbidities at baseline were independently associated with both improvement in HAQ and CDAI. Similarly, achieving CDAI low disease activity after treatment with ETN for at least 6 months, was associated with younger age of onset, lower baseline CDAI, shorter disease duration, male gender, and fewer comorbidities (Table 1).

Table 1. Regression Models for Change in HAQ, Change in CDAI and CDAI Low Disease Activity

	Change in HAQ		Change in CDAI		CDAI Low Disease Activity	
	Beta-Coeff (SE)	p-value	Beta-Coeff (SE)	p-value	OR (95% CI)	p-value
Age at onset (yrs)	0.01 (0.00)	<0.0001	0.06 (0.02)	0.0190	1.01 (1.00–1.02)	0.0027
Baseline CDAI/HAQ	−0.29 (0.02)	<0.0001	−0.68 (0.02)	<0.0001	1.04 (1.03–1.04)	<0.0001
Baseline Off Prednisone	0.02 (0.02)	0.5222	0.33 (0.58)	0.5704	1.09 (0.89–1.33)	0.4063
Baseline Negative RF	0.08 (0.03)	0.0095	1.79 (0.68)	0.0087	1.21 (0.96–1.53)	0.1105
Disease Duration	0.01 (0.00)	<0.0001	0.10 (0.04)	0.0079	1.02 (1.00–1.03)	0.0083
Gender (Female)	0.08 (0.03)	0.0083	1.22 (0.68)	0.0074	1.35 (1.07–1.71)	0.0116
# Comorbidities	0.05 (0.01)	0.0003	1.20 (0.32)	0.0002	1.18 (1.06–1.32)	0.0037
Race (Non-White)	0.00 (0.03)	0.8985	0.99 (0.76)	0.1933	1.23 (0.94–1.59)	0.1260

Conclusion: In a large prospective cohort of RA patients who received at least 6 months of ETN therapy, younger age of onset and fewer comorbidities were associated with HAQ/CDAI improvement and with CDAI low disease activity after adjusting for other clinically relevant variables. These results confirm the importance of the number of reported comorbidities and age of onset in impacting RA response to anti-TNF treatment, and suggest that physicians should consider these factors when initiating therapy.

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Assessment of Real Life Efficacy of Rituximab in Rheumatoid Arthritis: Predicting Factors of the Therapeutic Maintenance and Demonstration of a Corticosteroid Sparing Effect in the AutoImmunity and Rituximab Registry. Jacques-Eric Gottenberg[10], Philippe Ravaud[4], Thomas Bardin[6], Patrice Cacoub[5], Alain Cantagrel[11], Bernard Combe[8], Maxime Dougados[2], René-Marc Flipo[7], Bertrand Godeau[3], Loic Guillevin[2], Eric Hachulla[7], Xavier Le Loët[9], Thierry Schaeverbeke[1], Jean Sibilia[10], Gabriel Baron[4] and Xavier Mariette. [1]Bordeaux Hospital, [2]Cochin Hospital, [3]Henri Mondor Hospital, [4]Hotel Dieu Hospital, [5]La Pitié Hospital, [6]Lariboisière Hospital, [7]Lille Hospital, [8]Montpellier Hospital, [9]Rouen Hospital, [10]Strasbourg Hospital, [11]Toulouse Hospital

Objectives: Registries might provide useful information on efficacy of biological agents, provided that the selected outcome criteria take into account the variability of the follow-up of hundreds of patients among a large number of centers. We therefore evaluated the real life efficacy of rituximab (RTX) in rheumatoid arthritis (RA) by analyzing its maintenance and its corticosteroid sparing effect.

Patients and Methods: The French Society of Rheumatology has developed an independent registry, named AutoImmunity and Rituximab (AIR), available on-line (www.air-cri.org), in which data of tolerance and efficacy of RTX in refractory RA and also other refractory autoimmune diseases are prospectively collected every 6 months during 5 years.

Results:

- Predicting factors of retreatment with RTX

Among the 2005 patients with RA included in AIR registry (median age: 58 years, median RA duration: 13 years), 1057 patients (52.9%) have been retreated by RTX (2 cycles: 570, 3 cycles: 273, 4 cycles: 141, 5 cycles or more: 73).

570 patients have a follow-up of at least 18 months, including 459 patients (80.5%) who were retreated by subsequent cycles of RTX and 111 patients (19.5%) who received only one cycle before RTX discontinuation, as indicated in the crf and/or by the initiation of a new biological DMARD. RTX was discontinued because of absence of efficacy (n= 92) or problem of safety (n= 19). On univariate analysis, a higher proportion of retreated patients had not received any previous TNF antagonists (22% versus 13.7% in patients who received a single cycle, P=0.05), were RF-positive (82.1 vs 66.3%, P= 0.001) or anti-CCP positive (80.2% vs 61.7%, P<0.0001) or were RF or anti-CCP positive (91.9% vs 77.4%, P=0.04). In multivariate analysis, retreatment with RTX was significantly associated with anti-CCP positivity.

- Corticosteroid sparing effect

The proportion of patients treated with oral corticosteroids decreased from 79.1% at cycle 1 to 73.9% at cycle 2, 69.2% at cycle 3 and 69.4% at cycle 4 ($P< 0.0001$). Median dosage of corticosteroid decreased from 10.0 mg at 1st cycle to 6.0 mg at cycle 2, and 5.0 mg at cycle 3 and cycle 4 ($P< 0.0001$).

Conclusion: These results from the AIR registry show that anti-CCP positivity is a predicting factor of therapeutic maintenance in real life. These data also demonstrate the corticosteroid sparing effect of RTX in patients with RA.

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1791

Clinical and Functional Improvements in Early RA Following Treatment with Adalimumab Plus Methotrexate Compared with Methotrexate Monotherapy: 26-Week Results of the OPTIMA Trial. Arthur Kavanaugh[5], Roy Fleischmann[6], Paul Emery[3], Benoit Guérette[1], Laura Redden[2], Kaushik Patra[2] and Josef S. Smolen[4]. [1]Abbott Laboratories, Rungis, France, [2]Abbott Laboratories, Abbott Park, IL, [3]Leeds Teaching Hospital, Leeds, United Kingdom, [4]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [5]University of California San Diego, La Jolla, CA, [6]University of Texas Southwestern Medical Center, Dallas, TX

Background: The optimal treatment approach to achieve and sustain low disease activity (LDA) with TNF antagonists and methotrexate (MTX) in patients with early rheumatoid arthritis (RA) has not been resolved.

Methods: OPTIMA is an ongoing Phase 4, randomized, double-blind trial to determine the **O**ptimal **P**rotocol for **T**reatment **I**nitiation with **M**ethotrexate and **A**dalimumab (ADA) in MTX-naive patients with early RA. Subjects with RA <1 year, DAS28 >3.2, ≥6 SJC, ≥8 TJC, ESR ≥28 mm/h or CRP ≥1.5 mg/dL, and ≥1 of: >1 erosions or RF+ or anti-CCP+ were randomized 1:1 to ADA (40 mg eow) +MTX (titrated to 20 mg/wk by week 8) or placebo (PBO) +MTX for the first 26 weeks. ADA+MTX subjects achieving LDA (DAS28 <3.2) at weeks 22 & 26 were re-randomized to compare continued combination therapy versus ADA withdrawal for the 52-week Period 2; PBO+MTX subjects with LDA at weeks 22 & 26 remained blinded on MTX monotherapy. Any subject failing to meet LDA at week 22 and/or 26 was given open-label ADA+MTX. A high-field 1.5T MRI substudy was conducted on the metacarpophalangeal and wrist joints at baseline, week 26, and week 78.

Results: OPTIMA enrolled 1,032 subjects (PBO+MTX N=517, ADA+MTX N=515); a similar percentage of subjects discontinued prematurely in each treatment group (table). Baseline characteristics were comparable between groups: 74% female, 89% white, mean RA duration of 4.2 months, mean DAS28 of 6.0 with 81% having DAS28 ≥5.1, mean SDAI of 43.6, mean CDAI of 40.8, mean SJC66 of 18.1, mean CRP of 2.9 mg/dL, and mean HAQ disability index (HAQ-DI) score of 1.6. Subjects treated with ADA+MTX demonstrated a significantly more rapid response, with a greater proportion achieving clinical and functional improvements through 26 weeks compared with PBO+MTX subjects (table).

Table. Subjects' Disposition and Clinical Outcomes through 26 weeks of OPTIMA*

Subjects, n (%)	Randomized		Completed Period 1			
PBO+MTX	517		460 (89%)			
ADA+MTX	515		466 (91%)			
	Week 2		Week 12		Week 26	
	PBO+MTX	ADA+MTX	PBO+MTX	ADA+MTX	PBO+MTX	ADA+MTX
ACR 20/50/70, % pts	16/2/0	46/18/5	58/30/11	73/49/30	57/34/17	70/52/35
DAS28 <3.2, % pts	4	15	22	42	26	47
DAS28 <2.6, % pts	1	7	10	26	16	34
SDAI ≤3.3, % pts	0.4	2	5	14	10	20
CDAI ≤2.8, % pts	0.2	3	7	13	11	20
SJ (0–66), mean (SD)‡	14	11	9	7	8	5
CRP (mg/dL), mean (SD)‡	2.5	1	1.4	0.9	1.3	0.8
HAQ ≤0.5, % pts	10	25	30	41	33	45

*Results based on nonresponder imputation analysis unless otherwise noted; P <0.001 for all between-groups comparisons; ‡LOCF.

In the MRI sub-study, PBO+MTX (N=32) and ADA+MTX (N=27) subjects, respectively, had mean changes from baseline to week 26 in synovitis of −2.0 and -3.6 (P=0.003), in erosion of 1.4 and −0.8 (P=0.004), and in osteitis of 0.0 and −4.0 (P=0.006), suggesting more improvement of joint inflammation and damage in the ADA+MTX group. Serious adverse events occurred in 31 (6%) PBO+MTX and 36 (7%) ADA+MTX subjects. Serious infections occurred in 6 (1.2%) and 13 (2.5%) subjects in the PBO+MTX and ADA+MTX groups, respectively. There was 1 case of peritoneal TB in the ADA+MTX group, and opportunistic infections excluding TB occurred in 3 (0.6%) PBO+MTX and 1 (0.2%) ADA+MTX subjects. There were no cases of lymphoma or demyelinating disease. Six deaths occurred in the ADA+MTX group, 5 related to infection and 4 in subjects ≥65 years, compared with 1 death in the PBO+MTX group.

Conclusion: Treatment of early RA with ADA+MTX resulted in rapid, enhanced clinical and functional responses and improved MRI profiles, compared with MTX monotherapy through 26 weeks.

Disclosure: A. Kavanaugh: Abbott Laboratories, 2; **R. Fleischmann:** Abbott Laboratories, 2, 5; **P. Emery:** Abbott Laboratories, 2, 5, Bristol-Myers Squibb, 2, 5, Merck Pharmaceuticals, 2, 5, Pfizer Inc, 2, 5, Roche, 2, 5; **B. Guérette:** Abbott Laboratories, 1, 3; **L. Redden:** Abbott Laboratories, 1, 3; **K. Patra:** Abbott Laboratories, 1, 3; **J. S. Smolen:** Abbott Laboratories, 2, 5, Bristol-Myers Squibb, 2, 5, Centocor, Inc., 2, 5, Roche, 2, 5, Schering-Plough, 2, 5, UCB, Inc., 2, 5, Wyeth Pharmaceuticals, 2, 5.

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Clinical Response during Sequential Anti-Tumor Necrosis Factor Therapy in US Veterans Enrolled in the Veterans Affairs Rheumatoid Arthritis (VARA) Registry. Grant W. Cannon[4], Brian C. Sauer[5], Candace L. Hayden[5], Liron Caplan[2], Gail S. Kerr[7], J. Steuart Richards[8], Dannette S. Johnson[3], Ted R. Mikuls[6] and Andreas M. Reimold[1]. [1]Dallas VA and University of Texas Southwestern, Dallas, TX, [2]Denver VA and University of Colorado, Aurora, CO, [3]Jackson VA and University of Mississippi, Jackson, MS, [4]Salt Lake City VA and University of Utah, Salt Lake City, UT, [5]Salt Lake City VA and University of Utah, [6]Univ of Nebraska Med Ctr, Omaha, NE, [7]Washington VA and Georgetown and Howard Universities, Washington, DC, [8]Washington VA and Georgetown University, Washington, DC

Purpose: The linkage of pharmacy databases with objective clinical outcome measures provides an opportunity to evaluate rheumatoid arthritis (RA) therapies

in "real-world" clinical settings. Merging of data from the Veterans Affairs RA (VARA) registry, initiated in 2003, and the VA Pharmacy Benefits Management (PBM) database dating back to 1998 allowed the investigation of disease activity score (DAS28) in patients receiving anti-tumor necrosis factor (TNF) therapy with adalimumab (ADA), etanercept (ETA), and infliximab (INF).

Methods: VARA routinely collects DAS28 on RA patients in this prospective cohort study. For each anti-TNF prescription, PBM data was used to estimate duration of the prescription, total dose dispensed, and anticipated refill date. A treatment course duration was defined as time from the initial prescription until the expected refill date for the last treatment before a 90 day gap or discontinuation. The average DAS28 and ESR was calculated during each course of therapy greater than 90 days during the observation period from 90 days after initial prescription to the end of the course.

Patients with sequential treatment courses with either the same anti-TNF (no switch) or a different anti-TNF therapy (switch) were evaluated. EULAR response criteria were evaluated using average DAS28 in comparing the sequential therapies and reported as better (if good or moderate response criteria fulfilled), worse (if a reverse of the sequence fulfilled EULAR good or moderate response criteria), and no change if neither better or worse.

Results: Of the 1382 patients in the VARA cohort, 601 (44%) had received anti-TNF therapy in 1258 courses. Of these courses, 530 (42%) were of greater than 90 days in duration with at least one DAS28 recorded during the clinical observation period. Comparison of no switch patients (n=56) and switch patients (n=46) showed that the initial DAS28 score during the initial (first) and subsequent (second) evaluable courses were higher in switch patients ($p<0.001$) but no difference in ESR ($p=0.10$) were discernable. Compared to initial values, the sequential DAS28 scores and ESR measurements were not statistically significant by pair t-test. EULAR response measures for better, worse, and no change response also did not achieve statistical significance ($p=0.168$). Evaluations of the different combinations for switching or not switching for each anti-TNF were also not statistically significantly different.

Table 1. Use of Anti-TNF agents in the VARA cohort

	Initial anti-TNF (n=601)	Patients with any exposure (n=601)	Number of courses	Courses >90 days	Courses >90 days with DAS28
ADA	170 (28%)	309 (51%)	425	327	195
ETA	311 (52%)	349 (58%)	533	294	221
INF	120 (20%)	175 (29%)	300	159	122

Table 2. Patients switching and not switching anti-TNF therapy. Clinical outcome during initial (first) and subsequent (second) course

	EULAR response			DAS 28 during:		ESR during:	
Anti-TNF therapy	Better	No change	Worse	First anti-TNF	Second anti-TNF	First anti-TNF	Second anti-TNF
No Switch (n=56)	14 (25%)	31 (55%)	11 (20%)	3.6 ± 1.1	3.4 ± 1.1	28 ± 20	31 ± 21
Switch Rx (n=46)	18 (39%)	17 (40%)	11 (23%)	4.6 ± 1.2	4.4 ± 1.3	24 ± 22	23 ± 22

Conclusions: RA patients in the VARA registry who were switched to a second anti-TNF agent were more likely to have higher DAS28 scores than patients who were not switched. However, there was no evidence that a switch in anti-TNF therapy was associated with greater clinical improvement in patients who switched than patients who did not switch anti-TNF therapies, nor did any particular anti-TNF show superior efficacy.

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Clinical, Structural and Functional Remission in the Treatment of Rheumatoid Arthritis with Tocilizumab in Daily Clinical Practice–REACTION-2 Study. Tsutomu Takeuchi[2], Yoshiya Tanaka[5], Kouichi Amano[1], Eri Sato[4], Masao Nawata[6], Hayato Nagasawa[1], Daisuke Hoshi[4], Masayoshi Saito[6], Syunsuke Fukuyo[6], Kentarou Hanami[6], Hideto Kameda[3], Takahiko Kurasawa[1] and Hisashi Yamanaka[4]. [1]Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Saitama Medical Center, Saitama Medical University, Saitama, Japan, [2]Division of Rheumatology, School of Medicine, Keio University, Tokyo, Japan, [3]Division of Rheumatology, School of Medicine, Keio University, Tokyo, Japan, [4]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [5]The First Department of Internal Medicine, School of Medicine, University of Occupational & Environmental Health, Kitakyusyu, Japan, [6]The First Department of Internal Medicine, School of Medicine, University of Occupational & Environmental Health, Kitakyushu, Japan

Purpose: Anti-IL-6 receptor monoclonal antibody, tocilizumab (TCZ), is increasingly recognized as a powerful biological agent for the treatment of rheumatoid arthritis (RA). Comprehensive effectiveness of TCZ in daily clinical practice, in which the patients are advanced and even refractory to TNF inhibitors, is not fully understood. In this report, we evaluated the effectiveness of TCZ in the three major rheumatology centers as judged by clinical, structural and functional remission at 52 weeks in the advanced RA patients.

Patients and Methods: From May 2008 to March 2009, a total of 255 RA patients were enrolled and received 8 mg/kg every four weeks of TCZ treatment. Disease activity was assessed using DAS28-ESR, joint damage using the van der Heijde modified total Sharp score (mTSS), and functional disability using the health assessment questionnaire (HAQ) score. Safety was assessed by identifying adverse events for which a causal relationship with TCZ could not be ruled out. The last-observation-carried-forward method was used in each of the analyses.

Results: The mean (± SD) of each parameter at baseline were as indicated below, age; 59.1 ± 13.3 years, duration of RA; 12.4 ± 11.1 years, mTSS; 140 ± 101, prior biologics user; 62.8%, concomitant methotrexate (MTX) user; 55.6% (the mean dose was 5.31 ± 4.8 mg/week), and concomitant corticosteroid user; 67.0% (the mean dose was 3.9 mg/day).

With the 52 weeks TCZ treatment, the mean DAS28-ESR was significantly improved from 5.72 at baseline to 3.2 at week 52, and clinical remission was achieved in 42% of patients, and 55% of the patients reached low disease activity criteria. The individual parameters of DAS28-ESR decreased significantly until 24 weeks after starting treatment with TCZ, and this efficacy was maintained until 52 weeks.

The estimated yearly progression of mTSS was also significantly improved from 26.0 at baseline to 1.1 at week 52 ($p<0.0001$). Cumulative probability analysis showed that progression of joint damage was inhibited in 61.7% of patients. Similarly, erosion was inhibited in 75.8% and joint space narrowing was inhibited in 71.1% of patients.

Based on the HAQ scores, extremely severe functional disability was evident before treatment, with a mean score of 1.56. After treatment with TCZ for 52 weeks, the HAQ score decreased to 1.29 with a gradual decline. Defined as HAQ score ≤ 0.5, functional remission was achieved by 26.4% of patients.

The 52-week retention rate was approximately 72%, independent of history of prior therapy with biologics. In contrast, the patients taking MTX achieved the higher continuation rate, compared to those without MTX.

Conclusions: This study showed that clinical remission was achieved in 42% of the patients with 12.4 years of disease duration and progression of joint damage is inhibited appreciably by treatment with TCZ in daily clinical practice. Given the results that functional remission was obtained about one fourth of the patients, which is apparently lower than that of clinical remission, early treatment with TCZ before irreversible and progressed disability by structural damage is important to achieve higher rate for all three remission criteria.

Disclosure: T. Takeuchi: Chugai, 2, 5; **Y. Tanaka:** Chugai, 2, 5; **K. Amano:** Chugai, 2; **E. Sato:** None; **M. Nawata:** None; **H. Nagasawa:** None; **D. Hoshi:** None; **M. Saito:** None; **S. Fukuyo:** None; **K. Hanami:** None; **H. Kameda:** None; **T. Kurasawa:** None; **H. Yamanaka:** Chugai, 2, 5.

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Comparable Persistency and Effectiveness of Abatacept Versus Anti-TNF Agents in the Treatment of Biologic-Naïve Rheumatoid Arthritis Patients Using the CORRONA Registry. Leslie Harrold[3], George Reed[3], Lisa C. Rosenblatt[1], Monica Mody[1], Diane Moniz Reed[1] and Jeffrey Greenberg[2]. [1]Bristol-Myers Squibb, Princeton, NJ, [2]NYU Hospital of Joint Diseases, New York, NY, [3]University of Massachusetts Medical School, Worcester, MA

Background: For RA patients who are new candidates for biologic treatment, there is limited observational data to guide physician decision making with respect to the relative merits of an anti-TNF as compared to a non-anti-TNF biologic, such as abatacept (ABA).

Objective: To examine the persistency and effectiveness of ABA versus anti-TNF agents among biologic-naïve RA patients in a multi-centered observational registry within the United States.

Methods: Using data from the Consortium of Rheumatology Researchers of North America (CORRONA) from 2/20/02–12/31/09, RA patients who initiated ABA or an anti-TNF and were not in remission (based on Clinical Disease Activity Index; [CDAI]) at the time of initiation were identified. Anti-TNF to ABA initiators (3 to 4:1) were matched based on age, RA

duration, MTX use at initiation, initiation time frame (at or prior to index visit) and baseline CDAI. Persistency was evaluated 24 mths post-initiation using Kaplan–Meier curves. The likelihood of discontinuation was examined using Cox proportional hazard models, adjusting for clustering by physician, matched clusters and concomitant medications (MTX and prednisone). Effectiveness was measured at ~1 yr (±3 mths) after initiation of biologics by patient global assessment and pain, using an intention-to-treat (ITT; including all initiators) analysis as well as a completers analysis (only included those who remained on drug). Regression models were performed to adjust for clustering by physician matched clusters and baseline differences.

Results: After matching, there were 57 ABA initiators and 213 anti-TNF initiators. Both groups were mostly female (77–81%) with a mean age of 64–66 yrs, mean disease duration of 9–10 yrs and a mean CDAI of 17.8. At baseline, there were no differences between ABA and anti-TNF initiators, in terms of swollen and tender joint count, physician and patient global assessment, and ESR. Unadjusted persistency for ABA at 6, 12 and 24 mths was 84, 72 and 56%, respectively. Among anti-TNF users it was 81, 67 and 55%, respectively. The adjusted hazard ratio for discontinuing ABA as compared with anti-TNF over the 24-mth period was 0.88 (95% CI: 0.51–1.52). Among patients with a follow-up visit at 1 yr (ABA=37; anti-TNF=149), the estimated change in patient global assessment was 4.07 more in ABA patients (–4.07 [95% CI: –13.09 to 4.95]) as compared with anti-TNF patients in adjusted analyses among those who remained on drug at follow-up (ABA n=30/37; anti-TNF 106/149) and 2.62 more (–2.62 [95% CI: –10.82 to 5.58]) in the ITT population. In adjusted analyses, the estimated change in patient pain was 5.09 more in ABA patients (–5.09 [95% CI: –13.82 to 3.64]) as compared to anti-TNF patients among those who remained on drug at follow-up (ABA n=30/37; anti-TNF 108/149) and 4.76 more (–4.76 [95% CI: –12.9 to 3.44]) in the ITT population.

Conclusions: In this small sample of RA patients in a real world setting, treatment with ABA was comparable in persistency or effectiveness to anti-TNFs. This study suggests similar effectiveness of ABA and anti-TNFs in biologic-naïve RA patients, and further research with a larger sample size should be undertaken to confirm these findings.

Disclosure: L. Harrold: Bristol-Myers Squibb, 5; **G. Reed:** Corrona, 5; **L. C. Rosenblatt:** Bristol-Myers Squibb, 1, 3; **M. Mody:** Bristol-Myers Squibb, 1, 3, Eli Lilly and Company, 1, 3; **D. Moniz Reed:** Bristol-Myers Squibb, 1, 3; **J. Greenberg:** None.

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Comparative Effectiveness of Biological Treatment Options Following Tumor Necrosis Factor α Inhibitor Failure in Rheumatoid Arthritis: Systematic Review and Indirect Pairwise Meta-Analysis. Monika Schoels[1], John B. Wong[2], Daniel Aletaha[3] and Josef S. Smolen[4]. [1]2nd Department of Internal Medicine, Hietzing Hospital, Vienna, Austria; Div. of Clinical Decision Making, Informatics and Telemedicine, Tufts University School of Medicine, Boston, MA, [2]Div. of Clinical Decision Making, Informatics and Telemedicine, Tufts University School of Medicine, Boston, MA, [3]Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Austria, [4]Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Austria; 2nd Department of Internal Medicine, Hietzing Hospital, Vienna, Austria

Background: The optimal treatment for rheumatoid arthritis (RA) patients who fail tumor necrosis factor α inhibitors (TNFi) remains uncertain; direct randomized controlled trials comparing therapeutic options are lacking. Therefore, we indirectly compared drug efficacy and safety of biologic agents following inadequate response to TNFi. Additionally, we investigated the dependence of success rates on the number of previously failed TNFi.

Methods: We performed a systematic literature search and retrieved randomized controlled trials (RCTs) that enrolled patients who had experienced TNFi failure. After assessing the heterogeneity of trial populations at baseline, we performed an indirect meta-analysis with pairwise comparisons of drug efficacy and safety using a random effects model. We used published clinical trial data on abatacept (ABA), rituximab (RTX), and tocilizumab (TOC) to perform the analyses; for golimumab (GOL), we obtained ACR20, 50 and 70 response rates in the subpopulation of patients treated with concomitant methotrexate (MTX) for 24 weeks to match the other trials. We derived odds ratios (OR) for ACR response and ascertained risk differences (RD) for adverse events, serious adverse events and infection rates. In sub-analyses, we investigated whether multiple previous TNFi failures diminished the clinical response when compared to the efficacy of biologicals after one TNFi.

Results: In four RCTs with 24 week follow-up, direct comparisons of abatacept, golimumab, rituximab, and tocilizumab versus placebo showed statistically significant mean odds ratios for ACR20 (point estimates ranging from 3.3–8.9), ACR50 (5.5–10.2) and ACR70 (4.1–13.5). The risk for adverse events, serious adverse events, and serious infections was non-significant compared with placebo. Indirect pairwise comparisons of the four biologic agents showed no statistically significant differences in ACR50 and ACR70 outcomes. Golimumab had a significantly lower ACR20 response (OR 0.56–0.59) but significantly fewer adverse events (RD 0.13–0.18). Drug efficacy outcomes following multiple previous TNFi failures did not differ significantly from patients with a history of 1 TNFi (data for comparison was available for golimumab and tocilizumab, Figure).

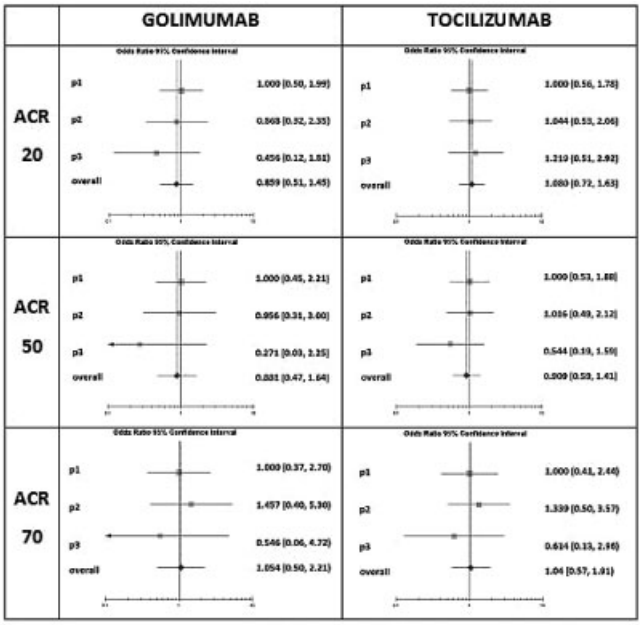

Figure. Response rates of GOL (left column) and TOC (right column). ACR20 (top panel), 50 (middle panel), and 70 (lower panel) of patients that had previously failed 2 (p2) and 3 (p3) TNFi, when compared to drug response rates after failure of 1 TNFi (p1).

Conclusions: In patients refractory to one or more TNFi, new biological agents provide significant improvement with good safety. In the absence of head-to-head trials, adjusted indirect meta-analysis enables evaluation of the comparative effectiveness and safety of biologics with each other and reveals similar effects of all biologicals.

Disclosure: M. Schoels: Abbott Laboratories, 5; **J. B. Wong:** None; **D. Aletaha:** Abbott Immunology Pharmaceuticals, 5, Bristol-Myers Squibb, 5, Hoffmann-La Roche, Inc., 5, Schering-Plough, 5, UCB, Inc., 5, UpToDate, 7, Wyeth Pharmaceuticals, 5; **J. S. Smolen:** Abbott Laboratories, 2, Amgen Inc., 5, Bristol-Myers Squibb, 2, Centocor, Inc., 5, Hoffmann-La Roche, Inc., 2, sanofi-aventis, 5, Schering-Plough, 2, UCB, Inc., 2, UpToDate, 7, Wyeth Pharmaceuticals, 2.

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Comparative Effectiveness of Rituximab in Combination with Either Methotrexate or Leflunomide in the Treatment of Rheumatoid Arthritis. Javier Narvaez[4], César Díaz Torné[2], José Miguel Ruiz[3], Maria Victoria Hernández[1], Vicens Torrente[2] and Sergio Ros[3]. [1]Department of Rheumatology, Hospital Clinic, Barcelona, Spain, [2]Department of Rheumatology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [3]Department of Rheumatology, Hospital de Viladecans, Barcelona, Spain, [4]Department of Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain

Background: Rituximab (RTX) has only been approved in combination with methotrexate (MTX) for patients with rheumatoid arthritis (RA) who have not responded to treatment with tumour necrosis factor (TNF) blocking agents. When MTX is contraindicated, RTX in combination with other DMARDs is increasingly used, despite a lack of specifically-designed, randomised clinical trials assessing these alternative combination therapies. In this context, real-world data on the effectiveness and safety of treatment combinations arising from observational cohort studies are the second-best source of evidence. One treatment option lacking sufficient supporting data is the combination of RTX with leflunomide (LEF). To date, only a small retrospective case series of ten patients has been published, with promising results.

Purpose: To compare the effectiveness of a combination of RTX with either MTX or LEF in the treatment of patients with active RA and inadequate response to anti-TNF agents or traditional DMARDs in a real-world setting.

Methods: Data from 77 consecutive unselected patients with active RA and treated with at least one cycle of RTX (1 g × 2 weeks) plus MTX or LEF were retrospectively collected. The primary endpoint of this retrospective analysis was the DAS28 response rate at month 6, according to the EULAR improvement criteria. Secondary efficacy endpoints included the percentage of patients in remission (DAS28 < 2.6) and with low disease activity (defined as DAS28 ≤ 3.2), the percentage of patients that fulfilled the ACR50 and ACR70 response criteria, and the variations in level of disability as established by the HAQ score. The ACR and EULAR response considered for the analysis was the maximal clinical response obtained between the end of month +4 and the end of month +6 of follow-up after the first cycle of RTX.

Results: Of the 77 patients, 45 received RTX+MTX and 32 RTX+LEF. At baseline there were no significant differences between the groups in terms of the main clinical and laboratory data, or in the number of previous DMARDs and anti-TNF agents used. The responses at six months are presented in the following table:

Treatment response rates at 6 months of therapy

	RTX+MTX (N=45)	RTX+LEF (N=32)	P
DAS28	4.24 (1.52)	3.85 (1.61)	0.2826[2]
Change in DAS 28	−1.68 (1.38)	−1.72 (1.43)	0.3103[2]
Change% in DAS28	−28.85 (−73, 35)	−26.41 (−92, 7)	0.7158[2]
EULAR response good-moderate	34 (75.5%)	25 (78.1%)	d=−2.6 CI: (020.5, 17.2) (>0.05)
Good	10 (22.2%)	8 (25%)	d=−2.8 CI: (−22.4, 15.5) (>0.05)
Moderate	24 (53.3%)	17 (53.1%)	d=0.2 CI: (−21.2, 21.8) (>0.05)
None	11 (24.4%)	7 (21.8%)	d=2.6 CI: (−17.2, 20.5) (>0.05)
DAS28 <3.2 (%)	11 (24.4%)	11 (37.3%)	0.3418[1]
DAS28 <2.6 (%)	4 (8.8%)	6 (18.7%)	0.303[4]
ACR50 responders (%)	6 (13.3%)	7 (21.8%)	0.324[1]
ACR70 responders (%)	1 (2.2%)	2 (6.2%)	0.3680[1]
HAQ	0.5 (0, 3)	0.75 (0, 3)	0.4612[3]
Change in HAQ	−0.68 (−3, 1)	−0.64 (−2, 2)	0.9149[3]
Change% in HAQ	−60.00 (−100, 100)	−50.00 (−94, 700)	0.2468[3]

Results are presented as mean (standard deviation), median (minimum, maximum) and counts and percentages. D=differences; CI=95%confidence interval.
[1]Chi-square, [2]t-test, [3]Median test, [4]Fisher test.

Minor adverse events occurred in 8.8% (4/45) of RTX+MTX patients and in 9.3% (3/32) of RTX+LEF patients. None of the patients had serious adverse events and none discontinued the treatment.

Conclusion: Current clinical practice is to use MTX as a first choice for combination with RTX. However, in a number of patients MTX has to be replaced by another DMARD. Our preliminary data support the view that LEF is a useful alternative if MTX is contraindicated, since its effectiveness and safety seem similar.

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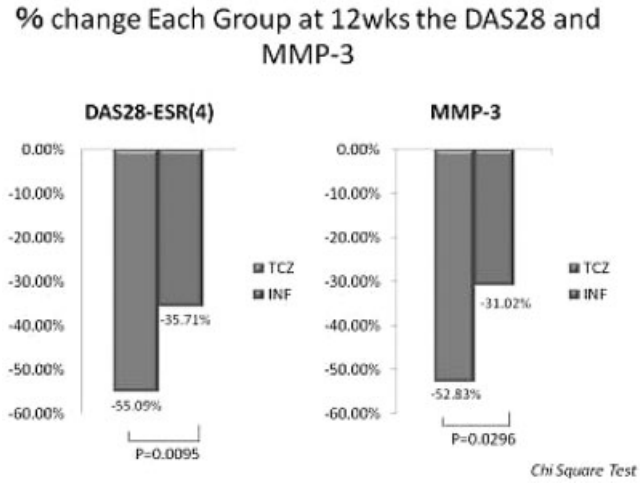
1797

Comparison of Tocilizumab and Infliximab Treatment for RA for a Duration of 12 Weeks, Based on MMP-3: Preliminary Report. Isamu Yokoe[1], Hitomi Kobayashi[2], Hiroshi Sato[2] and Shinya Nishio[2]. [1]Itabashi Chuo Medical Center, Tokyo, Japan, [2]Itabashi Chuo Medical Center

Purpose: MMP-3, an enzyme produced by synoviocytes, is a marker of synovitis, providing a more direct indication of actual joint destruction than CRP or ESR. It is potentially useful to detect synovitis at an early stage. A synergistic effect of IL-6 and either TNF or IL-1 induces MMP-3 production, and inhibition of IL-6 may alleviate synovitis by inhibiting both synergistic effects, but inhibition of only TNF or IL-1, only inhibits an additive effect. To measure this difference in RA treatments, infliximab (INF, an anti-TNF α antibody) and tocilizumab (TCZ, an anti-IL-6-receptor antibody) were given to groups of RA patients. Changes in MMP3 and improvement in the DAS were then compared between the INF and TCZ groups.

Methods: Consecutive Patients diagnosed with RA according to ACR criteria, were resistant to DMARDs, had moderate to severe activity, and complied with the Guideline for Biological Products of the Japanese College of Rheumatology, received either TCZ 8 mg/kg at Weeks 0, 4 and 8 or INF 3 mg/kg at Weeks 0, 2 and 6. Age, duration of illness, staging, classification, anti-CCP antibody, RF factor, PSL dose, mHAQ, DAS28 (ESR4), MMP-3, etc., were then compared between the 2 groups at baseline and after 12 weeks of administration. Chi-square test, Pearson test and Tukey-Kramer test were used to find statistical significance.

Results: TCZ and INF were respectively given to 20 and 24 patients, with a mean age of 60.2 ± 13.1 and 57.8 ± 12.4 years (P=0.40), and a mean duration of illness of 94.85 ± 93.5 and 70.0 ± 81.9 (P=0.45) months. Female ratio, staging, classification, anti-CCP antibody, RF factor, PSL dose (3 mg vs 4 mg, P=0.20), MTX dose (6 mg vs 7.3 mg, P=0.12), HAQ (0.675 vs 0.53, P=0.9) and MMP-3 (241 ng/mL vs 296 ng/mL, P=0.65) showed no significant differences between the 2 groups at baseline. In the TCZ group, 55% used MTX concomitantly, and 25% had not responded to TNF inhibitors previously. At baseline, the INF group included more patients with high disease activity than the TCZ group based on DAS28 (ESR4) (4.65 vs 5.33, P=0.027). After treatment, DAS28 (ESR4), mHAQ and MMP-3 values showed statistically significant improvement, but there were not significant differences between the 2 groups. The TCZ and IFX groups did, however, show significant changes in DAS28 score (−55% vs −36%, P=0.009) and MMP-3 level (−53% vs −31%, P=0.03).



MMP-3 and DAS28 (ESR4) were correlated in the 2 groups.

Conclusions: MMP-3 decreased earlier in the TCZ group than the IFN group, suggesting that TCZ can control progression of synovitis earlier than IFN. DAS28 also decreased in correlation with the MMP-3 value, so TCZ may suppress activity earlier than INF. However, the evaluated study population was very small and further study is required to draw a definite conclusion.

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1798

CTLA-4-Ig Fusion Protein (Abatacept) Modulate Inflammatory Activity of Cultured Synovial Macrophages from Rheumatoid Arthritis Patients. Maurizio E. Cutolo[6], Stefano Soldano[3], Paola Montagna[3], Alberto Sulli[3], Bruno Seriolo[3], Barbara Villaggio[4], Pier Franco Triolo[5], Paolo Clerico[5], Lamberto Felli[1], Luigi Molfetta[2] and Renata Brizzolara[3]. [1]Academic Orthopedic Department, University of Genova, Italy, [2]Orthopedic Unit, San Martino Hospital, Genova, Italy, [3]Research Laboratories and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Italy, [4]Research Laboratory of Nephrology, Department of Internal Medicine - University of Genova, Italy, [5]Rheumatoid Arthritis Unit – Orthopedic Surgery Department. CTO Hospital, Turin, Italy, [6]University of Genova, Genova, Italy

Background: CTLA-4-Ig, a biological agent employed in rheumatoid arthritis (RA) [1], is a fusion protein of the extra-cellular binding domain of human CTLA-4 with the Fc region of human IgG1. CTLA-4-Ig, like the native CTLA-4, binds more avidly than CD28 (T cells) to CD80(B7.1)/CD86(B7.2) on antigen presenting cells (APCs) [2], blocking CD28/B7 and CTLA-4/B7 interactions and downregulating immune activation in RA patients [3].

Our previous data in vitro demonstrated that CTLA-4-Ig blockade, in RA synovial macrophages/T cells co-cultures, resulted to induce anti-inflammatory effects [4].

The aim of this study was to investigate in vitro if CTLA-4-Ig directly affect the inflammatory activation of the cells of the monocytic lineage in monocultures of RA SM, in the absence of T cells.

Methods: RA SM were obtained from patients (5 females, 1 male; mean age 50±2 yrs; DAS28>5.2) who underwent therapeutic arthroscopic synoviectomy, after informed consent and in accordance with the local Ethical Committee. After 24 hours of culture, in the absence, as well as in the presence of CTLA-4-Ig at different in vitro concentrations (100, 500 μg/ml), RA SM were harvested and the expression of inflammatory cytokines (IL-6, TNFα, IL-1β) and TGFβ were evaluated by immunocytochemistry (ICC) (all mAbs diluited 1:100, Santa Cruz Biotechnology, Santa Cruz, CA, USA), with relative image analysis (Leica Q-Win image analysis system, Leica, Cambridge, UK) and western blot (WB) analysis. In addition, quantitative real-time PCR (qRT-PCR) analysis of mRNA was performed for IL-6, TNFα and IL-1β. Experiments were performed in triplicate.

Results: ICC image analysis revealed that the addition of CTLA-4-Ig 500 μg/ml in cultures of RA SM was able to significantly downregulate the cytokine expression ($p<0.001$ for IL-6 and TGFβ; $p<0.01$ for TNFα and IL-1β), compared to untreated RA SM. Moreover, the treatment with CTLA-4-Ig 100 μg/ml already showed a significant decrease for IL-6 ($p<0.001$) and IL-1β ($p<0.05$) and only TGFβ expression shown a significant variation for CTLA-4-Ig 100 μg/ml treatment compared to CTLA-4-Ig 500 μg/ml ($p<0.01$).

WB and qRT-PCR analysis confirmed these results and revealed a mild decrease in the amount of inflammatory cytokine production after CTLA-4-Ig 500 μg/ml treatment compared to untreated RA SM.

Conclusions: We provide evidence for a CTLA-4-Ig dose-dependent anti-inflammatory effect in vitro, in RA SM cultures. The addition of CTLA-4-Ig resulted in downregulating IL-6, TNFα, IL-1β and TGFβ production. Therefore, even if the best-defined mechanism of action of CTLA-4-Ig is the inhibition of the T cell co-stimulatory pathway, this study identifies the SM as further possibile target cells of CTLA-4-Ig treatment in RA.

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1799

Dosing of Anti-Tumor Necrosis Factor Biologics (Anti-TNFs) for Rheumatoid Arthritis (RA) and Psoriatic Arthritis (PsA) in Clinical Practice in the United States. J. Timothy Harrington[5], Dimitrios A. Pappas[2], Susan Messing[4], Xin Tu[4], Rui Chen[4], Kimberly Kaukeinen[4], Timothy Pietras[4], Jeffrey D. Greenberg[1] and Joel M. Kremer[3]. [1]Millburn, NJ, [2]Johns Hopkins University, Baltimore, MD, [3]The Center for Rheumatology, Albany, NY, [4]University of Rochester Medical Center, [5]University of Wisconsin, Madison, WI

Background: RA and PsA patients experience variable responses to biologics, and recommended doses and frequency of administration vary among the alternative anti-TNFs. Accelerated dosing is approved for infliximab (INFL) infusions, but varies for the other individual anti-TNFs. Switching among anti-TNFs and to biologics with alternative therapeutic targets has also not been well studied in a US population. Insurers often deny higher dosing of anti-TNFs as experimental treatment, while at the same time, therapeutic acceleration is being recommended to achieve optimal disease control and long term outcomes, as for example in the Treat to Target initiative.

Objective: To study rheumatologists' current choices of biologic agents in clinical practice, and the dosing of anti-TNFs in patients with RA and PsA enrolled in the CORRONA observational registry (Consortium of Rheumatology Researchers of North America, Inc.)

Methods: Biologic drug use is collected during routine office visits for the CORRONA enrolled RA and PsA patient populations. Food and Drug Administration (FDA) approved doses and frequencies are specified on the questionnaires, and space to indicate other dosing is also provided. Golimumab was not specified previously. Other doses, and/or frequencies of ant-TNF administration were pooled for this abstract into lower or higher than the specified categories. These data were obtained from the most recent visit report for all enrolled patients.

Results: Current biologic treatments were reported for 8706 of 22973 RA enrollees (38%) and 1742 of 3604 PsA enrollees (48%). For RA, these included: INFL (2733/8706, 31%), ETAN (2819, 32%), ADAL (1935, 22%), and all other biologics (1219, 14%). For PsA, these included: INFL (460/1742, 26%), ETAN (768, 44%, ADAL (495, 28%), and all other biologics (19, 1%). Anti-TNFs account for 86% of biologic use for RA, and 99% for PsA. Anti-TNF dosing for INFL, ETAN, and ADAL is shown in Table 1. Higher doses and/or frequencies of administration than those recommended are commonly reported.

Table 1. Dosing of Anti-TNFs (Number RA/Number PsA)

Infliximab (mg)	<300	3–<600	6–<900	9–<1200	>1200
	332/34	1806/261	508/133	68/24	19/8
Etanercept (mg)	Lower	25/wk*	25 2x/wk*	50/wk*	Higher
	26/17	119/23	410/121	1839/485	20/21
Adalimumab (mg)	Lower	40/2wks*	40/1.5wks	40/wk	
	19/8	1532/397	24/7	354/82	

*recommended doses for etanercept and adalimumab

Conclusions: 1. Choices and dosing of biologic drugs vary greatly across these RA and PsA populations. 2. Higher doses of anti-TNFs are commonly prescribed, suggesting that dosage acceleration is being considered for patients who experience a partial response to initial doses. 3. Further studies are needed regarding clinical outcomes, relative safety, and cost effectiveness of higher dose biologic treatment. 4. The results of these studies will likely differ in the US and other countries where biologic drugs are less commonly prescribed.

Disclosure: J. T. Harrington: Corrona, 5; **D. A. Pappas:** Corrona, 5, 9; **S. Messing:** None; **X. Tu:** None; **R. Chen:** None; **K. Kaukeinen:** None; **T. Pietras:** None; **J. D. Greenberg:** Corrona, 9; **J. M. Kremer:** Abbott Laboratories, 2, 5, Amgen Inc., 2, 5, Corrona, 9, Ortho Biotech Products L.P., 2, 5, UCB, Inc., 2, 5.

1800

Drug Free REmission after Cessation of Tocilizumab (Actemra) Monotherapy (DREAM Study). Norihiro Nishimoto. Wakayama Medical University, Ibaraki-City, Japan

Purpose: Tocilizumab (TCZ) has been demonstrated to frequently induce remission according to the DAS28 in patients with rheumatoid arthritis (RA). With long-term TCZ treatment reduced serum IL-6 levels have been observed in some patients, although TCZ does not directly act on IL-6, but inhibits the IL-6 receptor. It may be possible to discontinue TCZ in such patients without causing acute flare of the disease. We have previously reported that the serum IL-6 level correlates with actual in vivo IL-6 production and disease activity in patients with RA. Here we aimed to determine the rate of efficacy continuation at 52 weeks after cessation of TCZ treatment, and explore the factors that contribute to the duration of efficacy.

Methods: Patients who achieved DAS28<2.6 at the last observation of the previous Japanese TCZ clinical trials were enrolled and monitored for their disease activities without DMARDs. Patients with DAS28<3.2 were additionally enrolled to know if the disease activity at TCZ discontinuation might influence the efficacy duration. The loss of efficacy was defined as either DAS28>3.2 at two consecutive visits, initiation of additional RA treatments including increase in corticosteroid dose, or patient's request for retreatment. We estimated the efficacy continuation rate from Kaplan-Meier curves.

Results: A total of 187 patients were enrolled. Baseline characteristics of the patients were as follows: median disease duration, 7.8 years; median previous TCZ treatment for 4.0 years; median DAS28, 1.5 (remission rate 90%); 34.2% received corticosteroid and mean dose was 2.8 mg/day in these patients. The efficacy continuation rate was 35.1% at 24 weeks and 13.4% at 52 weeks. Efficacy continued in 24 patients as long as 52 weeks. Furthermore 19 patients were completely free from any drug. Multivariate Cox regression analysis revealed that baseline disease duration of the patients did not influenced efficacy duration after cessation of TCZ. However low serum IL-6 (<35 pg/mL) and normalization of MMP-3 level at TCZ discontinuation were identified as independent predictive markers for the longer efficacy duration. The estimated efficacy continuation rate in the patients both with serum IL-6 ≤12.9 pg/mL, which was calculated from receiver operating characteristic (ROC) curve, and with normal MMP-3 level was 70.6% at 24 weeks and 38.0% at 52 weeks, respectively. On the other hand, loss of efficacy among those with an IL-6 level higher than 35pg/mL was seen in 68.6% of patients within 12 weeks.

Conclusion: Efficacy continued after TCZ cessation without use of any DMRAD in 13.4% of the patients. Patients with normalization IL-6 and MMP-3 levels showed much longer duration of efficacy after cessation of TCZ.

Disclosure: N. Nishimoto: Chugai, 2, 5, 7, Roche, 5, Wyeth Pharmaceuticals, 2.

1801

Effect of Rituximab Treatment on Il-15 and T Cell Subpopulations in Rheumatoid Arthritis Patients. Cesar Diaz-Torne[1], Maria A. Ortiz[1], Carme Geli[1], Josep M. Llobet[1], Elisabeth Cantó[1], Elena Perez[1], Hector Corominas[2], Candido Juarez[1], Cesar R. Diaz-Lopez[1] and Silvia Vidal[1]. [1]Hospital de la Santa Creu i Sant Pau, [2]Hospital Moises Broggi

Rituximab is a therapeutic anti-CD20 antibody used for in vivo depletion of B cells. However, the mechanisms of action are not fully understood because clinical responses do not always correlate with the extent and duration of B cell depletion. This study was conducted to examine the effect of B cell depletion on peripheral T cells from rheumatoid arthritis patients after the first infusion and to compare the results with consecutive infusions.

Methods: 26 active RA patients received rituximab (1000 mg) on days 1 and 15. Following infussions were done depending clinical evolution (Never before six months) Peripheral blood samples were collected at baseline and at 30, 90 and 180 days postinfusion. The phenotype of T cell subsets of peripheral blood from RA patients were examined by cytometry and cytokine production was determined by ELISA and flow cytometry. Results from four consecutive infusions were compared and correlated with DAS28 activity index. Linear regression analysis was used to associate cellular changes and disease activity.

Results: Mean age was 61,5±11,5 years. 92,3% were women. Mean RA evolution was of 18,2±11,9 years. Previous DMARDs and biological therapies were 3,17±1,32 and 1,49±0,85 respectively. 50% were treated just with rituximab and the other 50% on combination with a DMARD. 96,2% were also using glucocorticoids. 96,2% had a positive antiCCP and/or rheumatoid factor. 89,5% had an erosive arthritis and 42,1% had a history of rheumatoid nodules. Patients previous DAS28 to treatment was 5,64±0,98.

According to our previous results, peripheral B cell depletion was fully effective by 30 days. No changes in the percentage of CD3+, CD4+, CD8+ and NK cells were found in the first as well as the two following infussions. Similarly to our observations in the first infussion, there was a comparative progressive diminution of CD8+CD45RO+ cells with the recovery starting at 180 days. DAS28 significantly correlated with CD8+CD45RO+ cells in the first and subsquent rituximab infussions. Since CD8+CD45RO+ diminution was coincident with the clinical response measured as DAS28, we investigated whether IL-15 could be responsible for this population changes in rheumatoid arthritis patients. As expected there was significant levels of IL-15 in the serum RA patients (110 ± 31 pg/ml) compared to healthy donors (< 10 pg/ml). Rituximab treatment decreased IL-15 levels in serum from rheumatoid arthritis patients. Although, no significant correlation was observed between IL-15 in the serum and CD8+CD45RO+ cells, levels of IL-15 trans-presented on the surface of neutrophils from RA patients significantly correlated with CD8+CD45RO+ ($p<0.01$) cells and CD8+CD45RO+/RA+ ratio ($p<0.001$).

Conclusions: This study demonstrates for the first time that rituximab treatment is able to reduce IL-15 levels. This reduction could be responsible for the observed CD45RO+ changes during the follow-up of these patients.

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1802

Effectiveness of Different DMARD Co-Therapies in Rituximab-Treated Rheumatoid Arthritis (RA) Patients–Results of a One-Year Follow Up Study from the CERRERA Collaboration. Cem Gabay[12], Katerina Chatzidionysou[11], Elisabeth Lie[5], Galina Lukina[9], Merete L. Hetland[2], Ulrik Tarp[3], Piet L. Van Riel[14], Dan Nordström[6], Juan J. Gomez-Reino[7], Karel Pavelka[1], Matija Tomsic[13], Evgeny L. Nasonov[8], Tore K. Kvien[4] and Ronald Van Vollenhoven[10]. [1]Charles Univ, Prague, Czech Republic, [2]Copenhagen Univ Hosp Hvidovre, Hvidovre, Denmark, [3]Copenhagen Univ Hosp Hvidovre, [4]Diakonhjemmet Hospital, Oslo, Norway, [5]Diakonhjemmet Hospital, Oslo, Norway, [6]Helsinki Univ Hosp, Helsinki, Finland, [7]Hospital Clinico Universitario, Santiago, Spain, [8]Institue of Rheumatology, Moscow, Russian Federation, [9]Institute of Rheumatology, Moscow, Russia, [10]Karolinska University Hospital, Stockholm, Sweden, [11]Karolinska, Stockholm, Sweden, Sweden, [12]Univ Hosp of Geneva, Geneva, Switzerland, [13]Univ Medical Center, Ljubljana, Ljubljana, Slovenia, [14]University Hosp Nijmegen, Nijmegen, The Netherlands

Background: Clinical trials have shown that rituximab (RTX) is efficacious in RA patients when prescribed in combination with methotrexate (MTX). However, some patients do not tolerate MTX, and are treated either with other DMARDs such as leflunomide (LEF) or without co-therapy. The purpose of this study was to compare the effectiveness and safety of rituximab alone or in combination with either MTX or LEF.

Methods: Ten European registries submitted anonymized datasets with baseline, 3, 6, 9 and 12 month clinical data for patients who had started RTX. Baseline and follow-up data included disease duration, number of previous biologic agents, disease activity (DAS28), functional disability (HAQ), concomitant DMARDs, corticosteroid use, and RTX retreatment. Patients were separated into three groups: RTX+MTX, RTX+LEF, and RTX alone. Patients receiving other DMARDs or combinations of DMARDs were excluded. Chi-square tests were used to compare the EULAR good response rates. Baseline values and mean changes were compared using ANOVA followed by Dunn/Bonferroni post-hoc testing. Logistic regression analyses were performed using co-therapies as independent variables.

Results: 2265 patients were analyzed: 1195 treated with RTX+MTX (mean dose (mg) of MTX was 14.4 ± 5.4 weekly), 177 with RTX+LEF, and 505 with RTX alone. At baseline, RTX alone patients were significantly older (55.2 ± 12.9 vs. 52.3 ±12.1 and 51.9 ±13.1), had longer disease (13.2 ± 10.1 vs. 11.4 ± 7.9 and 11.7 vs. 8.8), had more previous biological agents (1.1±1.1 versus 0.7±1.0 and 1.0±1.1) and previous DMARDs (2.8±1.8 versus 2.5±1.4 and 2.6±1.5) than RTX+LEF and RTX+MTX, respectively. Fewer patients on RTX+MTX were RF (74.5%) and anti-CCP positive (73.6%) than patients on RTX+LEF (77.6% RF+, 77.5% anti-CCP+) or RTX alone (78.8% RF+, 76.9% anti-CCP+).

Significantly more patients achieved a EULAR good response at 6 months when treated with RTX+LEF (29.1%) as compared to RTX+MTX (20.7%) and RTX alone (19.5%), P=0.04 and P=0.04, respectively. At 12 months an even greater percentage of good responders was observed in the RTX+LEF group (31.4%), while the percentage of good responders remained stable in the RTX+MTX and RTX alone groups (p=0.005 and p=0.01 respectively). RTX+LEF was significantly more often associated with a good EULAR response compared to RTX+MTX at 6 months (OR, 95% CI: 1.6, 1.0–2.5) and at 12 months (1.8, 1.2–2.8), P=0.04 and P=0.005, respectively. Similarly, RTX+LEF was also more often associated with a EULAR good response compared to RTX alone at 6 and 12 months (OR, 95% CI: 1.7, 1.0–2.8 and 1.8, 1.1–2.9, P=0.04 and P=0.01, respectively). Fewer patients with RTX + LEF were retreated during the first 12 months (19.2%) compared with RTX+MTX (27.9%) or RTX alone (21.8%). Adverse events occurred in 14.1%, 16.2%, and 16.4% of patients in RXT+LEF, RTX+MTX, and RTX alone, respectively.

Conclusion: The results of this large multinational cohort of patients show that LEF is effective and safe in combination with RTX. The finding that the efficacy of RTX in combination with LEF was greater than with MTX must be confirmed in further studies but suggests the possibility of a pharmacological synergism between the two agents.

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1803

Effects of Anti-TNF Agents on the Lung Function of Patients with Rheumatoid Arthritis: A Prospective Study. Meryem Can[1], Sait Karakurt[3], Atilla Bulur[1], Pamir Atagündüz[1], Sule Yavuz[2], Haner Direskeneli[2] and Nevsun Inanç[2]. [1]Marmara University Medical School, Division of Rheumatology, Istanbul, Turkey, [2]Marmara University Medical School, Division of Rheumatology, [3]Marmara University Medical SchoolDepartment of Pulmonary and Critical Care, Istanbul, Turkey

Background: The current evidence argues for caution in using TNF-targeted therapies in rheumatoid arthritis (RA) patients with pre-existing lung disease. Although the etiology of interstitial lung disease (ILD) in RA is still unclear, several cytokines are believed to play important roles in the pathogenesis of ILD.

Objective: To investigate both beneficial and adverse effects of anti-TNFα agents on the lung function of patients with RA in a 6 months follow-up study, to determine whether high resolution computed tomography (HRCT) findings correlated with clinical and pulmonary function test (PFT) abnormalities and to identify whether serum cytokines levels have an association with ILD in RA.

Methods: Fourty RA patients (F/M:33/7) were enrolled to the study. Infliximab (n=9), etanercept (n=12) and adalimumab (n=19) were started according to current guidelines in Turkey. The rate of concomitant metotrexate usage was 70%. Disease activity was assessed by DAS28. HRCT, pulmonary function test (PFT) and diffusing capacity of the lung for carbon monoxide (DLCO) were performed in all patients before and after 6 months of anti-TNFα treatment. Serum cytokines were measured by multiplex ELISA assay (IL1, IL6, MCP, TNF, VEGF, IFN gamma, IL10, IL12, IL13) at baseline and at 6 month's visit.

Results: Mean(SD) age was 48.8(11.8) and mean disease duration was 8.4(4.9) years. Anti-CCP and RF positivity were 55,6% and 80% respectively. Mean DAS28(SD) score was 5.5(1.1) and 4.2(3.2) at baseline and at 6 months' follow-up visit, respectively. None of the patients had severe respiratory involvement after starting treatment with anti-TNF agents. Significant improvements have been observed on respiratory parameters both by HRCT (77,5% vs 66,7%, p=0.01) and PFT (35.3% vs 30.8%, p=0.03) at 6 months' visit, however without a significant change in DLCO findings (14.7% vs 19.2%, p=0.3). At both evaluations bronchiectasis and interstitial lung disease were the most common pulmonary complications. When compared to the baseline findings, the number of patients with bronchiectasis and ILD also decreased (n=16/ 9 vs 10/6, respectively) at 6 months' visit. When the relationship of interstitial pulmonary involvement with the baseline HRCT, serum cytokine levels and serologic findings (RF, CCP) were analyzed, higher levels of IL10 (p=0.025), IL1beta (p=0.03) and MCP (p=0.027) were found to be associated with interstitial lung disease in RA.

Conclusion: Our results suggest that HRCT is sensitive for monitoring pleuropulmonary changes in RA patients. Anti-TNF agents seem to improve the chances of recovery in interstitial lung disease.

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1804

Effects of Subcutaneous and Intravenous Golimumab on Markers of Inflammation in Patients with Rheumatoid Arthritis. Mittie K. Doyle[4], Mahboob U. Rahman[4], Bart Frederick[2], Charles A. Birbara[6], Dick de Vries[1], Gary Toedter[3], Xiaoying Wu[3], Dion Chen[2], Mark Westerman[5] and Daniel E. Furst[7]. [1]Centocor B.V., Leiden, The Netherlands, [2]Centocor Research and Development, Inc., Malvern, PA, [3]Centocor Research and Development, Inc., [4]Centocor Research and Development, Inc./Univ. of Pennsylvania School of Medicine, Malvern, PA, [5]Intrinsic Life Sciences, [6]Univ. of Massachusetts City Campus, Worcester, MA, [7]University of California Los Angeles Medical School, Los Angeles, CA

Background: Treatment with the human anti-TNFα mAb golimumab, plus methotrexate, is effective in reducing the signs and symptoms of rheumatoid arthritis (RA). Elevated serum IL-6 and hepcidin have been associated with anemia of inflammation, common in RA pts, but the effects of golimumab on serum markers of inflammation and iron homeostasis are unknown.

Objectives: Assess early changes in inflammatory biomarkers, including CRP, IL-6, and hepcidin, in RA pts treated with golimumab (SC and IV).

Methods: In this phase 1, open-label study, pts ≥18 yrs with active RA for ≥3 months were randomized to receive SC injections of golimumab 100mg q4w through wk 20 or IV golimumab 2mg/kg at wks0&12. At wk24, the proportion of patients achieving ACR20/50/70 responses was determined. Blood samples for measuring serum levels of CRP, IL-6, SAA, TNFα, MMP-3, hyaluronic acid, ferritin, hepcidin, Hgb, and haptoglobin were collected at baseline, 24, 48, and 72 hrs, and at wks1, 2, 4, and 8. Urine hepcidin levels were measured at baseline, 48 hrs, and at wks2, 4, and 8.

Results: 49 pts were randomized to receive SC golimumab (n=33) or IV golimumab (n=16). Most patients were iron replete at baseline with mean ferritin >97ng/mL and mean transferrin saturations >22%. 5 pts (SC group) had mild anemia at baseline (Hgb=10.3–11.1 g/dL). For all pts, mean baseline CRP level was mildly elevated (1.1mg/dL), while mean hepcidin levels started and remained within normal ranges (17–286 ng/mL) throughout the study. Urine and serum hepcidin were positively correlated at all times. Overall, Hgb levels were maintained or increased. Mean serum CRP, IL-6, SAA, TNFα, MMP-3, haptoglobin, ferritin and hepcidin decreased rapidly within 2wks after the first golimumab administration and remained below baseline through wk8. Spearman's correlations showed decreases in serum hepcidin correlated with decreases in CRP and ferritin at most timepoints. At wk24, 62% of pts in SC group and 56% in IV group achieved ACR20, 31% and 25%, respectively, achieved ACR50, and 21% and 19%, respectively, achieved ACR70. Golimumab was generally well tolerated. Infections were the most common AEs (SC group, 39.4%; IV group, 31.3%). 2 pts in each group had SAEs, including noncardiac chest pain, pneumonia, and asthma; although none were considered related to golimumab therapy. There were no deaths in this study.

Conclusions: Both IV and SC golimumab were efficacious in reducing signs and symptoms of RA in this small phase 1 study. Very early decreases in mean serum levels of CRP, IL-6, SAA, TNFα, MMP-3, haptoglobin, ferritin, and hepcidin were evident. Decreases in CRP correlated with decreases in hepcidin, while concomitant decreases in ferritin were also observed, suggesting that golimumab treatment mobilized iron stores in these pts by reducing inflammation and in parallel, hepcidin levels. These observations support further study of hepcidin's role in RA and as a potential biomarker for clinical studies.

Disclosure: M. K. Doyle: Centocor Research and Development, Inc., 3; **M. U. Rahman:** Centocor Research and Development, Inc., 3; **B. Frederick:** Centocor Research and Development, Inc., 3; **C. A. Birbara:** Centocor Research and Development, Inc., 2, 9; **D. de Vries:** Centocor B.V., 3; **G. Toedter:** Centocor Research and Development, Inc., 2, 9; **X. Wu:** Centocor Research and Development, Inc., 3; **D. Chen:** Centocor Research and Development, Inc., 3; **M. Westerman:** Centocor Research and Development, Inc., 9; **D. E. Furst:** Centocor Research and Development, Inc., 2, 9.

1805

Efficacy and Safety of Certolizumab Pegol in a Clinically Representative Population of Patients (Pts) with Active Rheumatoid Arthritis (RA): Results of the REALISTIC Phase IIIb Randomized Controlled Study. Michael Weinblatt[2], Roy Fleischmann[8], Paul Emery[3], Niti Goel[11], Clifton O. Bingham[5], Janet Pope[9], Elena Massarotti[1], Ronald van Vollenhoven[6], Thomas W. J. Huizinga[7], Benjamin Duncan[10] and Maxime Dougados[4]. [1]Brigham and Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital, [3]Chapel Allerton Hospital, Leeds, United Kingdom, [4]Hospital Cochin, Paris, France, [5]Johns Hopkins University, Baltimore, MD, [6]Karolinska Institute, Stockholm, Sweden, [7]Leiden University Medical Centre, Leiden, The Netherlands, [8]MCRC, University of Texas, Dallas, TX, [9]St. Joseph's Health Care, University of Western Ontario, London, ON, Canada, [10]UCB, Raleigh, NC, [11]UCB, Smyrna, GA

Background: Certolizumab pegol (CZP) is effective and well tolerated in pts with active RA when used with methotrexate (MTX) or given as monotherapy.[1–3] The objective of this study was to further investigate the safety and efficacy of CZP in a broader active RA population more closely resembling routine clinical practice.

Methods: REALISTIC (RA Evaluation in Subjects Receiving TNF Inhibitor Certolizumab Pegol) was a multicenter (North America and Western Europe) Phase IIIb trial in active RA pts with inadequate response to ≥1 DMARD including pts with prior TNF-inhibitor exposure (NCT00717236), stratifying by baseline (BL) MTX use, prior TNF-inhibitor use and disease duration. In the 12-wk double-blind (DB) phase, pts were randomized to CZP 400 mg at Wks 0, 2 and 4 and 200 mg at Wks 6, 8 and 10 or placebo injection (control) every 2 wks (Q2W) added to their current treatment. From Wk 12, open-label (OL) CZP 200 mg Q2W was given for ≥16 wks. Primary outcome was ACR20 at Wk 12. ACR responses were determined using NRI, and DAS28(CRP) and HAQ-DI using LOCF.

Results: Of the 1063 pts aged 19–86 (mean 55.1) years (78.0% female) who were randomized (CZP = 851; control = 212), 37.6% had prior TNF-inhibitor exposure. Mean HAQ-DI and DAS28(CRP) scores at BL were 1.50 and 5.71 for CZP and 1.61 and 5.71 for the control group. Duration of RA was 0.2–52.0 (mean 8.7, SD 8.8) years. Most pts (88.7% overall; CZP: 89.5%, n = 762; control: 85.4%, n = 181) completed 12 wks' therapy and entered the OL phase. The primary objective was met; ACR20 was achieved in 51.1% of CZP vs 25.9% of control pts (p<0.001) at Wk 12. Wk 12 ACR50 and ACR70 responses were 26.6% and 13.0% for CZP pts vs 9.9% and 2.8% for control pts (p<0.001 for both). CZP clinical responses were rapid; ACR20/50 responses were significantly superior to control (31.8% vs 8.5% and 9.6% vs 1.4%, p<0.001 for both) from first time point (Wk 2) onwards. Significant improvements in DAS28(CRP) were reported with CZP vs control from Wk 2 (–1.07 vs –0.42; p<0.001) through to Wk 12 (–1.64 vs –0.79, p<0.001). DAS28(CRP) remission (DAS28 <2.6) was achieved in 16.3% of CZP and 5.7% of controls (p<0.001) at Wk 12. CZP pts also reported rapid and significant improvements in HAQ-DI vs control: mean change from BL at Wk 2: –0.29 vs –0.12; p<0.001 to Wk 12: –0.43 vs –0.21; p<0.001. In CZP pts, BL use of MTX (yes vs no) did not markedly affect ACR20 responses (52.4% vs 48.3%), nor did prior use of TNF-inhibitor (47.2% vs 53.5%) at Wk 12. Similar ACR20 results were seen regardless of disease duration, activity and geographic region. Adverse and serious adverse

event rates were comparable between CZP and control groups (65.1% vs 59.3%, and 5.4% vs 6.2%), with no new safety signals and no cases of TB observed.

Conclusion: In a diverse group of RA pts reflecting those seen in daily clinical practice (including those with prior TNF-inhibitor use), addition of CZP to current therapy was associated with a rapid clinical response consistent in all strata, improved function and reduced disease activity with a favorable risk benefit profile.

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1806

Efficacy and Safety of Certolizumab Pegol Plus Methotrexate in Patients with Rheumatoid Arthritis (RA): 3-Year Data from the RAPID 2 Study.

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Background: Certolizumab pegol (CZP) every other week (EOW) + methotrexate (MTX) had rapid and sustained efficacy with an acceptable tolerability profile over 2 years (yrs) in patients (pts) with active RA despite MTX.[1–3] Here we evaluate the sustainability of improvements in RA signs and symptoms, inhibition of joint damage progression and tolerability of CZP + MTX over 3 yrs in pts who completed 24 weeks (wks) of double-blind treatment with CZP 200 or 400 mg EOW + MTX (completers) in RAPID 2, and entered an open-label extension (OLE) of CZP 400 mg EOW + MTX.

Methods: ACR responses, DAS28(ESR), HAQ-DI, pain VAS (0–100 mm scale) are shown over 3 yrs (148 wks) from RAPID 2 baseline (BL) for CZP completers who entered the OLE; modified Total Sharp Scores (mTSS) are shown over 2.5 yrs (128 wks). Pts who withdrew from the OLE for any reason or took rescue medication in the OLE had data imputed from that time point onward. For mTSS, linear extrapolation (Lin ext) was used. For DAS28, HAQ-DI, and pain VAS, last observation carried forward (LOCF) was used for any missing data. For ACR responses, both nonresponder imputation (NRI) and observed data are reported. AEs were assessed in all pts at each visit (after first study drug administration) from RAPID 2 BL. Safety analyses were based on the ITT population. AEs and serious AEs (SAEs)/100 pt-yrs are presented for all pts who received ≥1 CZP dose. RAPID 2: NCT00160602; RAPID 2 OLE: NCT00160641.

Results: Of 494 pts treated with CZP + MTX, 355 completed RAPID 2; of these, 342 (96%) entered the OLE. Completers entering the OLE had high disease activity at RAPID 2 BL (mean: DAS28: 6.8; HAQ-DI: 1.6; pain VAS: 60.7); mean mTSS at RAPID 2 BL was 33.6. After 3 yrs, 79% of CZP completers continued to receive OL CZP; only 2 pts withdrew due to lack of efficacy. ACR responses and improvements in DAS28, HAQ-DI and pain from BL were sustained in the OLE to 3 yrs in CZP completers (Table). Inhibition of progression of structural damage observed during the placebo-controlled phase was sustained up to the last x-ray evaluation at 2.5 yrs. The incidence of AEs by Wk 148 was 108.17 cases/100 pt-yrs, and SAEs 13.35 cases/100 pt-yrs. Most AEs were mild to moderate; no new safety signals were identified. Serious infections were reported at a rate of 5.46 cases/100 pt-yrs, and malignancies at 0.64 cases/100 pt-yrs.

Table. Efficacy of CZP+MTX over 3 yrs in RA pts

	Wk 24		Wk 100		Wk 148	
	NRI	Observed[a]	NRI	Observed[a]	NRI	Observed[a]
ACR50 % responders	46.6	51.3	44.9	60.4	39.1	60.2
ACR70% responders	19.1	21.0	22.9	30.8	20.5	31.6
DAS28, mean (SD)[b]	4.0 (1.2)		3.8 (1.2)		3.8 (1.2)	
DAS28 change from BL, mean (SD)[b]	−2.8 (1.3)		−3.0 (1.3)		−3.0 (1.4)	
HAQ-DI, mean (SD)[b]	0.96 (0.60)		0.93 (0.61)		0.94 (0.62)	
HAQ-DI change from BL, mean (SD)[b]	−0.64 (0.50)		−0.66 (0.56)		−0.65 (0.58)	
Pain VAS change from BL (0–100 mm), mean (SD)[b]	−30.0 (22.4)		−30.9 (25.1)		−29.2 (25.8)	
mTSS change from BL, mean (95% CI)[c]	0.61 (0–1.3)		0.58 (0.1–1.1)		0.75 (0.2–1.3)[d]	

[a]Wk 24: N=310; Wk 100: N=240; Wk 148: N=206. [b]LOCF. [c]Lin ext. [b,c]The actual number of subjects in the summaries varies slightly from N=342 due to nonimputable missing data for each parameter. [d]Wk 128.

Conclusion: In pts with active RA despite MTX, the addition of CZP provides clinical improvements that are sustained over 3 yrs, inhibits joint damage progression, and is well tolerated.

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1807

Efficacy and Safety of Rituximab Treatment in Clinical Practice: Data from the CERERRA Collaboration.

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Background: The optimal regimen for treatment of RTX in RA has not yet been established. The purpose of this study was to analyze the efficacy of treatment and retreatment with RTX within 12 months after the first treatment and to identify predictors of response.

Methods: Ten European registries submitted anonymized datasets with baseline, 3, 6, 9 and 12 month data for patients who had started RTX. Heterogeneity between countries was analyzed by ANOVA. Predictors of response were identified by logistic regression analyses.

Results: Baseline data were available for 2265 patients. The mean (SD) age/disease duration of patients was 53.4 (13.2)/12.1 (9.1) years. 80.4% of them were female, 77.3% RF positive and 75.5% (574 out of 760 patients) were anti-CCP positive. The numbers of confirmed double seropositive and seronegative patients were 453 and 77 respectively. The mean (SD) numbers of previous DMARDs and biologics were 2.7 (1.6) and 1.1 (1.1) respectively. Significant heterogeneity was noted between countries for all baseline characteristics.

Significant reduction of DAS28 was observed at 6 [ΔDAS28 =1.92 (1.5)] and 12 months [ΔDAS28 =1.82 (1.5)]. HAQ was reduced from 1.63 (0.7) at baseline to 1.22 (0.7) and 1.27 (0.7) at 6 and 12 months, respectively. At 6

months 21.1% and 42.6% of patients were EULAR good and moderate responders, respectively; at 12 months the respective proportions are 20.8% and 40.6%. Seropositivity was associated with better response at 6 and 12 months (Table 1).

Table 1. Mean ± SD reductions in DAS28 at 6 and 12 months by serology.

	DAS28 improvement at 6 months (n=963)			DAS28 improvement at 12 months (n=539)		
	Positive	Negative	p	Positive	Negative	p
RF	1.95 ± 1.50	1.84 ± 1.50	NS	1.86 ± 1.49	1.67 ± 1.45	NS
ACPA	2.02 ± 1.52	1.42 ± 1.56	0.001	2.03 ± 1.45	1.58 ± 1.65	0.09
DOUBLE	2.02 ± 1.56	1.30 ± 1.47	0.006	2.0 ± 1.46	1.61 ± 1.66	NS

531 patients received retreatment by the end of 12 months. These patients achieved even higher DAS28 reductions at 12 months [ΔDAS28 =2.25 (1.4)] while for non-retreated patients a loss of effectiveness was observed [ΔDAS28 =1.46 (1.5)], (p<0.0001). A similar trend was observed in HAQ.

321 patients had an adverse event (AE) during the first year of treatment. The majority of the AE was infections and allergic reactions. 8 deaths occurred during the first year, 1 of them related to treatment (aspiration pneumonia). 193 patients discontinued RTX by the end of 12 months, 12 because of an AE, 92 because of inefficacy and the rest of the patients for other reasons. Retreatment was not associated with higher AE rate.

Predictors of EULAR Good Response at 12 months positive anti-CCP (p=0.002) and lower DAS28 at baseline (p=0.03).

Conclusions: RTX was effective and well tolerated for the majority of patients. Retreatment before 12 months lead to sustained efficacy and is generally safe. Anti-CCP positivity was associated with good response to treatment with RTX.

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1808

Efficacy and Safety of Tocilizumab in Patients with Moderate to Severe Active RA and a Previous Inadequate Response to DMARDs: The ROSE Study. Yusuf Yazici[3], Jeffrey R. Curtis[6], Akgun Ince[4], Herbert Baraf[5], Raymond L. Malamet[1], Carol Y. Chung[2] and Arthur Kavanaugh[7]. [1]Genentech, a Member of the Roche Group, South San Francisco, South San Francisco, CA, [2]Genentech, a Member of the Roche Group, South San Francisco, CA, [3]NYU Hospital for Joint Diseases, New York, NY, [4]St. Louis University School of Medicine, St. Louis, MO, [5]The Center for Rheumatology and Bone Research, Wheaton, Wheaton, MD, [6]University of Alabama at Birmingham, Birmingham, AL, [7]University of California at San Diego, La Jolla, CA

Purpose: Early and aggressive treatment of RA has been associated with improved outcomes. The objective of the Rapid Onset and Systemic Efficacy (ROSE) study was to assess the efficacy of tocilizumab (TCZ) versus placebo in combination with DMARDs in reducing signs and symptoms during 24 weeks of treatment in patients with moderate to severe RA who have had inadequate clinical response to DMARDs.

Methods: 619 patients were randomly assigned to TCZ 8 mg/kg + DMARDs (TCZ, n=412) or placebo + DMARDs (control, n=207). The primary efficacy end point was ACR50 response at week 24. Efficacy parameters were assessed every 4 weeks through week 24. Disease activity was also assessed at 1 week for a subset of 62 patients. Safety and laboratory parameters were assessed throughout the study.

Results: Most patients were female (81%) and Caucasian (81%); mean age was 55 y, mean disease duration was 8.6 y, mean number of previous DMARDs was 1.2, and mean DAS28 was 6.5. At week 24, there was a significantly higher percentage of ACR50 responders (primary end point) in the TCZ group than in the control group (30.1% vs 11.2%; $p<0.0001$). Significantly higher percentages of patients in the TCZ group than in the control group achieved ACR20 and ACR50 responses from week 4 through week 24 and ACR70 responses from week 8 through week 24 (Table). Patients in the TCZ group had significant improvement in RAPID3 scores from week 4 through week 24 and in FACIT-Fatigue scores from week 8 through week 24 compared with control (Table). In the TCZ group, improvements in CRP and Hb levels occurred early (week 4) and were sustained through week 24; CRP improvement was significant at all time points ($p<0.0001$). In the subset, DAS28 and patients' pain and global assessment scores significantly improved, and CRP levels normalized 1 week after TCZ treatment ($p\leq0.01$ vs control). SAE rates/100 PY (95% CI) were 24 (17, 33) and 19 (11, 31) for the TCZ and control groups, respectively. Serious infections were reported in 2.9% and 0.5% of patients in the TCZ and control groups, respectively. Malignancies were reported in 0.7% and 1.5% of patients in the TCZ and control groups, respectively. ALT shifts from normal at baseline to >3× ULN occurred in 3.2% of TCZ patients and in 1.1% of control patients. Clinically significant (grade 3/4) decreases in neutrophil counts were reported in 2.9%/0% of TCZ patients; no grade 3/4 decreases were reported in control patients. There were no occurrences of decreased platelet counts to clinically significant values (grade 3/4).

Conclusions: TCZ led to significant improvements in disease activity, ACR responses, and CRP and Hb levels as early as week 4 and in DAS28 response as early as week 1; responses persisted through week 24. Safety findings were consistent with the known safety profile of TCZ. With early and sustained efficacy, TCZ is an effective treatment option for patients with RA who have failed DMARDs.

Percentages of ACR20, ACR50, and ACR70 Responders, Mean Change From Baseline in RAPID3 and FACIT-Fatigue Scores, and Mean CRP Levels by Visit (ITT population: TCZ group, n=409; control group, n=205)

Week	TCZ	Control	p	TCZ	Control	p	TCZ	Control	p
	ACR20, %			ACR50, %			ACR70, %		
4	34.2	17.6	<0.0001	12.5	3.4	0.0002	4.4	1.5	0.0627
8	46.5	25.4	<0.0001	20.8	5.4	<0.0001	6.8	0.5	0.0002
24	44.7	25.4	<0.0001	30.1	11.2	<0.0001	15.4	1.5	<0.0001
	RAPID3 Score[a]			FACIT-Fatigue Score[a]			CRP[b], mg/dL		
4	−1.27	−0.52	<0.0001	3.97	2.99	0.1592	0.41	1.71	<0.0001
8	−1.70	−0.75	<0.0001	5.71	3.72	0.0110	0.28	1.72	<0.0001
24	−2.30	−1.37	<0.0001	8.49	5.76	0.0188	0.25	1.37	<0.0001

[a]Adjusted mean change from baseline, *p* adjusted for baseline value. [b]Mean values, *p* based on change from baseline adjusted for baseline value.

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1809

Efficacy of Abatacept and Tocilizumab in Rheumatoid Arthritis Patients Treated in Clinical Practice. Results from the Nationwide Danish DANBIO Registry. Henrik C. Leffers[4], Mikkel Ostergaard[4], Bente Glintborg[7], Niels Steen Krogh[10], Heidi Foged[6], Ulrik Tarp[1], Tove Lorenzen[9], Annette Hansen[3], Michael S. Hansen[2], Martin S. Jacobsen[8] and Merete L. Hetland[5]. [1]Aarhus University Hospital, Denmark, [2]Copenhagen University Hospital Gentofte, Denmark, [3]DANBIO Registry, and Copenhagen University Hospital Gentofte, Denmark, [4]DANBIO Registry, and Copenhagen University Hospital, Hvidovre and Glostrup, Hvidovre, Denmark, [5]DANBIO Registry, and Copenhagen University Hospital, Hvidovre and Glostrup, Denmark, [6]Frederiksberg Hospital, Denmark, [7]Holbæk Hospital, Denmark, [8]Randers Hospital, Denmark, [9]Vejle Hospital, Denmark, [10]Zitelab Aps, Denmark

Background: Abatacept (a selective T-cell costimulation modulator) and tocilizumab (an interleukin-6 (IL-6) receptor-inhibiting monoclonal antibody) have recently been approved for the treatment of rheumatoid arthritis (RA) based on their efficacy and safety in randomized controlled clinical trials. However, reports on their efficacy in clinical practice are scarce.

The aim of this study was to describe the disease activity, clinical response and drug survival in RA patients treated with abatacept or tocilizumab for the first time, based on prospectively registered data from the nationwide Danish DANBIO registry.

Methods: In the DANBIO registry we identified 150 and 178 RA patients treated with abatacept and tocilizumab, respectively. The clinical efficacy was assessed by changes in the 28 joints Disease Activity Score (DAS28), European League Against Rheumatism (EULAR) response rates after 24 and 48 weeks and drug survival. No imputation of missing values was done.

The small number of patients and the brief follow-up period did not allow for a direct comparison of the 2 drugs.

Results: Of the patients receiving abatacept and tocilizumab, respectively, 34%/42% (abatacept/tocilizumab) were male, median (interquartile range, IQR) age 54 (43–62)/56 (43–68) years, disease duration 8.5 (3–14)/9 (3–12) years and number of previous biological drugs 2 (2–3)/2 (2–3). Nearly all patients (95%/93%) had previously received ≥1 Tumor Necrosis Factor inhibitor (TNFi).

In the abatacept group, DAS28 was 5.3 (4.7–6.1), 3.4 (2.7–4.9) and 3.3 (2.5–4.3) at baseline, weeks 24 and 48, respectively, while 5.4 (4.7–6.2), 2.9 (2.3–4.0) and 2.5 (1.9–4.5) in the tocilizumab group. Changes in DAS28 variables over time seemed numerically very similar, except for C-Reactive Protein (CRP), which declined more rapidly in tocilizumab treated patients.

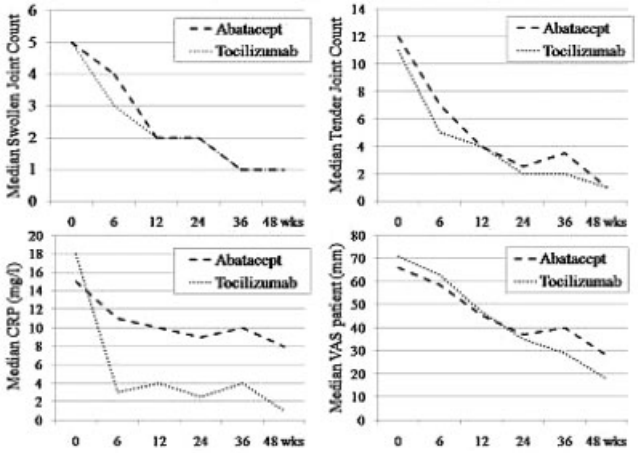

Figure 1. DAS28 variables. Time since treatment initiation (weeks).

DAS28 remission rates were 19% and 26% at week 24 and 48, respectively, in the abatacept group, while 39% and 58% in the tocilizumab group. Rates of EULAR moderate-/EULAR good response were 30%/40% and 32%/45% at week 24 and 48, respectively, in the abatacept group, while 43%/45% and 26%/58% in the tocilizumab group. After 1 year, 50% of abatacept patients and 60% of tocilizumab patients were still receiving the drug.

Conclusions: In RA patients (≥90% TNFi failures), abatacept and tocilizumab both significantly decreased the disease activity, and clinical response (EULAR good or moderate) were seen in the majority (≥70%) of patients. 50–60% of patients were still receiving the drug after 1 year. In the tocilizumab group, a steeper decline in CRP was observed than in the abatacept group, whereas changes in other outcome measures were similar.

Disclosure: H. C. Leffers: None; **M. Ostergaard:** Abbott Immunology Pharmaceuticals, 2, Centocor, Inc., 2, Roche, 2, Schering-Plough, 2, UCB, Inc., 2, Wyeth Pharmaceuticals, 2; **B. Glintborg:** None; **N. S. Krogh:** None; **H. Foged:** None; **U. Tarp:** None; **T. Lorenzen:** None; **A. Hansen:** None; **M. S. Hansen:** None; **M. S. Jacobsen:** None; **M. L. Hetland:** Abbott Immunology Pharmaceuticals, 2, Centocor, Inc., 2, Roche, 2, Schering-Plough, 2, UCB, Inc., 2, Wyeth Pharmaceuticals, 2.

1810

Efficacy of Rituximab on Pulmonary Rheumatoid Nodules: Data of 10 Patients from the French AIR/PR Registry. Baptiste Glace[7], Jacques E. Gottenberg[13], Xavier Mariette[1], Antoine Roche[5], Jean-Marie Berthelot[11], Maxime Dougados[3], Eric Toussirot[6], Thao Pham[9], Yannick Allanore[2], Damien Loeuille[10], Liana E. Euller-Ziegler[4], Thierry Lequerré[12] and Martin Soubrier[8]. [1]Bicetre Hospital/Paris Univ, Le Kremlin Bicetre, France, [2]Hopitaux de Paris Cochin, Paris, France, [3]Hospital Cochin, Paris, France, [4]L'Archet Hospital (University), Nice, France, [5]Radiology Department, CHU Clermont-Ferrand, [6]Rheumatology Department, CHU Besançon, [7]Rheumatology Department, CHU Clermont-Ferrand, [8]Rheumatology Department, CHU Clermont-Ferrand, [9]Rheumatology Department, CHU Marseille, [10]Rheumatology Department, CHU Nancy, [11]Rheumatology Department, CHU Nantes, [12]Rheumatology Department, CHU Rouen, [13]Strasbourg Hospitals, Strasbourg, France

Background: Pulmonary rhumatoid nodules (PRN) occur in 5 to 20% of patients having rheumatoid arthritis (RA). DMARDs (methotrexate, leflunomide) and TNF blockers may accelerate pulmonary nodulosis. The presence of B CD 20 lymphocytes on their outer rim has raised the potential impact of Rituximab (RTX) as emphasized in a recent report [1].

Objectives: We assessed the outcomes of patients with PRN from the French autoimmunity and RTX registry (AIR).

Method: AIR is an independent registry under the aegis of the French society of Rheumatology. Standardized information was gathered every 6 months for 5 years by trained clinical nurses in each centre taking part. RA patients with pulmonary nodules observed on CT-scan at baseline and at follow up were included. Scanner readings were centralized (AR). The nodules were assessed according to their number and size (long axis).

Results: Of the 2573 patients from 85 centres reviewed, 30 had PRN. 10 of these patients fitted the inclusion criteria: 8 women with a mean age of 66.5 ± 59/79 years and 2 men with a mean age of 56 ± 51/61 years. All the patients had erosive, seropositive, anti CCP positive RA. Nine patients had sub-cutaneous nodulosis. The nodules were found while the patients were undergoing treatment with methotrexate (MTX) (n=3), MTX in combination with etanercept (n=3) or adalimumab (n=1), adalimumab alone (n=1) and leflunomide in combination with etanercept (n=2). RTX was administred with MTX (n=4), leflunomide (n=2), salazopyrine and hydroxychloroquine (n=1) or alone (n = 3). Nine patients were receiving corticosteroids (prednisolone) with a mean dose of 10.8 ± (5.20) mg. With a mean follow-up of 11.5±8.2 months, twenty one out of the 27 nodules studied improved (78%) and the mean long axis decreased from 14.4 ± 7.8 mm to 8.5 ± 9mm (p=0.001). Fourteen nodules had improved after a mean follow-up of 8.3±2.7 months (mean long axis from 14.4±9mm to 11.3±8.9mm). Seven nodules had disappeared after a mean follow-up of 19.5±17.6 months (mean long axis at baseline: 15.5±5.5mm). Six nodules worsened after a mean follow-up of 14.8±0.7 months (mean long axis from 14.8±10mm to 17.8±9.8mm).

Conclusion: RTX seems to be effective in treating pulmonary rheumatoid nodules.

References:

[1] Favorable response of pulmonary rheumatoid nodule to Rituximab Oqueka T, Schultz H, Moosig F.Z Rheumatol. 2009 Jun;68(4):343–4.

Disclosure: B. Glace: None; **J. E. Gottenberg:** None; **X. Mariette:** None; **A. Roche:** None; **J.-M. Berthelot:** None; **M. Dougados:** None; **E. Toussirot:** None; **T. Pham:** None; **Y. Allanore:** None; **D. Loeuille:** None; **L. E. Euller-Ziegler:** None; **T. Lequerré:** None; **M. Soubrier:** None.

1811

Etanar® Therapy in Real-Life Patients with Rheumatoid Arthritis. Federico Rondon[11], Alain Bautista[4], Juan Carlos Salazar[1], Nohemí Casas[9], Pedro Santos[9], Francisco Vargas[6], Javier Márquez[2], Fredy Pumarejo[8], Fernando Fernández[3], Andrés Fernández[5], Rossana Mejía[1], Oscar Ruiz[1], Alberto Torrenegra[3], Jose Bernardo Martínez[7] and Rubén Darío Mantilla[10]. [1]CIREI, Bogota, [2]Hospital Pablo Tobon Uribe, Medellin, [3]Rheumatology, Barranquilla, [4]Rheumatology, Cucuta, [5]Rheumatology, Ibague, [6]Rheumatology, Medellin, [7]Rheumatology, Monteria, [8]Rheumatology, Valledupar, [9]Riesgo de Fractura-CAYRE IPS, Bogota, [10]Riesgo de Fractura-CAYRE IPS, Bogota, Colombia, [11]Universidad Nacional, Bogota

Objectives: Etanar®, a recombinant tumor necrosis factor receptor:Fc fusion protein, has been shown to be effective in suppressing disease activity in patients with rheumatoid arthritis (RA) who fail to respond to disease-modifying anti-rheumatic drugs (DMARDs). We present a 20-week analysis of the efficacy and safety of treating patients with long-standing, multi-DMARD resistant RA with Etanar® in a 'real-life' setting.

Methods: This multicenter observational before-after study enrolled patients with active RA despite treatment with DMARDs who started Etanar® treatment (25 mg s.c. injection twice weekly) and were followed for 20 weeks. Demographics and clinical characteristics including functional status (HAQ) and activity of disease (DAS28) were registered every 4 weeks.

Results: 110 patients were enrolled (82% women, mean age: 52.5 ± 14.5 yrs, mean duration of RA: 9.7 ± 8.9 yrs). Comorbidity was present in 43 (39.1%) patients with arterial hypertension, observed in 20 (18.2%) patients, being the most frequent. Methotrexate (MTX) was administered for 85.3% of the patients. Of the patients, 28.5% were receiving monotherapy and 71.5% were on combination therapy, MTX-Sulfasalazine and MTX-Leflunomide were the most frequently used in 21.5% and 20.6% respectively. DAS28 declined from 5.76 ± 0.81 to 3.48 ± 1.12 ($p < 0.001$, by Friedman test), and HAQ declined from 2.5 ± 1.1 to 1.1 ± 0.9 ($p < 0.001$). Side-effects were registered in 11 (10%) cases, and the main causes of discontinuation of anti-TNF therapy were lack of efficacy

(n=2), heart failure (n=2), nausea and dizziness (n=2), pneumonia (n=2) and asthma (n=1).

Conclusions: Etanar® can effectively control disease activity in real-life patients with active RA and poor responses to MTX but also other DMARDs. Safety and tolerability assessment indicates Etanar to be well tolerated.

Disclosure: F. Rondon: Lafrancol, 2; **A. Bautista:** Lafrancol, 2; **J. C. Salazar:** Lafrancol, 2; **N. Casas:** Lafrancol, 2; **P. Santos:** Lafrancol, 2; **F. Vargas:** Lafrancol, 2; **J. Márquez:** Lafrancol, 2; **F. Pumarejo:** Lafrancol, 2; **F. Fernández:** Lafrancol, 2; **A. Fernández:** Lafrancol, 2; **R. Mejía:** Lafrancol, 2; **O. Ruiz:** Lafrancol, 2; **A. Torrenegra:** Lafrancol, 2; **J. B. Martínez:** Lafrancol, 2; **R. D. Mantilla:** Lafrancol, 2.

1812

Etanercept (ETN) Plus Methotrexate (MTX) Combination Therapy Resulted in a Better Radiographic Outcome Than ETN Monotherapy Even in Patients with Active Rheumatoid Arthritis Despite MTX Treatment: 104-Week Results from the JESMR Study. Hideto Kameda[2], Katsuaki Kanbe[7], Eri Sato[7], Yukitaka Ueki[5], Kazuyoshi Saitoh[8], Shouhei Nagaoka[9], Toshihiko Hidaka[10], Tatsuya Atsumi[1], Michishi Tsukano[4], Tsuyoshi Kasama[6], Shunichi Shiozawa[3], Yoshiya Tanaka[8], Hisashi Yamanaka[7] and Tsutomu Takeuchi[2]. [1]Hokkaido University Graduate School of Medicine, [2]Keio University, [3]Kobe University Hospital, [4]Kumamoto Orthopaedic Hospital, [5]Sasebo Chuo Hospital, [6]Showa University School of Medicine, [7]Tokyo Women's Medical University Medical Center, [8]University of Occupational and Environmental Health, [9]Yokohama Minami Kyosai Hospital, [10]Zenjinkai Shimin-No-Mori-Hospital

Background: The radiographic superiority of the continuation of methotrexate (MTX) to its discontinuation at the commencement of etanercept (ETN) in patients with active rheumatoid arthritis (RA) despite MTX therapy has not been clarified.

Objectives: An important aim of the JESMR study is to compare the radiographic efficacy of continuation versus discontinuation of MTX at the commencement of ETN for two years in patients with active RA despite MTX therapy.

Methods: In total, 151 patients with active RA despite treatment with MTX were randomized to either ETN 25 mg twice a week with 6–8 mg/week of MTX (the E+M group), or ETN alone (the E group). The radiographic progression was assessed by van der Heijde-modified Sharp score at baseline, weeks 24, 52 and 104. The last observation carried forward and linear imputation were used for the analysis of clinical and radiographic efficacy, respectively, for missing data.

Results: Demographic and clinical features between groups at baseline were similar. The cumulative probability plot of ACR-N at week 104 clearly demonstrated the superior response in the E+M group to that in the E group. The ACR 20, 50 and 70 response rates at week 52 were 82.2%, 68.5% and 46.6%, respectively, in the E+M group, all of which were significantly greater than 59.4% (p=0.003), 39.1% (p=0.001) and 23.2% (p=0.005), respectively, in the E group. The mean progression in total score (ΔTSS) tended to be smaller in the E+M group than in the E group (1.2 versus 6.6, p=0.09), and a significant difference was observed in the erosion score change at week 104 (−0.5 versus 3.1, respectively, p=0.045). Furthermore, ACR-N < 50 predicted a risk for radiographic progression only in the E group.

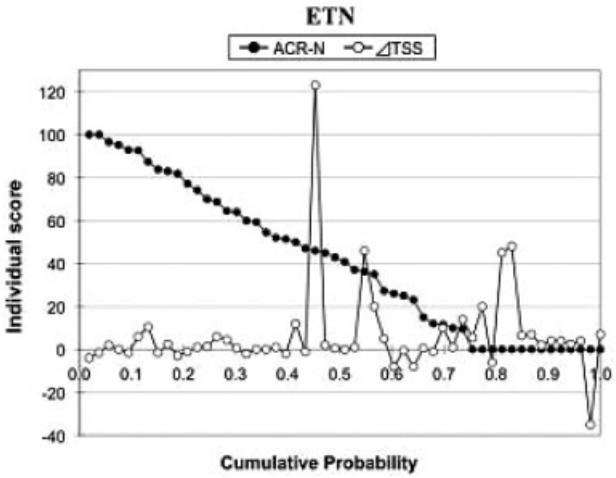

Figure 1.

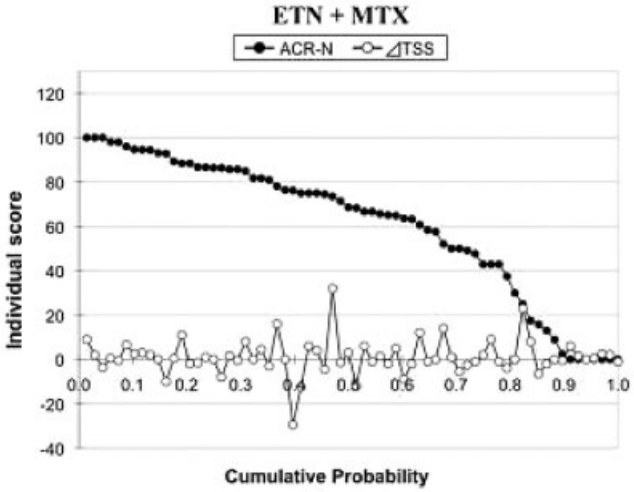

Figure 2.

Conclusion: The continuation of MTX at the commencement of ETN therapy is clinically and radiographically beneficial even in RA patients who had shown an inappropriate response to MTX.

Disclosure: H. Kameda: Pfizer Inc, 8; **K. Kanbe:** Pfizer Inc, 8; **E. Sato:** None; **Y. Ueki:** None; **K. Saitoh:** None; **S. Nagaoka:** Pfizer Inc, 2, 8; **T. Hidaka:** Pfizer Inc, 8; **T. Atsumi:** Pfizer Inc, 8; **M. Tsukano:** Pfizer Inc, 2, 8; **T. Kasama:** Pfizer Inc, 2, 8; **S. Shiozawa:** Pfizer Inc, 2; **Y. Tanaka:** Pfizer Inc, 8; **H. Yamanaka:** Pfizer Inc, 2, 8; **T. Takeuchi:** Pfizer Inc, 2, 8.

1813

Etanercept Normalizes Systemic Bone Metabolism in Rheumatoid Arthritis Patients. Won Park[2], Mie Jin Lim[1], Seong Ryul Kwon[1], Ji Yeol Yoon[1], Chang Gi Moon[1] and Go Eun Ju[1]. [1]Inha University Hospital, Incheon, Republic of Korea, [2]Inha University Hospital, Choong-Gu Incheon, Korea, Republic of

Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease accompanied by bone loss. Etanercept is soluble TNF-α receptor which is effective in suppressing RA activity.

Objective: Our aim is to assess bone metabolism in TNF naïve RA patients and to figure out effects of etanercept on bone turnover markers and inflammatory mediators.

Methods: Twenty-one RA patients (19 women and 2 men; age 46.29 ± 11.6 years) were included. They were required to be active RA, thus meeting the criteria of DAS28 ≥ 3.2 and either ESR ≥ 28 mm/hr or CRP ≥ 2.0 mg/dL and morning stiffness ≥ 45 minutes.

Age and sex matched control group were recruited.

Etanercept was administered at standard dose, twice a week.

Venous blood was drawn at baseline in both groups and at week 14–16 after etanercept use in RA patient. Bone metabolism was assessed using bone specific alkaline phosphatase (BSAP), osteoprotegerin (OPG), sclerostin for bone formation and receptor activator for nuclear factor κB ligand (RANKL), serum c-telopeptide (CTX) for bone resorption. Serum level of inflammatory mediators including ESR, CRP and IL-6 were also determined.

Differences between two groups were examined for statistical difference by Wilkoxon signed ranks test. A p value of less than 0.05 was denoted statistically significant.

Results: At baseline the sclerostin level was significantly decreased in RA patients than in control group while serum CTX was decreasing. However after etanercept use, both serum CTX and sclerostin markedly increased (Table 1).

Table 1. Bone metabolism in TNF naïve RA patients and changes observed after etanercept use

	Baseline	Week 14–16 after etanercept use	*p*
ESR (mm/hr)	39 ± 31.2	26 ± 25	0.013
CRP (mg/dL)	0.98 ± 0.866	0.43 ± 1.118	0.013
IL-6 (pg/mL)	3.58 ± 3.371	0.77 ± 0.726	0.001
OPG (pmol/L)	2.36 ± 1.081	2.2 ± 0.786	0.619
BSAP (U/L)	20 ± 6.97	20.3 ± 7.45	0.887
RANKL (pmol/L)	0.25 ± 0.37	0.22 ± 0.422	0.07

Table 2. Bone turnover markers and inflammatory mediators after etanercept administration in RA patients

	Age and sex matched control	RA patients baseline	*P* (control vs. RA patients baseline)	week 14–16 after etanercept	*P* (RA patients baseline Vs. Week 14–16)
Sclerostin (pg/mL)	2.2 ± 1.61	1.63 ± 2.26	0.03	2.95 ± 4.18	0.046
Serum CTX (ng/mL)	0.38 ± 0.18	0.28 ± 0.13	0.114	0.34 ± 0.17	0.048

BSAP and OPG were slightly affected by etanercept. RANKL mildly decreased after treatment.

Inflammatory mediators responded to the treatment as ESR, CRP and IL-6 all significantly decreased (Table 2).

Conclusions: Our study showed lower level of serum CTX and sclerostin in RA patients than in control group, which suggested slow bone resorption rate coupled with low bone production. However after etanercept use, bone turnover markers rose while inflammation was decreasing. Therefore we conclude that etanercept stimulates depressed bone metabolism in RA patients as it suppresses inflammation.

Disclosure: W. Park: None; **M. J. Lim:** None; **S. R. Kwon:** None; **J. Y. Yoon:** None; **C. G. Moon:** None; **G. E. Ju:** None.

1814

Golimumab, a Human Anti-TNFα Monoclonal Antibody Administered Subcutaneously Every Four Weeks as Monotherapy in Patients with Active Rheumatoid Arthritis Despite DMARD Therapy: 24-Week Results of Clinical and Radiographic Assessments. Tsutomu Takeuchi[5], Masayoshi Harigai[8], Yoshiya Tanaka[10], Hisashi Yamanaka[9], Naoki Ishiguro[7], Kazuhiko Yamamoto[11], Takuya Oba[4], Mahboob U. Rahman[1], Toru Yoshinari[6], Nobuyuki Miyasaka[2] and Takao Koike[3]. [1]Centocor Research and Development, Inc., Malvern, PA, [2]Graduate School of Medical and Dental Sciences, Tokyo, Japan, [3]Hokkaido University Graduate School of Medicine, [4]Janssen Pharmaceutical K.K., [5]Keio University, Toyko, Japan, [6]Mitsubishi Tanabe Pharma Corporation, [7]Nagoya University, [8]Tokyo Medical and Dental University, Tokyo, Japan, [9]Tokyo Womens Med Univ, Shinjuku-ku, Tokyo, Japan, [10]University of Occupational and Environmental Health, Kitakyushu, Japan, [11]University of Tokyo Graduate School of Medicine, Tokyo, Japan

Objective: To assess the efficacy and safety of golimumab (GLM) as a monotherapy in Japanese patients with active rheumatoid arthritis (RA) despite DMARD therapy.

Methods: In this multicenter, randomized, double-blind, placebo (PBO)-controlled study, patients with active RA with ≥6 swollen and ≥6 tender joints (SJC/TJC) despite treatment with DMARD were randomized to subcutaneous injections of PBO, GLM 50mg, or GLM 100mg administered q4 wks. Starting at wk 16, GLM 50mg was administered q4 wks to patients in the PBO group. The primary endpoint was the proportion of patients achieving ACR20 at wk 14. Secondary endpoints included the proportion of patients achieving ACR50, ACR70 response, DAS28 (ESR) response, and improvement in Health Assessment Questionnaire (HAQ) at wk 14, and change from baseline in van der Heijde/Sharp-Score (vdH-S) at wk 24. Data was analyzed using Full Analysis Set (modified Intent-To-Treat: all patients receiving one dose of study treatment included) population. The results of the non-parametric data analyzed using van der Waerden method is being reported.

Results: 308 patients received treatment (105 PBO, 101 GLM 50mg, and 102 GLM 100mg). Treatment groups were balanced for baseline demographic and disease characteristics [mean (SD) values for all patients: CRP 2.46(2.62) mg/dL, ESR 47.9(30.18) mm/hr, SJC 12.9(6.49), TJC 15.7(9.25), DAS 28(ESR) 5.89(1.04)]. The baseline vdH-S(TSS) for the GLM 50mg and 100mg groups were 44.05(50.80) and 56.66(56.74), respectively. At wk 14, the GLM 50mg and 100mg groups were significantly better than PBO in improving signs and symptoms of RA and physical function (Table). At wk 24, the GLM 100mg group significantly inhibited radiographic progression compared with PBO; the median and IQ ranges clearly showed better inhibition with the GLM 100 mg dose. Through wk 16, the overall incidence of adverse events (AEs) was 63.8%, 62.4%, and 59.8% in the PBO, GLM 50mg, and GLM 100mg groups, respectively; serious AEs occurred in 1.9%, 1.0%, and 2.0% of the patients in the PBO, GLM 50mg, and GLM 100mg groups, respectively. Serious infections occurred in 1.0%, 0%, and 1.0% of patients, respectively, in the PBO, GLM 50mg, and GLM 100mg. Injection site reactions occurred in 6.7%, 7.9%, and 7.8% of patients, respectively. There were no reports of tuberculosis or death.

Conclusion: Both doses of GLM significantly improved signs, symptoms, and physical function compared with PBO. In addition GLM 100 mg significantly inhibited progression of structural damage compared with PBO. Injection site reactions were mild and not increased compared with PBO. GLM monotherapy was well-tolerated with safety profile similar to other anti-TNF agents.

Tables. Efficacy at Wk 14 and Wk 24

Assessment	PBO	GLM 50 mg	GLM 100 mg
Patients treated (n)	105	101	102
Primary Endpoint			
ACR 20 at Wk 14	20 (19.0)	51 (50.5)*	60 (58.8%)*
Secondary Endpoints			
Wk 14			
ACR 50	6 (5.7%)	29 (28.7%)*	33 (32.4%)*
ACR 70	1 (1.0%)	13 (12.9%)**	12 (11.8%)***
DAS28 (ESR) moderate responders	26 (27.7%)	69 (71.1%)*	74 (74.0%)*
Improvement from baseline in HAQ (mean [SD]), range	−0.042 (0.546) (−1.88, 1.75)	0.255 (0.507)* (−1.88, 1.38)	0.330 (0.450)* (−0.750, 1.75)
Wk 24			
Change from baseline in vdH-S (TSS)			
Mean (SD), (range)	2.58 (4.69) (−2.5, 29.8)	1.87 (4.09) (−1.8, 23.0)	2.13 (10.42) (−2.5, 102.5)
Median (IQ range)	1.00 (0.00, 3.50)	0.50 (0.00, 2.00)	0.00 (−0.50, 2.00)
p-value		0.1802	0.0043
Change from baseline in joint space narrowing score			
Mean (SD), (range)	0.90 (1.89) (−1.0, 9.5)	1.02 (2.83) (−1.5, 17.5)	0.96 (5.05) (−2.0, 48.5)
Median (IQ range)	0.00 (0.00, 1.00)	0.00 (0.00, 0.50)	0.00 (0.00, 0.50)
p-value		0.3373	0.0832
Change from baseline in bone erosion score			
Mean (SD), (range)	1.28 (2.49) (−2.5, 14.5)	0.98 (2.06) (−1.5, 11.5)	1.13 (5.69) (−2.5, 54.0)
Median (IQ range)	0.50 (0.00, 2.00)	0.50 (0.00, 1.00)	0.00 (0.00, 1.00)
p-value		0.5895	0.0316

*p<0.0001; **p=0.0007; ***p=0.0013

Disclosure: T. Takeuchi: Centocor Research and Development, Inc., 2, 5, 8, 9, Centocor Research and Development, Inc., Mitsubishi-Tanabe Pharma, 2, 5, 8, 9, Jansen Pharma, Mitsubishi-Tanabe Pharma, Wyeth KK, Takeda Pharma LTD, Abbott, Eisai Pharma, Chuga; **M. Harigai:** Centocor Research and Development, Inc., 2, 5, 9, Centocor Research and Development, Inc., Mitsubishi-Tanabe Pharma, Wyeth Pharma, Chugai Pharma, Abot Japan, Eisai Pharma, Takeda Pharma LTD, Bristol-Myers, 2, 5, 9, Mitsubishi-Tana; **Y. Tanaka:** Centocor Research and Development, Inc., 2, 5, 8, 9, Centocor Research and Development, Inc., Mitsubishi-Tanabe Pharma, Takeda Pharma, Banyu Pharma, Chugai Pharma, Eisai Pharma, Astellas Pharma, Abbott Immunology Pharma, Janssen Ph; **H. Yamanaka:** Centocor Research and Development, Inc., 2, 5, 9, Centocor Research and Development, Inc., Janssen Pharma, Mitsubishi-Tanabe Pharma, Wyeth KK, Takeda Pharma LTD, 2, 5, 9, Janssen Pharma, Mitsubishi-Tanabe Pharma, Wyeth KK, Taked; **N. Ishiguro:** Centocor Research and Development, Inc., 2, 8, 9, Centocor Research and Development, Inc., Takeda Pharma, Mitsubishi-Tanabe Pharma, Astellas Pharma, Chugai Pharma, Eisai Pharma, 2, 8, 9, Takeda Pharma, Mitsubishi-Tanabe Pharma, A; **K. Yamamoto:** Astellas, Janssen Pharmaceutical, Mitubishi-Tanabe, 1, 2, 5, 8, 9, Centocor Research and Development, Inc., Santen Pharma, Mitsubishi-Tanabe Pharma, 1, 2, 5, 8, 9, Immunofuture Inc., 1, 2, 5, 8, 9, Mitsubishi-Tanabe Pharma, Abbot; **T. Oba:** Janssen Pharmaceutica Product, L.P., 3; **M. U. Rahman:** Centocor Research and Development, Inc., 3; **T. Yoshinari:** Mitsubishi-Tanabe Pharma, 3; **N. Miyasaka:** Centocor Research and Development, Inc., 2, 5, 9, Centocor Research and Development, Inc., Tanabe-Mitsubishi Pharma, Chugai Pharma, Abbott Japan, Eisai Pharma, Takeda Pharmaceutical Co LTD, Daiichi-Sankyo Pharma, Astellas Pharma; **T. Koike:** Centocor Research and Development, Inc., 2, 5, 8, 9, Centocor Research and Development, Inc., Janssen Pharma, Mitsubishi-Tanabe Pharma, 2, 5, 8, 9, Mitsubishi-Tanabe Pharma, Pfizer Inc., Takeda Pharma LTD, Abbott, Eisai Pharma, Chu.

1815

Golimumab, a Human Anti-TNFα Monoclonal Antibody Administered Subcutaneously Every Four Weeks in Patients with Active Rheumatoid Arthritis Despite Methotrexate Therapy: 24-Week Results of Clinical and Radiographic Assessments. Yoshiya Tanaka[10], Masayoshi Harigai[8], Tsutomu Takeuchi[4], Hisashi Yamanaka[9], Naoki Ishiguro[6], Kazuhiko Yamamoto[7], Takuya Oba[3], Mahboob U. Rahman[1], Toru Yoshinari[5], Nobuyuki Miyasaka[8] and Takao Koike[2]. [1]Centocor Research and Development, Inc., Malvern, PA, [2]Hokkaido University Graduate School of Medicine, [3]Janssen Pharmaceutical K.K., [4]Keio University, Toyko, Japan, [5]Mitsubishi Tanabe Pharma Corporation, [6]Nagoya University, [7]The University of Tokyo, [8]Tokyo Medical and Dental University, Tokyo, Japan, [9]Tokyo Womens Medical University, Shinjuku-ku, Tokyo, Japan, [10]University of Occupational and Environmental Health, Kitakyushu, Japan

Objective: To assess the efficacy and safety of golimumab(GLM) in Japanese pts with active RA despite MTX therapy.

Methods: In this multicenter, randomized, double-blind, placebo-controlled study, pts with active RA despite MTX therapy with ≥4 swollen and ≥4 tender joints (SJC/TJC) were randomized to receive subcutaneous injections of PBO, GLM 50mg, and GLM100mg administered q4wks. All pts received MTX 6–8 mg orally/wk. Pts with <20% improvement in SJC/TJC entered early escape at wk16 in a blinded manner, as follows: PBO+MTX → GLM50mg+MTX and GLM50mg+MTX → GLM100mg+MTX. Pts receiving GLM100mg+MTX remained on the same dose. The primary endpoint was the proportion of pts achieving ACR20 at wk14. Secondary endpoints were the proportion of pts achieving ACR20 at wk24, ACR50, ACR70 response at wks14 and 24, change from baseline in DAS28 (ESR) scores and improvement in Health Assessment Questionnaire (HAQ) at wks14&24, and change from baseline in van der Heijde/Sharp-Score(vdH-S) at wk24. Data was analyzed using Full Analysis Set (modified Intent-To-Treat:all pts receiving one dose of study treatment included) population. The results of the non-parametric data analyzed using van der Waerden method is reported.

Results: 261 pts received treatment (88 PBO+MTX, 86 GLM50mg+MTX, and 87 GLM100mg+MTX). Treatment groups were balanced for baseline demographic and disease characteristics [mean(SD) values for all pts: CRP 1.86(2.29) mg/dL, ESR 44.3(29.94) mm/hr, SJC 11.5(6.60), TJC 13.1(7.92), DAS 28(ESR) 5.52(1.05), vdH-S(TSS) 55.10 (58.09)]. Both doses of GLM+MTX were significantly better than PBO+MTX in improving signs and symptoms/physical function and in inhibiting radiographic progression (Table). Through wk24, 80.7%, 81.4%, and 82.8% of pts had ≥1 adverse event (AE) in the PBO + MTX, GLM 50mg + MTX, and GLM 100mg + MTX groups, respectively. Serious AEs occurred in 1.1%, 2.3%, and 3.4% of pts, respectively. Serious infections occurred in 0.0%, 0.0%, and 1.1% of pts, in the PBO+MTX, GLM50mg+MTX, and GLM100mg+MTX groups respectively. Injection site reactions occurred in 9.1%, 9.3%, and 11.5% of pts, respectively. One pt in the GLM50mg+MTX group had a bone neoplasm (thoracic vertebra tumor; hemangoendothelioma, of low malignancy potential). There were no reports of tuberculosis or deaths.

Conclusions: Both GLM+MTX doses had significantly greater improvement in signs and symptoms and physical function, as well as significantly better inhibition of progression of structural damage compared with PBO+MTX in pts with RA. Injection site reactions were mild and not increased compared with PBO+MTX. GLM+MTX was well-tolerated with safety profile similar to other anti-TNF agents.

Table. Efficacy results through Wk 14 and Wk 24

Assessment	PBO+MTX	GLM+MTX GLM 50 mg	GLM+MTX GLM 100 mg	GLM+MTX Combined
Pts treated (n)	88	86	87	173
Primary Endpoint				
ACR 20 at wk 14	24 (27.3%)	62 (72.1%)*	65 (74.7%)*	127 (73.4%)*
Secondary Endpoints				
Wk 14				
ACR 50	8 (9.1%)	37 (43.0%)*	33 (37.9%)*	70 (40.5%)*
ACR 70	2 (2.3%)	19 (22.1%)	12 (13.8%)**	31 (17.9%)***
DAS28 (ESR) moderate responders	32 (37.6%)	66 (79.5%)*	71 (85.5%)*	137 (82.5%)*
Improvement from baseline in HAQ (mean [SD]), range	0.067 (0.495) (−1.750, 1.750)	0.315 (0.397)* (−0.625, 1.375)	0.388 (0.418)* (−0.375, 2.000)	0.352 (0.408)* (−0.625, 2.000)
Wk 24				
ACR 20	29 (33.0%)	61 (70.9%)*	65 (74.7%)*	126 (72.8%)*
ACR 50	13 (14.8%)	36 (41.9%)*	42 (48.3%)*	78 (45.1%)*
ACR 70	5 (5.7%)	23 (26.7%)†	19 (21.8%)‡	42 (24.3%)†
DAS28 (ESR) moderate responders	41 (48.8%)	68 (84.0%)*	74 (90.2%)*	142 (87.1%)*
Improvement from baseline in HAQ (mean [SD]), range	0.027 (0.582) (−1.750, 2.125)	0.330 (0.417)* (−0.375, 1.625)	0.453 (0.431)* (−0.375, 2.000)	0.392 (0.428)* (−0.375, 2.000)
Change from baseline in vdH-S (TSS)				
Mean (SD), (range)	2.51 (5.523) (−8.5, 33.5)	1.05 (3.705) (−6.3, 22.5)	0.33 (2.655) (−3.5, 19.0)	0.69 (3.230) (−6.3, 22.5)
Median, (IQ range)	0.25 (0.00, 3.00)	0.00 (0.00, 1.00)	0.00 (−0.50, 0.50)	0.00 (−0.50, 1.00)
p-value		p=0.0363	p<0.0001	p=0.0003
Change from baseline in Joint Space Narrowing Score				
Mean (SD), (range)	0.83 (2.313) (−6.5, 11.0)	0.71 (2.905) (−2.5, 22.0)	0.29 (1.486) (−2.0, 10.0)	0.50 (2.305) (−2.5, 22.0)
Median, (IQ range)	0.00 (0.00, 1.00)	0.00 (0.00, 0.50)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
		p=NS	p=0.0085	p=0.0391
Change from baseline in Bone Erosion Score				
Mean (SD), (range)	1.66 (3.734) (−2.5, 22.5)	0.54 (1.615) (−2.5, 8.0)	0.03 (1.444) (−3.5, 9.0)	0.28 (1.548) (−3.5, 9.0)
Median, (IQ range)	0.00 (0.00, 1.75)	0.00 (0.00, 1.00)	0.00 (−0.50, 0.50)	0.00 (−0.50, 0.50)
p-value		p=0.0358	p<0.0001	p=0.0002

*p<0.0001; **p=0.0050; ***p=0.0003; †p=0.0002; ‡p=0.0019

Disclosure: Y. Tanaka: Centocor Research and Development, Inc, Mitsubishi-Tanabe Pharma, Takeda Pharma, Banyu Pharma, Chugai Pharma, Eisai Pharma, Astellas Pharma, Abbott Immunology, Jansen Pharma, 2, 5, 8, 9, Centocor Research and Development, Inc., 2; **M. Harigai:** Centocor Research and Development, Inc., 2, 5, 9, Centocor Research and Development, Inc., Mitsubishi-Tanabe Pharma, Wyeth Pharma, Chugai Pharma, Abbot Japan, Eisai, Takeda LTD, Mristol-Myers, 2, 5, 9, Mitsubishi Tanabe Pharma, Wy; **T. Takeuchi:** Centocor Research and Development, Inc, Mitsubishi-Tanabe Pharma, 2, 5, 8, 9, Centocor Research and Development, Inc., 2, 5, 8, 9, Janssen Pharma, Mitsubishi-Tanabe Pharma, Wyeth KK, Takeda Pharma LTD, Abbott, Eisai Pharma, Chuga; **H. Yamanaka:** Centocor Research and Development, Inc, Janssen Pharma, Mitsubishi-Tanabe Pharma, Wyeth KK, Takeda Pharma LTD, Abbott, Eisai Pharma, Chugai Pharma, Otsuka Pharma, Bristol Myers Squibb KK, 2, 5, 9, Centocor Research and Developmen; **N. Ishiguro:** Centocor Research and Development, Inc., 2, 8, 9, Centocor Research and Development, Inc., Takeda Pharma LTD, Mitsubishi-Tanabe Pharma, Astellas Pharma, Chugai Pharma, Eisai Pharma, 2, 8, 9, Takeda Pharma, Mitsubishi-Tanabe Pharm; **K. Yamamoto:** Astellas, Janssen Pharma, Mitsubishi-Tanabe Pharma, 2, 5, 8, 9, Centocor Research and Development, Inc., 2, 5, 8, 9, Centocor Research and Development, Inc., Santen Pharma, Mitsubishi-Tanabe Pharma, 2, 5, 8, 9, Mitsubishi-Tanabe; **T. Oba:** Janssen Pharma KK, 3; **M. U. Rahman:** Centocor Research and Development, Inc., 3; **T. Yoshinari:** Mitsubishi-Tanabe Pharma, 3; **N. Miyasaka:** Centocor Research and Development, Inc., 2, 5, 9, Centocor Research and Development, Inc., Mitsubishi-Tanabe Pharma, Chugai Pharma, Abbott Japan, eisai Pharma, Takeda Pharma LTD, Daiichi-Sankyo Pharma, Astellas Pharma, Teijiin Ph; **T. Koike:** Centocor Research and Development, Inc., 2, 5, 8, 9, Centocor Research and Development, Inc., Janssen Pharma, Mitsubishi-Tanabe Pharma, 2, 5, 8, 9, Mitsubishi-Tanabe Pharma, Pfizer Inc, Takeda Pharma LTD, Abbott, Eisai Pharma, Chuga.

1816

Impact of Abatacept on Circulating Dendritic Cells and Regulatory T Cells in Rheumatoid Arthritis Patients with Inadequate Response or Intolerance to TNF-alpha Blockers. Emilie Shipley[1], Christophe Richez[1], Thomas Barnetche[2], Cécile Contin-Bordes[2], Patrick Blanco[2] and Thierry Schaeverbeke[1]. [1]Hôpital Pellegrin, Bordeaux, France, Metropolitan, [2]Hôpital Pellegrin, France, Metropolitan

Objectives: To assess the variation of circulating dendritic cells (DCs) and T cell subsets, including regulatory T cells (Treg), in rheumatoid arthritis (RA) patients with inadequate response (IR) or intolerance to TNF blockers receiving abatacept and methotrexate for at least 6 months. To evaluate whether these variations correlate with EULAR response criteria and to identify predictive factors of response to abatacept.

Methods: Circulating DCs, including myeloid DCs (mDCs) and plasmacytoid DCs (pDCs), and different T-cell subsets were longitudinally evaluated (M0, M3 and M6) by flow cytometry. Wilcoxon's signed-rank test was used for the analyses of matched pairs. Correlation between cells numbers and activity markers were assessed using Spearman's rank. $P < 0.05$ was considered statistically significant.

Results: Seventeen RA patients with inadequate response or intolerance to TNF blockers initiated with abatacept + MTX, were assessed at baseline, 3 and 6 months. 86% were female. These patients had mean age 61 years, disease duration 13 years, DAS28 4.9 (+/−1.4) and CRP 1.4 mg/dl (+/−1.7). 75% were rheumatoid factor positive and 62.5 % were anti-CCP positive. RA patients were classified as either good or moderate EULAR responders (11pts, 65%) or non-responders (6pts, 35%) at 3 months.

At baseline, no correlation was found in the total population between disease activity and levels of different immune cells, whereas in the responders group, DAS28 negatively correlated with the absolute number of circulating T cells ($r = -0.90$, $p = 0{,}0003$, CD4+T cells ($r = -0.88$, $p = 0{,}0008$, Tregs ($r = -0.68$, $p = 0.03$), mDCs ($r = -0.87$, $p = 0.001$), pDCs ($r = -0.79$, $p = 0.006$) and activated mDCs ($r = -0.82$, $p = 0.02$).

Between M0 and M3, blood CD4+ T cells (595 +/− 362 × 10^3cells/ml at M0 vs. 743 +/− 523 × 10^3cells/ml at M3, p=0.04) and plasmacytoid DCs (3936 +/− 3466 cells/ml at M0 vs. 7277 +/− 5262 cells/ml at M3, p=0.02) levels increased substantially in RA patients treated by abatacept. Interestingly, EULAR responders showed a significant increase at M3 in their numbers of circulating CD3+ T cells (865 +/− 336 × 10^3cells/ml at M0 vs. 1045 +/− 428 × 10^3cells/ml at M3, p=0.02) and myeloid DCs (3177 +/− 2621 cells/ml at M0 vs. 9867 +/− 1145 cells/ml at M3, p=0.03).

Conclusion: Our data suggest that patients with active RA and responding to abatacept are characterized by a decrease at baseline in circulating DCs and T cells including Tregs, which are probably recruited in the target tissues. Efficient abatacept therapy restores levels of these immune cells. Inclusion of additional patients in this ongoing study and analysis of immune cells levels at M3 and M6 should precise the impact of abatacept on DCs/T cells and eventually define predictive factors.

Disclosure: E. Shipley: None; **C. Richez:** Wyeth Pharmaceuticals, 5; **T. Barnetche:** None; **C. Contin-Bordes:** None; **P. Blanco:** None; **T. Schaeverbeke:** Abbott Laboratories, 5, Bristol-Myers Squibb, 2, 5, Merck Pharmaceuticals, 5, Pfizer Inc, 5, Roche, 5.

1817

Impact of Abatacept on Synovitis and Structural Damage in Methotrexate (MTX)—Inadequate Responders with Active Rheumatoid Arthritis (RA): A Randomized, Controlled Magnetic Resonance Imaging (MRI) Exploratory Study. Philip G. Conaghan[9], Patrick Durez[8], Rieke Alten[6], Gerd Burmester[4], Paul P. Tak[1], Lars Klareskog[5], Corine Gaillez[2], Manuela Le Bars[2], Xianhuang Zhou[3] and Charles Peterfy[7]. [1]Academic Medical Center/University of Amsterdam, Amsterdam, The Netherlands, [2]Bristol-Myers Squibb, Rueil-Malmaison, France, [3]Bristol-Myers Squibb, Princeton, NJ, [4]Charité-Universitatsmedizin, Berlin, Germany, [5]Karolinska University Hospital, Stockholm, Sweden, [6]Schlosspark-Klinik, University Medicine Berlin, Germany, [7]Spire Science LCC, San Francisco, CA, [8]Université Catholique de Louvain, Brussels, Belgium, [9]University of Leeds, Leeds, UK

Background: X-ray can detect erosions in established RA, but is less sensitive for early changes[1]. MRI has the potential to study synovial inflammation and measure bone damage at an earlier stage and with greater sensitivity than X-ray.

Objective: Evaluate the impact of abatacept or placebo, + MTX, on MRI changes in wrist synovitis, osteitis and bone erosion in patients with RA and an inadequate response to MTX.

Methods: In this double-blind, randomized, Phase IIIb study of abatacept (~10 mg/kg) versus placebo, + MTX, patients had active RA despite MTX, defined as either DAS28 (CRP) >3.2, or ≥6 tender and swollen joints and CRP above the upper limit of normal. Patients had clinically detectable synovitis of ≥1 wrist, and had ≥1 X-ray erosion or were positive for anti-CCP or RF. Patients had 1.5T MRI (coronal fat-suppressed 3D gradient-echo ± IV gadolinium-contrast) of one wrist at baseline and Month 4. The primary endpoint was mean change at Month 4 in wrist synovitis score (OMERACT-RAMRIS method[2]). Wrist and hand osteitis and erosion scores were secondary endpoints. Exploratory efficacy analyses included DAS28 (CRP), LDAS (≤3.2) and remission (<2.6). Comparisons in wrist synovitis change between groups were based on non-parametric ANCOVA. Efficacy was reported for the intent-to-treat population. Safety was reported for patients who received ≥1 abatacept dose.

Results: Of 27 and 23 patients randomized to abatacept + MTX or placebo + MTX, 26 and 23 completed 4 months. Baseline characteristics were generally similar between groups: mean (SD) RA duration was 25.7 (18.0) and 28.2 (17.0) months, and DAS28 scores were 5.3 (1.1) and 5.3 (0.9) for abatacept and placebo, respectively. However, 55.6 and 48.1% of patients in the abatacept and 82.6 and 73.9% in the placebo group were RF and anti-CCP positive, respectively. Mean change from baseline to Month 4 in synovitis score was –0.44 for abatacept and 0.52 for placebo (p=0.103). For osteitis and erosion scores, mean changes were –1.94 and 0.45 for abatacept versus 1.54 and 0.95 for placebo (treatment difference [95% CI]: –0.50 [–1.77, 0.76] and –3.48 [–6.00, –0.96], respectively). The percentage of patients with newly involved joints at Month 4, by synovitis, osteitis and erosion scores was 8, 28 and 20% for abatacept versus 13, 30 and 30% for placebo. At Month 4, mean (95% CI) change from baseline in DAS28 was –1.68 (–2.15, –1.21) for abatacept and –0.55 (–0.95, –0.16) for placebo. Percentages (95% CI) of patients with LDAS and remission were 50.0 (30.8, 69.2) and 15.4% (1.5, 29.3) in the abatacept and 13.6 (0.0, 28.0) and 0.0% (0.0, 0.0) in the placebo group. Safety events were similar to previously reported abatacept trials.

Conclusions: The sensitivity of MRI is again demonstrated, in that even with small patient numbers and wrist-only assessments, abatacept + MTX treatment was associated with reductions in osteitis and erosion scores, and a trend toward reduced MRI synovitis scores versus placebo + MTX. The beneficial clinical outcomes were consistent with those in other large-scale abatacept clinical trials.

References:

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[2]Ostergaard M, et al. *Ann Rheum Dis* 2005;**64**(Suppl1):i3–i7

Disclosure: P. G. Conaghan: AstraZeneca, 8, Bioiberica, 8, Bristol-Myers Squibb, 8, Centocor, Inc., 8, Merck Pharmaceuticals, 8, Novartis Pharmaceuticals Corporation, 8, Pfizer Inc, 2, 8, Roche, 8; **P. Durez:** Bristol-Myers Squibb, 8, Schering-Plough, 8, Wyeth Pharmaceuticals, 8; **R. Alten:** Bristol-Myers Squibb, 2, 8; **G. Burmester:** Bristol-Myers Squibb, 2, 5, 8; **P. P. Tak:** Bristol-Myers Squibb, 2, 5; **L. Klareskog:** None; **C. Gaillez:** Bristol-Myers Squibb, 3; **M. Le Bars:** Bristol-Myers Squibb, 1, 3; **X. Zhou:** Bristol-Myers Squibb, 3; **C. Peterfy:** Spire Sciences LLC, 3.

1818

Key Pharmacological Parameters Support Monthly Dosing for Golimumab. Mahboob U. Rahman[2], Ann Cai[1], Eilyn Lacy[1], Jonathan Kay[4], Ed C. Keystone[5], Eric L. Matteson[3], Chuanpu Hu[1], Honghui Zhou[1] and Dave Shealy[1]. [1]Centocor Research and Development, Inc., [2]Centocor Research and Development, Inc./ Univ. of Pennsylvania School of Medicine, Malvern, PA, [3]Mayo Clinic, Rochester, MN, [4]UMass Memorial Medical Center, Worcester, MA, [5]University of Toronto, Toronto, ON, Canada

Purpose: To compare the molecular characteristics and clinical pharmacology of SC golimumab (GLM) and adalimumab (ADA), two human anti-TNFα antibodies with similar half-lives but different dosing frequencies.

Methods: Affinity to soluble TNFα was measured by surface plasmon resonance. Evaluation of *in vitro* neutralization efficiency (NE) was accomplished using bioassays for TNFα-induced cytotoxicity on a human rhabdomyosarcoma cell line (KYM-1D4) and E-selectin expression by primary human umbilical vein endothelial cells. A PK/PD model was developed using serum GLM concentrations (conc) and ACR20/50/70 results from GO-FORWARD (Ph 3 trial) using the MTX + PBO, MTX + GLM 50 mg, and MTX+GLM 100 mg grps. Mixed-effect logistic regression was used with a latent variable approach, in conjunction with an inhibitory indirect effect model, to model ACR20/50/70 results simultaneously. The PK/PD model linked time profiles of GLM conc and ACR20/50/70. Results from a Ph 2 dose-ranging study evaluating efficacy of GLM 50 or 100 mg SC q2 or 4wk in pts with active RA despite MTX are presented. The GLM 50 and 100 mg q2 wk grps are combined into a (q2 wk) grp; GLM 50 and 100 mg q4 wk grps are combined into another (q4 wk) grp to assess the relative clinical efficacy of q2 and q4 wk dosing. Primary endpoint was ACR20 at wk 16. ACR20 is presented over time from wks 2–16.

Results: Affinity (mean; range) of GLM for TNFα (18pM; 9–27 pM) was significantly greater than ADA (127 pM; 99–154; p=0.018). Neutralization efficiency (NE) was compared as moles of antibody required to achieve 50% inhibition/mole of TNFα. NE for GLM in the cytotoxicity assay was 22.1 vs 124 for ADA (p<0.001); in the E-selectin assay, NE for GLM was 1.32 vs 4.32 for ADA (p=0.008). A 3 to 6 fold higher conc of ADA was necessary to neutralize the same level of TNFα as GLM *in vitro*. The EC_{50} value (*in vivo* potency) for GLM by the current exposure-response model, using GO-FORWARD data, was estimated to be 454 ± 296 ng/mL, which was smaller than the reported EC_{50} for ADA by PK/PD analysis (810 ± 370 ng/mL) (Nestorov et al. 2004). Although analyzed by different PK/PD methods, this appears consistent with the *in vitro* potency comparison. In the Ph 2 GLM dose ranging study, the proportions of pts who achieved ACR 20 at wk 16 (primary analysis) were 58.0% (p=0.045) and 64.7% (p=0.008) for GLM q4wk + MTX (n=69) and GLM q2wk + MTX (n=68) grps, respectively (vs 37.1% for the PBO + MTX grp [n=35]). Fig 1 shows q4 wk and q2 wk dosing had comparable efficacy.

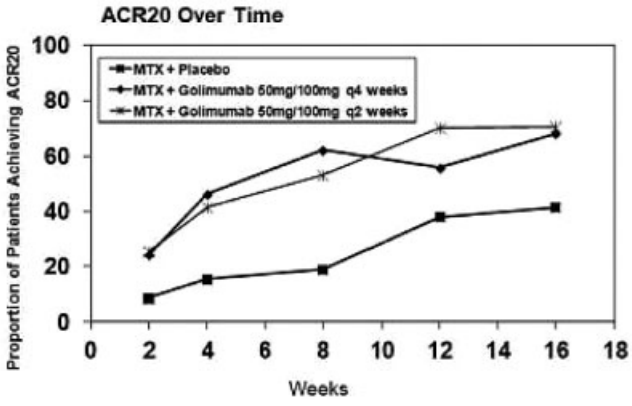

Figure 1.

Conclusions: Compared with ADA, GLM demonstrates greater affinity to TNFα and capacity to neutralize TNFα, in *in vitro* assays, and lower EC_{50} in PK/PD modeling. These data suggest that similar conc of GLM would maintain efficacy for longer duration than those of ADA and allow less frequent dosing, despite similar half-lives. A Ph2 dose ranging study also supports monthly dosing of GLM by demonstrating comparable clinical efficacy with q2 wk and q4 wk dosing.

Disclosure: M. U. Rahman: Centocor Research and Development, Inc., 3; **A. Cai:** Centocor Research and Development, Inc., 3; **E. Lacy:** Centocor Research and Development, Inc., 3; **J. Kay:** Centocor Research and Development, Inc., 2, 9; **E. C. Keystone:** Centocor Research and Development, Inc., 2, 9; **E. L. Matteson:** Centocor Research and Development, Inc., 2, 9; **C. Hu:** Centocor Research and Development, Inc., 3; **H. Zhou:** Centocor Research and Development, Inc., 3; **D. Shealy:** Centocor Research and Development, Inc., 3.

1819

LITHE: Tocilizumab (TCZ) Inhibits Radiographic Progression and Improves Physical Function in Rheumatoid Arthritis (RA) Patients (pts) at 3 Years with Maintenance of Clinical Efficacy over Time. Joel M. Kremer[1], Daniel E. Furst[6], Ruben Burgos-Vargas[3], Jean Dudler[2], Christopher M. Mela[5], Emma Vernon[5] and Roy M. Fleischmann[4]. [1]Albany Medical College, Albany, NY, [2]Hôpital Orthopédique, Epalinges, Switzerland, [3]Hospital General de México and Universidad Nacional Autónoma de México, Mexico City, México, Mexico, [4]Metroplex Clinical Research Center, Dallas, TX, [5]Roche, Welwyn, United Kingdom, [6]UCLA Medical Center, Los Angeles, CA

Purpose: To report 3-yr data from the extension of a 3-arm, randomized, double-blind, placebo-controlled, phase 3 trial of TCZ in pts with moderate to severe RA who were MTX inadequate responders.

Methods: A total of 1190 pts were randomly assigned (1:1:1) to receive TCZ (4 mg/kg [TCZ4] or 8 mg/kg [TCZ8]) or placebo (control) every 4 wks plus MTX (10–25 mg/wk). After wk 52, pts switched to open-label treatment with TCZ8, an option chosen by the majority of pts (62%-68% across all 3 treatment groups). Radiographs of hands and feet were analyzed by Genant-modified Total Sharp Score (GmTSS) for any pt who had a baseline, wk 52, wk 104, and at least 1 post-wk 104 assessment. If a patient had a post-wk 104 but not a wk 152 value, linear extrapolation was used to impute up to wk 152. Signs and symptoms data and safety data are reported as pooled data (All TCZ) in all pts who received at least 1 dose of TCZ; data are presented from the first dose of TCZ to August 28, 2009 (mean duration, 2.43 yrs). LOCF was used for missing tender and swollen joint counts; no imputation was used for missing HAQ score, CRP, ESR, and VAS assessments.

Results: The radiographic population consisted of 704 pts, accounting for approximately 80% of the pts who ultimately would have a post-wk 104 assessments: 244, 241, and 219 pts had been initially assigned to TCZ8, TCZ4, and control, respectively. The majority of pts had received open-label TCZ8 for at least 2 of 3 yrs of the study; 9% of placebo and 19% of TCZ4 pts had remained on original blinded treatment at 1 yr. The mean change in GmTSS from baseline to yr 3 was 60% lower in pts who were randomly assigned to TCZ compared with those initially receiving control, demonstrating inhibition of joint damage by TCZ (Table). The majority of radiographic progression in pts randomly assigned to control was observed in the first yr before switching to TCZ. By yr 3, no radiographic progression was observed in a greater proportion of pts initially assigned to TCZ8 and TCZ4 than to control.

The All TCZ group included 1149 pts with 2790 pt-yrs (PY) of exposure. ACR response and DAS28 remission rates were high, demonstrating continued clinical benefit (Table). At wk 104, 34% (257/768) of pts had HAQ scores <0.5; the proportion of pts with HAQ scores <0.5 was maintained through wk 152.

Overall rates/100 PY of serious adverse events and serious infections were 11.0 and 3.2; overall rates/100 PY of deaths and deaths from infections were 0.39 and 0.14. Malignancies occurred at an overall rate of 0.7/100 PY, including solid cancers (0.6/100 PY) and nonmelanoma skin cancer (n = 1; 0.0/100 PY).

Table. Outcomes at Week 152

GmTSS	TCZ8 n=244	TCZ4 n=241	Control n=219
Mean (SD) change from baseline	0.72 (2.56)[a,b]	0.71 (2.14)[b,c]	1.78 (3.64)
Pts with no progression (GmTSS change from baseline ≤0), % (n)	69 (169)[a,d]	67 (162)[d,c]	51 (111)
Signs and Symptoms		**All TCZ**	
ACR20, % (n/n)		80 (472/591)	
ACR50, % (n/n)		59 (346/591)	
ACR70, % (n/n)		36 (212/591)	
DAS28 remission, % (n/n)		57 (325/572)	
TJC and SJC= 0, % (n/n)		21 (137/656)	
HAQ <0.5, % (n/n)		37 (202/552)	

n/n=no, patients achieving end point/no. patients reaching time point with valid assessments.
[a]$p<0.0001$ vs control. [b]p calculated by Van Elteren test stratified by region. [c]$p=0.0002$ vs control.
[d]p calculated by logistic regression analysis adjusted for region. [c]$p=0.0008$ vs control.

Conclusions: During long-term treatment, TCZ + MTX continued to inhibit radiographic progression. Improvements in physical function and other clinical benefits were maintained at high levels. The safety profile did not change compared with the 2-yr analysis.

Disclosure: J. M. Kremer: Genentech, 2, 5, 8, Roche, 2, 5; **D. E. Furst:** Abbott Laboratories, 2, 5, Actelion Pharmaceuticals US, 2, 5, Amgen Inc., 2, Amgen, 2, 5, Biogen Idec, 5, Bristol-Myers Squibb, 2, 5, Centocor, Inc., 5, Corrona, 3, Genentech, 2, 5, Gilead Sciences, Inc., 2, Gilead, 2, 5, GlaxoSm; **R. Burgos-Vargas:** Abbott Laboratories, 5, 8, Pfizer Inc, 5, 8, Roche, 5, 8, Schering-Plough, 5, 8, Wyeth Pharmaceuticals, 5, 8; **J. Dudler:** Amgen Inc., 5, Gebro Pharma, 5, MSD, 5, Pfizer Inc, 5, Roche, 5; **C. M. Mela:** Roche, 3; **E. Vernon:** Roche, 3; **R. M. Fleischmann:** Roche, 2.

1820

Long-Term Efficacy of Tocilizumab (TCZ) in Patients (Pts) with Rheumatoid Arthritis (RA) Treated up to 3.7 Years. Majed Khraishi[3], Rieke Alten[8], Juan J. Gomez-Reino[2], Warren Rizzo[1], Joy Schechtman[6], Andre Kahan[4], Emma Vernon[5], Monet Taylor[5] and Josef Smolen[7]. [1]Advanced Arthritis Care, Scottsdale, AZ, [2]Hospital Clínico U. de Santiago, Santiago, Spain, [3]Memorial University of Newfoundland, St. John's, NL, Canada, [4]Paris Descartes University, Paris, France, [5]Roche, Welwyn, UK, [6]SunValley Arthritis Center, Peoria, AZ, [7]University Clinic for Internal Medicine, Vienna, Austria, [8]University of Berlin, Berlin, Germany

Background: Efficacy and safety of TCZ have been shown in RA pts in phase 3 trials for up to 2 y. Efficacy data from ongoing extension studies for up to 3.7 y (wk 192) are presented for pts treated with TCZ ± MTX/other DMARDs.

Methods: This analysis was in 2 populations from long-term extensions (GROWTH95, GROWTH96, open-label phase of LITHE) of phase 3 trials. One population comprised pts who were previous inadequate responders to DMARDs (DMARD-IR: OPTION, TOWARD, LITHE), and the other comprised pts who were never exposed to or who had never failed MTX (AMBITION). Pts received at least 1 dose of TCZ + DMARDs/MTX in the phase 3 or extension trials except pts in AMBITION, who received TCZ monotherapy. Pts from AMBITION with <50% reduction from baseline in tender and swollen joint counts (TJC, SJC) could receive DMARDs/MTX in the extension. Outcomes were assessed every 4 wks in the original studies and, in the extensions, every 8 (LITHE) or 12 (GROWTH95/96) wks from initial TCZ exposure to Aug 28, 2009; data were assigned to the nearest 12-wk point for pooling. Numbers of pts with assessments decreased over time because some pts had not yet reached later assessments or withdrew. Results include pts who had assessments at each visit; no imputation was performed for missing data. Data were included until <10% of the baseline pt number was reached.

Results: The analysis was in 2904 DMARD-IR pts and 618 pts who were never exposed to or had never failed MTX. By the cutoff date, 27.7% of DMARD-IR pts and 24.6% of never exposed/never failed MTX pts had withdrawn. In DMARD-IR pts, TCZ efficacy was shown by continuously increasing absolute numbers achieving ACR50, LDA (DAS28 ≤3.2), and DAS28 remission (DAS28 ≤2.6) through wk 96 and ACR70 through wk 120 (Table). In never exposed/never failed MTX pts, efficacy was shown by sustained absolute numbers achieving ACR50/70, LDA, and DAS28 remission to wk 96 (Table). While proportions who achieved ACR50/70, LDA, and DAS28 remission were maintained to wks 168 and 192, data must be interpreted with caution due to lower absolute numbers reaching these visits in the extensions (Table). By wk 144, 20% (396/1980) of assessed DMARD-IR pts and 27% (105/390) of assessed never exposed/never failed MTX pts had achieved the major clinical response of ACR70 maintained for 24 consecutive wks. At wk 120, 52.3% (1118/2139) and 38.4% (821/2139) of assessed DMARD-IR pts and 59.5% (278/467) and 38.3% (179/467) of assessed never exposed/never failed MTX pts, respectively, had ≤1 SJC and ≤1 TJC; 38.4% (772/2008) of DMARD-IR pts and 48.4% (216/446) of never exposed/never failed MTX pts had HAQ-DI scores ≤0.5.

Table.

Week	0	24	48	72	96	120	144	168	192
DMARD-IR [n=2904], % (n/n)									
ACR50	N/A	**35** (929/2693)	**45** (1088/2439)	**50** (1162/2312)	**53** (1183/2227)	**56** (1154/2047)	**56** (1028/1825)	**61** (802/1323)	**66** (469/716)
ACR70	N/A	**16** (423/2693)	**24** (581/2439)	**30** (692/2312)	**31** (698/2227)	**35** (714/2047)	**35** (638/1825)	**43** (562/1323)	**45** (325/716)
LDA	**2** (50/2889)	**43** (1137/2658)	**54** (1302/2396)	**62** (1403/2261)	**65** (1409/2158)	**68** (1352/1978)	**69** (1208/1755)	**70** (887/1268)	**73** (500/689)
DAS28 remission	**1** (22/2889)	**27** (722/2658)	**40** (962/2396)	**47** (1066/2261)	**50** (1083/2158)	**54** (1061/1978)	**54** (951/1755)	**57** (718/1268)	**61** (420/689)
Never exposed to or never failed MTX [n=618], % (n/n)									
ACR50	**N/A**	**40** (223/563)	**49** (256/521)	**53** (256/487)	**54** (257/477)	**58** (256/442)	**60** (208/348)	**62** (110/178)	**N/A**
ACR70	**N/A**	**22** (126/563)	**32** (164/521)	**31** (152/487)	**35** (169/477)	**38** (169/442)	**43** (151/348)	**45** (80/178)	**N/A**
LDA	**5** (32/616)	**50** (277/556)	**62** (312/502)	**67** (314/471)	**67** (310/461)	**71** (298/421)	**73** (239/329)	**71** (120/170)	**N/A**
DAS28 remission	**3** (20/616)	**37** (204/556)	**48** (243/502)	**52** (243/471)	**51** (236/461)	**55** (232/421)	**56** (184/329)	**57** (97/170)	**N/A**

Baseline (wk 0) was first active TCZ dose. For pts randomly assigned to TCZ in initial studies, this was at core study baseline. For pts assigned to placebo, first active dose of TCZ was at initiation of rescue or at first dose received in the open-label or exclusion studies. Data points with <10% of original sample size are not presented. n/n = pts with response/evaluable pts. For TJC and SJC. LOCF was used for any missing individual joint; total joint count used data available at that time point No imputation for missing HAQ-DI score. CRP, ESR, or VAS assessment. CRP was used to calculate ACR response If missing, ESR was used. LDA=DAS28≤3.2; DAS28 remission=DAS28<2.6.

Conclusions: Efficacy during long-term TCZ treatment was demonstrated by increasing numbers and/or proportions of pts achieving ACR50/70, LDA, and DAS28 remission until at least wk 96; for pts who reached wk 192, these benefits were maintained. These data support TCZ as an effective, long-term treatment for RA pts.

Disclosure: M. Khraishi: Abbott Laboratories, 2, 5, Amgen Inc., 2, 5, 8, Bristol-Myers Squibb, 5, 8, Merck Pharmaceuticals, 5, 8, Pfizer Inc, 5, 8, Roche, 5, 8, UCB, Inc., 5, Wyeth Pharmaceuticals, 2; **R. Alten:** Abbott Laboratories, 5, 6, 8, Bristol-Myers Squibb, 5, 6, 8, Novartis Pharmaceuticals Corporation, 5, 6, 8, Roche, 5, 6, 8, Wyeth Pharmaceuticals, 2; **J. J. Gomez-Reino:** Bristol-Myers Squibb, 8, Hoffmann-La Roche, Inc., 5, Roche, 2, 8, Schering-Plough, 2, 5, 8, UCB, Inc., 5, 8, Wyeth Pharmaceuticals, 2; **W. Rizzo:** None; **J. Schechtman:** Abbott Laboratories, 5, 8, Amgen Inc., 5, 8, 9, Array, 5, 8, 9, AstraZeneca, 5, 8, Bristol-Myers Squibb, 9, Canfite Pharma, 9, Centocor, Inc., 5, 8, 9, Covidien, 5, 8, 9, Design Write, 5, 8, 9, Eli Lilly and Company, 5, 8, 9, E; **A. Kahan:** Chugai, 2, Roche, 2; **E. Vernon:** Roche, 3; **M. Taylor:** Roche, 3; **J. Smolen:** Roche, 2, 6.

1821

Mechanism of Inhibition of Joint Destruction by Rituximab in Rheumatoid Arthritis. Maria J. H. Boumans[2], Rogier M. Thurlings[3], Koen Vos[4], Danielle M. Gerlag[3] and Paul P. Tak[1]. [1]Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, [2]Academic Medical Center/University of Amsterdam, Amsterdam, Noord-Holland, The Netherlands, [3]Academic Medical Center/University of Amsterdam, [4]Academic Medical Center/University of Amsterdam/Jan van Breemen Institute

Background: The RANK/RANKL/OPG system regulates osteoclast differentiation and activation. Osteoclasts are essential for the resorption of mineralised cartilage and subchondral bone in chronic arthritis. Treatment with rituximab may reduce the progression of joint destruction in rheumatoid arthritis (RA) patients, even in the absence of a clinical response. The underlying mechanisms are at present poorly understood.

Objective: To examine the effects of rituximab treatment on the RANK/RANKL/OPG system.

Methods: Twenty-eight rheumatoid factor positive and/or ACPA positive RA patients were treated with rituximab. Methylprednisolone pre-medication was omitted to study the specific effects of rituximab. Serum OPG was measured using multiplex analysis before and 16 weeks after treatment. Serum RANKL was measured by ELISA. OPG and RANK expression was measured in synovial biopsy samples of 20 patients before and 16 weeks after treatment using immunohistochemistry. Stained sections were evaluated by digital image analysis. Changes after treatment were assessed using the Wilcoxon's signed rank test.

Results: We found a significant decrease in serum levels of both OPG and RANKL 16 weeks after initiation of rituximab treatment (20 %, $P = 0.001$ and 40 %, $P = < 0.0001$ respectively) while the OPG/RANKL ratio increased ($P = 0.006$). In the synovial tissue, there was a significant decrease of 99 % in RANK-positive osteoclast precursors ($P = 0.018$), while OPG expression showed a non-significant decrease (25 %, $P = 0.069$).

Conclusion: The decrease in synovial osteoclast precursors associated with the increased OPG/RANKL ratio in the serum may explain in part the protective effect of rituximab treatment against progression of joint destruction.

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1822

Monocyte Migration to the Synovium in Rheumatoid Arthritis Patients Treated with Adalimumab. Marieke Herenius[3], Rogier Thurlings[4], Carla Wijbrandts[4], Roelof Bennink[5], Serge Dohmen[6], Carlijn Voermans[6], Diana Wouters[2], Elena Izmailova[7], Daniëlle Gerlag[4], Berthe van Eck-Smit[5] and Paul P. Tak[1]. [1]Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, [2]Department of Immunopathology, Sanquin Research, Amsterdam, Noord Holland, The Netherlands, [3]Division of Clinical Immunology and Rheumatology, Academic Medical Center/University of Amsterdam, Amsterdam, The Netherlands, [4]Division of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [5]Division of Nuclear Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [6]Landsteiner Laboratory, Department of Experimental Immunohematology, Sanquin Research, Amsterdam, The Netherlands, [7]Millennium Pharmaceuticals, Inc, Department of Research and Development, Cambridge, MA

Background: The mechanism of action of treatment with tumor necrosis factor –α (TNF-α) blockers in rheumatoid arthritis (RA) is still not completely understood. Since the recognition of synovial tissue as the primary site of inflammation, studying the synovium has provided insight into the pathogenesis of the disease and the mechanism of action of different therapies. Anti-TNF antibody treatment has been shown to result in marked reduction of synovial inflammation in both RA and psoriatic arthritis early after initiation of therapy. This early reduction in synovial inflammation could not be explained by apoptosis induction at the site of inflammation. This leaves either reduced cell influx or enhanced cell efflux to explain this process. The aim of this study was to test if adalimumab treatment could affect the influx of monocytes into the synovium.

Methods: We used a novel technique to analyze the migration of labelled autologous monocytes using scintigraphy. CD14+ monocytes were isolated from patients with RA, using a positive selection procedure with magnetic-activated cell sorting, and labeled with 99mTc-HMPAO. Scintigraphic scans were made 1 hour, 2 hours and 3 hours after re-infusion. This procedure was performed at three time points with a two weeks interval. Adalimumab treatment was started after the second set of scans.

Results: Re-infusion lead to a stable number of monocytes in the joint of interest after 1, 2 and 3 hours on all days. Already 14 days after the start of treatment with adalimumab a significant decrease in DAS28 was shown. There was no significant change in monocyte influx 1, 2 and 3 hours after re-infusion from day -14 to day 1, which was before the start of adalimumab treatment ($p=0.33$, $p = 0.67$, $p=0.21$, respectively). Of interest, the influx of monocytes did not decrease after re-infusion of monocytes comparing day 14 to baseline, indicating that adalimumab treatment did not affect the influx of monocytes early after initiation of treatment.

Conclusions: The results of this mechanistic study indicate that CD14+ monocyte influx into the synovium is not altered two weeks after the start of adalimumab treatment. As previous studies showed a rapid decrease in macrophage infiltration after anti-TNF- antibody therapy, which could not be explained by increased cell death, this points to an important role for enhanced efflux of inflammatory cells from the synovium. These data are in line with the recent observation that monocytes migrate towards the inflamed RA synovium at a slow macrophage-replacement rate and with the recently shown increase in lymphatic vessels in the synovium after TNF-α blockade.

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1823

Multiple Regression Analysis on the Clinical Parameters Associating with Clinical, Structural and Functional Remission at 52 Weeks in RA Patients Treated with Anti-IL-6 Receptor Antibody, Tocilizumab – REACTION-2 Study. Tsutomu Takeuchi[2], Yoshiya Tanaka[5], Kouichi Amano[1], Eri Sato[4], Masao Nawata[5], Hayato Nagasawa[1], Daisuke Hoshi[4], Kazuyoshi Saito[5], Syunsuke Fukuyo[5], Kentarou Hanami[5], Takahiko Kurasawa[1], Hideto Kameda[3] and Hisashi Yamanaka[4]. [1]Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Saitama Medical Center, Saitama Medical University, Saitama, Japan, [2]Division of Rheumatology, School of Medicine, Keio University, Tokyo, Japan, [3]Division of Rheumatology, School of Medicine, Keio University, Tokyo, Japan, [4]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [5]The First Department of Internal Medicine, School of Medicine, University of Occupational & Environmental Health, Kitakyushu, Japan

Purpose: In order to identify the baseline clinical parameters associating with remission in RA patients treated with anti-IL-6 receptor monoclonal, tocilizumab (TCZ), we attempt to analyze clinical, laboratory and radiographic date set of REACTION-2 study by multiple logistic regression analysis.

Patients and Methods: In REACTION-2 study, a total of 255 RA patients were treated with TCZ 8 mg/kg every four weeks in three major rheumatic centers as daily clinical practice. In the assessment of disease activity, DAS28-ESR score <2.6 was defined as clinical remission, and non-responder imputation was used for missing data. For joint damage, modified TSS ≤0.5 was defined as structural remission, and for functional disability, HAQ score ≤0.5 was defined as functional remission. The associations with each type of remission were analyzed by multiple logistic regression analysis. The last-observation-carried-forward method was used in each of the analyses.

Results: Baseline characteristics of 255 patients showed that the mean age was 59.1 ± 13.3 years, the mean duration of RA was 12.4 ± 11.1 years, Methotrexate was used by 55.6% of patients, with the mean dose 5.31 ± 4.8 mg/week, and the mean steroid dose was 3.9 mg/day. Although a large proportion of patients, 62.8%, had been previously treated with biologics, the mean DAS28-ESR was 5.72.

Logistic regression analysis of baseline clinical parameters and clinical remission at 52 weeks demonstrated that clinical remission was significantly associated with younger age, lower DAS28-ESR, lower HAQ score, higher MTX dose and lower steroid dose at baseline. Multiple regression analysis of these associations confirmed that all the above factors independently influenced the achievement of clinical remission.

Similarly, multiple regression analysis revealed that HAQ score at baseline independently influenced the achievement of structural remission, while logistic regression analysis identified two significant parameters such as HAQ score and steroid dose at baseline.

Finally, multiple regression analysis demonstrated that only HAQ score at baseline independently influenced the achievement of functional remission, while logistic regression analysis showed six significant parameters including age, duration of RA, DAS28-ESR, HAQ score, mTSS score and MTX dose at baseline.

Conclusions: In this analysis, we identified the baseline clinical parameters influencing the various types of remission at 52 weeks by treatment with TCZ in clinical practice. It appears that baseline HAQ score before TCZ treatment is an important factor that influences clinical, structural and functional remission.

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1824

Outcome of Interstitial Lung Disease (ILD) after Administration of Biologics in Patients with Pre-Existing ILD in RA. Shinji Motojima[1], Tamao Nakashita[1], Akira Inoue[1], Kei-ichi Inoue[1] and Natsuki Fujio[2]. [1]Department of Rheumatology and Allergy, Kameda Medical Center, Kamogawa, Chiba, Japan, [2]Department of Rheumatology and Allergy, Kameda Medical Center, Japan

Purpose: Development or exacerbation of interstitial lung disease (ILD) is a problem when biologics are administrated in patients with RA, and not a few fatal cases have been reported in Japan. According to the post-marketing surveillance report of TNF blockers, the development/exacerbation rate of ILD was 0.5 %. In our department, however, the rate was 4 % probably because we have many RA cases with ILD. Although the majority of the development/exacerbation is seen in patients with pre-existing ILD, there are no reports showing how frequently ILD exacerbates and what the outcome of ILD is in patients with pre-existing ILD. This study was carried out focusing on this viewpoint.

Method: Subjects were 34 patients with RA, with the mean age of 65. As a part of workup before administration of biologics, chest CT scan was done. After administration of biologics, chest X-ray film (CXR) was taken at least every 3 months. When newly developed shadows were found on CXR or when patients complained of respiratory symptoms for more than 2 weeks, chest CT scan was done again. The severity of ILD was graded into 4, grades 0 to grade 3, according to the extent of ILD on chest CT. The biologics administrated were infliximab (IFX) for 8, etanercept (ETN) for 24 and adalimumab (ADA) for 2, respectively. The duration of observation was from 1 to 46 months with the median of 9 months.

Results: The ILD of 18, 10 and 6 patients were graded into grade 1, 2 and 3, respectively. The ILD exacerbated in 11 subjects (32.3 %); the duration from the introduction of biologics to the exacerbation was from 1 to 27 months with the median of 9 months. The biologics used at the exacerbation of ILD were IFX in 5, ETN in 5 and ADA in 1, respectively. IFX induced the exacerbation of ILD more frequently than other biologics ($p < 0.05$). There were no differences between the subjects with ILD exacerbation and those without it in age, gender, RF titer, the ILD grade, KL-6 concentration, the dose of prednisolone and MTX, and DAS28-ESR. The biologics were withdrawn in 8 of 11 subjects with ILD exacerbation, and 2 subjects with ILD grade 2 and 3 died due to respiratory failure.

Conclusions: The exacerbation rate was very high in patients with pre-existing ILD when biologics were administrated. Unfortunately we could not extract the factors that predict the ILD exacerbation.

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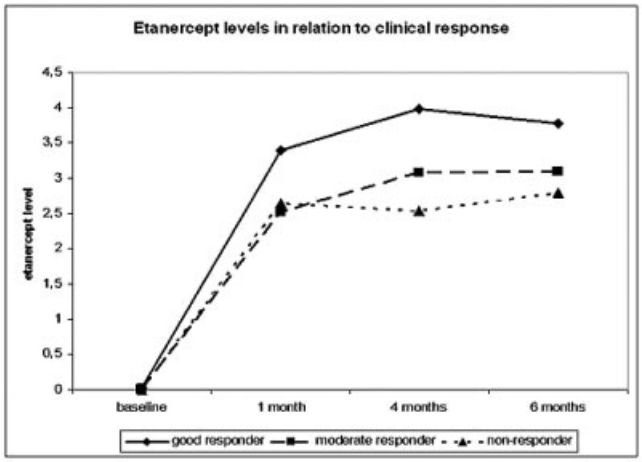
1825

Patients Not Responding to Etanercept Obtain Lower Trough Etanercept Concentrations Compared to Responding Patients. Anna Jamnitski[1], Michael T. Nurmohamed[1], Margreet M. Hart[2], Ben A. Dijkmans[3], Lucien Aarden[2] and Gerrit Jan Wolbink[1]. [1]Jan van Breemen Institute, [2]Sanquin Research, [3]VU Medical Center

Purpose: A substantial proportion of the patients with rheumatoid arthritis (RA) failed to respond on treatment with etanercept. Previous research has shown that etanercept appeared to be less immunogenic compared to adalimumab and infliximab. The goal of this study is to investigate the relationship between etanercept levels and clinical response in a large cohort of RA patients.

Methods: Between 2004 and 2008, 292 consecutive patients with active RA (DAS28 > 3.2) and a new etanercept prescription were included in an observational cohort at the Jan van Breemen Institute, Amsterdam. Clinical response variables and etanercept levels were collected at baseline and after 1, 4 and 6 months of etanercept treatment. Trough serum etanercept levels were measured by ELISA (Sanquin research, The Netherlands). Last observation carried forward (LOCF) data was used for patients who discontinued the treatment with etanercept before 28 weeks. Differences between EULAR responders and non responders were evaluated by using an independent t-test, confounding analyses were performed using multiple regression analysis.

Results: After 6 months of etanercept treatment 103 patients were good, 115 were moderate and 74 were non responders according to EULAR response criteria. Etanercept levels were undetectable at baseline (<0.001 mg/l). Patients with good EULAR response had significantly higher trough etanercept concentrations than EULAR non responders, $p = 0.009$ at 1 month and $p<0.001$ at both 4 and 6 months. To know, 3.40 (2.22 – 4.62) at 1 month, 3.98 (2.72 – 5.35) at 4 months and 3.78 (2.53 – 5.17) at 6 months in EULAR responders compared to 2.64 (1.20 – 3.89) at 1 month, 2.54 (1.12 – 3.94) at 4 months, and 2.80 (1.27 – 3.93) at 6 months in EULAR non responders. No antibodies were detected against etanercept.



Conclusion: This study demonstrates for the first time that patients with good EULAR response obtain significantly higher levels of etanercept than patients not responding to etanercept treatment. Furthermore this study confirms that etanercept is less immunogenic than another TNF-inhibitors.

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Prevalence and Persistence of Low Infliximab Serum Trough Levels in RA Patients with Low Disease Activity in Daily Clinical Practice. Aatke van der Maas[3], Alfons A. Den Broeder[4], Gert-Jan Wolbink[1], Frank H. J. van den Hoogen[4], Piet L. C. M. van Riel[5] and Bart J. F. van den Bemt[2]. [1]Department of Immunopathology, Sanquin Research, Amsterdam, The Netherlands, [2]Department of Pharmacy, St. Maartenskliniek, Nijmegen, The Netherlands, [3]Department of Rheumatology, St. Maartenskliniek, Nijmegen, The Netherlands, [4]Department of Rheumatology, St. Maartenskliniek, Nijmegen, The Netherlands, [5]Department of Rheumatology, St. Radboud UMCN, Nijmegen, The Netherlands

Treatment of RA with infliximab requires optimal dosing to balance maximum effect and minimal dose related side effects and costs. DAS driven dose de-escalation can be used in patients with low disease activity, but costs time and can lead to flaring. Since infliximab serum trough levels and presence of HACA's (Human Anti-Chimeric Antibodies) demonstrated a correlation with clinical effect in cross-sectional studies, they could be used as predictors for successful de-escalation. There is however not much data on prevalence and persistence of serum trough levels and HACA's in RA patients with low disease activity. This prospective observational study aims to study prevalence and longitudinal course of serum trough levels and HACA's and their persistence within patients treated in daily clinical practice, focussing on patients with low disease activity.

Methods: All RA patients treated with infliximab at the Sint Maartenskliniek Nijmegen for at least 6 months were included and followed in a 1.5 year period. At every visit DAS28, serum trough levels and HACA's were measured. Cross sectional analysis of the prevalence of low serum trough levels (<1.0 μg/ml) and/or HACA's was done in all patients and in a subgroup with stable low DAS28 ≤ 3.2 for at least 3 consecutive visits. Persistence at 2 consecutive visits in patients with stable DAS28 and infliximab dosing was analysed by means of a Spearman correlation coefficient and Wilcoxon test for serum trough levels, and with kappa analysis for HACA's presence.

Results: 147 RA patients were included, 65 and 40 patients had a DAS28 $<$ 3.2 and 2.6 respectively. In 35% of the patients with a DAS28$\leq$2.6 and in 31% with a DAS28$\leq$3.2 non-measurable/low serum trough levels were found. 30% was associated with presence of HACA's (see table 1). The longitudinally analysis showed that, in patients with stable low DAS28, 38% had low to non measurable serum trough levels, with nearly 50% showing HACA's. There was no statistical difference between trough levels at 2 consecutive visits in patients with stable DAS28 and dosing ($p=0.38$). The correlation between serum trough levels between two consecutive visits was very high ($r=0.97$, $p=0.00001$), as was the agreement for the presence of HACA's between visits (kappa 1.0).

Table 1. Number of patients with low and high infliximab serum trough levels and HACA's in patients with low and high DAS28.

DAS28	Infliximab serum trough levels		HACA's		Total
	Low* (%, [95% CI])	High* (%, [95% CI])	Yes (%, [95% CI])	No (%, [95% CI])	
≤3.2	20 (31%, [19–42])	45 (69%, [58–81]))	7 (11%, [3–19])	58 (89%, [81–97])	65
≤2.6	14	26	5	35	
2.6–3.2	6	19	2	23	
>3.2	39 (48%, [37–59])	43 (52%, [41–63])	25 (30%, [59–80])	57 (70%, [20–41])	82
Total	59	88	32	115	147

*Low serum trough levels are defined as <1.0 μg/ml, high as >1.0 μg/ml

Discussion: Among patients with sustained low disease activity low to non measurable serum trough levels are prevalent both in cross sectional and longitudinal analyses. In patients with stable treatment and DAS28 there is a high persistence between two consecutive measurements of trough levels and HACA's. Therefore, infliximab serum trough levels and HACA are promising candidates to be tested for their predictive value for successful dose de-escalation.

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Regulatory T Cells from Patients with Rheumatoid Arthritis Are Not Affected by Adalimumab and Etanercept. Thierry Lequerré[3], Céline Blache[2], Stéphanie Beuteux[2], Arnaud Roucheux[1], Ingrid Dedreux[1], Serge Jacquot[1], Xavier Le Loët[4], Olivier Boyer[1] and Olivier Vittecoq[4]. [1]Department of Immunology, Inserm905, Rouen University Hospital, University of Rouen, [2]Inserm905, University of Rouen, [3]Rheumatology Department, Inserm905, Rouen University Hospital, University of Rouen, Rouen, France, [4]Rheumatology Department, Inserm905, Rouen University Hospital, University of Rouen

Background: Despite the overall benefits of TNFα blocking agents [adalimumab (ADA), etanercept (ETA), infliximab (INF)], their immune effects on $CD4^+CD25^+$ regulatory T cells (Tregs) in rheumatoid arthritis (RA) patients have not been fully characterized and is still controversial. It was suggested that INF increased significantly the number of Tregs in RA patients responding to INF. To our knowledge, any study compared the TNFα blocking agent effects' differentiating antibodies and soluble receptor on the number of Tregs cells. The objective is to analyse the ETA and ADA treatment effects' on the Tregs population in RA patients.

Material and Methods: RA patients (n = 48) were treated with either ADA (n = 28) or ETA (n = 20) associated with stable dose of methotrexate or leflunomide. Demographic and clinical data were collected at baseline, after 6 and 12 weeks of treatment. The disease activity score 28 (DAS28) criteria for response to these drugs were applied to assess clinical efficacy after 12 weeks of treatment, that led us to compare the Tregs population in responders [including good responders (GR) and moderate responders (MR)] and no responders (NR). Human blood mononuclear cells were isolated from whole venous blood by Ficoll–Hypaque centrifugation and samples were used fresh to perform flow cytometry analysis. Tregs were defined by different gating strategies ($CD4^+CD25^{hi}$, $CD4^+FoxP3^+$, $CD4^+CD25^+CD127^{lo}$). For all the statistical analyses, values less than 0.05 were considered significant.

Results: The overall mean ($\pm$ SD) disease duration was 9.54 $\pm$ 9.8 years and the DAS28 score indicated that all these patients had highly active RA (5.46 $\pm$ 0.9) at baseline. Prior to treatment, all variables were similar for ADA and ETA subsets. The majority of RA patients (57.1% in ADA group and 65% in ETA group) received corticosteroids. After 12 weeks of treatment, the percentages of GR, MR and NR were respectively 46.5, 35.7 and 17.8% in ADA group and 30, 20 and 50% in the ETA group. The percentage of Tregs was 5.5 $\pm$ 0.04% for ADA group and 4.95 $\pm$ 0.02% for ETA group before treatment. Stratifying our RA patients based on corticosteroids status did not reveal any differences in Tregs frequencies before treatment. Overall, and also when stratifying RA patients according to the drug, the TNFα blocking agent had no effect on the percentage and on the absolute number of $CD4^+CD25^+$ cells in these patients after 6 weeks or 12 weeks of treatment. Moreover, the percentage of Tregs did not change at 6 and 12 weeks in RA patients responding to ADA or ETA as compared to RA patients nonresponding. Furthermore, the $CD4^+CD25^+CD45RA^+$, $CD4^+CD25^+CD45RO^+$ and $CD4^+CD25^+CD62L^+$ cells populations were unaffected by TNFα blocking agents whatever the response to these drugs.

Conclusion: This is the first study analyzing the impact of ADA and ETA on the Tregs compartment of a substantial number of RA patients. None of these two molecules modified the phenotype and the percentage or the absolute number of blood Tregs after 6 and 12 weeks of treatment whatever the phenotype used to assay these Tregs. However, we can not exclude that ADA and ETA may have more subtle effects such as on the functionnal capacity of tregs to regulate cytokines production.

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Relationship between Rituximab Serum Levels and Progression of Structural Damage in Rheumatoid Arthritis Patients. Maria J. H. Boumans[2], Y. K. O. Teng[6], Rogier M. Thurlings[3], Koen Vos[4], Steven O. Stapel[7], Gertjan Wolbink[5], Janneke Tekstra[8] and Paul P. Tak[1]. [1]Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, [2]Academic Medical Center/University of Amsterdam, Amsterdam, Noord-Holland, The Netherlands, [3]Academic Medical Center/University of Amsterdam, [4]Academic Medical Center/University of Amsterdam/Jan van Breemen Institute, [5]Jan van Breemen Institute, Sanquin Research, Amsterdam, [6]Leiden University Medical Center, [7]Sanquin Research, Amsterdam, [8]University Medical Centre, Utrecht

Background: Treatment with rituximab reduces disease activity in patients with rheumatoid arthritis (RA). The current dosing schedule of rituximab has been shown to induce and maintain a clinical response, and is also protective against progression of joint destruction. Studies on the relationship between serum levels of rituximab and its effects on structural damage may provide insights that may facilitate further optimisation of dosing regimens.

Objective: To determine whether low rituximab serum levels are associated with progression of structural damage in RA patients.

Method: Sixty-three RA patients were treated with two infusions of 1000 mg rituximab (days 1 and 15) in three different centres. The change in total Sharp score (TSS) after 1 year was used as radiographic endpoint and patients were divided into progressors (increase in TSS $\geq$ 5) versus non-progressors. Rituximab serum levels were measured by sandwich ELISA after 4 and 12 weeks (LUMC and UMCU) or 4 and 16 weeks (AMC). Differences were analyzed using the Mann-Whitney test.

Results: There was no (trend towards a) difference in rituximab levels between progressors versus non-progressors 4 weeks and 12/16 weeks after treatment in the different cohorts (week 4: LUMC: $P = 0.8$, UMCU: $P = 0.38$ and AMC: $P = 0.5$; week 12: LUMC: $P = 0.47$, UMCU: $P = 0.14$; week 16: AMC: $P = 0.46$)). There was also no difference in rituximab levels between progressors and non-progressors when the data of the cohorts were pooled (week 4: $P = 0.58$ (all 3 cohorts); week 12: $P = 0.64$ (LUMC and UMCU)) (Table 1).

Table 1. Rituximab serum levels 4, 12 and 16 weeks after initiation of treatment.

Week 4			
	Progressors	**Non-progressors**	**P-value**
LUMC	125 (57–149) n=12	81 (118–153) n=12	0.8
UMCU	188 (81–194) n=3	152 (64–179) n=6	0.38
AMC	112 (45–172) n=4	128 (103–160) n=19	0.5
3 cohorts pooled	126 (63–187) n=19	128 (99–161) n=37	0.58
Week 12			
	Progressors	**Non-progressors**	**P-value**
LUMC	4.4 (3.2–11.4) n=13	10.8 (2.9–21.6) n=12	0.47
UMCU	13.2 (2.5–28.2) n=6	2.6 (0.06–8.2) n=7	0.14
2 cohorts pooled	5.9 (3.2–19.4) n=15	6.6 (0.5–16.6) n=19	0.64
Week 16			
	Progressors	**Non-progressors**	**P-value**
AMC	1.8 (0.3–22.7) n=4	3.5 (1.3–7.8) n=19	0.46

Values represent the median and the interquartile range.

Conclusion: The rituximab serum levels between 4 and 16 weeks after initiation of treatment were similar between progressors and non-progressors. The results do not support the use of higher dosages of rituximab to inhibit progression of joint destruction.

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Response, Remission, and Flare during Early Treatment of Rheumatoid Arthritis with Infliximab. Ronald F. Van Vollenhoven[2], Dimitrios Boumpas[10], Rene Westhovens[9], Marek Brzosko[7], Karin E. Svensson[8], Olav Bjorneboe[3], Cees Meeuwisse[5], Shankar Srinivasan[4], Nathan Vastesaeger[6] and Philippe Gaudin[1]. [1]CHU Hôpital Sud, Echirolles Cedex, France, [2]Karolinska University Hospital, Stockholm, Sweden, [3]Martina Hansens Hospital, Gjettum, Norway, [4]Merck and Company, Inc, Kenilworth, NJ, [5]MSD, Oss, The Netherlands, [6]MSD, Brussels, Belgium, [7]Pomeranian Medical University, Szczecin, Poland, [8]Skövde Hospital, Skövde, Sweden, [9]University Hosp KU Leuven, Leuven, Belgium, [10]University Hospital of Heraklion, Heraklion Crete, Greece

Background: For RA patients who are treated with infliximab (IFX), increases in dose and/or frequency can maximize benefit. Our objective was to investigate response patterns during first 14 weeks of treatment with IFX to identify patients who may be candidates for dose optimization

Methods: This was a phase-IV, multicenter, observational study conducted in Europe. Enrollees were IFX- naïve adults with RA for whom treatment with IFX 3 mg/kg had been chosen per label. The relationship between patient characteristics and baseline DAS28 was explored using descriptive statistics. In the efficacy-evaluable population, subjects were retrospectively classified into 3 groups: disease duration $<$ 3 yr/anti-TNF naïve (group 1); disease duration $\geq$ 3 yr/anti-TNF naïve (group 2); failed/did not tolerate prior anti-TNF (group 3). EULAR criteria for response and remission and inverse EULAR criteria for flare were used to describe change in disease activity during induction (infusions weeks 0, 2 and 6) and the first 8-week infusion interval (week 14).

Results: 728 patients were enrolled—78.4% female, mean age 54.1 years (SD 13.1), mean disease duration 9 years (SD 9.0). Weak correlations with baseline DAS28 were found for age ($r = 0.1402$, $P < 0.005$) and weight ($r = 0.1152$, $P < 0.005$), but not for gender and disease duration. Of 662 patients evaluable for efficacy, 76 (11.5%) were in group 1, 447 (67.5%) were in group 2, and 123 (18.6%) were in group 3, with 2.4% unclassified. The mean baseline DAS28 was 5.2 (SD 1.2) and core DAS28 components were similar among groups, with the exception of mean CRP, which was higher in group 1 than in 2 and 3 (33.6, 21.4, and 22.0 mg/L, respectively).

EULAR response (moderate/good) was achieved in 74% of all patients by week 6, and by week 14 this proportion had increased to 81.8% in group 1, remained stable in group 2, and decreased to 67.3% in group 3 (differences not significant). Remission was achieved in 25% of patients in group 1, 25% in group 2, and 15.7% in group 3 at week 6; by week 14, 23% of all patients were in remission with no significant differences between groups. Of the 463 patients who had EULAR response at week 6, 75 (16.2%) had disease flare at week 14 (13.5% group 1, 15.1% group 2, 20.5% group 3). Of core DAS28 components, CRP showed an increase from 9.0 mg/L at week 2 to 18.3 mg/L at week 14, whereas others remained stable or continued to improve. Interestingly, the proportional contribution of global health VAS to the total DAS28 score increased from 35.7% at baseline to 43.4% at week 14 ($P < 0.01$). The most common adverse event (AE) was infections (13.2%). Serious AEs were reported by 5.5% of patients, and 6.8% discontinued IFX because of AEs.

Conclusion: Most patients treated with IFX achieve moderate/good EULAR response early in treatment. Response rates at 16 weeks are highest in patients naïve to anti-TNF agents. Early disease flare is uncommon and may be more frequent in prior anti-TNF users. Close monitoring with DAS28 during IFX treatment may help identify candidates for dose optimization.

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Rituximab (RTX) Is More Effective in Active Sero-Positive RA Than Sero-Negative RA. Abdul Khan[3], Taher Mahmud[4], Tony Hammond[1], Mike Batley[2] and Alison Leak[5]. [1]Maidstone General Hospital Hermitage Lane Maidstone Kent, Maidstone, Kent, United Kingdom, [2]Maidstone General Hospital Maidstone Kent, Maidstone, Kent, United Kingdom, [3]Maidstone General Hospital, Maidstone, Kent, Maidstone, Kent, United Kingdom, [4]Pembury Hospital, Pembury, Kent, United Kingdom, [5]Queen Elizabeth Queen Mother Hospital, Margate, Kent, United Kingdom

Introduction: The efficacy of Rituximab (RTX) was established in an open label study of 161 patients with sero-positive RA (Edwards J *et al* 2004). Evidence is now accumulating from clinical trials that patients with sero-positive RA respond better to RTX than those with sero-negative disease (Isaacs J *et al* EULAR 2009, Tak P *et al* EULAR 2009). NICE guidance in the UK states that RTX is indicated for severe active RA (usually DAS28 > 5.1) when patient has had inadequate response to DMARDs, and also failed anti-TNF therapy. NICE defines an adequate response to RTX as improvement in DAS28 by 1.2 or more. We have retrospectively analysed the response to one course of RTX in all 139 RA patients treated within Kent & Medway Rheumatology Network, comparing sero-positive and sero-negative patients.

Methods: All 10 rheumatologists in the K&M Network treating RA patients with RTX agreed to submit data for audit purposes to define local practice. This abstract is based on a review of the hospital notes of all 139 patients known to have had at least 6 months follow-up after their first course of RTX (dosage 1000mg on day 1 and 15) for active RA. Data was analysed for age, sex, disease duration, prior DMARD and anti-TNF treatment, positivity of Rheumatoid factor and anti-CCP antibodies, and response to RTX (with current DMARDs). Categorical variables were compared using Fisher's exact test; normally distributed continuous measures were compared using unpaired t-test and variables not normally distributed were compared using Mann-Whitney test.

Results: There were 85 patients with sero-positive RA (RF+CCP+ 28, RF+CCP- 36, RF+CCP not done 7, CCP+RF- 14), and 54 patients with sero-negative RA (all RF negative, 50 CCP negative, 4 CCP not done). There were no differences between groups for age, sex, disease duration or number of prior anti-TNF drugs, nor current DMARD treatment with RTX, but sero-negative RA had more DMARDs prior to RTX 5.8 (SD1.4), compared to sero-positive RA 5.2 (SD1.5) $p = 0.03$.

Prior to treatment with RTX seropositive RA had a significant higher DAS28 score, mean 6.1, compared to 5.8 for sero-negatives ($p= 0.02$). However, post RTX sero-positive RA had significant lower DAS (mean 3.9) than sero-negatives (5.1), and reduction in DAS was significant greater in sero-positive RA (mean 2.2), compared to mean 0.6 in sero-negatives (both $p<0.001$)

81% of sero-positive RA had a good EULAR response, compared to only 22% for sero-negative RA ($p<0.001$). 67% of sero-positive RA reached low DAS (<3.2) and 15% remission (DAS<2.6), compared to 4% sero-negative RA ($p <0.001$), and none remission ($p =0.002$).

RTX Response

	Category	Seronegative Number (%)	Seropositive Number (%)	P-value
DAS28 pre treatment	<5.1	11 (20%)	9 (11%)	0.13
	5.1–6.5	35 (65%)	54 (64%)	
	>6.5	8 (15%)	22 (26%)	
Below 5.1 post treatment	Yes	22 (41%)	73 (86%)	<0.001
	No	32 (59%)	12 (14%)	
Low disease state post treatment	Yes	2 (4%)	57 (67%)	<0.001
	No	52 (96%)	28 (33%)	
Remission post treatment	Yes	0 (0%)	13 (15%)	0.002
	No	54 (100%)	72 (85%)	
EULAR response	No response	32 (59%)	8 (9%)	<0.001
	Moderate response	10 (19%)	8 (9%)	
	Good response	12 (22%)	69 (81%)	
EULAR outcome	None	38 (70%)	9 (11%)	<0.001
	Moderate	14 (26%)	49 (58%)	
	Good	54 (4%)	85 (32%)	

Conclusions: In this UK cohort, sero-positive RA patients respond more effectively to RTX than sero-negative RA, even when well matched for disease activity, disease duration and prior treatment.

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Safety and Efficacy of IL-1 Trap in Resistant Adult Onset Still's Disease: 24 Month Follow-Up of Open Label Treatment and Biomarkers of Response. Cailin Henderson, Mildred Wilson, Tuyet-Hang Pham, Gregory Dolan, Adriana Gobbo, Christopher Snyder, Elizabeth Joyal and Raphaela Goldbach-Mansky. NIAMS/NIH

Purpose: To investigate IL-1 pathogenesis in adult onset Still's disease (AOSD) by studying the efficacy and safety of treatment with IL-1 Trap. Outcomes were clinical disease activity indicators, inflammatory markers, safety, and serum cytokine levels.

Methods: Prospective, open-label dose escalation treatment study with IL-1 Trap over 24 months in patients with treatment refractory AOSD. Patients were treated with 100mg weekly subcutaneous doses and escalated to 320 mg weekly in the event of an incomplete response.

Results: 5 patients (3 female, 2 male) with active disease were enrolled. Mean age on entry was 30 years and mean disease duration was 74.2 months (range 14–204 months). All patients had failed DMARDs including methotrexate (5/5), TNF-inhibiting drugs (4/5), thalidomide (1/5), azathioprine (1/5), rituximab (1/5), cyclophosphamide (1/5), and anakinra (3/5). Disease flares occurred in all patients necessitating dose escalation to 320 mg / week. Improvements were observed in mean abnormal WBC, hemoglobin, and platelet counts. Inflammatory markers including ferritin, SAA, ESR, and CRP decreased. Three patients met ACR 20% response criteria and two of these three met ACR 50% response criteria. The two non-responders required intermittent rescue therapy with systemic steroids for ongoing disease activity. At 24 months, the three responders had lower patient global scores, daily prednisone doses, ferritin, SAA, CRP, and ESR levels. Patients had significantly higher TNFα, IL-6, and IL-18 at baseline compared healthy controls. The reduction in IL-6 and TNFα but not IL-18 at 24 weeks tended to be higher in the responders. Patients responding to IL-1 Trap had higher levels of IL-18 at baseline than non-responders (34412 vs. 3943). Adverse events included macrophage activation syndrome in one patient and mycobacterial infections in two patients; one with bursitis and one with a skin infection.

	Responders (n=3)				Non-Responders (n=2)				Total (n=5)			
Outcome (SD)	Month 0	Month 6	Month 12	Month 24	Month 0	Month 6	Month 12	Month 24	Month 0	Month 6	Month 12	Month 24
Patient Global	4.8 (1.7)	3.7 (3.1)	3.6 (3.6)	3.0 (1.3)	4.98 (3.4)	4.8 (4.8)	4.4 (2.9)	5.1 (4.3)	4.9 (2.1)	4.1 (3.3)	3.9 (3.0)	3.8 (2.6)
Tender Joint Count	21.3 (11.7)	18.3 (13.6)	16.3 (20.0)	9.7 (9.3)	5.5 (2.1)	5.0 (4.2)	4.5 (2.1)	6.0 (7.1)	15.0 (12.0)	13.0 (12.3)	11.6 (15.6)	8.2 (7.7)
Swollen Joint Count	11.3 (5.8)	10.7 (10.1)	9.3 (8.6)	7.0 (8.9)	10.5 (7.8)	13.0 (0)	7.5 (0.7)	10.5 (3.5)	11.0 (5.7)	11.6 (7.2)	8.6 (6.2)	8.4 (6.8)
Prednisone Dose mg/d	20.8 (21.3)	16.7 (12.6)	15.0 (0)	7.2 (2.6)	11.5 (9.2)	14.0 (5.7)	15.0 (7.1)	14.5 (7.8)	17.1 (16.5)	15.6 (9.5)	15.0 (4.1)	10.1 (5.9)
WBC K/ul	8.9 (3.0)	9.1 (2.4)	9.4 (1.8)	6.1 (1.6)	13.1 (0.6)	9.6 (2.6)	10.2 (2.7)	10.2 (0.2)	10.6 (3.1)	9.3 (2.1)	9.7 (1.9)	7.7 (2.5)
Hemoglobin mg/dl	10.9 (1.1)	11.7 (0.7)	12.2 (1.1)	12.3 (0.1)	11.6 (2.8)	12.3 (2.1)	12.7 (1.8)	11.8 (0.2)	11.1 (1.6)	11.9 (1.2)	12.4 (1.2)	12.1 (0.3)
Platelets K/ul	274.7 (68.6)	259.3 (46.3)	241.0 (35.8)	234.7 (62.6)	391.5 (24.8)	323.5 (78.5)	339.5 (68.6)	301.0 (15.6)	321.4 (81.3)	285.0 (62.0)	280.4 (68.8)	261.2 (57.8)
Ferritin mg/dl	242.7 (316.7)	197.3 (262.1)	1093.0 (1834)	39.0 (13.1)	520.0 (42.4)	126.0 (99.0)	74.0 (7.1)	166.0 (93.3)	353.6 (271.5)	168.8 (195.8)	685.4 (1412)	89.8 (84.3)
SAA mg/L	253.0 (144.1)	134.7 (96.7)	51.7 (62.6)	29.0 (26.9)	626.5 (542.4)	370.5 (487.2)	243 (224.9)	551 (221.3)	402.4 (354.6)	229.0 (284.1)	128.2 (160.0)	289.8 (327.5)
CRP mg/dl	5.5 (1.6)	2.8 (1.3)	1.5 (1.1)	2.2 (2.3)	13.1 (4.6)	3.0 (3.2)	1.5 (1.0)	5.7 (1.9)	8.5 (4.9)	2.9 (1.9)	1.5 (0.9)	3.6 (2.7)
ESR mm/hr	40.3 (19.7)	25.7 (12.4)	27.7 (26.3)	26.3 (18.2)	99.0 (12.7)	40.0 (15.6)	31.5 (6.4)	61.5 (33.2)	63.8 (35.6)	31.4 (14.1)	29.2 (19.0)	40.4 (28.5)

Conclusions: Open label treatment of refractory AOSD patients with IL-1 Trap resulted in meaningful clinical improvements in 3/5 patients. 2/3 patients achieved a response after one year of treatment and dose adjustments suggesting that longer term treatment may be necessary to optimally control disease. Patients showed increased levels of IL-6, IL-18, and TNFα compared to controls and higher levels of serum IL-18 may predict a successful response. This proof of concept study detected differential responses to treatment with IL-1 Trap in patients with refractory Still's disease and suggests biomarkers that may be useful in predicting response to treatment.

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Safety, Efficacy, and Sustained Improvements in Household Productivity and Daily Activities with Certolizumab Pegol (CZP) Monotherapy over 2 Years in Patients with Active Rheumatoid Arthritis (RA). Roy M. Fleischmann[4], Ernest Choy[3], Ronald van Vollenhoven[2], Niti Goel[6], Oana Purcaru[5], Kristel Luijtens[5] and Vibeke Strand[1]. [1]Division of Immunology and Rheumatology, Stanford University School of Medicine, Palo Alto, CA, [2]Karolinska Institute, Stockholm, Sweden, [3]Kings College Hospital, London, United Kingdom, [4]MCRC, University of Texas, Dallas, TX, [5]UCB, Brussels, Belgium, [6]UCB, Smyrna, GA

Background: CZP was effective and well tolerated as monotherapy vs placebo (P) when given as 400 mg every 4 wks (Q4W) for 24 wks in the FAST4WARD double-blind (DB) Phase III study in patients (pts) with active RA previously failing on DMARDs.[1] We present 2-yr data on safety (primary), efficacy (secondary), and effects on household work and daily activities from an open-label extension (OLE).

Methods: Pts who completed FAST4WARD or withdrew on/after Wk 12 were eligible for CZP 400 mg Q4W in the OLE. The majority of pts (75%)

enrolled were from the USA. Adverse event (AE) and serious AE (SAE) cases per 100 pt-yrs were analyzed according to original DB randomization and through Wk 112 for all those receiving ≥1 CZP dose during the DB phase or OLE. Efficacy, including ACR response rates (NRI) and components (LOCF), was assessed over 112 wks from FAST4WARD baseline (BL) in CZP completers entering the OLE and for the ITT (NRI/LOCF). Household productivity and impact on family/social/leisure activities were assessed from BL (Q4W for 6 months, then Q12W) using the Work Productivity Survey (WPS-RA).[2] FAST4WARD: NCT00548834; FAST4WARD OLE: NCT00160693.

Results: Of 220 randomized pts (111 CZP, 109 P), 104 completed and 116 withdrew (35 CZP, 81 P); 32 were excluded for methotrexate use. Of 188 pts included in this safety analysis, 170 received CZP in the DB phase or OLE. Total mean CZP exposure at Wk 112 was 17.2 months (Table). No evidence of an increased incidence of AEs following longer-term CZP exposure and no new safety signals were observed. The majority of AEs were mild or moderate in intensity (Table). Infections (Table) and cardiac disorders were the most frequently reported SAEs. AEs led to withdrawal in 26 CZP-treated pts. 3 pts died during the OLE: 1 each from acute MI, cardiac arrest, and metastatic lung cancer. No cases of tuberculosis were reported. In 69 CZP completers entering the OLE, ACR20 and 50 response rates (70.3% and 34.4%, respectively, at Wk 112), and individual ACR subcomponent improvements, were sustained throughout. ITT analysis yielded similar ACR20 and 50 response rates (56.3% and 25.2%). The CZP completers also had on average fewer 1) household days lost, 2) days with reduced household productivity, and 3) missed days of family/social/leisure activities per month at Wk 100 compared with BL (1.0 vs 10.1; 1.1 vs 12.1 and 0.3 vs 5.0, respectively). Improvements seen as early as Wk 4 were sustained to Wk 100.

Table. Treatment-emergent AEs (safety population)

	DB phase		DB+OLE
	P (n=92)	CZP (n=96)	CZP (n=170)
Total mean exposure (months)	3.9	5.2	17.2
AEs (cases/100 pt-yrs)			
Any AE	297.1	387.5	206.9
Mild AE	156.7	218.0	114.9
Moderate AE	163.0	165.4	95.4
Severe AE	28.0	17.0	16.1
SAEs	10.1	19.6	14.5
Serious infection	0	4.8	4.1

Conclusion: There was no evidence of increased incidence of AEs with longer-term exposure to CZP 400 mg monotherapy Q4W in the OLE. This treatment regimen conferred sustained improvements in RA signs, symptoms and productivity in the home, and was associated with increased participation in family/social/leisure activities over 2 yrs.

References:

1. Fleischmann R, et al. Ann Rheum Dis 2009;69:805–11.
2. Osterhaus J, et al. Arthritis Res Ther 2009;11:R73.

Disclosure: R. M. Fleischmann: Abbott Laboratories, 2, 5, Amgen Inc., 2, 5, Biogen Idec, 2, Bristol-Myers Squibb, 2, 5, Centocor, Inc., 2, 5, Eli Lilly and Company, 2, Genentech and Biogen IDEC Inc, 2, 5, Lexicon, 2, 5, Pfizer Inc, 2, 5, Regeneron Pharma; **E. Choy:** Abbott Laboratories, 2, 5, 8, Allergan, 2, 5, 8, Boehringer Ingelheim, 2, 5, 8, Chelsea Therapeutics, 2, 5, 8, Chugai, 2, 5, 8, Eli Lilly and Company, 5, 8, GlaxoSmithKline, 2, 5, 8, Jazz Pharmaceuticals, 2, 5, 8, MedImmune, 2, 5, 8; **R. van Vollenhoven:** UCB, Inc., 2, 5; **N. Goel:** UCB, Inc., 1, 3; **O. Purcaru:** UCB, Inc., 3; **K. Luijtens:** UCB, Inc., 3; **V. Strand:** Abbott Immunology Pharmaceuticals, 5, Alder, 5, Amgen Inc., 5, AstraZeneca, 5, Biogen Idec, 5, Canfite Pharma, 5, CBio, 5, Centocor, Inc., 5, Chelsea Therapeutics, 5, Crescendo, 5, Cypress Biosciences, Inc., 5, Euro-Diagnostica Inc.

1833

Statins Inhibit the Anti-Rheumatic Effects of Rituximab in Rheumatoid Arthritis—Results from the Dutch Rheumatoid Arthritis Monitoring (DREAM) Registry.

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Objective: Rituximab (RTX) is used in the treatment of lymphomas and Rheumatoid Arthritis (RA). In lymphoma studies, it has been suggested that statins may inhibit the efficacy of RTX by impairing its binding to CD20. However, evidence is ambiguous. This study aims to investigate whether in RA, the combination of statins and RTX, compared with RTX alone, reduces its effect on disease activity at 6 months.

Methods: All (N=187) RA patients who started on RTX in the DREAM registry were included in this prospective cohort study, 23 patients were exposed to the combination of statins and RTX. The primary outcome was disease activity (DAS28) at 6 months, analyzed using ANCOVA. Power was calculated in advance and exceeded 0.80, α=0.05. The secondary outcome was drug survival of the first RTX course, analyzed using Cox-proportional hazards regression.

Results: Patients exposed to statins were older and more frequently male. Disease duration, ESR, DAS28, rheumatoid factor, previous DMARDS, use of glucocorticoids, and concomitant MTX use did not differ ($p>0.05$) at baseline. At 6 months DAS28 scores differed significantly ($p=0.023$) between patients exposed (mean 4.8, SD 1.5) and unexposed (mean 4.3, SD 1.1) to statins. RTX survival was significantly shorter in the exposed group, HR (95%CI) of 2.3 (1.4–3.9). Baseline DAS28 and rheumatoid factor were included as covariates in all models.

Conclusion: In RA, concomitant use of statins significantly reduces the effect of RTX on disease activity. This lends support to the hypothesis that statins can reduce the clinical effects of RTX, possibly through cholesterol depletion.

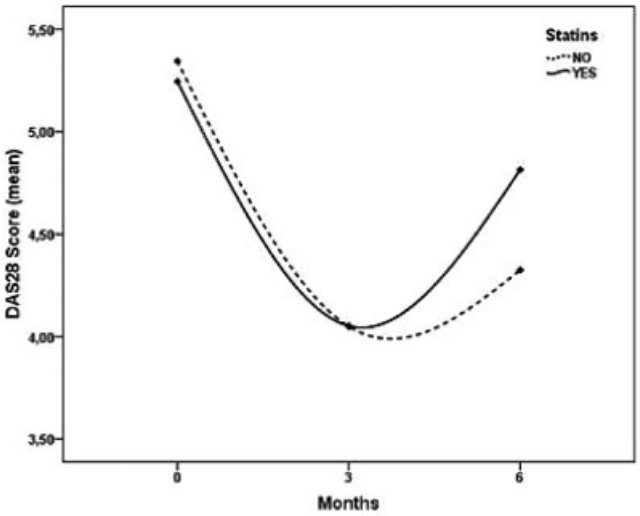


Figure 1.

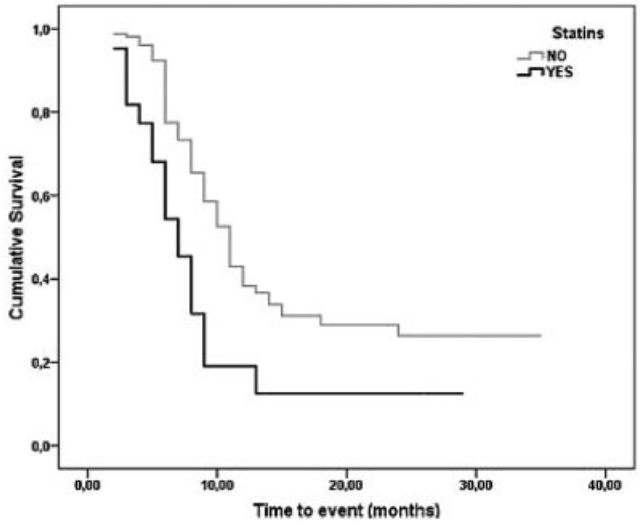


Figure 2.

Disclosure: E. Arts: None; **T. L. Jansen:** None; **A. Den Broeder:** None; **H. E. Vonkeman:** None; **E. Dutmer:** None; **M. A. F. J. Van de Laar:** None; **P. L. C. M. Van Riel:** None; **J. Fransen:** None.

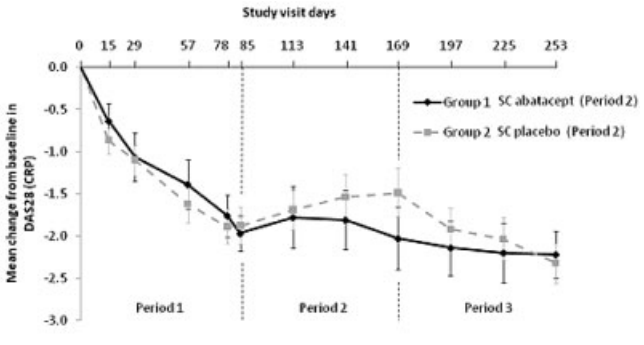
1834

Subcutaneous (SC) Abatacept Is Well-Tolerated, Demonstrates Clinical Efficacy and Is Associated with Low Immunogenicity Following Withdrawal and Re-Introduction: Phase III Evaluation in Rheumatoid Arthritis (RA) Patients Responding to Abatacept. Jeffrey L. Kaine[6], Geoffrey S. Gladstein[5], Ingrid Strusberg[4], Manuel Robles[2], Ramesh Pappu[1], Ingrid Delaet[1], Miranda Pans[1] and Charles L. Ludivico[3]. [1]Bristol-Myers Squibb Co, Princeton, NJ, [2]Centro Médico Toluca, Metepec, Mexico, [3]East Penn Rheumatology Associates, East Stroudsburg, Philadelphia, PA, [4]Instituto Reumatológico, Strusberg, Cordoba, Argentina, [5]New England Research Associates, Trumbull, CT, [6]Sarasota Arthritis Center, Sarasota, FL

Background: In clinical practice, patients (pts) may temporarily interrupt their RA biologic therapy leading to reduced drug concentrations and immunogenicity, which can impact safety and efficacy, particularly during re-administration. We examine the impact of withdrawal and re-introduction of SC abatacept on safety, immunogenicity and efficacy in pts with RA receiving background methotrexate (MTX).

Methods: Pts with mild-to-moderate RA (receiving MTX for ≥3 mths) were enrolled in this randomized, double-blind, Phase III withdrawal trial. During a 12-wk, open-label (OL) period (I) pts received weekly SC abatacept 125 mg. On Day 1, pts also received an intravenous (IV) loading dose (~10 mg/kg according to weight range). Period I responders (DAS28 [CRP] reduction from baseline of ≥0.6) were randomized (1:2) in Period II to either continue SC abatacept (Group 1) or to receive placebo (PBO; Group 2) for 12 wks. All Period II-treated pts could enter the 12-wk, OL Period III; Group 1 pts continued SC abatacept, while Group 2 pts re-initiated SC abatacept with or without an IV loading dose (Groups 2a and 2b, respectively). Pts who received ≥1 dose of abatacept were monitored for safety, and events are presented by Period. Immunogenicity (pts with ELISA-detected anti-abatacept antibodies) and disease activity (DAS28) data are presented for pts who entered Period II (as-observed).

Results: Of 167 pts who entered Period I, 10 (6%) discontinued, 37 (22%) were non-responders, and 120 (72%) entered Period II (Group 1 n=40; Group 2 n=80); 40 from Group 1 and 79 from Group 2 entered Period III, of whom 40 and 77 completed Period III. At baseline (Period II population), mean age was 49.0 (SD: ± 13.2) yrs, disease duration was 6.6 (± 6.5) yrs, DAS28 was 4.8 (± 0.8). Serious adverse events (SAEs) were infrequent during Periods I–III (<2.5% of pts across groups), with no change in trend over time. Local injection-site reactions were reported in two pts in Period I. One serious infection (cellulitis, considered unrelated) was reported in Period I. No autoimmune disorders or malignancies were reported. Immunogenicity was low throughout, with a non-significant numerical increase upon drug withdrawal in Group 2; 0/38 and 7/73 pts in Groups 1 and 2, respectively, were seropositive at the end of Period II (p=0.119). At the end of Period III, seropositivity was observed in 1/38 and 2/73 of pts in Groups 1 and 2; immunogenicity was comparable between Groups 2a and 2b. At the end of Period III, reductions from baseline in DAS28 were comparable for both groups (Figure).



Visit day	15	29	57	78	85	113	141	169	197	225	253
Group 1, n	38	40	40	33	40	39	38	38	40	39	39
Group 2, n	75	80	79	76	78	80	76	75	79	77	74

Conclusions: Three-month interruption and subsequent re-introduction of SC abatacept is well-tolerated and does not negatively impact efficacy and safety. Furthermore, immunogenicity was consistent with the IV experience, and was not significantly affected by this stop-start schedule, an important consideration for the clinical use of SC abatacept.

Disclosure: J. L. Kaine: Bristol-Myers Squibb, 2; **G. S. Gladstein:** New England Research Associates, LLC, 2; **I. Strusberg:** Bristol-Myers Squibb, 5, 8, 9; **M. Robles:** None; **R. Pappu:** Bristol-Myers Squibb, 3; **I. Delaet:** Bristol-Myers Squibb, 1, 3; **M. Pans:** Bristol-Myers Squibb, 3; **C. L. Ludivico:** None.

1835

Subcutaneous Golimumab Sustains Effects of Intravenous Golimumab in Patients with Active Rheumatoid Arthritis: Results of the GO-LIVE Long Term Extension. Joel M. Kremer[4], Peter Taylor[3], Alan Mendelsohn[2], Daniel G. Baker[1], Lilianne Kim[2] and Christopher T. Ritchlin[5]. [1]Centocor Research and Development, Inc., Malvern, PA, [2]Centocor Research and Development, Inc., [3]Imperial College of London, [4]The Center for Rheumatology, Albany, NY, [5]University of Rochester Medical Center, Rochester, NY

Objectives: To evaluate the efficacy and safety of SC golimumab (GLM) in RA pts who previously received IV GLM q12 wks with and without MTX.

Methods: Adult RA pts(n=643), with persistent disease activity while receiving MTX≥15mg/wk for at least 3mos, were randomized to IV placebo + MTX (n=129) or GLM 2- or 4mg/kg, both with and without MTX, q12wks (n=514) up to Wk96 [median 68.4 wks]. Pts who received IV GLM completing the Wk48 database lock were eligible to participate in the long term extension (LTE) and receive open label GLM 50mg SC q4wks for an additional 24wks (E-0 to E-24) and 16wks of safety follow-up (E-24 to E-40) with and without MTX. At Wk E-14, changes in concomitant RA medication (including MTX) were permitted at the investigators discretion.

Results: Of the 505 pts who entered the LTE, 186 pts who did not change dosing strategy during the IV phase (GLM IV 2mg/kg IV + MTX [n=82]; GLM IV 4mg/kg + MTX [n=104]) participated in the LTE at Wk E-0; baseline demographics and disease characteristics were comparable between both groups. Through Wk E-0, ACR20, ACR50, and DAS28-CRP (good or moderate) response was achieved by 67.5%, 61.9%, 43.4% and 39.2%, 87.7% 82.1% in the IV GLM 2mg/kg and 4 mg/kg groups, respectively. Overall efficacy (ACR20, ACR50) and improvements in ACR components were sustained or improved in a majority of pts through Wk E-24 regardless of GLM IV dose(Table). Compared with the IV phase, DAS 28 response and CRP measures improved with SC GLM. The rates of GLM SC discontinuations from Wk E-0 through Wk E-24 were 2.4% and 4.8% in pts previously treated with IV GLM 2- and 4mg/kg, respectively, most commonly for adverse events(AEs). A total of 77.5% and 83.0% of patients in the GLM IV 2- and 4 mg/kg groups, respectively, experienced ≥1 AEs through Wk E-0. Rates of infusion reactions remained lower in GLM-treated pts compared with placebo-treated pts. During the LTE (Wk E-0 through Wk E-40), 69.5% of SC GLM-treated pts experienced ≥1 AE; 13.7% and 14.0% of pts previously treated with GLM IV 2- and 4 mg/kg, respectively, experienced ≥1 serious AE. Injection site reactions were rare [0.6% (19/3443)].

Conclusion: In pts switched to SC GLM 50mg through the LTE, overall efficacy was sustained or improved regardless of whether pts previously received IV GLM 2-or 4mg/kg. Both IV and SC GLM were well tolerated with acceptable safety profiles.

Wk 24 GLM Treatment Assignment	GLM IV 2mg/kg +MTX	GLM IV 4mg/kg + MTX
ACR20 at Wks E-0 relative to BL	56/82 (68.5%)	65/104 (62.5%)
Wk E-14/Wk E-24	40/56(87.5%) / 46/56(85.7%)	60/65(92.3%) / 59/65(90.8%)
ACR50 at Wks E-0 relative to BL	36/82 (43.9%)	39/104 (37.5%)
Wk E-14/ Wk E-24	31/36(86.1%) / 26/36(72.2%)	35/39(89.7%) / 32/39(82.1%)
SJC median % improv at E-0 relative to BL	77%	69%
Wk E-14 / Wk E-24	75% / 78%	80% / 80%
TJC median % improv at E-0 relative to BL	73%	80%
Wk E-14 / Wk E-24	78% / 82%	81% / 83%
CRP median % improv at E-0 relative to BL	25%	31%
Wk E-14 / Wk E-24	50% / 44%	50% / 53%
DAS28CRP good/ mod at WkE-0 relative to BL	70/82 (88%)	85/104 (82%)
WkE-14/ WkE-24	59/70(84.3%) / 65/70(92.9%)	78/85(91.8%) / 80/85(94.1%)

Disclosure: J. M. Kremer: Centocor Research and Development, Inc., 2, 9; **P. Taylor:** Centocor Research and Development, Inc., 2, 9; **A. Mendelsohn:** Centocor Research and Development, Inc., 3; **D. G. Baker:** Centocor Research and Development, Inc., 3; **L. Kim:** Centocor Research and Development, Inc., 3; **C. T. Ritchlin:** Centocor Research and Development, Inc., 2, 9.

1836

Sustained and Clinically Meaningful Improvements in Both Day- and Night-Time Aspects of HRQoL Are Observed with Abatacept Treatment in Patients with Rheumatoid Arthritis (RA) and Previous Inadequate Response to MTX: 5-Year Data from the AIM Trial. Joel Kremer[2], Anthony S. Russell[3], Rene Westhovens[5], Julie Teng[1], Lisa Rosenblatt[1] and Paul Emery[4]. [1]Bristol-Myers Squibb, Princeton, NJ, [2]Center for Rheumatology, Albany Medical College, Albany, NY, [3]University of Alberta Hospital, Edmonton, AB, Canada, [4]University of Leeds, Leeds, United Kingdom, [5]UZ Gasthuisberg, Leuven, Belgium

Background: RA significantly impairs patients' quality of life and limits their ability to participate in daily activities. Long-term, sustainable improvements in HRQoL are important treatment goals for this chronic disease, and capturing this information is key to improving patient care. Here we report 5-year data from the AIM trial, examining the long-term impact of abatacept across multiple day- and night-time aspects of HRQoL in patients with established RA.

Methods: In the double-blind (DB), placebo-controlled AIM trial, patients were randomized to abatacept (~10 mg/kg) or placebo, plus methotrexate (MTX), for 1 year; patients who completed the 1-year period were eligible to enter an open-label (OL) long-term extension (LTE), during which all patients received abatacept (~10 mg/kg) plus MTX. Sleep quality (Medical Outcomes Study Sleep-Problem Index [SPI] scored 0–100) and fatigue (visual analog scale [0–100 mm]) were assessed up to Year 5 (1 year DB + 4 years OL), and activity (Activity Limitations Score, 0–30 days) up to Year 4 (1 year DB + 3 years OL). Minimal clinically important (MCI) changes in sleep, fatigue and activity were estimated at –6 units, –10 units and –4 days respectively.[1,2] Data are summarized over time by original randomization group using point estimates for patients who received ≥1 dose of abatacept in the LTE (as-observed data).

Results: 433 and 219 patients were randomized and treated with abatacept or placebo in the 1-year DB period; 378 and 161, respectively, entered and were treated in the LTE, of which 390 (72.4%) have completed 5 years. At baseline, the mean age of patients entering the LTE was 50.8 years, mean duration of RA was 8.5 years, and mean tender and swollen joint counts were 31.6 and 21.9, respectively; mean baseline values for sleep, fatigue and activity were similar between groups (Table). Initial improvements in HRQoL over 1-year DB treatment were greater for abatacept versus placebo (Table). Over 4–5 years' treatment, patients initially treated with abatacept sustained clinically important improvements, i.e. above the MCI threshold, in all HRQoL domains. Over time, patients who switched to abatacept plus MTX after 1 year of MTX plus placebo showed similar HRQoL improvements as those seen in patients continuously treated with abatacept.

Table. Mean changes from baseline over time in sleep problems, fatigue and activity limitations

	Year										
	BL	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5
Sleep problem index (0–100): MCI is −6 units											
Abatacept	42.2*	−10.9	−10.8	−11.4	−10.9	−12.2	−11.9	−12.2	−11.7	−11.2	−10.6
Placebo	43.6*	−9.3	−8.0	−10.9	−11.3	−12.0	−11.3	−10.1	−10.4	−11.6	−9.1
Fatigue, VAS (0–100 mm): MCI is −10 units											
Abatacept	63.5*	−26.9	−28.0	−29.4	−31.2	−29.7	−32.8	−30.3	−32.2	−30.9	−30.3
Placebo	65.3*	−23.6	−22.6	−31.1	−30.0	−30.6	−31.3	−31.2	−32.6	−32.3	−32.0
Activity limitation, number of days of limitation (0–30): MCI is −4 days											
Abatacept	13.7*	−8.7	−9.0	−9.2	−9.6	−9.4	−10.1	−10.0	−9.7	-	-
Placebo	13.4*	−5.6	−6.4	−9	−8.2	−9.2	−8.7	−8.3	−10.3	-	-

*Baseline value equals mean for subjects entering long-term extension with data available at baseline and Day 29; Data represent mean change from baseline; higher scores for all variables represent more severe impairment; BL=baseline; VAS=visual analog scale.

Conclusions: In patients with RA and an inadequate response to MTX, abatacept provides sustained, long-term, MCI improvements across both day- and night-time measures of HRQoL, and reduces the limitation of patients' usual daily activities caused by their disease. These improvements represent tangible benefits to patients.

References:
[1]Wells G, et al. *J Rheumatol* 2007;**34:**280–9
[2]Todd KH, et al. *Ann Emerg Med* 1996;**27:**485–9.

Disclosure: J. Kremer: Abbott Laboratories, 2, 5, Amgen Inc., 2, 5, Bristol-Myers Squibb, 2, 5, Centocor, Inc., 2, 5, Genentech and Biogen IDEC Inc, 2, 5, Merck Pharmaceuticals, 2, 5, Pfizer Inc, 2, 5, Roche, 2, 5; **A. S. Russell:** Bristol-Myers Squibb, 5, 8, 9, GlaxoSmithKline, 5, 8, 9, Pfizer Inc, 5, 8, 9; **R. Westhovens:** Bristol-Myers Squibb, 5, 8, Centocor, Inc., 5, Roche, 5, Schering-Plough, 5, UCB, Inc., 2; **J. Teng:** Bristol-Myers Squibb, 1, 3; **L. Rosenblatt:** Bristol-Myers Squibb, 1, 3; **P. Emery:** Amgen Inc., 5, Bristol-Myers Squibb, 5, Centocor, Inc., 5, Roche, 5, Schering-Plough, 5.

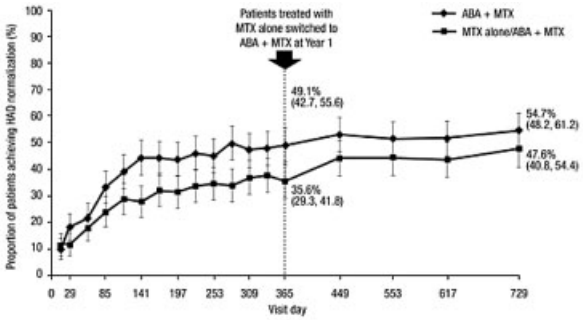
1837

Sustained and Clinically Meaningful Improvements in Physical Function and Fatigue and Reductions in Activity Limitation Are Observed in MTX-Naïve Patients with Early Rheumatoid Arthritis (RA) Treated with Abatacept over 2 Years of the AGREE Trial. Rene Westhovens[5], Jurgen Wollenhaupt[4], Boulos Haraoui[2], Jean-Claude Becker[1], Allison Covucci[1], Lisa Rosenblatt[1] and Joan Bathon[3]. [1]Bristol-Myers Squibb, NJ, [2]Institut de Rumatologie de Montreal, Montreal, QC, Canada, [3]John Hopkins University School of Medicine, Baltimore, MD, [4]Klinikum Eilbek, Hamburg, Germany, [5]UZ Gasthuisburg, Leuven, Belgium

Background: The ability to participate in normal work and/or social daily activities is central to a patient's (pts) Health-Related Quality of Life (HRQoL) and sense of well being. RA-associated fatigue and functional disability can significantly limit activities and have a profound impact on psychological and social health. Here for the first time in MTX-naïve pts with early RA and poor prognostic factors, we assess physical function and HRQoL from the pt perspective, over 2 yrs of abatacept treatment.

Methods: During the 1-yr double-blind period of the AGREE trial[1], RA pts with poor prognostic factors were randomized 1:1 to ABA (~10 mg/kg) + MTX or placebo + MTX (MTX alone). All pts continuing in the 1-yr open-label (OL) period received ABA + MTX. Normalization of physical function (Health Assessment Questionnaire-Disability index [HAQ-DI] ≤0.5), fatigue (100 mm visual analog scale [VAS]) and activity limitation (number of days/month a pt could not perform usual activities due to RA) were evaluated. Mean change from baseline (BL) is presented for pts who entered the OL period and had data available at the visit of interest (as observed), with consideration of established minimal clinically important differences (MCID).

Results: Pts had high BL disease activity (mean Disease Activity Score 28 [C-reactive protein]: 6.3; HAQ-DI: 1.7) and short disease duration (6.1–6.9 mths). Mean BL values for HRQoL outcomes were comparable between groups (fatigue: 64.3–65.8 mm; activity limitation: 15.4–16.0 days/month). The proportions of pts achieving normalized physical function increased from BL to Yr 2 in both treatment arms (Figure). Reductions in fatigue were maintained over 2 yrs in the ABA + MTX group (–36.1 at Yr 1; –40.2 at Yr 2) and exceeded the MCID of 10[2]; further reductions were noted at Yr 2 relative to Yr 1 for pts who switched to ABA + MTX from MTX alone (–28.0 at Yr 1; –37.0 at Yr 2). By Yrs 1 and 2, pts randomized to ABA + MTX gained 11.4 and 12.1 days/month of activity vs BL, respectively, surpassing the MCID of 4 days[2], with just 4.6 and 3.6 days/month of activity limitation reported. Improvements were also noted in the original MTX alone group at Yrs 1 and 2, with gains of 8.3 and 11.5 days/month vs BL, with 7.1 and 4.1 actual days/month of activity limitation reported.



Visit day	15	29	57	85	113	141	169	197	225	253	281	309	337	365	449	553	617	729
ABA + MTX, n	231	230	229	231	230	230	229	229	228	231	229	231	225	230	226	227	225	223
MTX alone, n	224	223	226	225	225	226	224	223	219	222	224	222	225	225	–	–	–	–
MTX alone, switched to ABA + MTX, n	–	–	–	–	–	–	–	–	–	–	–	–	–	–	220	221	216	208

Error bars represent 95% confidence intervals.

Conclusions: Treatment with ABA + MTX resulted in normalization of physical function and reductions in fatigue that were maintained over 2 yrs, and reduced RA-related limitation of daily activities. Pts originally treated with MTX alone demonstrated improvements in these patient-reported

outcomes in Yr 2 after addition of abatacept at Yr 1. These data support the early use of abatacept to provide meaningful improvements in QoL and daily functioning in MTX-naïve pts with early RA and poor prognostic factors.

[1]Westhovens R, et al. *Ann Rheum Dis* 2009;**68:**1870–7
[2]Wells G, et al. *J Rheumatol* 2007;**34:**280–9

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1838

TNF-alpha Antagonist Therapy Leads to an Expansion of IL-17 Expressing CD4+ T Cells Both In Vitro and In Vivo. Hayley G. Evans[2], Nicola J. Gullick[3], Bruce W. Kirkham[1] and Leonie S. Taams[3]. [1]Guy's & St Thomas' NHS Foundation Trust, [2]Kings College London, London, United Kingdom, [3]Kings College London

Purpose: TNF-alpha is a highly pro-inflammatory cytokine, which contributes to inflammation and joint damage progression in patients with Rheumatoid Arthritis (RA). Use of TNF-alpha antagonists has had considerable success in the clinic, by reducing disease activity and inhibiting joint damage progression. We have previously demonstrated that TNF-alpha can induce IL-17 expression and secretion from CD4+ T cells when produced in combination with IL-1-beta by in vitro activated monocytes. IL-17 has also been shown to induce tissue inflammation and bone destruction in RA. In the present study we investigated how the presence of IL-17-producing CD4+ T cells is affected by TNF-alpha antagonist therapy.

Methods: PBMC and CD4+ T cells from healthy controls (n=13) or patients with RA (n=34) were stimulated ex vivo with PMA/ionomycin and analysed via intracellular flow cytometry and ELISA for their production of IL-17 and IFN-gamma. PBMC (0.5×10^6 in a 48 well plate) and CD4+ T cell/monocyte (0.5×10^6:0.5×10^6, in a 24 well plate) co-cultures were also cultured in the absence or presence of Infliximab, Etanercept or Adalimumab followed by stimulation and analysis via flow cytometry and ELISA.

Results: The percentage of IL-17+ CD4+ T cells is significantly enriched in the blood of RA patients when compared to healthy controls (0.6±0.6% vs. 1.4±1.2%, p=0.003. When separated by treatment regimes, we observed a further enrichment of IL-17+ CD4+ T cells in patients treated with TNF-alpha antagonists compared to those on DMARD therapy (1.1±0.8% vs. 2.3±1.7%, p=0.02). This enrichment could not be explained by the method of stimulation, naïve/memory cell ratio, the age, sex, and disease duration or disease activity of the patients. Instead this may be a direct drug effect since in vitro experiments demonstrated that the presence of TNF-alpha antagonists can stimulate the expression of IL-17 by CD4+ T cells (63±41%, n=6). Finally, preliminary data indicate a rise in the percentage CD4+IL-17+ expressing T cells in the blood when measured ex vivo pre and post anti-TNF-alpha therapy.

Conclusions: Treatment of RA patients with TNF-alpha antagonists leads to an increase of Th17 cells in the peripheral blood. In vitro experiments suggest this may not simply be the result of re-distribution of joint Th17 cells. We propose that the presence of this primed pool of pro-inflammatory T cells may contribute to relapse of disease when anti-TNF-alpha therapy is ceased.

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1839

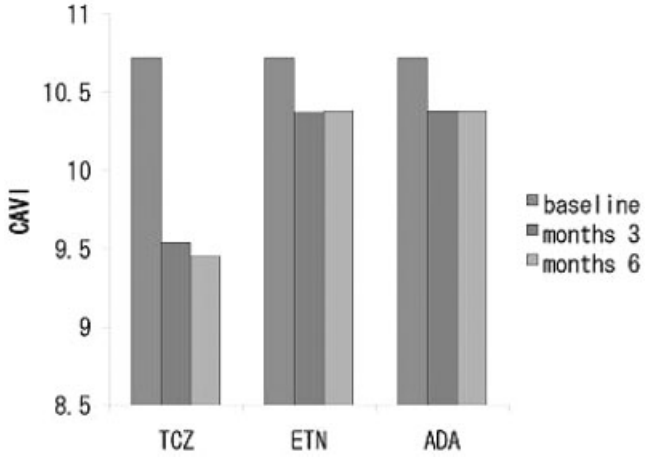
Tocilizumab Monotherapy Improves Arterial Stiffness Compared with Other Biologics Monotherapy in Rheumatoid Arthritis. Kensuke Kume[1], Kanzo Amano[1], Susumu Yamada[1] and Hiroyuki Ohta[2]. [1]Hiroshima Clinic, Hiroshima, Japan, [2]IGL School, Hiroshima, Japan

Background: Methotrexate (MTX) plus TNF inhibitor is very effective in rheumatoid arthritis (RA). But sometimes we choice biologics monotherapy, when it is difficult to use MTX. By the way, patients with RA have an increased cardiovascular (CV) risk. We should have strategies for prevent CV primary in RA patients. And some biologics reduce arterial stiffness and may improve CV morbidity in RA patients.

Objective: to examine the effect of tocilizumab (TCZ) alone, etanercept (ETN) alone, and Adalimumab (ADA) alone, compared respectively on arterial stiffness in RA patients in an open label randomized study design.

Methods: RA patients were eligible if they had active disease and no prior treatment with MTX or a TNF inhibitor. All patients have no previous history of CV. 32 RA patients with moderate to severe active disease(DAS 28>3.2) were randomly assigned to receive TCZ alone (n=11), ETN alone (n=11), or ADA alone (n=10). Arterial stiffness was assessed with augmentation index corrected for a heart rate of 75 beats per minute (AIx@75) and cardio-ankle vascular index (CAVI) at baseline, 3 months, and 6 months follow-up. Clinical data was collected at regular visits. CAVI measures arterial stiffness independent of blood pressure and it is superior to brachial ankle pulse wave velocity as an index of arterial stiffness.

Results: Each groups of characteristics (DAS 28, CRP, diastolic blood pressure, age, gender, disease duration, class) at baseline are no significantly different. Treatment with TCZ (36.3 ± 11, 33.8 ± 3and 33.9± 3%; P = 0.032), ETN (36.4 ± 8, 33.8 ± 5 and 33.5 ± 6%; P = 0.038), ADA (37.1 ± 8, 33.0 ± 5 and 34.1 ± 7%; P = 0.047) attenuated the Aix@75 significantly from baseline to 3 months and 6 months follow-up. Treatment with TCZ (10.82 ± 1.58, 9.62 ± 0.94 and 9.55 ± 1.42%; P = 0.028), ETN (10.92 ± 1.38, 10.29 ± 0.53 and 10.28 ± 1.31%; P = 0.035), ADA (10.74 ± 1.78, 10.38 ± 0.75 and 10.35 ± 0.98%; P = 0.025) attenuated the CAVI significantly from baseline to 3 months and 6 months follow-up. And the CAVI of the TCZ group has most significantly decreased in comparison with the CAVI of ETN or IFX group in 3 and 6 months follow-up.



Conclusions: Monotherapy of TCZ, ETN, and ADA reduces arterial stiffness in RA patients. TCZ monotherapy improves arterial stiffness more significantly compared with other biologics monotherapy in RA patients.

Disclosure: K. Kume: None; **K. Amano:** None; **S. Yamada:** None; **H. Ohta:** None.

1840

Tocilizumab Treatment in Patients with Rheumatoid Arthritis and an Inadequate Response to DMARDs and/or TNF Inhibitors: ACT-SURE Preliminary Results. Vivian P. Bykerk[7], Jose Álvaro-Gracia[3], Jose Andres Roman Ivorra[4], Michael T. Nurmohamed[6], Karel Pavelka[5], Corrado Bernasconi[8], Andrea Stancati[8], Jean Sibilia[2] and Andrew Östör and the ACT-SURE Study Group[1]. [1]Addenbrookes Hospital, Cambridge, United Kingdom, [2]Hautepierre Service de Rhumatologie, Strasbourg, France, [3]Hospital Universitario de La Princesa, IIS Princesa, Madrid, Spain, [4]Hospital Universitario Dr. Peset, Valencia, Spain, [5]Institute of Rheumatology, Prague, Czech Republic, [6]Jan van Breemen Institute, Amsterdam, The Netherlands, [7]Mount Sinai Hospital, Toronto, ON, Canada, [8]Roche, Basel, Switzerland

Background: Safety and efficacy of TCZ have been demonstrated in 7 phase 3 controlled studies in pts with RA and DMARD-IR or TNFi-IR but not in pts who switched to TCZ without TNFi washout. The ACT-SURE study evaluated TCZ safety and efficacy in pts who were DMARD-IR or TNFi-IR, treated in tertiary academic and non academic centers as well as in private practice setting.

Methods: ACT-SURE was a phase 3b, open-label, single-arm, 6-mo study of DMARD-IR/TNFi-IR pts with active RA treated with TCZ 8 mg/kg Q4W alone or in combination with DMARDs. Safety endpoints included adverse events (AEs) and serious AEs (SAEs). Efficacy endpoints included ACR and DAS28 responses. Analyses were stratified by prestudy TNFi use: TNFi-naive (DMARD-IR) pts, previous TNFi users (>2 mos since TNFi use) or recent TNFi users (≤2 mos since TNFi use). Subanalysis of pts who received TCZ monotherapy was also performed.

Results: Of 1681 evaluable pts, 58% were DMARD-IR, 18% were previous TNFi users and 24% were recent TNFi users. Mean age of pts was 54 years; 81% were women. Mean RA duration was 8.2 years in DMARD-IR pts and 11.2/11.7 years in previous/recent TNFi users. Baseline DAS28 was similar among groups (5.9–6.2). Overall, 12.8% pts withdrew, 4.8% for safety-related reasons; infections were the primary safety-related cause of withdrawal (1.1% of pts or 1.8/100 patient-years [PY]). Rates/100 PY AEs/SAEs and serious infections were slightly lower in TNFi-naive pts than in those with previous TNFi exposure (Table). ALT shifts from normal at baseline to >3′ ULN occurred in <3% of pts (Table). Onset of efficacy was rapid and increased over time: among the groups, DAS28 remission was achieved by 24%–38% of pts at wk 8 and 49%–62% of pts at wk 24. Clinical response tended to be higher in DMARD-IR pts, with little difference between recent and previous TNFi users (Table). At wk 24, mean DAS28 values were 2.34, 2.83 and 2.76 in DMARD-IR pts, previous TNFi users and recent TNFi users. Improvement in physical function was similar across groups: 74.1%, 71.1% and 70.2% of DMARD-IR pts, previous TNFi users and recent TNFi users achieved ≥0.22 point change from baseline in HAQ-DI. In the subgroup of pts who received TCZ monotherapy, 66.9%, 43.5% and 23.8% achieved ACR20/50/70 response at wk 24; 49.8% achieved DAS28 remission.

Conclusions: ACT-SURE was performed in a setting closer to clinical practice than is typical of phase 3 studies and confirmed the safety profile of TCZ shown in previous phase 3 trials. TCZ is effective when used in DMARD-IR pts as the first-line biologic and in TNFi-IR pts. TCZ was effective as monotherapy or with DMARDs. Efficacy was characterized by rapid onset of action and increasing response over time. These results did not show a difference in TCZ safety for pts who were previous or recent TNFi users, which supports treating pts with TCZ immediately after stopping TNFi use.

Table. Safety and Efficacy Outcomes at Wk 24

	AE Rate/ 100PY	SAE Rate/ 100PY	Serious Infections Rate/100PY	Infusion Reactions % (n)[a]	ALT Shift From Baseline to >3×ULN % (n)
DMARD-IR	551.1	18.6	4.2	6.8 (66)	2.4 (23)
TNFi-IR, previous use	654.4	28.7	7.6	7.4 (22)	3.0 (9)
TNFi-IR, recent use	652.6	18.0	6.0	6.1 (25)	0.7 (3)
	ACR20 % (n)	**ACR50 % (n)**	**ACR70 % (n)**	**ACR90 % (n)**	**DAS28 Remission % (n/n)**
DMARD-IR	70.5 (688)	51.9 (507)	31.8 (310)	10.3 (101)	61.6 (534/867)
TNFi-IR, previous use	60.7 (181)	35.2 (105)	17.8 (53)	6.4 (19)	48.5 (117/241)
TNFi-IR, recent use	62.7 (255)	42.3 (172)	19.7 (80)	6.6 (27)	50.4 (175/347)

n/n=no. pts who responded/no. evaluable pts.
[a]Infusion reaction=AE occurring during infusion of TCZ.

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1841

Treatment with TNF-Inhibitors Reduces Radiographic Joint Destruction in Rheumatoid Arthritis Patients Treated in Clinical Practice. Lykke M. Ørnbjerg[1], Mikkel Østergaard[1], Pernille Bøyesen[12], Anja Thormann[1], Ulrik Tarp[6], Wolfgang Böhme[13], Ditte Dencker[13], Hanne Lindegaard[15], Uta Poulsen[14], Anette Hansen[2], Vibeke Ringsdal[5], Anette Schlemmer[5], Niels Graudal[10], Anne R. Andersen[16], Jakob Espesen[4], Gina Kollerup[7], Torben G. Christensen[11], Randi Pelck[3], Bente Glintborg[3], Ole R. Madsen[2], Dorte V. Jensen[8], Ole Majgaard[9] and Merete L. Hetland[1]. [1]DANBIO Registry and Depts. of Rheumatology, Copenhagen University Hospitals at Hvidovre and Glostrup, Denmark, [2]Dept. of Internal Medicine and Rheumatology, Gentofte University Hospital, Denmark, [3]Dept. of Internal Medicine, Copenhagen University Hospital at Holbæk, Denmark, [4]Dept. of Internal Medicine, Hospital Lillebaelt at Vejle, Denmark, [5]Dept. of Rheumatology, århus University Hospital at ålborg, Denmark, [6]Dept. of Rheumatology, århus University Hospital, Denmark, [7]Dept. of Rheumatology, Copenhagen University Hospital at Frederiksberg, Denmark, [8]Dept. of Rheumatology, Copenhagen University Hospital at Hørsholm, Denmark, [9]Dept. of Rheumatology, Copenhagen University Hospital at Næstved, Denmark, [10]Dept. of Rheumatology, Copenhagen University Hospital at Rigshospitalet, Denmark, [11]Dept. of Rheumatology, Copenhagen University Hospital at Slagelse, Denmark, [12]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [13]Dept. of Rheumatology, Hospital of South West Jutland at Esbjerg, Denmark, [14]Dept. of Rheumatology, King Christian Xth Hospital, Gråsten, Denmark, [15]Dept. of Rheumatology, Odense University Hospital, Denmark, [16]Depts. of Rheumatology, Copenhagen University Hospitals at Hvidovre and Glostrup, Denmark

Background: Real-life studies concerning the impact of tumour necrosis factor inhibitor (TNF-I) treatment on radiographic progression in rheumatoid arthritis (RA) patients are few.

Objectives: To compare radiographic progression (delta total Sharp (dTSS); erosion (dES); and joint space narrowing (dJSN) scores) during treatment with disease-modifying antirheumatic drugs (DMARDs) and during subsequent treatment with TNF-I in RA patients in clinical practice.

Methods: Conventional radiographs (CR) of hands and wrists were obtained ~2 years before start of TNF-I (time-point A), at the start of TNF-I (B) and ~2 years after start of TNF-I (C). Clinical data from the DANBIO registry and the patientfiles was collected for the patients with CRs. The CRs were scored blinded to chronology according to the van der Heijde modified Sharp score. Annual radiographic progression rates during DMARD (delta A-B) and TNF-I (delta B-C) treatments were calculated.

Results: 522 RA patients (76% women, 80% rheumatoid factor positive, 65% anti-CCP positive, 27% current smokers, age 54 (21–86) years (median (range)); disease duration 5 (0–67) years) had complete A-B-C series. At time-point A, 28-joint disease activity score (DAS28) was 4.4 (1.4) (mean (SD)) and patients received the following treatments: methotrexate (MTX) (45%), sulphasalazine (22%), hydroxychlorochine (12%), leflunomide (5%), other DMARDs (6%) or no DMARDs (10%). At time-point B, DAS28 was 5.0 (1.1) and treatment with infliximab (61%), etanercept (15%), or adalimumab (24%), was started (combination with MTX (78%), combination with other DMARDs (10%), monotherapy (12%)). At time-point C, 60% were on the initial TNF-I, 29% had switched to another TNF-I and 11% withdrawn from TNF-I. Mean DAS28 was 3.1(1.2). The duration of Period A-B was median 735(interquartile range 484–1002) days and of period B-C 562 (405–766) days. Radiographic data are shown in Table 1. The progression rate (deltaTSS) during TNF-I treatment was reduced by 61% compared to DMARD.

Table. Radiographic progression during treatment with DMARDs and subsequent treatment with TNF-I in RA patients in clinical practice.

	A DMARD	B TNF-I start	C 2 yr follow-up	Delta A-B/yr	Delta B-C/yr	P value
TSS mean(SD)	21.0 (29.8)	25.7 (32.0)	27.0 (32.8)	2.1 (3.8)	0.67 (2.3)	<0.0001 (1)
TSS median (IQR)	7 (1–31)	13 (2–40)	14 (3–42)	0.73 (0–2.9)	0 (0–0.89)	<0.0001 (2)
ES mean(SD)	13.1 (19.9)	15.5 (21.3)	16.2 (21.7)	1.04 (2.0)	0.36 (1.4)	<0.0001 (1)
ES median (IQR)	4 (0–18)	6 (1–23)	7 (1–24)	0.2 (0–1.4)	0 (0–0)	<0.0001 (2)
JSN mean(SD)	7.8 (11.5)	10.2 (12.7)	10.8 (13.2)	1 (2.6)	0.31 (1.2)	<0.0001 (1)
JSN median (IQR)	2 (0–12)	5 (0–16)	6 (0–17)	0 (0–1.4)	0 (0–0)	<0.0001 (2)
Progressing patients (%)				59	31	<0.0001 (3)

(1) Paired T-test (2) Paired Wilcoxon-test (3) Chi-square test A, 2 years before TNF-I treatment start; B, TNF-I treatment start; C, 2 years after TNF-I treatment start; TSS, total van der Heijde Sharp score; ES, erosion score; JSN, joint space narrowing; SD, standard deviation; IQR, inter quartile range; Delta A-B/yr, annual progression rate time A to B; Delta B-C/yr, annual progression rate time B to C.

Conclusion: Real-life data from a large nationwide observational cohort showed that use of TNF inhibitors in RA patients treated for ~2 years in

routine care significantly reduces the rate of joint damage progression when compared to the previous ~2 years on conventional treatment.

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ACR Poster Session C
Systemic Lupus Enrythematosus - Clinical Aspects and Treatment - Epidemiology and Health Services III
Wednesday, November 10, 2010, 9:00 AM–6:00 PM

1842

Accumulation of Traditional Risk Factors for Coronary Heart Disease in Patients with Systemic Lupus Erythematosus. Rosa W. Telles[2], Cristina C. D. Lanna[2], Fabricia F. Simil[1], Luana G. Machado[1], Fabiana L. Sousa[1], Luciana A. Rodrigues[2] and Antonio L. Ribeiro[3]. [1]Hospital das Clinicas, [2]School of Medicine, [3]School of Medicine-Universidade Federal de Minas Gerias-Brazil

Objective: to examine the accumulation of traditional risk factors for Coronary Heart Disease (CHD) in patients with SLE.

Patients and Methods: 157 patients included in a prospective study of atherosclerosis in lupus patients were followed during 39(37–42) months. Traditional risk factors for CHD were collected at entry (T_0), trough out the follow up (considered positive when the risk factors were identified in two different occasions for a period ≥1 year) and at the last study visit (T_1). The hypothesis of risk factors accumulation was investigated comparing the prevalence of those factors between T_0 and T_1 using either McNemar or Wilcoxon tests. The annual mean incidence of the risk factors was determined.

Results: median (IR) age at entry and age at lupus diagnosis of the 157 patients were 38(29–46) years and 27.3(21.5–34.7) years, respectively (96.2%: female gender; 75.8%: non-white). Median (IR) duration of lupus was 7.7(4.3–11.4) years. The prevalence of the following traditional risk factors increased during study interval (T_0 *x* T_1): positive family history for coronary heart disease (12.7% *x* 15.9%; p=0.025), postmenopausal status (38.2% *x* 45.2%; p=0.001), hypertension (46.5% *x* 55.4%; p=0.003), obesity (19.7% *x* 29.3%; p=0.006) and abdominal obesity (42% *x* 60.5%; p<0.001). The number of current smokers did not differ (14% *x* 12.1%; p=0.250). Although the prevalence of LDL≥130mg/dl (16,6% *x* 22,9%; p=0,036) and the total cholesterol≥200mg/dl (19,7% *x* 28,7%; p=0,024) increased, the prevalence of HDL<40mg/dl did not change (26,8% *x* 20,4%; p=0,268). The number of traditional risk factors (age and sex, hypertension, diabetes mellitus, dyslipidemia, hypertiglyceridemia, family history for CHD and smoking habit) per patient also increased during the study interval [1(0–2) *x* 2(1–3); p=0.015]. The annual mean incidence of the traditional risk factors were: hypertension 4%, diabetes mellitus 0.8%, dyslipidemia 10%, triglycerides≥150mg/dl 5.1%, obesity (BMI>30kg/m^2) 5.1% and abdominal obesity (abdominal circumference >102cm in men and >88cm in women) 11.5%.

Conclusion: the prevalence of traditional risk factors for CHD increased in a short-period in young patients with SLE. Some of these risk factors have already been associated with clinical and subclinical atherosclerosis in lupus. Lupus patients should be monitored for cardiovascular risk factors in a regular basis and appropriate treatment instituted.

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1843

Analysis of the Level of Agreement between Different Measures of Disease Flare in an Exploratory Study of Abatacept in Systemic Lupus Erythematosus (SLE). Caroline Gordon[3], Jean-Claude Becker[1], Sheila Kelly[1], Yun Peng[2], Michael Kinaszczuk[1] and Joan T. Merrill[4]. [1]Bristol-Myers Squibb, Princeton, NJ, [2]Bristol-Myers Squibb, Pennington, NJ, [3]University of Birmingham, Birmingham, United Kingdom, [4]University of Oklahoma, Oklahoma City, OK

Background: This Phase II exploratory trial of abatacept used BILAG A/B flare (adjudicated per protocol) as the primary endpoint[1]. *Post-hoc* analyses examined other BILAG and physician- defined flare measures.

Methods: This was a double-blind, Phase II study in which SLE patients with active polyarthritis, serositis and/or discoid lesions were randomized to abatacept (~10 mg/kg) or placebo (PLC) for 1 year. Prednisone (30 mg/day or equivalent) was given for 1 month, then tapered by protocol. The primary endpoint was new adjudicated BILAG A/B flare (classic BILAG index)[2] over 1 year after the start of steroid taper. *Post-hoc* assessments included BILAG A only flare (adjudicated), or physician-defined flare in response to the question 'Since the last visit, does the patient exhibit symptoms of an acute SLE flare?' (yes/no). Treatment modifications were recorded on visits when physician-defined flares occurred. Analyses are based on data for all randomized and treated patients.

Results: 118 abatacept and 57 PLC patients were assessed. Proportions of patients with ≥1 BILAG A/B flare, BILAG A only flare or physician-assessed flare, respectively, were 79.7, 40.7 and 63.6% for abatacept versus 82.5, 54.4 and 82.5% for PLC. In the abatacept group, physician's assessment agreed with BILAG A/B flare in 71/165 (43%) cases: when the flare definition was restricted to BILAG A only, agreement occurred in 23/33 (70%) cases (Table). Most BILAG-defined flares that physicians did not rate as flares were B events (84/94 in abatacept-treated patients). 45.8% of physician-assessed flares occurred when no BILAG A/B flare was recorded. In instances where physicians recorded flare, BILAG A/B flare coincided with treatment modification the majority of the time (49/71 [69.0%]). Results in the PLC group were similar to abatacept.

Cross-tabulation of the presence/absence of flare according to BILAG and physician-defined measures

		Abatacept (n=118)			Placebo (n=57)		
		Total n	Yes n (%)	No n (%)	Total N	Yes n (%)	No n (%)
		Adjudicated BILAG A or B flare					
Physician assessment of flare	Yes	131	71 (54.2)	60 (45.8)	82	47 (57.3)	35 (42.7)
	No	1178	94* (8.0)	1084 (92.0)	533	32 (6.0)	501 (94.0)
		Adjudicated BILAG A flare					
Physician assessment of flare	Yes	131	23 (17.6)	108 (82.4)	82	17 (20.7)	65 (79.3)
	No	1178	10 (0.8)	1168 (99.2)	534	1 (0.2)	533 (99.8)

*10 were A flares; the remaining 84 were B flares

Conclusions: These data demonstrate some discordance between BILAG adjudication- and physician-determined flares. This may be due to: a) BILAG flare rules being based on an item worsening after improving at 2 prior visits (to avoid recording non-significant fluctuations in disease severity), whereas physicians may have recorded worsening irrespective of prior visits; b) physicians recording flare when items were the same over 4 prior weeks (not just when new, or worse after improving); c) the classic BILAG index may fail to capture some flare features detected by physicians. Some BILAG A/B flares occurred when no physician-defined flares were recorded; BILAG flares were more likely to be confirmed by the physician when restricted to BILAG A, suggesting increased ability of BILAG A to define events that physicians considered significant. These data provide valuable insight into issues encountered when assessing flare in clinical trials of SLE, and may help inform future trial design.

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1844

Anti-NR2A Antibody as a Predictor for Neuropsychiatric Systemic Lupus Erythematosus. Masanori Hanaoka[3], Takahisa Gono[3], Yasushi Kawaguchi[1], Hirotaka Kaneko[2], Katsuji Nishimura[2], Yasuhiro Katsumata[2], Yuko Okamoto[2], Sayumi Baba[2], Sayuri Kataoka[2] and Hisashi Yamanaka[4]. [1]Tokyo Women's Medical Univ, Tokyo, Japan, [2]Tokyo Women's Medical Univ, [3]Tokyo Women's Medical University, [4]Tokyo Womens Med Univ, Shinjuku-ku, Tokyo, Japan

Purpose: N-methyl-D-aspartate receptors (NMDAR) are ligand-gated ion channels with crucial roles in synaptic transmission and plasticity of central

nervous system (CNS). Additionally, NMDAR are located on non-neuronal tissues, such as bone, skin, pancreas and megakaryocyte. Anti-NMDAR subunit 2A/2B (NR2A/2B) antibody has been reported to react against the peptide DWEYSVWLSN in systemic lupus erythematosus (SLE). Although DWEYS was reported as residues 283–287 in NR2A/2B, the actual sequence of residues 283–287 is DWDYS in NR2A and DEWDY in NR2B. This will make DWDYS-peptide more specific than DWEYS-peptide in NR2A, even though most reports that have measured anti-NR2 antibody by enzyme-linked immunosorbent assay (ELISA) have used DWEYS-peptide. The aim of the present study is to establish a method to detect serum anti-NR2A antibody by ELISA and to evaluate the relationship between anti-NR2A antibody and various tissue damages in SLE.

Methods: Measurement of anti-NR2A antibody in sera was performed by ELISA using either DWEYS- or DWDYS-peptide as autoantigen. Clinical characteristics were compared between anti-NR2A antibody-positive 27 patients (P group) and -negative 80 patients (N group) in SLE, using DWDYS-peptide.

Results: The optical density (OD) value using DWDYS-peptide correlated significantly ($r = 0.94$, $P < 0.0001$) with the one using DWEYS-peptide in SLE patients. The median OD value was significantly higher ($P < 0.0001$) in DWDYS-peptide than DWEYS-peptide. The median OD value [interquartile range] using DWDYS-peptide were 0.449 [0.327–0.622] and 0.197 [0.14–0.29] in 107 SLE patients and 74 non-SLE patients, respectively. There was a strikingly significant difference between two subsets ($P < 0.0001$). Additionally, SLE Disease Activity Index (SLEDAI) was significantly higher ($P = 0.023$) in P group. The frequency of serositis, nephritis and neuropsychiatric SLE (NP SLE) was significantly higher ($P = 0.039$, 0.015 and 0.0002, respectively) in P group. The frequency of diffuse CNS form and focal CNS form was significantly higher ($P = 0.036$ and 0.01, and odds ration 3.5 and 5.3, respectively) in P group. The leukocyte count and hemoglobin was significantly decreasing ($P = 0.021$ and 0.0008, respectively) in P group. Although no correlation were found between anti-NR2A antibody and the titer of anti-DNA antibody, significant correlations were found between anti-NR2A antibody and leukocyte count ($r = -0.31$, $P = 0.001$) and hemoglobin ($r = -0.42$, $P < 0.0001$). NP SLE was a most significant independent variable ($P = 0.0008$), associated with anti-NR2A antibody-positivity, estimated by multiple liner regression analysis. The leukocyte count and hemoglobin were also significant variables ($P = 0.0095$ and 0.013, respectively) associated with anti-NR2A antibody-positivity.

Conclusion: Serum anti-NR2A antibody can be a predictor for NP SLE and may damage also non-nervous tissues. The usage of peptide including DWDYS is more preferable for detecting anti-NR2A antibody in ELISA.

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1845

Assessing the ANA Test as a Screening Tool: Utility or Futility? Aryeh M. Abeles and Micha Abeles. University of Connecticut Health Center

Introduction: Current ANA testing may be overly sensitive, resulting in frequent false positives as well as unnecessary follow-up testing and misdiagnosis. Several studies have focused on ANA prevalence and predictive value, but the purpose of this investigation was to evaluate the clinical utility of a positive ANA test in a real-world setting, by reviewing the outcomes of patients referred to a tertiary rheumatology clinic for evaluation of a positive ANA test. No prior study has directly addressed this question.

Method: We reviewed records for all consultation patients presenting to the authors at the UCHC rheumatology clinic between July 2007 and July 2009. Patients were included in the evaluation if they had been referred for a positive ANA. Patients presenting with an already-diagnosed ANA-associated rheumatic disease (AARD) were excluded. All ANA tests and all referrals had been ordered by non-rheumatologists. A complete review of systems and physical examination was performed on each patient. 91 out of 101 patients with ANA titers ≥1:320 had the following labs drawn: antibody (Ab) panel (Anti-dsDNA, SSA/SSB, Sm, RNP), C3, C4, CH50, CBC, and ESR. Of 67 patients with ANA ≥1:640, 64 had lab evaluations performed as above. Referring physician reasons for ordering ANA testing were also collated.

Results: Of 1,306 initial consultation visits to our clinic, 232 were referrals for a positive ANA, with titers ranging from 1:40 to greater than 1:5120. Initial ANA testing had been performed at several different laboratories (the majority at UCHC). 98% of all initial ANA tests had been run using immunofluoresence assay with Hep-2 cells.

9.1% of patients evaluated (21/232) had an AARD (5 SLE, 12 Sjogren's syndrome, 3 scleroderma, 1 MCTD). The remainder of patients had no AARD, of whom twenty-one (9.1%) had isolated autoimmune thyroid Ab present. No patient with an ANA ≤1:80, and only 1 patient with ANA≤1:160, had a rheumatic disease. There was no correlation between the highest ANA titers with a specific rheumatic illness. The most common reason for ordering ANA testing was widespread pain and tenderness (54/232, 23.2%) but also included, among others, chronic lower back pain, episodic chronic rhinitis, palpitations, thinning hair, unilateral heel pain, and lateral buttock pain. The positive predictive value of an ANA test in our cohort of patients was 2.2% for lupus and 9.1% for any AARD.

Conclusion: In this retrospective study, over 90% of patients referred to a tertiary rheumatology clinic for positive ANA testing had no evidence of an AARD. The poor predictive value of a positive ANA test may in part be attributable to poor patient selection with concomitant low pretest probabilities. The extremely low positive predictive value of ANA tests at titers below or equal to 1:160 suggests that the cutoff of a "positive" ANA may need to be re-evaluated by testing laboratories. Even at high titers, however, many patients referred for a positive ANA had no discernible AARD, corroborating previously noted lack of predictive value of ANA testing.

Disclosure: A. M. Abeles: None; **M. Abeles:** None.

1846

Atherosclerosis in SLE; a Cross Sectional Study of 223 Patients with 223 Individually Matched Population Controls. Johanna T. Gustafsson[2], Kerstin Urstad Jensen[1], Marie Herlitz-Lindberg[1], Sonia Möller[4], Susanne Petterson[3], Iva Gunnarsson[2] and Elisabet Svenungsson[2]. [1]Department of Clinical Physiology, Södersjukhuset, Karolinska Institute, Stockholm, Sweden, [2]Department of Medicine Solna, Karolinska Institute. Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden, [3]Department of Neurobiology, Care Sciences and Society (NVS), Division of Nursing, Karolinska Institutet, Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden, [4]Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden

Objective: Accelerated atherosclerosis is believed to contribute to premature cardiovascular disease (CVD) in patients with Systemic Lupus Erythematosus (SLE). We investigated the prevalence of subclinical atherosclerosis in SLE patients and controls.

Patients and Methods: 223 SLE patients/ 223 population controls, individually matched for age, sex and region of living were included after overnight fasting. All were investigated clinically including CVD risk factors and inflammatory biomarkers. The same investigator performed B-mode ultrasonography of carotid arteries. Intima media thickness (IMT) and plaques occurrence (local intima-medial thickening >1mm) were tabulated

Results: Mean age was 48,5 ± 14,3 years in patients and 48,7 ±14,2 in controls. Manifest CVD (ischemic heart, cerebro- and peripheral vascular disease) was more common in SLE patients (13 % vs. 3 %, $p < 0.0001$). Patients were more likely to smoke, have antihypertensive and lipid lowering treatment, lower high density lipoprotein, and higher triglycerides (TG). They had lower low density lipoprotein levels ($p<0.05$ for all).

Patients had thicker mean IMT than controls ($p=0.02$), but there was no difference in plaque occurrence, 21% and 17% respectively.

After age adjustment:

Manifest CVD was associated with plaques in the SLE group, but not with IMT.

In SLE, IMT was positively associated with systolic blood pressure (sBP, <0.0001), TGs ($p=0.008$) and hemoglobin levels($p=0.04$) and negatively with discoid skin lesions ($p=0.03$) and leukopenia($p=0.03$). Plaques were positively associated with TGs ($p=0.01$) and systolic blood pressure ($p=0.02$) and negatively with discoid skin lesions ($p=0.04$).

In controls, IMT was associated with high CRP levels ($p=0.02$) and sBP (<0.0001). Smoking ($p=0.03$) and TG levels ($p=0.03$) were associated with plaques.

Multivariable adjusted models:

In patients age and sBP remained associated with IMT ($p<0.001$ for both) and plaques ($p<0.001$ and $p=0.01$ respectively). In controls age ($p<0.001$) and sBP ($p=0.001$) remained associated with IMT and age ($p<0.001$) and smoking ($p=0.03$) with plaques.

Conclusions: This is to our knowledge the largest study of subclinical atherosclerosis in SLE patients. Patients had thicker IMT, but we could not confirm the increased prevalence of carotid plaques previously reported. Selection of controls, definition of plaques and possibly ethnicity are possible underlying explanations. Plaques and IMT were mainly associated with

traditional CVD risk factors in both patients and controls. The relative contribution of subclinical atherosclerosis for hard outcomes i.e. events in SLE needs to be investigated and should be in focus of future studies.

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1847

Autoantibodies Predate the Onset of Systemic Lupus Erythematosus. Solbritt Rantapää-Dahlqvist[2], Catharina Eriksson[1], Heidi Kokkonen[1], Martin Johansson[1], Göran Hallmans[1] and Göran Wadell[1]. [1]Umeå, Sweden, [2]Rheumatology, Umeå, Sweden

Objective: To identify the presence of autoantibodies in a Northern European population antedating disease onset of SLE using blood samples donated to the Medical Biobank of Northern Sweden before onset of symptoms and relate the predating antibodies with first symptoms of disease.

Methods: The register of patients fulfilling the ACR criteria for SLE and the given date for the onset of symptoms was co-analysed with the register of the Medical Biobank and the Maternity cohort of northern Sweden. Thirty-eight patients (35 females and 3 males) were identified as donating blood samples prior to disease onset. A nested case-control study, designed 1:4, was performed with 152 age and sex matched controls being identified. Antibodies (abs) against SSA (60 and 52 kDa), SSB, Sm, RNP, Scl-70, Jo-1, dsDNA, Centromere B and histones were analysed using a multiplex detection kit, ANA-II Plus Test System (Athena Multi-Lyte®) on a Bio-Plex Array Reader (Luminex200, LabmapTM). Autoantibody tests for ANA were performed by indirect immunofluorescence on HEp2-cells at a sample dilution of 1:100.

Results: In 22/35 (63 %) of the patients with SLE autoantibodies against nuclear antigens were detected in the blood 5.6 (±4.7; mean±SD) years before the onset of symptoms and 8.7 (±5.6) years before diagnosis. The sensitivity was highest for ANA at 45.7% with a specificity of 95%, followed by anti-dsDNA and anti-SSA abs both with a sensitivity of 20.0% at a specificity of 98.7% and 97.4%, respectively. The odds ratio (OR) for anti-DNA predicting disease was 18.13 (CI 95%: 3.58–91.84), and for ANA 11.5 (CI 95%: 4.54–28.87). The sensitivity for the other autoantibodies varied between 14.3% and 2.9% with specificity ranging between 97.4% and 100%. The autoantibody appearing first, i.e., 6.6±2.5 (mean±SD) years prior to the onset of symptoms is anti-SSA antibodies whilst those closest to disease onset are anti-Centromere B antibodies at 0.2 years, anti-Sm at 0.7 years, and anti-Scl70 at 1.4±0.6 years. The number of individuals with antibodies present increased the closer to onset of symptoms. The mean number of antibodies present in pre-diseased individuals was 1.4 and after disease onset 3.1 ($p < 0.001$). The time predating disease was shorter, and the number of antibodies greater, in those individuals with serositis as a presenting symptom in comparison to those with arthritis and skin manifestations.

Conclusion: Autoantibodies against nuclear antigens can be detected in the blood of patients with SLE several years before the onset of symptoms and diagnosis. The most sensitive autoantibodies were ANA, SSA and dsDNA, with the highest predictive OR for anti-dsDNA abs. The autoantibody appearing first was anti-SSA abs.

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1848

Belimumab, a BLyS-Specific Inhibitor, Improved Fatigue and SF-36 Physical and Mental Component Summary Scores in Patients with SLE: BLISS-76 and -52 Studies. V. Strand[8], R. A. Levy[3], R. Cervera[2], M. A. Petri[6], H. Rudge[1], L. Pineda[5], W. Freimuth[5], Z. J. Zhong[4], A. E. Clarke[7] and for the BLISS-76 and −52 Study Group. [1]GlaxoSmithKline, Uxbridge, Uxbridge, UK, [2]Hospital Clinic, Barcelona, Spain, [3]Hospital Universitário Pedro Ernesto, Rio de Janeiro, Brazil, [4]Human Genome Sciences, Inc, Rockville, MD, [5]Human Genome Sciences, Inc, Rockville, Rockville, MD, [6]Johns Hopkins University School of Medicine, Timonium, MD, [7]McGill University Health Centre, Montreal, QC, Canada, [8]Stanford University, Palo Alto, Portola Valley, CA

Purpose: To evaluate the effects of belimumab on fatigue and other health-related quality-of-life (HRQOL) measures in patients with seropositive (ANA ≥1:80 and/or anti-dsDNA ≥30 IU/mL) SLE.

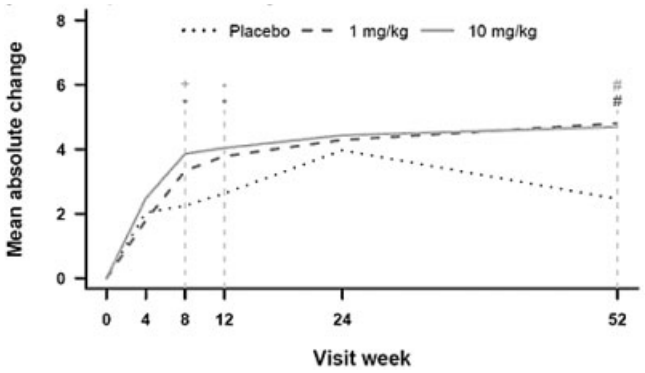
Methods: BLISS-76 (NCT00410384) and BLISS-52 (NCT00424476) were phase 3, multicenter, randomized, double-blind, placebo-controlled studies of 819 and 865 seropositive SLE patients, respectively. Patients with screening SELENA-SLEDAI scores ≥6 were randomly assigned to receive belimumab 1 or 10 mg/kg plus standard of care (SOC) SLE therapy, or placebo plus SOC, with dosing on d 0, 14, and 28, and then q28d for 72 or 48 wk. The primary endpoint in both studies was patient response (SLE Responder Index) at wk 52. HRQOL assessments included SF-36 and FACIT-Fatigue questionnaires at multiple time points throughout the study, including baseline and wk 52. Data for the 2 studies are presented separately and pooled.

Results: In BLISS-76, mean improvements (MIs; absolute change from baseline) in SF-36 physical and mental component summary (PCS and MCS, respectively) and FACIT-Fatigue scores were significantly greater with belimumab 1 mg/kg vs placebo at wk 52 (Table 1). In BLISS-52, MIs from baseline in SF-36 PCS and FACIT-Fatigue scores were significantly greater with belimumab 1 and 10 mg/kg vs placebo at wk 52 (Table 1). Based on pooled data, MIs from baseline were significantly greater with belimumab 1 and 10 mg/kg for SF-36 PCS, and with 1 mg/kg for MCS vs placebo at wk 52 (Table 2). Both belimumab treatment groups demonstrated greater MIs in FACIT-Fatigue score vs placebo at wk 8, 12, and 52 (Figure 1).

Table 1. PCS, MCS, and FACIT-Fatigue Data: BLISS-76 and -52

			BLISS-76			BLISS-52		
			SOC+ Placebo	SOC+ Belimumab		SOC+ Placebo	SOC+ Belimumab	
	Assessment		n=275	1 mg/kg n=271	10 mg/kg n=273	n=287	1 mg/kg n=288	10 mg/kg n=290
SF-36		n	274	270	269	286	283	284
	Baseline PCS	Mean ± SE	36.5 ± 0.6	36.7 ± 0.6	36.3 ± 0.6	41.3 ± 0.5	41.4 ± 0.6	41.7 ± 0.5
	MI at wk 52	Mean ± SE	2.9 ± 0.5	4.4 ± 0.5*	3.4 ± 0.5	3.0 ± 0.5	4.2 ± 0.5*	4.2 ± 0.5*
		n	274	270	269	286	283	284
	Baseline MCS	Mean ± SE	41.2 ± 0.7	41.4 ± 0.7	40.3 ± 0.8	40.9 ± 0.6	41.1 ± 0.6	40.0 ± 0.6
	MI at wk 52	Mean ± SE	1.4 ± 0.7	3.1 ± 0.6*	2.7 ± 0.7	2.7 ± 0.6	3.7 ± 0.6	3.8 ± 0.6
FACIT-Fatigue		n	272	271	269	281	283	278
	Baseline FACIT-Fatigue	Mean ± SE	27.4 ± 0.8	26.5 ± 0.7	25.8 ± 0.8	33.5 ± 0.6	33.6 ± 0.6	33.3 ± 0.6
	MI at wk 52	Mean ± SE	2.9 ± 0.7	5.7 ± 0.7**	4.6 ± 0.6	2.1 ± 0.6	3.9 ± 0.6**	4.8 ± 0.6***

*p<0.05, **p<0.01, ***p<0.001; otherwise p not significant
SE, standard error.



#: p < 0.001; +: p < 0.01 *: p < 0.05

Figure 1. Mean improvement in FACIT-Fatigue scores: BLISS-76/-52 pooled data.

Table 2. BLISS-76/-52 Pooled Data

			SOC + Placebo	SOC+Belimumab	
	Assessment		n=562	1 mg/kg n=559	10 mg/kg n=563
SF-36		n	560	553	553
	Baseline PCS	Mean ± SE	39.0 ± 0.4	39.1 ± 0.4	39.1 ± 0.4
	MI at wk 52	Mean ± SE	2.9 ± 0.3	4.3 ± 0.4**	3.8 ± 0.3*
		n	560	553	553
	Baseline MCS	Mean ± SE	41.1 ± 0.5	41.3 ± 0.5	40.1 ± 0.5
	MI at wk 52	Mean ± SE	2.0 ± 0.5	3.4 ± 0.4**	3.3 ± 0.5
FACIT-Fatigue		n	553	554	547
	Baseline FACIT-Fatigue	Mean ± SE	30.5 ± 0.5	30.1 ± 0.5	29.6 ± 0.5
	MI at wk 52	Mean ± SE	2.5 ± 0.4	4.8 ± 0.4***	4.7 ± 0.4***

*p<0.05, **p<0.01, ***p<0.001; otherwise p not significant.

Conclusion: Patients with seropositive SLE receiving belimumab treatment had improved SF-36 PCS and MCS scores at wk 52. Improvement in fatigue was noted as early as wk 8.

Disclosure: V. Strand: GlaxoSmithKline, 5, Human Genome Sciences, Inc., 5; **R. A. Levy:** GlaxoSmithKline, 8, Human Genome Sciences, Inc., 5, 8, 9; **R. Cervera:** GlaxoSmithKline, 5, Human Genome Sciences, Inc., 5, 9; **M. A. Petri:** GlaxoSmithKline, 5, Human Genome Sciences, Inc., 2, 5, 6, 9; **H. Rudge:** GlaxoSmithKline, 1, 3; **L. Pineda:** Human Genome Sciences, Inc., 1, 3; **W. Freimuth:** Human Genome Sciences, Inc., 1, 3; **Z. J. Zhong:** Human Genome Sciences, Inc., 1, 3; **A. E. Clarke:** GlaxoSmithKline, 5, Human Genome Sciences, Inc., 9; **for the BLISS-76 and −52 Study Group:** None.

1849

Causes and Predictors of Death in 181 Brazilian Patients with Systemic Lupus. Rosa W. Telles[2], Cristina C. D. Lanna[2], Rodrigo C. P. Reis[4], Fabiana L. Sousa[1], Luciana A. Rodrigues[2] and Antonio L. Ribeiro[3]. [1]Hospital das Clinicas, [2]School of Medicine, [3]School of Medicine-Universidade Federal de Minas Gerais-Brazil, [4]Statistics Department

Objective: To determine the causes and predictors of death in SLE patients.

Patients and Methods: 181 outpatients were enrolled from May 2005 to February 2006 (T_0) in a prospective study. These patients were followed up to either the last visit at outpatient clinic, death or end of study visit (from October 2008 to July 2009). Causes of death were defined on the basis of death certificates, medical records and information collected from doctors and relatives. Variables predicting mortality were assessed by Kaplan-Meier and Cox regression methods. The final multivariate model was selected according to clinical and biological plausibility and was corrected for optimism.

Results: Two patients were lost to follow up. Median (IR) age at diagnosis and age at the T_0 of the 179 patients were 26.7(21.8–34.6) and 38(29–46) years, respectively. Median (IR) disease duration was 8.2(4.3–12.4) years. After a median (IR) follow up of 3.3(3.1–3.5) years, 13(73%) patients died due to end-organ failure (5), infection (5), disease activity (1) and atherosclerosis (1). The cause of the mesenteric ischemia of one patient could not be determinate. These 13 patients died a median (IR) of 9.6(7.6–19.3) years after being diagnosed as having SLE. Predictors of mortality observed at T_0 were: nephritis, chronic renal disease (creatinina clearance$<$60ml/min/1,73m^2), antiphospholipid syndrome, higher modified SLEDAI-2k and higher damage index score, cyclophosphamide intravenous use, higher daily dose of prednisone and higher systolic blood pressure, univariate analysis ($p<0.05$). Independent predictors of mortality in Cox regression model were a higher damage index score (HR: 1.401; CI95%: 1.076–1.824), cyclophosphamide use (HR: 3.800; CI95%: 1.313–12.766), and antiphospholipid syndrome (HR: 3.818; CI95%: 1.073–13.587)

Conclusion: This study presents a high frequency of late mortality in lupus patients due to SLE itself and infection. This result is not in agreement with the proposed bimodal pattern of lupus mortality and with the high frequency of atherosclerosis as a cause of death in developed countries. The most important predictors of death were related to lupus itself.

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1850

Cigarette Smoking and Cutaneous Damage in Patients with Systemic Lupus Erythematosus. Josiane Bourré-Tessier[5], Christine A. Peschken[13], Lawrence Joseph[5], Patrick Belisle[5], Ann E. Clarke[7], Sasha R. Bernatsky[3], Marie Hudson[6], Carol A. Hitchon[14], Shikha Mittoo[13], Janet E. Pope[8], Paul R. Fortin[11], C. Douglas Smith[10], Hector Arbillaga[2], Dafna D. Gladman[12], Murray B. Urowitz[9], Michel Zummer[1], CANIOS 1000 Canadian Faces of Lupus Investigators[15] and Christian A. Pineau[4]. [1]Ch Maisonneuve-Rosemont, Montreal, QC, Canada, [2]Chinook Regional Hospital, [3]McGill UHC/RVH, Montreal, QC, Canada, [4]McGill Univ Health Center, Montreal, QC, Canada, [5]McGill University, [6]McGill University and Jewish General Hospital, [7]Montreal General Hospital, Montreal, QC, Canada, [8]St Joseph Health Care London, London, ON, Canada, [9]The Toronto Western Hospital, Toronto, ON, Canada, [10]TOH Riverside Campus, Ottawa, ON, Canada, [11]Toronto Western Hospital, Toronto, ON, Canada, [12]Toronto Western Hospital, Toronto, ON, Canada, [13]Univ of Manitoba, Winnipeg, MB, Canada, [14]University of Manitoba, Winnipeg, MB, Canada, [15]Various Sites

Background: In patients with systemic lupus erythematosus (SLE), cutaneous damage is common and can produce considerable morbidity. Moreover, since smoking may decrease the effectiveness of antimalarial agents, tobacco use may be associated with increased skin manifestations in SLE patients. We examined the association between cigarette smoking and cutaneous involvement in a multicenter Canadian SLE cohort.

Methods: Adults with SLE were enrolled in a multicenter cohort. Various cutaneous elements, as recorded at last visit by the SLICC/ACR Damage Index (SDI; alopecia, extensive scarring and skin ulceration) and the ACR criteria (discoid rash, malar rash and photosensitivity) were used as primary outcomes. Cross-sectional analysis with multivariate logistic regression models were used to estimate the association between cigarette smoking (defined as smoking regularly 3 or more months in the lifetime) and cutaneous involvement. Other potentially associated factors included age, sex, lupus duration, medication including antimalarials, and laboratory data.

Results: In our cohort of 1724 adults, most (83.3%) were female, mean age (SD) was 40.7 years (17.9), mean disease duration was 12.4 years (10.1) and 36.1% had smoked regularly in their lifetime. Cutaneous involvement included malar rash (59.9%), photosensitivity (50.7%), alopecia (11.0%), extensive scarring (3.5%), discoid rash (3.4%) and skin ulceration (0.2%). In multivariate analysis, smoking was associated with discoid rash (OR 1.96; 95%CI 1.41–2.71) and photosensitivity (1.52; 1.17–2.00). We did not find an association between smoking and alopecia, extensive scarring, skin ulceration or malar rash. An association between antimalarials and skin manifestations was expected since antimalarials are regularly used to treat cutaneous involvement in SLE. Indeed, the use of hydroxychloroquine was associated with discoid rash (2.23; 1.10–4.53) and malar rash (2.0; 1.02–3.93) in multivariate analysis.

Conclusion: Cigarette smoking is associated with discoid rash and photosensitivity in this large cohort of SLE patients. Our results emphasize the need to counsel patients on smoking cessation.

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1851

Clinical and Serologic Characteristics of Filipino Multiplex Systemic Lupus Erythematosus (SLE). Helmar F. Soldevilla and Sandra V. Navarra. University of Santo Tomas, Philippines

Purpose: To describe the clinical and serologic characteristics of multiplex systemic lupus erythematosus (SLE) in a Filipino Lupus Database, and compare these with patients with simplex or sporadic SLE from the same database.

Methods: An active search for multiplex SLE patients i.e. belonging to families with at least 2 first degree relatives diagnosed with SLE, was done among patients included in the Lupus Database of the University of Santo Tomas (UST) in Manila, Philippines. Simplex SLE patients i.e. ascertained by review of medical records and verified by phone interview to have no first to third degree family history of SLE or other autoimmune disease, were chosen from the same database to match disease duration. The demographic and cumulative clinical characteristics based on American College of Rheumatology (ACR) criteria and other SLE-related manifestations were compared between the 2 groups, with statistical significance at a p value <0.05.

Results: There were 166 patients (138 females) with an average age at diagnosis of 28.61$\pm$13.07 SD years (range 1–73), belonging to 75 multiplex families. The relationships included 21 parent-child and 54 siblings including three sets of twins. The average age at diagnosis of the simplex SLE patients (N=309, 257 females) was 36.53 $\pm$ 15.04 SD years (range 4–85). The mean disease duration was 98.28 $\pm$ 65.21 months SD (range 1–300) and 96.46 $\pm$ 47 months SD among the multiplex and simplex patients respectively, p=0.77. Among the clinical manifestations, serositis (multiplex=36, 22.08% vs. simplex= 36, 11.65%, p=0.0027), neurologic manifestations (multiplex =25, 15.33% vs. simplex = 26, 8.41%, p=0.0283) and cutaneous vasculitis (multiplex = 27, 17.0% vs simplex= 23, 8.04%, p= 0.0042) were more common in multiplex patients. The other clinical manifestations and serology including antinuclear antibody (ANA) and anti-dsDNA were comparable between both groups.

Conclusions: SLE patients from multiplex families were younger with relatively higher number of males than in those with sporadic SLE. Serositis, neurologic manifestations and cutaneous vasculitis were more frequently recorded in multiplex patients. These findings suggest a role for genetics in the clinical expression of SLE, with potentially more serious organ involvement among patients from multiplex families.

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1852

CNS Lupus: The Prevalence and Antibodies Depend on the Definition. Results from the 1000 Faces of Lupus Cohort. Alan Borowoy[3], Christine A. Peschken[2] and Janet E. Pope[1]. [1]St Joseph Health Care London, London, ON, Canada, [2]Univ of Manitoba, Winnipeg, MB, Canada, [3]University of Western Ontario, London, ON, Canada

Background: Neuropsychiatric involvement in SLE (NPSLE) is common and encompasses a broad spectrum of neurologic and psychiatric syndromes with significant impact on morbidity and mortality and prevalence varies depending on the definition used (from 12–80%). We determined the prevalence of NPSLE and associated factors in 1000 Faces of Lupus, a large multi-centre Canadian cohort.

Methods: Adults were enrolled who satisfied the ACR classification for SLE and had completed SLEDAI, SLAM and SLICC damage indices. NPSLE was defined as: (i) NPSLE by ACR classification criteria (seizure or psychosis), (ii) ACR, SLEDAI (seizure, psychosis, organic brain syndrome, cranial nerve disorder, headache and CVA), SLAM (CVA, seizure, cortical dysfunction and headache) and SLICC (cognitive impairment, psychosis, seizures, CVA, cranial or peripheral neuropathy or transverse myelitis) with and without (iii) NPSLE syndromes considered minor and nonspecific, and (iv) ACR criteria and SLEDAI NP indices. Factors associated with NPSLE were explored using univariate and multivariate regression including antibodies, # of ACR criteria, disease duration, disease activity, ethnicity, education and income.

Results: Cohort size was 1417, mean disease 12±10 years, mean age 41±16 years, 86% females. Subgroup size was dependent on the specific definition of NPSLE. The prevalence of NPSLE was: (i) 6.4%, (ii) 38.6%, (iii) 28.7% and (iv) 10.2%. In univariate analysis, Aboriginals had increased NPSLE (>twice as common) versus Caucasians, Asians and Blacks {p=0.04 in Group (i)}. Anti-SSA/Ro was increased in groups (i) and (iv) and antiphospholipid (aPL) was increased in (i), (ii) and (iii). In group (iv) absence of anti-Sm was significant. NPSLE was not increased in those with positive anti-DNA, anti-SSB/La, anti-RNP, LAC (lupus anticoagulant) or aCL(anti-cardiolipin antibody). Total number of ACR criteria, SLAM, age at diagnosis, disease duration and gender were not associated with NPSLE. If thromboembolic events were excluded, aPL was no longer associated. Education level was not associated with NPSLE (p=0.32) and income was only significant in group (i) (p=0.03). The results are shown below for Group (i).

Characteristics Group (i)	NPSLE (n=80)	Non-NPSLE (n=1173)	p-value
Age at diagnosis	29.9 +/− 12.3	32.0 +/− 14.0	0.19
Disease duration	13.2 +/− 10.4	12.7 +/− 10.2	0.67
Gender *n*	69:10	1021:110	0.88
(% F:M)	90.8 : 9.2 %	90.3 : 9.7 %	
Ethnicity (%)			0.04
Aboriginal	9 (12.5)	56 (5.3)	
Asian	14 (19.4)	162 (15.3)	
Black	5 (6.9)	106 (10.0)	
White	44 (61.1)	732 (69.3)	
Total ACR criteria	5.9 +/− 1.5	6.1 +/− 1.7	0.31
SLAM-2 Score	5.8 +/− 4.1	5.8 +/− 4.0	1.0
Antibody positive (%)			
anti-dsDNA	26 (61.9)	448 (48.8)	0.12
Anti-Smith	18 (24.0)	305 (28.6)	0.43
Anti-RNP	18 (25.4)	291 (26.7)	0.89
Anti-Ro	36 (51.4)	369 (34.1)	0.004
Anti-La	14 (20.0)	136 (12.6)	0.19
LAC	3 (4.0)	26 (2.4)	0.43
aCL	10 (13.3)	76 (7.1)	0.66
aPL	27 (36.0)	191 (18.0)	<0.001

Conclusions: The prevalence and factors associated with NPSLE varied depending on the definition used and was highest in the Aboriginal group, and may be higher if positive anti-Ro or aPL. SLAM, SLICC and SLEDAI include mild subjective disease manifestations, which contributed to a 10% higher prevalence of NPSLE compared to a strict definition. NPSLE may be less frequent in this database than other publications as it may be decreasing, or due to selection bias of those who enter an observational cohort.

Disclosure: A. Borowoy: None; **C. A. Peschken:** None; **J. E. Pope:** None.

1853

Cognitive Disfunction in Young Patients within the Early-Years If the Disease. An Inception-Cohort Study. Ali Duarte-Garcia[2], Sandra Juárez-Arellano, Juanita Romero-Diaz, Hilda Fragoso-Loyo and Jorge Sánchez-Guerrero[1]. [1]Insituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, México, [2]Instituto Nacional de Nutricion Salvador Zubiran

Cognitive dysfunction is considered a late manifestation in SLE patients. It is still undefined the factors associated with its presentation as well as the time of onset during lupus evolution. We aimed to identify time of onset, and lupus-related factors associated with cognitive dysfunction in an inception cohort of SLE patients.

Methods: We included 76 patients (96% females) with SLE of recent-onset at enrollment. At entry, a standardized medical evaluation was done assessing lupus characteristics, medications, cardiovascular risk-factors, and laboratory tests. Patients were seen every 3–6 months, and assessed for disease activity and medications. Information was updated yearly and a blood sample drawn.

At 6.2 (0.6–9.8) years of follow-up, all the 76 patients were evaluated for cognitive dysfunction using the following tests: Trail Making test, Digit Span, California Verbal Learning test, Rey-Osterrieth complex figure test, the Stroop Color-Word test, WAIS III letter-number sequencing, Animal naming test, Controlled Oral Word association, WAIS-R/III digit symbol substitution test, Grooved pegboard test, and WAIS-R/III similarities. Tests were grouped in 7 cognitive domains: memory, attention/executive function, visuo-spatial, motor, psycho-motor speed, language, and problem solving. Cognitive dysfunction was present when results were at least -2 SD in 2 or more cognitive domains.

Results: At enrollment, mean (SD) age of lupus patients was 25.2 (9.1) years, lupus duration 5.4 (3.8) months, and SLEDAI-2K score 6.9 (5.8). At screening, mean age of patients was 30 (19–51) years. Eleven patients (14%) were diagnosed with cognitive dysfunction, females (91%). Cognitive dysfunction was observed as early as age 21–30 years, after 3 years of evolution.

Comparing patients with and without cognitive dysfunction, the single difference was observed in education 9 (5–16) vs. 12 (8–17) years, P=0.05. No difference was observed in body mass index, hypertension, diabetes mellitus, lipid profile (total cholesterol, c-LDL, c-HDL, triglycerides, Lp(a), Apo-B), glucose, homocystein, and hsCRP. Also, the Framingham risk scores were similar in both groups.

Comparing patients with and without cognitive dysfunction, SLE characteristics did not differ between groups: age at diagnosis 23 (17–43) vs. 24 (14–46) yrs, disease duration 7.1 (3.2–9.4) vs. (6.–.–.8) yrs, P=0.45, disease activity–SLEDAI-2K AUC 18.7 (9.3–26.3) vs. 14.2 (0–35.5), P=0.10, adjusted mean SLEDAI-2K 5.67 vs. 3.98, P=0.32, and SLICC/DI score 0 (0–3) vs. 0 (0–4), respectively. The prevalence of anti ds-DNA, Sm, RNP, SSA, SSB, anti-cardiolipin and anti-b2-glycoprotein-I antibodies did not differ. The cumulative dose of prednisone was 19.8 and 16.5 grams, respectively (P=0.58). No difference was observed with the use and cumulative dose of immunosuppressants, as well as the use of antimalarials and low-dose aspirin

Conclusions: In this inception cohort of young lupus patients, cognitive dysfunction was observed from age 21–30 years, and after 3 years of lupus. The single association observed was with a lower education level, but no lupus-related variables were identified.

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1854

Cognitive Dysfunction in Patients with SLE: A Prospective Study. Andres Piatti[2], Tara Adhikari[2] and Michael Luggen[1]. [1]University of Cincinnati College of Medicine, Cincinnati, OH, [2]University of Cincinnati College of Medicine

Background: Cognitive dysfunction (CD) has been reported to occur frequently in SLE. It is unclear, however, it this CD is transient, persistent, or progressive. Published reports have estimated persistence or progression in anywhere from 17% to 93% of patients. These widely divergent results may be due in part to the definition of CD and the control population employed. Chronic rheumatic diseases cause pain, fatigue, and depression which may affect cognitive function. All studies of progression to date have employed normal healthy individuals as controls. Definitions of CD relative to this population will identify some pts whose major problems are depression, pain, or fatigue, which may improve, and some who have structural CNS disease,

which may not. Previous work from our group utilizing an age, sex, and race matched RA control population and a community based cohort of SLE pts suggested that the frequency of CD was low (17.2%), but that most patients had persistent deficits. This work extends those observations.

Methods: Patients with SLE by ACR Criteria from several sources were examined at baseline and again after ≥ 6 months. Cognitive function was assessed by the ANAM (Automated Neuropyschologic Assessment Metrics), a validated, computerized, cognitive testing battery, utilizing as the primary outcome measure the total throughput score (TTS=total number of correct responses/time). Disease activity, damage, and treatment variables were ascertained at baseline and at 6 mos. Abnormality was defined as having scores 1.5 SD below the mean of a comparable RA control population. Results were compared using paired t-tests or Wilcoxon sign rank test and by Fisher's exact test.

Results: Thirty-eight (38) patients have been examined to date on at least 2 occasions. Four (10.6%) had CD at baseline. CD persisted in all pts at 6 mos. None, however, showed progression and no additional subjects developed CD. Pts with CD were significantly older than those without (58.3 ± 8.9 vs 44.1 ± 9.0, $p < 0.05$). Other differences were found but none were statistically significant, perhaps due to small numbers with CD. TTS improved significantly in those without CD (increase of 9.4% (95% CI: 0.1%, 19.0%) but decreased in those with CD by 4.0% (95% CI: −13.9%, 5.8%).

Conclusions: Using RA controls, 10.6% of SLE pts had CD and all remained unchanged over a 6 month interval. Age was a significant correlate of CD. Pts without CD improved scores over 6 mos perhaps demonstrating a learning effect. Those with CD had no such improvement. This may represent another measure of CD.

Disclosure: A. Piatti: None; **T. Adhikari:** None; **M. Luggen:** None.

1855

Cognitive Dysfunction in Systemic Lupus Erythematosus: Development of a Screening Tool. Tara Adhikari[2], Andres Piatti[2] and Michael Luggen[1]. [1]University of Cincinnati College of Medicine, Cincinnati, OH, [2]University of Cincinnati College of Medicine

Background: Cognitive Dysfunction (CD) is said to occur frequently is SLE and to be associated with increased unemployment rates and decreased quality of life. Yet, it is oftentimes undiagnosed because of difficulties in doing so. There are only two validated tools for detecting the CD in SLE patients. Traditional neuropsychologic testing (NPT), which consist of a variable battery of tests, administered and interpreted by a clinical psychologist, requiring 4 to 6 hours to complete, and costing oftentimes over $1000. And, the Automated Neuropsychologic Assessment Metrics (ANAM), a computerized battery of tests which assess some of the same cognitive domains as NPT, requires approximately 45 minutes, and costs approximately $400 for a software license. While more efficient and less costly, the ANAM is neither readily available nor practical for clinic administration or for screening larger populations. What is needed for both situations is a brief, sensitive, and reliable screening questionnaire.

Methods: The Montreal Cognitive Assessment Questionnaire (MoCA) has been developed and tested to identify mild cognitive impairment in the elderly. It is a brief (<10 mins), performance-based questionnaire that has been utilized in a number of other diseases with fair sensitivity (85–90%) and variable specificity (53–87%). The MoCA has never been utilized to screen for CD in patients with lupus.

Patients with SLE fulfilling American College of Rheumatology criteria were recruited and evaluated. Demographic, clinical, and treatment information was obtained. In addition, depression was assessed using the Beck Depression Inventory (BDI) and fatigue, pain, and overall well being scored on a 10 cm visual analogue scale. All subjects were administered the ANAM as the gold standard and the MoCA.

The total throughput score (TTS) is a standard measure of cognitive performance of the ANAM. It is the average of the total number of correct responses/time required for those responses. Abnormal was defined as any score 2 SD or more below the mean established for a comparable rheumatoid arthritis population. The scores of the MoCA were compared to the TTS and the classification of normal or abnormal by the ANAM compared to that of the MoCA using various cutoffs.

Descriptive statistics of the study population were computed. Using various cutpoints for the MoCA, the sensitivity, specificity, accuracy, predictive values, and likelihood ratios were also computed.

Results: Fourty-four (44) patients have been recruited to date. Eleven (25%) were identified by the ANAM as being impaired in comparison to 13 (29.5%) by the MoCA. The scores of the two tests were significantly correlated ($r = 0.57$, $p < .001$). Using the standard cut-off of 26, the sensitivity of MoCA was 83%, specificity 73%, accuracy 75%, with a positive predictive value of 50% and negative predictive value of 92% compared to ANAM. Other cut points were less efficient.

Conclusion: The MoCA appears to be a useful screening tool for the detection of CD in SLE using the standard cutoff of 26. However, improved performance might be obtained by weighting individual questions differently or by developing additional items with enhanced discrimination.

Disclosure: T. Adhikari: None; **A. Piatti:** None; **M. Luggen:** None.

1856

Determinants of Treatment Adherence in Patients with Systemic Lupus Erythematosus (SLE). Shazia A. Beg[1], Sofia de Achaval[2], Michael A. Kallen[2], Vanessa L. Cox[2], Marsha N. Richardson[2], John D. Reveille[3] and Maria E. Suarez-Almazor[4]. [1]Baylor College of Medicine, Houston, TX, [2]The University of Texas M. D. Anderson Cancer Center, Houston, TX, [3]Univ Texas Health Sci Ctr, Houston, TX, [4]University of Texas, MD Anderson Cancer Center, Houston, TX

Objective: Patients' health-related beliefs may ultimately influence their health-related behaviors, including their adherence to medications. The Health Belief Model (HBM) has been widely used to explain individual health behaviors under different chronic disease conditions. This study examines the relationships between HBM domains and medication adherence in SLE patients.

Methods: We examined a cohort of 110 ethnically diverse SLE patients from publicly funded hospitals in Houston, Texas. At baseline, 12 and 24 months patients completed a HBM questionnaire and two adherence questionnaires—the Compliance Questionnaire Rheumatology (CQR), with scores ranging from 0 to 100 and higher scores indicating better adherence; and the Adult AIDS Clinical Trials Group-Adherence (AACTG-Adh) with scores ranging from 0 to 3 and higher scores indicating worse adherence. HBM domains of study interest included perceived severity of disease, perceived benefits and risks of treatment, self efficacy and barriers to treatment. Statistical analyses included Pearson correlational analysis and multi-variable stepwise linear regression modeling.

Results: Of 110 SLE patients, 90% were female; mean age was 37 years; 55% were African-Americans and 38% Hispanic. Mean CQR score was 69.6 (sd=11.6), while mean AACTG-Adh score was 0.7 (sd=0.5). Both adherence measures showed similar correlational results; however, AACTG-Adh results are presented here, as these were consistently of higher magnitude. At baseline, HBM domains that were statistically significantly associated with better adherence included: (i) elements of self-efficacy i.e. function (r=0.20), optimism (r=0.22), pain (r=0.34), and symptoms (r=0.41); and (ii) perceived effectiveness (r=0.28). Domains significantly associated with worse adherence included: (i) perceived disease severity (r=0.39) and perceived threat (r=0.36); (ii) barriers i.e. access (r=0.21), transportation (r=0.39), financial (r=0.36), and clinic logistics (r=0.37); (iii) forgetting (r=0.58); (iv) perceived toxicity (r=0.44); and (v) lack of benefit (r=0.45). In the multi-variable regression analysis using AACTG-Adh as the dependent variable, the following beliefs were independent predictors in the final stepwise model: self-efficacy about symptom control which was associated with increased adherence; financial barriers, forgetting, perceived toxicity and perceived disease severity which were all associated with decreased adherence. Throughout the study's time period, most HBM constructs and treatment adherence itself remained at generally constant levels, highlighting the stability of beliefs and behaviors in the absence of targeted interventions.

Conclusions: Several HBM dimensions are closely associated with adherence in SLE patients. While some barriers may be difficult to modify, educational interventions outlining medication benefits and risks, introducing strategies to remember taking medications and enhancing self efficacy could potentially increase treatment adherence in this patient population.

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1857

Discordance between Self-Report and Physician-Assessed Disease Activity in Patients with Systemic Lupus Erythematosus (SLE): Implications for Clinical Trial Design and Clinical Care. Anca D. Askanase[3], Isabel Castrejón[4], Jill P. Buyon[5], Yusuf Yazici[1] and Theodore Pincus[2]. [1]Hospital for Joint Diseases, Hastings on Hudson, NY, [2]New York University Hospital for Joint Disease, Hastings-on-Hudson, NY, [3]NYU Hospital for Joint Diseases, New York, NY, [4]NYU Hospital for Joint Diseases, [5]NYU School of Medicine, New York, NY

Purpose: To analyze agreement levels between patient (PT) and physician (MD) assessments in 50 patients with SLE seen in usual care, including ***a)*** global PT and MD estimates of status; ***b)*** patient self-report scores on the SLAQ (Systemic Lupus Activity Questionnaire) and MDHAQ (Multidimensional Health Assessment Questionnaire) for physical function (FN), pain (PN), patient global estimate (PTGL), fatigue (FT), RAPID3 (FN, PN, and PTGL), and review of systems checklist (SX); ***c)*** physician-scored indices SLEDAI-2K (SLE Disease Activity Index), BILAG (British Isles Lupus Assessment Group index), SLAM (SLE Activity Measure) and ECLAM (European Consensus Lupus Activity Measurement).

Methods: A cross-sectional study was performed in 50 consecutive SLE patients of one rheumatologist. Patients completed the SLAQ and MDHAQ, including PTGL. The rheumatologist scored a physician global estimate (MDGL) (scored 0–3 in 0.1 increments) without knowledge of PTGL, and completed the SLEDAI 2K, BILAG, SLAM, and ECLAM. Agreement levels of various measures were analyzed using Spearman rank order correlations.

Results: The study included 45 women and 5 men, mean age 38.7 years, mean disease duration 7.3 years, 36% Caucasian, 18% Black, 26% Hispanic, 18% Asian. The mean MDGL (1.10±0.62), PTGL (3.11 ±2.81) and SLE indices (SLEDAI 5.02±3.75; BILAG 4.60±4.31; SLAM 3.86±2.92; ECLAM 1.97±1.37) indicated mild/moderate lupus activity. The correlation between MDGL and PTGL of rho=0.14 was not statistically significant. Correlations between MDGL and SLE indices were significant, rho=0.60–0.72 ($p<0.001$). Correlations between PTGL and patient measures also were significant, rho=0.58–0.87 ($p<0.001$). However, PTGL was correlated at lower levels with SLE indices – significantly with BILAG and SLAM (0.35–0.40; $p<0.01$), and not significantly with SLEDAI or ECLAM. MDGL was not correlated significantly with any patient measure or index.

		PTGL	MDGL
Patient Measures	SLAQ		
	• Total score	0.60*	−0.08
	• # positives	0.58*	−0.06
	• VAS activity	0.69*	0.34
	MDHAQ		
	• FN	0.68*	0.08
	• PN	0.87*	0.08
	• FT	0.79*	−0.02
	• PTGL	-	0.14
	• # SX	0.66*	0.03
Physician Measures	MDGL	0.14	-
	SLEDAI	0.16	0.72*
	BILAG	0.35†	0.70*
	SLAM	0.40*	0.64*
	ECLAM	0.26	0.60*

*$p<0.0001$; †$p<0.01$

Conclusion: MDGL and PTGL are not correlated significantly, an observation made previously. MDGL was correlated significantly with all physician-derived indices, and PTGL was correlated significantly with all patient-derived measures and indices. By contrast, MDGL was correlated at much lower, non-significant levels with patient-derived measures and indices, and PTGL was correlated at lower levels with physician-derived indices. Further analysis of these discordances may clarify the clinical relevance of various measures in clinical trials, and may lead to improved care and compliance in patients with SLE.

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1858

Ethnicity Affects the Frequency of CNS Manifestations of SLE. Maryna Shayuk[2], Hong Fang[2] and Michelle A. Petri[1]. [1]Timonium, MD, [2]Johns Hopkins University

Purpose: The new SLICC classification criteria have added mononeuritis multiplex, myelitis, peripheral or cranial neuropathy and acute confusional state to the previous CNS manifestations (psychosis and seizure) of the neurologic criterion for SLE. We investigated the frequency of these neurologic manifestations, as well as depression, lupus headache and stroke in a prospective SLE cohort.

Method: 1889 SLE patients (88.5% female, 56.5% Caucasians, 36.9% African-Americans) were included. Neurologic manifestations were recorded at cohort entry and updated at every visit.

Result:

Table 1. Neurologic manifestations, by ethnicity

	Caucasian	Af-Am	P-value*	Odds Ratio**	95% CI (Odds Ratio)
Seizure	105/1135 (9.25%)	80/744 (10.75%)	0.2853	0.8461	0.6226–1.1499
Psychosis	34/11 (3.00%)	36/743 (4.85%)	0.0389	0.6070	0.3763–0.9792
OBS	54/1135 (4.76%)	39/743 (5.25%)	0.6313	0.9017	0.5909–1.3761
Meningitis	21/1135 (1.85%)	17/743 (2.29%)	0.5100	0.8050	0.4219–1.5363
Stroke	40/1135 (3.52%)	42/742 (5.66%)	0.0268	0.6088	0.3908–0.9484
Depression	455/1134 (40.12%)	239/741 (32.25%)	0.0006	1.4075	1.1587–1.7097
Headache from SLE	102/1135 (8.99%)	67/741 (9.04%)	0.9675	0.9933	0.7190–1.3722
Mono. Multiplex	11/1134 (0.97%)	25/742 (3.37%)	0.0002	0.2809	0.1374–0.5744
Cog. Impairment	81/1116 (7.26%)	37/731 (5.06%)	0.0591	1.4679	0.9834–2.1912
Optic Neuritis	16/1117 (1.43%)	7/732 (0.96%)	0.3663	1.5051	0.6162–3.6766
Cranial Neuropathy	25/1117 (2.24%)	11/730 (1.51%)	0.2664	1.4964	0.7318–3.0601
Peripheral Neuropathy	86/1117 (7.70%)	48/730 (6.58%)	0.3626	1.1852	0.8218–1.7092
Transverse Myelitis	9/1113 (0.81%)	9/729 (1.23%)	0.3635	0.6522	0.2577–1.6508

*based on chi-square test for the binary outcomes
**the ratio of the odds of the event occurring in Caucasian to the odds of it occurring in Af-Am

Conclusion: Caucasians have significantly more depression, but African-Americans have significantly more psychosis, stroke, and mononeuritis multiplex. Depression is the most common neurologic manifestations in both ethnicities. The addition of acute confusional state, mononeuritis multiplex, optic neuritis, other cranial neuropathies, peripheral neuropathy and myelitis allow an additional 21% of SLE patients to meet the neurologic classification criterion who did NOT have seizures or psychosis.

Disclosure: M. Shayuk: None; **H. Fang:** None; **M. A. Petri:** None.

1859

Five Year Follow-Up Study of Bone Mineral Density in Patients with Systemic Lupus Erythematosus: The Influence of Corticosteroid Treatment. Anna M. Schilder, Jonathan Jacobs, Lindy-Anne Korswagen, Ben A. C. Dijkmans, Willem F. Lems, Alexandre E. Voskuyl and Irene E. M. Bultink. VU University Medical Center, Amsterdam, The Netherlands

Introduction and Objective: The influence of corticosteroids on bone mineral density (BMD) in systemic lupus erythematosus (SLE) is still under debate. Various studies have reported an association between corticosteroid use and low BMD in SLE but other studies did not demonstrate a significant relationship. This discrepancy might be explained partially by the cross-sectional design of the far majority of studies. Only a few longitudinal studies on BMD change and the associated factors in patients with SLE have been performed. However, in these studies, the numbers of patients were small and the duration of follow-up was relatively short (three years).

The aim of this study was to assess change in BMD during long-term follow-up in patients with SLE and to identify factors associated with BMD loss. In particular the effect of corticosteroid treatment on BMD change was studied.

Methods: We prospectively studied 82 patients with SLE. Demographic and clinical data were collected and BMD measurements of the lumbar spine and total hip were performed by dual energy x-ray absorptiometry at baseline and at follow-up. Osteoporosis was defined as a T score less than -2.5 SD and osteopenia as a T score less than −1.0 SD in at least 1 region of measurement. Statistical analysis was performed using independent sample t-test for comparison of means, univariate and multiple regression analysis.

Results: At baseline, osteopenia was present in 49% of the patients and osteoporosis in 9% (93% female, mean age 38.8 years, mean disease duration 6.3 years). During the observation period, 67.1% of the patients were treated with corticosteroids. The mean cumulative dose of prednisone used between baseline and follow-up was 13.4 ± 8.5 grams. The mean daily dose of prednisone was 6.6 ± 3.9 mg in the corticosteroid users.

After a mean follow-up of 5.7 years, no significant change in BMD of the total hip or the lumbar spine was observed at group level. However, higher cumulative corticosteroid dose during the observation period was significantly

associated with BMD loss in the lumbar spine, but not at the hip (p = 0.851). A mean daily dose of more than 7.5 mg prednisone was associated with significant BMD loss at the lumbar spine as compared to patients receiving less than 7.5 mg per day (P = 0.003).

Conclusion: In this long-term follow-up study, no significant change in BMD of the lumbar spine or the total hip is observed in patients with SLE. However, higher mean daily and cumulative corticosteroid dose is associated with BMD loss in the lumbar spine. The high prevalence of reduced BMD and the negative influence of corticosteroid use on bone density in the lumbar spine underline the importance of permanent attention for monitoring and treatment of low BMD in SLE, especially in patients using higher doses of corticosteroids.

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High Prevalence of Fetal Loss and Pregnancy Complications in African-American Lupus Patients: A Retrospective Case-Control Study. Kirk C. Eddleman[2] and Vikas Majithia[1]. [1]University of Mississippi Medical Center, Jackson, MS, [2]University of Mississippi Medical Center

Introduction: Pregnancy in Systemic Lupus Erythematosus (SLE) patients is associated with a high rate of fetal loss and pregnancy complications which are about 2–4 times higher than non-SLE patients. The rates are felt to be even higher in African-American (AA) patients, but an exact prevalence and risk is not yet characterized. We undertook this study to assess the risk of fetal loss and complications in SLE patients at University of Mississippi Medical Center, caring for predominantly (gt]90%) AA patients.

Methods: A retrospective chart review of pregnancies in 83 women with SLE and 99 age-matched controls was performed for time-period between 2004 and 2006. Patients were identified by cross referencing billing codes 710.0 (Lupus) and 648.1 or 648.3 (Pregnancy). Data included: demographics, SLE related information, medications, compliance with follow-up visits (>60%), fetal outcomes and complications. Odds ratio were calculated and statistical significance was determined using Fischer's Exact test.

Results: Mean age of two groups were 22 years and both groups had 95 % AA patients. Results are summarized below.

Table 1. Fetal loss in SLE versus non-SLE patients

	SLE group	Control group	Odds ratio	P-value
Overall Fetal Loss	16.9% (n=83)	3% (n=99)	6.49	0.001
Overall Fetal loss in hydroxycholoroquine users	6% (n=30)	3% (n=99)	2.28	NS
Overall Fetal loss in compliant patients*	3% (n=67)	1% (n=54)	1.6	NS

(*compliance=> 60% follow-up visits).

Table 2. Maternal Complications in pregnancy for SLE versus non-SLE patients

	SLE group	Control group	Odds ratio	P-value
Pre-term Labor	50.7%	31.2%	2.26	0.01
Baseline Hypertension	33.7%	9%	5.09	<0.0001
Pre-Eclampsia	31.3%	18.2%	2.05	0.04
HELLP Syndrome*	6%	2%	3.10	NS
Hyperglycemia	2%	3%	NS	NS

(HELLP=Hypertension, Elevated Liver enzymes and Low platelets)

Discussion: We found SLE significantly increased the risk of fetal loss in 2nd and 3rd trimesters (OR 6.49). The risk was similarly increased in this study for miscarriage (fetal loss<20 weeks) and stillbirth (fetal loss>20 weeks). In contrast, patients who were being treated with hydroxychloroquine (OR 2.28) or were compliant (OR 1.6) only had a minor increase in the risk as compared to control group. SLE patients had increased likelihood of having baseline hypertension, pre-eclampsia and pre-term labor. There was no increase in likelihood of association with hyperglycemia, C-sections, HELLP syndrome, anti-phospholipid antibodies or lupus activity markers in our comparison.

Our data suggest the likelihood of the fetal loss (6 vs 4 times), any complication (80% vs 50%), pre-eclampsia(33% vs 20%) or pre-term labor (50% vs 33%) may be higher than previously reported. The AA ethnicity may be a contributing factor here but a small sample size limits further characterization of the specific factors contributing to the increased risk.

Conclusion: There is a marked increase in risk of fetal loss and adverse pregnancy complications in African-American SLE patients many of which are higher than previously reported. Plaquenil and compliance with physician care seem to help decrease the likelihood of these adverse outcomes.

Disclosure: K. C. Eddleman: None; **V. Majithia:** None.

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Hyperuricemia Is a Predictor of Subclinical CVD in SLE Patients but Not Controls. Joseph L. Enama[2], Robert Gilkeson[1] and Lisabeth Scalzi[2]. [1]Case Western Reserve University, [2]Penn State Univ Hershey, Hershey, PA

Purpose: Both systemic lupus erythematosus (SLE) and hyperuricemia are non-traditional risk factors for atherosclerotic cardiovascular disease (CVD). We compared the associations of serum uric acid levels (UA) and subclinical CVD, while adjusting for traditional CVD risk factors, between patients with SLE and controls.

Methods: 222 patients (140 with SLE, 82 controls), all without clinical CVD, were recruited from rheumatology clinics at two academic medical centers. Demographic information and fasting blood samples were collected from each patient. Coronary artery calcium scores (CAC) were calculated in each patient. Subclinical CVD (lCAC) was defined by [log (CAC +1)]. Associations of uric acid with traditional predictors of CVD were examined in univariate analyses. Traditional and non-traditional CVD risk factors—including dyslipidemia, body mass index (BMI), hypertension (HTN), high sensitivity C-reactive protein, smoking history, diabetes (DM), race, age, and UA—were examined as independent predictors of subclinical CVD. Variables were analyzed using either Chi-square or Student's t-test, dependent on whether they were ordinal versus continuous measures respectively. Final linear regression models were calculated for SLE and controls, including all significant covariates ($p < 0.1$) for the analyses.

Results: Mean serum UA levels did not significantly differ between SLE and control patients. (6.0 mg/dL versus 6.4 mg/dL, p = 0.9). UA was significantly associated with advanced age (p = 0.01), hypertension ($p < 0.01$), and BMI ($p < 0.01$) in SLE patients. Significant covariates for lCAC in the control group included dyslipidemia (p = 0.05), HTN (p = 0.01), DM (p = 0.037), age ($p < 0.01$), and UA ($p < 0.01$). Significant covariates for lCAC in SLE patients included smoking history (p = 0.01), age ($p < 0.01$), and UA ($p < 0.01$). The linear regression model in controls demonstrated that only age was a significant predictor for lCAC (p = 0.01). UA was found to be a significant predictor for lCAC in SLE patients, when controlling for age and smoking (p = 0.03). SLE patients with UA in the upper tertile (uric acid ≥ 4.7 mg/dL) had a significantly higher lCAC (p = 0.04).

Conclusions: In patients with SLE, the presence of hyperuricemia in patients may predict CVD, independent of other traditional CVD risk factors. Larger studies are needed to determine if uric acid-lowering interventions may lower the risk of CVD in SLE.

Disclosure: J. L. Enama: None; **R. Gilkeson:** None; **L. Scalzi:** None.

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Identifying Modifiable Risk Factors for Depression in Systemic Lupus Erythematosus. David Karol[2], Lisa G. Criscione-Schreiber[2] and Megan E. B. Clowse[1]. [1]Duke Univ Med, Durham, NC, [2]Duke University, Durham, NC

Background: Depression is common (40%) in individuals with systemic lupus erythematosus (SLE), and may be exacerbated by disease activity and chronic pain. We aimed to measure the rate of depression in our SLE cohort, and to identify modifiable factors associated with depression.

Methods: Upon enrollment in our university-based SLE registry, each patient completed a questionnaire that included the Beck Depression Inventory II (BDI-II), pain scores, and demographic information. Disease activity was measured by the treating rheumatologist using the physician's global assessment (PGA) and SLE disease activity index (SLEDAI). Current medications were recorded. For statistical analysis, patients were divided into two groups: depressed (BDI-II≥18) and not depressed (BDI-II<18). Student's t-test was used to compare the means of continuous variables and z-test was used for dichotomous variables.

Results: The BDI-II was completed by 105 patients, 40 (38.1%) of whom were depressed (BDI≥18). Depression was associated with several measures of disease activity, prednisone and antidepressant use. It was not associated with demographic characteristics, including race, income, type of insurance, or age. (Table) Half of the patients with depression had clinically evident

arthritis as indicated on the SLEDAI (2 or more joints with current inflammation), but only 17% of those without depression had arthritis (p=0.0003). On the other hand, SLE rash, which can be disfiguring and lead to social isolation, was not associated with depression. The other individual measures of SLE activity in the SLEDAI, including hypocomplementemia and anti-dsDNA antibody, were not associated with depression. Prednisone dose and antidepressant use were associated with depression. Only 40% of patients with depression, however, were currently taking a selective serotonin-reuptake inhibitor (SSRI). In a multivariate analysis that included the measures that were independently associated with depression (including PGA, SLEDAI arthritis, current pain, prednisone dose, and antidepressant use), only the level of current pain remained significantly correlated with moderate to severe depression.

Conclusions: We found that depression was statistically significantly associated with pain, arthritis, lupus activity, prednisone dose and antidepressant use. In multivariate analysis, pain appeared to be the most important predictor of depression. It is unclear whether pain promotes depression or vice versa. However, pain may be a modifiable risk factor for depression in SLE patients, and treatment will likely be most successful when addressing both components.

Table. Demographics and independent variables in SLE patients with and without depression.

	Not Depressed (N=65)	Depressed (N=40)	P value
	Demographics:		
Female no. (%)	60 (92%)	37 (93%)	0.97
Race			
Caucasian	31 (48%)	25 (63%)	0.16
African-American	29 (45%)	13 (33%)	
Age	38 ± 12	40 ± 12	0.61
	Measures of Lupus Activity		
PGA‡	0.6 ± 0.7	0.9 ± 0.7	0.012
SLEDAI¶	3.4 ± 3.7	4.9 ± 4.6	0.06
SLEDAI arthritis	11 (17%)	20 (50%)	0.0003
SLEDAI rash	14 (22%)	8 (20%)	0.85
Current pain (0–10)	3.0 ± 3.0	6.0 ± 2.5	0.00001
	Medications		
Prednisone dose (mg)	5.6 ± 9.3	11.2 ± 16.7	0.03
Antidepressant use	13 (20%)	16 (40%)	0.0004

‡PGA: Physician's Global Assessment, scale 0 (no activity) to 3 (severe activity)
¶SLEDAI: Systemic Lupus Erythematosus Disease Activity Index

Disclosure: D. Karol: None; **L. G. Criscione-Schreiber:** None; **M. E. B. Clowse:** None.

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In Systemic Lupus Erythematosus (SLE) Patients, Patient Reported Outcomes and Physician Assessment of Disease Activity Are Poorly Correlated: Implications for Outcome Measures in SLE. Magaly Villafradez Diaz[1], Ashwini Shadakshari, Andy McCracken, Christopher Swearingen, Daniel Ricciardi and Yusuf Yazici[2]. [1]Long Island College Hospital, [2]NYU Hospital for Joint Diseases

Purpose: To evaluate the correlation of patient vs physician reported outcome measures in a routine care SLE cohort.

Methods: The first recorded physician global observations in patients with the primary diagnosis of systemic lupus were identified; corresponding demographic, patient reported functional outcomes and current usage of prednisone, hydroxychloroquine and non-steroidal anti-inflammatory medications and immunosupressive medication use were abstracted. Current medication usage was operational defined as medications taken prior to and including the visit date; patient discontinuations prior to the selected visit and medication initiations at the selected visit were defined as non-current usage. Summary statistics for demographic, outcome measures and median visit of physician global observation were estimated by current medication usage. Lin's concordance correlation was estimated for each patient reported functional outcome compared to the physician global. Spearman's correlation coefficient were calculated for patient and physician measures.

Results: 180 patients were included in this analysis (mean age 42, disease duration 0.7 years, 93% female, education 14 years). On average patients had active disease, with (mean (SD)) pain 5.0 (3.0), function 2.5 (1.9), fatigue 6.1 (3.0) patient global assessment of disease activity 4.9 (2.6) and physician global assessment of disease activity 2.4 (1.7), (all measures' range 0–10). Mean RAPID3 score (range 0–30) was 12.8 (6.1). Spearman and concordance correlations are given in Table 1. There was only moderate correlation seen with physician assessment of disease activity with all patient reported outcomes and the RAPID3 composite index.

Table 1. Spearman and Concordance Correlations (95% Confidence Intervals) between Physician Global and Patient Reported Outcomes in SLE

MD Global Association	Spearman	Concordance
Function	0.356 (0.189, 0.504)	0.334 (0.177, 0.492)
Pain	0.365 (0.207, 0.504)	0.160 (0.076, 0.245)
Global	0.391 (0.235, 0.527)	0.179 (0.091, 0.268)
RAPID3	0.431 (0.259, 0.576)	0.264 (0.141, 0.387)
Fatigue	0.279 (0.110, 0.432)	0.108 (0.033, 0.182)

Conclusions: In this cohort of SLE patients seen in routine care, there was moderate correlation between what the patients reported about their disease activity and physicians perceptions of their disease activity. Measures that primarily depend on physician assessment o disease activity may be poor correlates of SLE activity and may not be ideal measures to be sued in clinical trials of SLE.

Disclosure: M. V. Diaz: None; **A. Shadakshari:** None; **A. McCracken:** None; **C. Swearingen:** None; **D. Ricciardi:** None; **Y. Yazici:** None.

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Incidence and Predictors of Hospitalization in Systemic Lupus Erythematosus (SLE): Results from a Large Contemporary Multi-Ethnic Cohort. June Lee[3], Janet E. Pope[1], Christine A. Peschken[2] and The 1000 Faces of Lupus. [1]St Joseph Health Care London, London, ON, Canada, [2]Univ of Manitoba, Winnipeg, MB, Canada, [3]University of Western Ontario, London, ON, Canada

Background: Annual rates of hospitalization for lupus are as high as 30 to 40%. The aim of this study was to determine the rate of, causes for, and determinants of hospitalization in a large contemporary SLE cohort.

Methods: Data from the 1000 Canadian Faces of Lupus (a prospective multi-centre cohort study) were used. Data on hospitalization, lupus flares, demographics, medication history, disease activity and damage, and co-morbidities are collected annually. Univariate and regression analyses were performed.

Results: Data on hospitalization (yes or no) were available on 724 participants; 68 reported hospitalizations related to SLE (hospitalization rate of 9.4% overall and an annual hospital rate of 7.2%). The most common causes of SLE-related hospitalization were hematologic (18.1%), serositis (16.9%), musculoskeletal (13.3%), and renal (12.0%). Some were hospitalized for more than one reason. The occurrence of hospitalization was significantly associated with: Aboriginal compared to Caucasian, Asian and Blacks (p=0.003), having a lower household income (p=0.01), being work disabled (p=0.001), having greater disease activity as indicated by the SLAM-2 (p=0.004), having a greater number of ACR criteria (p=0.006), positive anti-Sm (anti-Smith) antibody (p=0.018) and use of azathioprine (p=0.039). There was no significant relationship between hospitalization and gender, age, number of co-morbidities (as indicated by the Charlson Co-morbidity Score), or number of medications used.

Table. Demographic Characteristics of the 2 Groups

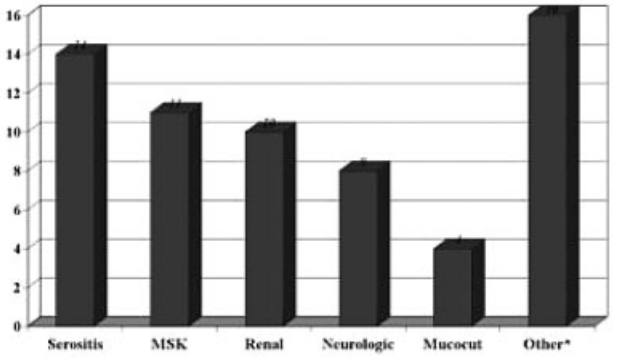
	No. (%) of Patients	
	Non-Hospitalized	Hospitalized
Total	656 (90.6)	68 (9.4)
Gender, Ratio F:M	8.8:1	8.5:1
Age, mean (SD), years	40.5 (17.4)	39.8 (16.9)
Ethnicity†		
Caucasian	417 (92.7)	33 (7.3)
Black	56 (93.3)	4 (6.7)
Asian	118 (95.9)	5 (4.1)
Aboriginal*	44 (81.5)	10 (18.5)
Work Disabled**	102 (15.5)	25 (36.6)
High School Education	55 (81.0)	468 (71.3)
Income Level††		
<$15,000***	63 (85.1)	11 (14.8)
$15,000–$29,999	72 (94.7)	4 (5.3)
$30,000–$49,999	123 (95.3)	6 (4.7)
≥$50,000	247 (96.1)	10 (3.9)

†Excluded 37 participants whose ethnicity not available or belonged to ethnic group other than the 4 of interest.
*Significant relationship between being of Aboriginal race and hospitalization (p=0.004).
**p=0.001.

Table. Disease Activity and Co-Morbidities

	Mean (SD)	
	Non-Hospitalized	Hospitalized
ACR Criteria*	5.2 (1.4)	5.9 (1.7)
SLAM Score**	5.4 (3.9)	6.9 (4.7)
SLEDAI-2K Score	4.4 (4.3)	4.8 (5.0)
SLICC Score	1.3 (1.8)	1.3 (1.7)
Charlson Co-Morbidity Score	1.4 (0.9)	1.7 (1.2)

*p=0.006
**p=0.004



*Other reasons for hospitalization reported were gastrointestinal, infection, pulmonary hypertension, adrenal insufficiency, hepatitis, and thromboembolic events. Some patients had more than one reason for hospitalization

Figure 1. Reasons for hospitalization by number of patients.

Conclusions: The rate of hospitalization of patients with SLE was lower than expected; however this may indicate that the care of lupus is improving, that the cohort is biased towards healthy patients, or that flares are more likely to be handled as an outpatient. Also some renal lupus may be followed solely by a nephrologist. Some hospitalizations may have been under ascertained and we did not record hospitalizations for non-lupus reasons such as pregnancy. The causes of hospitalization were varied and different than what other studies have shown. Several predictors of hospitalization are related to ethnicity, socioeconomic factors and disease activity, which is consistent with results of other studies.

Disclosure: J. Lee: None; **J. E. Pope:** None; **C. A. Peschken:** None; **The 1000 Faces of Lupus:** None.

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Measuring Therapeutic Adherence in Systemic Lupus Erythematosus (SLE) Using the Medication Event Monitoring System (MEMS®). Maria F. Marengo, Christian A. Waimann, Sofia de Achaval, Vanessa L. Cox, Araceli Garcia Gonzalez, Marsha N. Richardson and Maria E. Suarez-Almazor. The University of Texas M. D. Anderson Cancer Center, Houston, TX

Background: Treatment adherence is crucial in chronic diseases such as SLE. Multiple methods for measuring adherence have been proposed. Electronic monitoring is considered one of the most accurate measures of adherence. The objective of our study was to quantify adherence to medical therapy in patients with SLE with electronic monitoring.

Methods: This study was part of a 2– year prospective cohort of 110 patients with SLE from 2 publicly-funded county hospitals, in which 74 patients agreed to have their SLE drug therapy electronically monitored, with MEMS® caps (AARDEX). These are medication bottle caps with a microchip which records the time and date of bottle openings. Adherence to daily medications was determined as the percentage of days with correct number of doses taken. Adherence to weekly methotrexate (MTX) was determined as the percentage of doses taken within intervals of 7 ± 1.75 days. We also estimated percentage of prescribed doses taken (not considering dosing interval). MEMS® data was downloaded with each refill. Patient outcomes were assessed at baseline, 3, 6, 12, 18 and 24 months including Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Systemic Lupus International Collaborating Clinics Damage Index (SLICC), SF-12 and flares. We also collected baseline Medical Outcome Study social support (MOS), Center for Epidemiologic Studies Depression Scale 10 items (CDES-10) and sociodemographic variables. 85% of the patients completed 2 years follow-up; for the remainder we used the last observation for analysis. Statistical analysis was performed with SAS

Summary of Results: 89% were female, 49% African-American, and 46% Hispanic; mean age was 36y (±11), disease duration 6y (±5), SLEDAI 3.2 (±3.2) and SLICC 0.8 (±1.2); 97% received prednisone, 92% hydroxychloroquine, 30% mycophenolate mofetil, 13% MTX, 8% azathioprine (not all medications were monitored with MEMS) (table). Adherence for doses taken on schedule (day/wk) was 64% for prednisone and 46% to 62% for the other drugs. Only 15 (20%) of the patients had an average adherence ≥ 80%. Depression was associated with worse adherence ($r=-0.24$, $p<0.04$), and increasing SF-12 mental scores (MCS) with better adherence ($r=0.31$, $p=0.02$). Mean SLEDAI decreased significantly overtime ($p<0.002$); % doses taken had a small but significant correlation with decrease in SLEDAI for all drugs ($r=-0.25$, $p<0.04$) and for prednisone alone ($r=-0.31$, $p<0.02$); % doses on schedule showed similar trends but did not reach statistical significance. No differences were observed for SLICC.

Drugs	N	Total days monitored	Mean dose	% prescribed doses taken on schedule	% prescribed doses taken
Prednisone	65	511 (±260)	12 mg/day	64.3 (±24)	75.9 (±24.6)
Hydroxychloroquine	51	556 (230)	248 mg/day	56.2 (±26.2)	72.0 (±26.1)
Methotrexate	7	350 (267)	134 mg/week	62.0 (±28.7)	94.6 (±30.9)
Micophenolate Mofetil	3	459 (178)	1087 mg/day	46.3 (±20)	67.1 (±22.6)
Average all drugs	74	–	–	58.6 (±24.9)	73.3 (±25.2)

Conclusion: Adherence to drug therapy measured by electronic monitoring appears to be low in patients with SLE, and related to depression and overall mental health. Only 1 out of 5 patients was at least 80% adherent. Low adherence appeared to have a detrimental effect on health outcomes.

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Mycophenolate Mofetil (MMF): Physician Prescribing Practices. Seema Malani[1] and Ellen M. Ginzler[2]. [1]SUNY Downstate Medical Center, Brooklyn, NY, [2]SUNY-Downstate Medical Center, Brooklyn, NY

Aim: To determine physician prescribing practices for mycophenolate mofetil (MMF, CellCept®) in North America

Purpose: MMF is commercially available and used off-label for the treatment of SLE but consensus guidelines for its use in lupus and other autoimmune diseases are lacking. We were interested in learning the prescribing practices for MMF among rheumatologists and nephrologists, and their experience with efficacy and toxicity.

Method: Approximately 700 adult and pediatric rheumatologists and nephrologists interested in SLE from the U.S. and Canada were invited via e-mail to complete an electronic survey, including 20 questions regarding their practice setting, ethnic composition of patients treated, dose and duration of MMF use, ethnic differences in response to MMF, and MMF use for extra-renal lupus and other autoimmune diseases.

Results: 141 physicians responded to the survey. The majority were rheumatologists (95.5%) with 3.5% nephrologists; 55% practice in an academic institution. The majority (60%) treat 10–50 SLE patients/month. African-American/Afro-Caribbeans and Caucasians were the predominant population.

57% of respondents prescribe steroids with MMF as first line therapy for active lupus nephritis, predominantly for class III and IV nephritis; 36% favor steroids plus IV cyclophosphamide (IVC). 38% of respondents continue to prescribe MMF for treatment of severe active nephritis with worsening renal function. 85% of academic vs. 71% of private physicians prescribe MMF for both induction and maintenance in lupus nephritis ($p=0.04$). For patients who relapse on maintenance MMF, a similar number of respondents prescribe IVC for reinduction followed by maintenance MMF vs. azathioprine maintenance. Most respondents (75%) attempt a target MMF dose of 3 grams/day. 52% prefer to continue MMF indefinitely while 41% taper and discontinue the dose after achieving remission.

53% of respondents found no racial difference in response to MMF, while 23% did not have a heterogeneous racial population. Few commented on a need for a higher MMF dose in African-American patients.

MMF use for extra-renal lupus manifestations was reported for pulmonary disease (65%), hematologic (57%), cutaneous (48%), neuropsychiatric (44%), and arthritis (41%). MMF use in other autoimmune disease included systemic vasculitis (56%), inflammatory myopathies (50%), interstitial lung disease (44%), systemic sclerosis (33%).

Most respondents change from MMF to other maintenance drugs only for side effects or insurance coverage issues. GI side effects were the most common adverse events reported (84%), followed by infection (30%), and hematologic events (27%).

Conclusion: Despite a lack of guidelines for MMF use, it is the first choice therapy both in remission induction and maintenance of lupus nephritis. Most physicians continue MMF for a long duration. There also appears to be considerable use of MMF for treatment of extra-renal manifestations of SLE.

Disclosure: S. Malani: None; **E. M. Ginzler:** None.

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Novel Cardiovascular Risk Prediction Models in Patients with Systemic Lupus Erythematosus. Vivian K. Kawai[2], Annette M. Oeser[4], Joseph Solus[3], Young H. Rho[3], Paolo Raggi[1], Aihua Bian[3], Tebeb Gebretsadik[3], Ayumi Shintani[3] and C. Michael Stein[2]. [1]Emory University, [2]Vanderbilt University, Nashville, TN, [3]Vanderbilt University, [4]VUMC 23rd Ave South Pierce, Nashville, TN

Background: Women with systemic lupus erythematosus (SLE) have accelerated atherosclerosis and increased coronary heart disease (CHD), but the Framingham risk score (FRS) underestimates risk. Several new approaches have improved prediction of CHD risk in the general population. These include the Reynolds risk score (RRS), that is of particular interest because it includes a measure of inflammation (C-reactive protein), and novel risk scores that substitute "coronary age" in place of chronological age. We examined the hypothesis that these new CHD risk prediction models would better identify increased risk of CHD in women with SLE, particularly in those with subclinical coronary atherosclerosis.

Methods: We studied 121 women with SLE and 65 age-matched female-controls without a previous cardiovascular event. Demographic and clinical data were recorded and FRS and RRS calculated. Coronary artery calcium (CAC) was measured by computed tomography using the Agatston score, and coronary age was derived as described by McClelland. Coronary age-modified risk scores (camFRS, camRRS) were calculated in which chronological age in the existing FRS and RRS calculations was replaced with coronary age. Risk scores were compared in patients with SLE and controls, and in SLE patients with and without CAC, using Wilcoxon rank sum tests. We examined the association between risk scores and CAC using proportional odds logistic regression models. Paired analyses were performed using Wilcoxon signed-rank test or McNemar's test, as appropriate. All analyses used a 5% two-sided significance level.

Results: Coronary artery calcium was present in 21 patients with SLE (17%) and 4 controls (6%) (P=0.033). However, despite more frequent and severe atherosclerosis in SLE, the FRS, camFRS, RRS and camRRS did not differ significantly among women with SLE and controls ($p>0.05$). In women with SLE with CAC the FRS (OR=1.42, 95%CI (1.06–1.90), P=0.017) and RRS (OR=1.29, 95% CI (1.11–1.51), P=0.001) were higher than in those without CAC, however few patients (≤5%) with CAC had 10-year risk scores ≥10% - the threshold used to determine moderate CHD risk. Coronary age-modified risk scores were significantly lower than their respective conventional risk scores in lupus patients without CAC, and higher in those with CAC (both P values <0.001). Coronary age-modified risk scores assigned more patients with CAC to a risk category of ≥10% (camFRS 48%, cam RRS 29%) than conventional scores (FRS 0%, RRS 5%) (P =0.004 and P=0.073, respectively).

Conclusions: The RRS, a novel 10-year risk prediction model that includes C-reactive protein in the risk calculation, was of limited use in women with SLE. Incorporation of coronary age, calculated from CAC scores, into risk prediction models increases the number of patients with CAC with a predicted CHD risk above the 10% 10-year threshold. The ability of models that include coronary age to predict risk of cardiovascular events will be of interest.

Disclosure: V. K. Kawai: None; **A. M. Oeser:** None; **J. Solus:** None; **Y. H. Rho:** None; **P. Raggi:** None; **A. Bian:** None; **T. Gebretsadik:** None; **A. Shintani:** None; **C. M. Stein:** None.

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Optimal Frequency of Visits for SLE Patients To Capture Disease Activity over Time. Dominique Ibañez[3], Dafna D. Gladman[2] and Murray B. Urowitz[1]. [1]The Toronto Western Hospital, Toronto, ON, Canada, [2]Toronto Western Hospital, Toronto, ON, Canada, [3]University of Toronto Lupus Clinic, Toronto Western Hospital, Toronto, ON, Canada

Objective: Disease activity in SLE patients, measured by SLEDAI-2K, is evaluated at each clinic visit and covers a period of 30 days prior to the assessment. Having consecutive monthly clinic visits would capture the entire disease activity for that period of time. Adjusted Mean SLEDAI (AMS) calculates the areas under the curve of SLEDAI-2K over time. AMS evaluated using monthly visits would be the gold standard for disease activity over time. The usual clinical practice is to see patients every 3–6 months. The aim of this study is to compare the AMS obtained over a one year period when visits are done monthly and compare it to AMS obtained using quarterly, semi-annual or annual visits.

Methods: Patients followed monthly for 12 consecutive visits are included. AMS is evaluated using all of the SLEDAI-2K (AMS_{GOLD} using all 12 visits), only quarterly visits (AMS_3, using visits 3 months apart), semi-annual visits (AMS_6, using 1st, middle and last visits only) and annual visits (AMS_{12} using only the 1st and last visits). Comparisons between AMS_3, ASM_6 and AMS_{12} with AMS_{GOLD} are made using descriptive statistics.

Results: 78 patients were seen monthly for a year. 72 (92%) were women with mean (std) age at SLE diagnosis of 30.1 (11.4) years and mean age and disease duration at study start of 46.2 (12.0) years and 15.5 (9.7) years respectively. The SLEDAI-2K values seen have a mean (std) of 2.05 (2.07) and range in values from 0 to 15, with 7% of all visits having a SLEDAI-2K ≥ 5. The mean (std) AMS_{GOLD} for the entire year is 2.05 (1.66), for AMS_3 = 1.99 (1.65), for AMS_6 = 2.12 (1.87) and for AMS_{12} = 2.08 (1.83). Mean (std) of the absolute differences with AMS_{GOLD} are: for AMS_3 = 0.29 (0.33), for AMS_6 = 0.45 (0.59) and for AMS_{12} = 0.61 (0.58). Differences which were < 0.5 were considered minimal while those ≥ 1 were deemed important. Comparing AMS_{GOLD} to AMS_3, 82% of the differences were minimal and 3% were important. When comparing to AMS_6, 68% were minimal and 10% were important while when comparing to AMS_{12}, 50% were minimal and 21% were important.

Conclusion: Usual clinical visits occurring quarterly offer a good estimation of disease activity over a one year period and are preferred over semi-annual and annual visits.

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1869

Optimal Frequency of Visits To Capture Disease Activity over Time in SLE Patients with Varying Levels of Disease Activity. Dominique Ibanez[2], Murray B. Urowitz[3] and Dafna D. Gladman[1]. [1]Toronto Western Hospital, Toronto, ON, Canada, [2]University of Toronto Lupus Clinic, Toronto Western Hospital, [3]University of Toronto Lupus Clinic, Toronto Western Hospital, Toronto, ON, Canada

Objective: Disease activity in SLE patients, measured by SLEDAI-2K, is evaluated at each clinic visit. Adjusted Mean SLEDAI (AMS) calculates the area under the curve of SLEDAI-2K over time. A previous study in patients with mild disease activity showed that quarterly visits offer a good estimation of disease activity. The aim of this study was to extend the study by using patients with varying levels of disease activity and to compare the AMS obtained over a 3-year period in patients with regular quarterly visits to AMS obtained using semi-annual, annual visits or visits every 18 months.

Methods: Patients followed every 3 months over a 36 month period are included. AMS is evaluated using all of the visits (AMS_3), using only the semi-annual visits (AMS_6), the annual visits (AMS_{12}), and the visits 18 months apart (AMS_{18}). Based on AMS_3, patients' disease activity is classified as Minimal (AMS_3 <3), Mild (AMS_3 ≥3 and <7) or Moderate (AMS_3 ≥7). Comparisons between AMS_6, AMS_{12} and AMS_{18} with AMS_3 are made using descriptive statistics. An important error is measured as the increase in AMS_3 associated with each additional flare.

Results: 202 patients were seen quarterly for a 3-years period. 178 (88%) were women with mean (std) age at SLE diagnosis of 30.1 (12.8) years and disease duration at study start of 9.7 (8.1) years. 82 patients are Minimal, 80 are Mild and 40 are Moderate. The mean (std) AMS_3 for the entire period is 5.0 (3.0), for AMS_6 = 5.1 (3.0), for AMS_{12} = 5.0 (3.1) and for AMS_{18} = 5.2 (3.4). In the 3 years interval, 179 (89%) of the patients experienced at least 1 flare. The presence of each flare is associated with an increase in AMS_3 of magnitude 1.0. Therefore, absolute differences which were < 0.5 were considered minor, those between 0.5 and 1 acceptable, those ≥1 were deemed important and those ≥3 were considered serious.

Percent of Errors Based on Visit Frequency and Level of Disease Activity

	Level of Disease Activity			
	Minimal (n=82)	Mild (n=80)	Moderate (n=40)	All Patients (n=202)
Using Semi-annual Visits				
Minor	56%	51%	45%	52%
Acceptable	35%	31%	17%	30%
Important	9%	18%	38%	18%
Serious	0%	1%	3%	1%
Using Annual visits				
Minor	45%	34%	30%	37%
Acceptable	23%	16%	7%	18%
Important	32%	50%	63%	45%
Serious	2%	7.5%	18%	7.5%
Using Visits 18 months apart				
Minor	35%	26%	15%	28%
Acceptable	26%	16%	5%	17%
Important	39%	58%	80%	55%
Serious	6%	15%	28%	14%

Conclusion: Quarterly visits are preferred over visits further apart. In patients with lower disease activity, semi-annual visits are a good estimation of disease activity over time while in patients with more active disease, shorter times between visits are necessary.

Disclosure: D. Ibanez: None; **M. B. Urowitz:** None; **D. D. Gladman:** None.

1870

Performance of Anti-Nucleosome, Anti-C1q and Anti-dsDNA Antibodies for the Diagnosis of Concurrent Disease Activity of Systemic Lupus Erythematosus. Chi Chiu Mok, Ling Yin Ho, Hoi Wah Leung and Lap Gate Wong. Tuen Mun Hospital

Objectives: To evaluate the specificity and sensitivity of anti-nucleosome, anti-C1q and anti-dsDNA antibodies in the diagnosis of disease activity in systemic lupus erythematosus (SLE)

Methods: Consecutive patients with SLE were recruited for serological testing of anti-dsDNA (Euro-diagnostica, Arnhem, Netherlands), IgG-anti-nucleosome and IgG-anti-C1q (Euroimmun, Lubeck, Germany) antibodies by ELISA and complement levels by immunonephelometry (Siemens, Germany). Concurrent renal and extra-renal disease activity was assessed by SLEDAI-2K and physician global assessment (PGA). Correlation among levels of these antibodies, complements and disease activity scores was made by spearman's rank correlation test. The specificity and sensitivity of these antibodies in diagnosing concurrent renal and extra-renal activity was calculated.

Results: 245 SLE patients were studied (95% women). The mean age was 40.6±12.2 years at the time of blood tests; and the duration of SLE was 8.7±7.1 years. The prevalence of positive anti-dsDNA (≥50IU/ml), anti-nucleosome (≥20RU/ml) and anti-C1q antibodies (≥20RU/ml) was 55%, 44% and 21%, respectively. All the 3 antibodies correlated significantly with complement levels (C3 and C4), SLEDAI (with deduction of scores due to elevation of anti-dsDNA and depression of complements) and PGA scores ($P<0.001$ in all). Positive anti-dsDNA and anti-C1q, but not anti-nucleosome antibodies correlated significantly with the presence of active renal disease as scored by the SLEDAI. The sensitivity of anti-dsDNA, anti-nucleosome and anti-C1q antibodies for the presence of active renal disease was 75%, 47% and 53%, respectively. The specificity was highest for anti-C1q for active lupus renal disease (84%), followed by anti-nucleosome (57%) and anti-dsDNA antibodies (49%). The specificity of combined anti-dsDNA and anti-C1q for active renal disease was 88%. The negative predictive value of a negative anti-dsDNA and anti-C1q for active renal disease was 91%. For the prediction of concurrent extra-renal SLE activity, the specificity was also highest with anti-C1q (83%), followed by anti-nucleosome (60%) and anti-dsDNA (48%) antibodies.

Conclusions: Anti-nucleosome does not perform better than anti-dsDNA for the presence of concurrent SLE activity. Anti-C1q antibodies, however, is more specific than anti-dsDNA for both renal and extra-renal lupus activity. The absence of both anti-dsDNA and anti-C1q has a high negative predictive value for concurrent active renal disease.

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1871

Predictive Value of High Levels of Antinuclear Antibodies in People without Other Feature of Autoinmunity. A Prospective Study. Ignacio Villa-Blanco[4], Marcos Lopez-Hoyos[1], Ana Ruibal[2] and Jaime Calvo-Alen[3]. [1]Hospital "Marques de Valdecilla", [2]Hospital "Txagorritxu", [3]Hospital Sierrallana, Torrelavega, Spain, [4]Hospital Sierrallana, Spain

Background: Low levels of antinuclear antibodies (ANA) are not an uncommon finding in otherwise healthy people but the presence of high levels of ANA is a far less common situation. On the other hand, different studies have shown that diseases as systemic lupus erythematosus (LES) may be heralded by the presence of these autoantibodies several years before. Therefore, it is possible to hypothesize that people with high ANA titers may portend and special risk for the development of autoimmune diseases but prospective data to this regard are lacking.

Objective: To analyze the outcome of healthy people with high levels of ANA.

Methods: All patient of our centre with a positive ANA test with a titter ≥1/1280 obtained between January of 1996 and December of 2006 were identify regardless the reason to order such test. A medical record review was performed in all cases and only those cases where any type of inflammatory or autoimmune disease had been excluded at the moment when the ANA test was performed and with a minimum time of follow up (from the date when the positive ANA test was obtained up the time of study onset) of 36 months were selected. In all cases, the development of any autoimmune disease during the follow up was established by chart review and then the rest of patient were contacted for further clinical and laboratory evaluation at he outpatient clinic.

Results: Overall, 133 patient were identified with a positive ANA test with a titter ≥1/1280. Out of them, 68 had been diagnosed of having different types of inflammatory or autoimmune disease (11 Rheumatoid arthritis, 11 Sjögren syndrome (SS), 8 autoimmune hepatitis, 5 LES, 4 undifferentiated connective tissue disease, 4 CREST syndrome, 3 primary biliary cirrhosis (PBC), 3 Dermatomyositis, 3 Inflammatory Bowel disease, 2 Morfea, 2 pernicious anaemia, 1 polymyalgia rheumatica, 1 Sweet, 1 antiphospholipid syndrome, 1 VIH, 1 VHC, 2 Hashimoto thyroiditis, 1 myelodisplastic syndrome, 1 mixed connective tissue disease, 1 sarcoidosis, 1 BONO, 1 ankylosing spondylitis. In 65 patients [78% women; mean age (range) 60.7 years (20–92)] this type of diseases were excluded. During the follow up [mean time (range) 86 months (36–120)], 8 patients (12%) developed systemic diseases: 2 LES with renal involvement after 96 and 48 months from the initial ANA test, 2 SS (45 and 59 months after the initial ANA test), 2 PBC (36 and 38 months after the initial ANA test), 1 autoimmune hepatitis (95 months after the initial ANA test) and 1 incomplete CREST syndrome (46 months after the initial ANA test). No other findings suggestive of autoimmune diseases were identify in the rest of 57 patients but in 39 % of them, ANA titters remained high (≥1/1280).

Conclusions: According to our data, during the follow up, a significant percentage (12%) of asymptomatic patients with high titters of ANA develop an autoimmune disease. Patients with persistent positive ANA test have a special risk for the development of autoimmune disease and may need longer periods of follow up.

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1872

Preliminary Comparison of Health-Related Quality of Life in Children with Lupus across Different Continents. Lakshmi Nandini Moorthy[14], Claudia Saad-Magalhães[1], Juliana Oliveira Sato[1], Claudio A. Len[10], Maria O. Hilário[10], Flavio Sztajnbok[9], Rozana Gasparello de Almeida[9], Feng Qi Wu[2], Xiaolan L. Huang[2], Fernanda Falcini[13], Donato Rigante[11], Rolando Cimaz[12], Jordi Antón Lopez[8], Consuelo Modesto[7], Rubén J. Cuttica[5], Lisette W. A. van Suijlekom-Smit[3], Marieke H. Otten[3], Maria J. Baratelli[14], Margaret G. E. Peterson[6], Afton L. Hassett[15] and Thomas J. A. Lehman[4]. [1]Botucatu Medical School-São Paulo State University, Brazil, [2]Capital Institute of Pediatrics, China, [3]Erasmus MC, Sophia Childrens Hospital, The Netherlands, [4]Hosp for Special Surgery, New York, NY, [5]Hospital de Pediatría Pedro de Elizalde, Argentina, [6]Hospital for Special Surgery, [7]Hospital Infantil Valle de Hebron, Spain, [8]Hospital Sant Joan de Déu, Spain, [9]Universidade do Estado do Rio de Janeiro, Brazil, [10]Universidade Federal de São Paulo, Brazil, [11]Università Cattolica Sacro Cuore, Italy, [12]University of Firenze, Firenze, Italy, [13]University of Florence, Florence, Italy, [14]University of Medicine and Dentistry of NJ-Robert Wood Johnson Medical School, New Brunswick, NJ, [15]University of Michigan Medical School, Ann Arbor, MI

Background: Simple Measure of Impact of Lupus Erythematosus in Youngsters© (SMILEY©) is a brief 24-item health-related quality of life (HRQOL) assessment tool for pediatric systemic lupus erythematosus (SLE). Responses are in the form of a 5-faces scale for easy comprehension. Higher percentage scores indicate better HRQOL. SMILEY is valid in US-English and has been translated and adapted to 21 languages. Currently, we are conducting cross-cultural validation of SMILEY. We are also preliminarily exploring differences in HRQOL using SMILEY across different countries and examining factors influencing these differences.

Objective: We conducted preliminary analysis of SMILEY scores from various countries in South America, Europe and Asia.

Methods: Children ≤18 years with SLE and parents completed the appropriate SMILEY translation, and gold standard quality of life and physical function scales. Physicians completed the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI). Across the countries, we compared age, SMILEY and PedsQL generic total scores, Child Health Assessment Questionnaire (CHAQ) disability index, and SDI. Contingent upon the data distribution of the above variables, we used one-way ANOVA or the Kruskal-Wallis (KW) test. Because of the limited sample size for each country, we have combined data by similar geographic regions (continents).

Results: 125 children (106 girls) and parents participated from South America (Brazil= 45, Argentina=11), Europe (Italy=16, Spain=15, Netherlands=10), and Asia (China=28). Table 1 shows the means/medians of child and parent reports of SMILEY and PedsQL generic total scores; parent CHAQ disability index; age; and SDI. Children from Asia had the highest SMILEY and PedsQL scores (indicating higher HRQOL), and lowest age. Significant differences between continents were found for age, parent PedsQL and child SMILEY scores. Parents' PedsQL and SMILEY scores were lower compared to child scores and this difference was most pronounced for children from South America.

Table 1. HRQOL, SDI, SLE-duration and age across the continents

	South America	Europe	Asia	p value
SMILEY total*				
Mean ± SD (range, n)				
Child	68 ± 15 (33–97, 52)	70 ± 16 (26–93, 41)	77 ± 13 (58–96, 28)	0.03 (ANOVA)
Parent	64 ± 16 (36–100, 54)	69 ± 16 (35–94, 38)	72 ± 16 (39–100, 28)	0.1 (ANOVA)
PedsQL total*				
Mean ± SD (range, n)				
Child	74 ± 15 (38–98, 42)	74 ± 21 (24–100, 30)	81 ± 11 (57–99, 27)	0.14 (ANOVA)
Parent	66 ± 22 (15–100, 40)	73 ± 19 (32–96, 28)	79 ± 19 (35–100, 28)	0.03 (ANOVA)
CHAQ score				
Median (range, n)				
Parent	0 (0–2.375, 42)	0 (0–1.25, 25)	Not completed	0.3 (KW)
SDI				
Median (range, n)	0 (0–4, 45)	0 (0–4, 40)	0 (0–3, 11)	0.7 (KW)
Duration (months)				
Median (range, n)	27 (1–116, 54)	31 (1–150, 40)	23 (1–188, 25)	0.2 (ANOVA)
Age (years)				
Mean ± SD (range, n)	14 ± 3 (6–18, 52)	15 ± 2 (7–18, 40)	12 ± 3 (5–16, 27)	0.005 (ANOVA)

*Higher percentage scores indicate better HRQOL

Conclusion: On preliminary analysis, differences in HRQOL and age were found across continents. Children from Asia (China) were the youngest and had the highest HRQOL. Age and cultural differences can influence HRQOL. Parents seemed to perceive a lower HRQOL for children with SLE; either reflecting a greater perception of their child's vulnerability, their own anxiety, or HRQOL. We are expanding our sample and exploring these differences further.

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1873

Prevalence and Risk Factors of Glucocorticoid-Induced Diabetes Mellitus in Patients with Systemic Lupus Erythematosus. You Jung Ha[1], Kwang-Hoon Lee[2], Se-jin Jung[1], Yoon Kang[1], Min-Chan Park[3], Sang-Won Lee[1], Soo Kon Lee[1] and Yong-Beom Park[1]. [1]Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea, Republic of, [2]Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea, Republic of, [3]Gangnam Severance Hospital, Seoul, Korea, Republic of

Background and Purpose: Glucocorticoid is a main strategy for the treatment of systemic lupus erythematosus (SLE). Although it is well known that glucocorticoid may cause diabetes mellitus (DM), there have been only few studies about glucocorticoid-induced DM in patients with SLE. This study was performed to investigate the prevalence and risk factors of glucocorticoid-induced DM in patients with SLE.

Methods: Patients with SLE who had received high-dose glucocorticoid therapy (prednisolone ≥1mg/kg/day) were recruited in Yonsei University Medical Center, Seoul, Korea from January 1999 through June 2009. Patients diagnosed with DM before glucocorticoid therapy were excluded. Risk factors for the development of glucocorticoid-induced DM were identified by univariate and multivariate analysis.

Results: A total of 127 patients with SLE were studied (9 males and 118 females). The mean age of the patients was 34.9 ± 12.7 years. Sixteen (12.6%) of the 127 patients developed glucocorticoid-induced DM after high-dose glucocorticoid therapy. Median duration from high-dose glucocorticoid treatment to the development of DM was 34 days. Univariate analysis showed that old age, family history of DM, hypertension, higher body mass index, and concurrent use of mycophenolate mofetil would increase the risk for glucocorticoid-induced DM. In multivariate analysis, age (OR 1.08, 95% CI 1.03–1.14), family history of DM (OR 9.60, 95% CI 2.22–41.47) and concurrent use of mycophenolate mofetil (OR 4.50, 95% CI 1.29–15.68) were determined as independent risk factors for glucocorticoid-induced DM.

Conclusion: DM was developed among 12.6% of patients with SLE after high-dose glucocorticoid treatment. Old age, family history of DM, and concurrent use of mycophenolate mofetil were the factors responsible for increased risk of developing glucocorticoid-induced DM.

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1874

Prolonged Serologically Active Clinically Quiescent (SACQ) Systemic Lupus Erythematosus (SLE): Novel Predictors of Flare? Amanda Steiman[1], Murray B. Urowitz[2], Joan E. Wither[4], Dominique Ibañez[1], Timothy Li[3] and Dafna D. Gladman[1]. [1]Toronto Western Hospital, Toronto, ON, Canada, [2]Toronto Western Hospital, Toronto, ON, Canada, [3]Toronto Western Hospital, [4]University Health Network, Toronto, ON, Canada

Purpose: Anti-double stranded DNA antibodies (anti-dsDNA) and complement levels are routinely used to predict flare in SLE patients. Some SLE patients, however, are clinically quiescent despite persistent serologic activity, as evidenced by elevated anti-dsDNA and/or hypocomplementemia. Past studies reveal that nearly 60% of such SACQ patients flare, but do so only after average 182 weeks. In these patients changes in total serum anti-dsDNA and/or C3/C4 levels measured at routine clinic visits were not predictive of flare. Some studies suggest that anti-chromatin (-nucleosome) antibodies are more sensitive than anti-dsDNA to detect active SLE, and that the time to first flare after a SACQ period was significantly correlated with their presence. This study investigates whether levels of anti-dsDNA and anti-chromatin isotypes, measured during a prolonged SACQ period, differed in SACQ patients who remained SACQ versus those who flared.

Methods: Archived serum samples of patients with a prolonged SACQ period, stored at −80 °C, were retrieved and divided by disease activity (during a SACQ period vs during flare). Serum levels of IgM, IgA, IgG, IgG1, IgG2, IgG3, and IgG4 anti-dsDNA and anti-chromatin antibodies were measured by ELISA. H1-stripped chromatin was prepared from the human cell line, MOLT4. ELISA plates were coated overnight with dsDNA (40 ug/ml) and chromatin (8 ug/ml) diluted in PBS at 4°C. Serum was diluted 1/100 for measurement of IgM, IgA, and IgG, or 1/50 for IgG1–4. SACQ was defined as at least a two year sustained period with SLEDAI of 2 or 4 from serologic activity only, during which patients could be taking antimalarials, but not steroids or immunosuppressives. Flare was defined as any increase in clinical disease activity. P-values were reported using Wilcoxon rank sum tests.

Results: Thirty-eight serum samples which corresponded to a prolonged SACQ period (from 23 patients) were analyzed. Fifteen of the 38 (39%) samples corresponded to patients whose SACQ period ended in flare. Anti-chromatin total IgG levels were significantly lower in SACQ patients who flared than in those who remained SACQ (0.361 ± 0.277 vs 0.835 ± 0.700, p=0.007; normal < 0.147), however there was no significant difference between these groups when IgG was broken down by subtype. Anti-chromatin IgM and IgA values were comparable between groups. Anti-dsDNA IgA (but not IgM or IgG) was significantly lower in SACQ patients who flared compared to those who remained SACQ (0.028 ± 0.025 vs 0.081 ± 0.095, p=0.018). When only the most recent sample from each SACQ patient was analyzed (9/23 (39%) of whom flared), there was no difference between anti-chromatin or anti-dsDNA isotype levels between patients who flared and those who remained SACQ.

Conclusions: In this small pilot study neither anti-chromatin nor anti-dsDNA antibody levels were predictive of flare in SACQ patients. Alternate serum biomarkers must be sought.

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1875

Racial Disparities in Treatment Preferences among Lupus Patients. Ernest R. Vina, Christopher M. Masi, Stephanie L. Green and Tammy O. Utset. University of Chicago Medical Center, Chicago, IL

Background: Worse health outcomes among African-American compared to white SLE patients are well documented. While racial differences in patient treatment decisions have been identified in other diseases, this phenomenon has not been explored in SLE. The objectives of this study are: (1) to determine whether there are differences between African American and white SLE patients' willingness to a) receive an immunosuppressive medication (cyclophosphamide, CTX) when clinically indicated and b) participate in clinical trials involving novel, experimental medications; and (2) to determine whether demographic, psychosocial and clinical characteristics explain racial differences in either measure of medical management.

Methods: Data from 25 African-American and 25 white lupus patients were evaluated. Structured telephone interviews were conducted to determine treatment preferences, as well as characteristics and beliefs that may affect these preferences. Chart reviews were conducted to evaluate clinical characteristics (disease duration, SLEDAI, SLICC Damage Index, Charlson Comorbidity). Serial hierarchical multivariate logistic regression analyses using forward selection of variables with $p<0.20$ were conducted.

Results: Compared to white SLE patients, African American SLE patients were less willing to receive CTX (96% vs. 56%, $p=0.001$). They also had lower incomes ($p<0.005$), were less likely to have private insurance ($p=0.001$), and were more likely to believe that prayer can affect health outcomes ($p=0.016$). Lupus patients willing to receive CTX were more likely to be older ($p=0.027$), to have higher incomes ($p=0.004$), to have private insurance ($p=0.034$), to be more educated ($p=0.047$) and to perceive CTX to be effective ($p=0.001$). Multivariate logistic regression analysis showed that age (OR=1.13, $p=0.042$), educational level (OR=8.90, $p=0.025$) and perception of effectiveness of treatment (OR=1.67, $p=0.025$) were significant predictors of willingness to receive CTX. After adjustment for these variables, willingness to receive CTX was higher among whites compared to African Americans (OR=11.74) but this effect did not reach significance ($p=0.056$).

In contrast, no significant racial differences were observed in willingness to participate in a clinical trial (84% among whites vs. 68% among African-Americans, $p=0.185$). Willingness to participate in a clinical trial was positively associated with being married ($p=0.015$), having private insurance ($p=0.05$) and having a physician with a participatory decision-making (PDM) style ($p=0.001$). A logistic regression model showed that the CES-D score (OR=0.91, $p=.017$) and physician PDM style (OR=1.08, $p=0.003$) were significant predictors of willingness to participate in a clinical trial.

Conclusions: We found a trend toward decreased likelihood of accepting CTX among African American compared to white lupus patients after adjusting for multiple covariates. In contrast, African American and white SLE patients did not differ in willingness to participate in a clinical trial. We continue to collect data and will determine whether these results persist with larger cohorts of African-American and white SLE patients.

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Risk Factors Associated with the Presence of Pneumonia in Patients with Lupus Erythematosus (SLE): A Nested Case-Control Study. Iñigo Rúa-Figueroa[1], Francisco J. Nóvoa[2], Celia Erausquin[2], Miguel Garcia-Bello[2], Felipe Rodríguez de Castro[2], Juan C. Quevedo[2], Isabel García-Laorden[2], Carlos Rodriguez-Gallego[2], Felix Francisco[2] and Carlos Rodriguez-Lozano[2]. [1]Hospital Dr Negrin, Las Palmas GC, Spain, [2]Hospital Dr Negrin

Purpose: To determine the incidence of pneumonia and the associated risks factors in a monocentric SLE cohort.

Methods: We included SLE patients (1997 criteria) with pneumonia and 196 age and sex-matched SLE controls. Clinical data, comorbidity and risk factors for pneumonia were retrospectively collected. Katz severity index (SI) and weighted SLICC/ACR damage index (wDI) were recorded. The standardized incidence ratio (SIR) of pneumonia was estimated. MBL, FCγR IIA, MASP-2, C2, IL6–174, SPD y SPA1 y 2 single nucleotide polymorphisms (SNP) were studied based on previous evidence of association with pulmonary infection. Differences were analysed using Pearson's χ^2 or Fisher's exact test as appropriate, and Student's t-test or Wilcoxon for qualitative variables.

Results: Mean age at diagnosis: 31 years (p25-p75: 24–40); mean disease duration: 12 years (6–18); 92% were women; mean follow up: 6.7 (2.2–11.5). Leukopenia 48%; SLE criteria: 6 (5–7); SI 3 (2–5); wDI: 2 (0–5); exitus 14 (6%). 36 patients presented one or more pneumonia (29 defined, 7 probable); 9 patients suffered from pneumonia before SLE onset. 58% had received steroids, 16% at high doses, and 44% immunosuppressors at any time. Only 13% of patients were taking immunosuppressors at the moment of pneumonia. The SIR for pneumonia was 7.2. Excluding pneumonia cases after SLE onset, we also found an increased ratio (1.3). An association with a SNP of SPA2 1A1/1A0 gene, a protein crucial in pulmonary innate immunity, was found but the significance disappeared after Bonferroni correction. Excluding patients with immunosuppressors at the time of pneumonia, associations were found with SI (OR 1.2; 95% CI 1–1.4; $p=0.016$), wDI: $p=0.044$, number of SLE criteria ($p=0.04$), number of hospital admissions: (OR 17; 95%CI 2.4–130; $p<0.01$), and a strong trend for exitus (OR 3.2; 95% IC: 9–11.1; $p=0.07$) in univariate analysis. We found also association with high doses steroids treatment any time (OR 2; 95% CI 0.9–4.6; $p= 0.087$), immunosuppressors (OR 2.2; 95% IC: 1–4.9; $p=0.049$), cutaneous ulcers (OR 6.7; 95% IC: 2.1–21; $p<0.01$) and vasculitis (OR 3; 95% IC: 1.3–7.2; $p =0.008$). Furthermore, a trend was found for other infections ($p=0.130$) and admissions for non-pulmonary infections ($p=0.087$). In the multivariate analysis, adjusting for immunosuppressor treatment, the single statistically significant risk factor was SI ($p=0.023$).

Conclusions: The incidence of pneumonia in patients with SLE is higher than in the general population and this probably also happens before the onset of SLE. Most patients were not receiving immunosupressive therapy at the moment of the pneumonia. Pneumonia is more frequent in severe SLE, independently of immunosupressive therapy.As suggested by current literature, infections - pneumonia in our study -, could be a severity marker in SLE.

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SLE and Atherosclerotic Risk Factors by Ethnicity and Geographic Distribution at Inception in a International Cohort of SLE. Murray B. Urowitz[33], Dafna D. Gladman[22], Dominique Ibanez[32], Caroline P. Gordon[29], Sang-Cheol Bae[6], Ann E. Clarke[15], Sasha R. Bernatsky[15], F. Jorge Sanchez-Guerrero[9], John G. Hanly[19], David A. Isenberg[24], Anisur Rahman[25], Paul R. Fortin[33], Daniel J. Wallace[1], Ellen M. Ginzler[20], Joan T. Merrill[18], Graciela S. Alarcón[28], Barri J. Fessler[23], Ian N. Bruce[13], Gunnar K. Sturfelt[27], Ola Nived[27], Kristjan Steinsson[12], Munther A. Khamashta[21], Michelle A. Petri[2], Rosalind Ramsey-Goldman[17], Susan Manzi[34], Mary Anne Dooley[31], Ronald V. Vollenhoven[11], Cynthia B. Aranow[4], Thomas Stoll[10], Manuel Ramos[7], Kenneth C. Kalunian[26], Asad A. Zoma[5], Guillermo Ruiz-Irastorza[8], Peter J. Maddison[16], Diane L. Kamen[14], S. Sam Lim[3] and Christine A. Peschken[30]. [1]West Hollywood, CA, [2]Timonium, MD, [3]Emory University, Atlanta, GA, [4]Feinstein Institute, Manhasset, NY, [5]Hairmyres Hospital, East Kilbride, United Kingdom, [6]Hanyang University Medical Center, Seoul, Korea, Republic of, [7]Hospital Clinico I Provincial, [8]Hospital de Cruces, Universidad del Pais Vasco, [9]Instituto Nacional Nutricion, Mexico City, DF, Mexico, [10]Kantansspital Schaffhausen, Schaffhausen, Switzerland, [11]Karolinska University Hospital, [12]Landspitalinn University Hospital, [13]Manchester Royal Infirmary, Manchester, United Kingdom, [14]Medical University of South Carolina, Charleston, SC, [15]Montreal General Hospital, Montreal, QC, Canada, [16]North West Wales NHS Trust, Colwyn Bay, United Kingdom, [17]Northwestern University, Chicago, IL, [18]Oklahoma Medical Research Foundation, Oklahoma City, OK, [19]Queen Elizabeth II Health Services Center, Halifax, NS, Canada, [20]SUNY-Downstate Medical Center, Brooklyn, NY, [21]The Rayne Institute, London, United Kingdom, [22]Toronto Western Hospital, Toronto, ON, Canada, [23]UAB Rheumatology, Birmingham, AL, [24]UCL Div of Medicine, London, United Kingdom, [25]UCL Div of Medicine, [26]UCSD School of Medicine, La Jolla, CA, [27]University Hospital Lund, Lund, Sweden, [28]University of Alabama, Oakland, CA, [29]University of Birmingham, Birmingham, United Kingdom, [30]University of Manitoba, Winnipeg, MB, Canada, [31]University of North Carolina at Chapel Hill, Chapel Hill, NC, [32]University of Toronto Lupus Clinic, Toronto Western Hospital, [33]University of Toronto Lupus Clinic, Toronto Western Hospital, Toronto, ON, Canada, [34]West Penn Allegheny Health System, Pittsburgh, PA

A large multicentre multinational inception cohort was established to study risk factors for atherosclerosis (AS) in SLE. We have previously shown that a significant number of atherosclerotic disease risk factors are present within the first year of SLE. This study examines the presence of SLE and atherosclerotic risk factors at inception in a multicenter, international cohort of SLE patients according to ethnic groups and by geographic distribution.

Methods: 30 centres from 11 countries assembled an inception cohort of SLE patients according to a standardized protocol between 2000 and 2010 to study risk factors for atherosclerosis. Simple statistics are provided. Comparisons between ethnic groups and geographic distributions were made using chi square tests and analysis of variance.

Results: Of the inception cohort of 1593 SLE patients 89% were female and age at diagnosis was 35±13 yrs. Patient characteristics were as follows:

Table 1. Distribution by Geographical Area of Residence

	Asia	Canada	Europe	Mexico	USA	P value
N	168 (10.6)	352 (22.1)	425 (26.7)	202 (12.7)	446 (28.0)	
Sex F	89%	89%	91%	90%	88%	0.85
Age at diagnosis	29 ± 10	38 ± 15	37 ± 14	28 ± 9	36 ± 13	<0.0001
SLEDAI-2K	7.4 ± 6.1	6.3 ± 5.6	3.9 ± 5.0	6.8 ± 6.1	4.6 ± 4.5	<0.0001
SDI	0.25 ± 0.70	0.31 ± 0.70	0.16 ± 0.59	0.25 ± 0.56	0.41 ± 0.86	0.009
SF36 PCS	43 ± 8	39 ± 11	39 ± 11	42 ± 10	39 ± 11	<0.0001
MCS	44 ± 11	45 ± 12	44 ± 12	45 ± 12	45 ± 12	0.93
Hypertensive	32%	33%	32%	41%	34%	0.20
Cholesterolemia	35%	41%	31%	36%	37%	0.09
Current Smoker	7%	18%	17%	9%	17%	0.0004
Metabolic Syndrome	8%	12%	11%	25%	15%	<0.0001
Family History of CAD	8%	27%	23%	15%	31%	0.03
Steroids	95%	60%	63%	93%	61%	<0.0001
Antimalarial	73%	73%	64%	48%	68%	<0.0001
Immunosuppressive	50%	35%	35%	65%	33%	<0.0001

Table 2. Distribution by Ethnic Group

	Asian	Black	Caucasian	Hispanic	Other	P value
N	257 (16.2)	247 (15.2)	772 (48.5)	250 (15.7)	65 (4.1)	
Sex F	90%	90%	88%	90%	95%	0.27
Age at diagnosis	30 ± 11	34 ± 11	38 ± 15	29 ± 10	35 ± 14	<0.0001
SLEDAI-2K	7.1 ± 6.1	4.7 ± 5.0	4.5 ± 5.0	6.8 ± 5.9	5.7 ± 4.8	<0.0001
SDI	0.28 ± 0.73	0.37 ± 0.88	0.23 ± 0.60	0.29 ± 0.70	0.26 ± 0.81	0.44
SF36 PCS	42 ± 9	37 ± 11	38 ± 11	40 ± 10	37 ± 11	<0.0001
MCS	45 ± 11	45 ± 12	45 ± 12	44 ± 12	44 ± 11	0.97
Hypertensive	31%	48%	30%	38%	25%	<0.0001
Cholesterolemia	37%	43%	33%	34%	41%	0.06
Current Smoker	7%	13%	20%	9%	27%	<0.0001
Metabolic Syndrome	7%	14%	13%	22%	15%	0.0001
Family History of CAD	18%	32%	24%	23%	46%	0.07
Steroids	89%	79%	53%	88%	67%	<0.0001
Antimalarial	71%	61%	70%	52%	61%	<0.0001
Immunosuppressive	47%	43%	30%	60%	42%	<0.0001

SLEDAI-2K was higher in Asians and Hispanics and also in the geographical areas in which they are a majority. SDI on the other hand is not associated with ethnicity but is higher in the United States. Metabolic syndrome is higher in Mexicans and in Hispanics in general. Hypertension does not show a geographic distribution but is associated with Black ethnicity.

Conclusion: There are differences in the features of SLE and atherosclerotic risk factors at inception when studied by geographic and ethnicity origins. Whether there will be differences in the development of CAD events among these ethnic groups remains to be elucidated.

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Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) Responder Index (SRI)-50: A Valid Index for Measuring Improvement in Disease Activity. Zahi Touma[2], Dafna D. Gladman[1], Dominique Ibañez[2] and Murray B. Urowitz[2]. [1]Toronto Western Hospital, Toronto, ON, Canada, [2]University of Toronto Lupus Clinic, Toronto Western Hospital, Toronto, ON, Canada

Background: We have previously described the development of SRI-50, an index that can describe partial improvement in disease activity between visits in lupus patients.

Objective: To determine whether SRI-50 would capture patients who have improved by ≥50% as determined by physician global assessment (PGA), construct validity of SRI-50 for assessing improvement in disease activity in SLE.

Methods: All patients attending the Lupus Clinic from September 2009 to December 2009 were enrolled in a prospective longitudinal study. Of the 298 patients enrolled 141 had a follow-up visit and were studied further. SLEDAI-2K and SRI-50 scores were determined initially and on a follow-up visit at 1–3 months. During the first visit a PGA was determined on a visual analog scale (VAS) line of 100 mm, with anchors of 0 "no disease activity" and 10 for very active disease". During the follow-up visit a PGA was determined on a 7-point Likert VAS; 7 much, 6 moderately, and 5 slightly improved, 4 unchanged, 3 slightly, 2 moderately, and 1 much worse. We defined a 50% improvement as PGA≥6. An external clinician evaluated patients' records and grouped them on follow-up visit into: improved, same and worse using standardized predefined definitions. The external construct was the Likert VAS. We hypothesized that patients who had ≥50% improvement (PGA≥6) would be captured by SRI-50 and the change in their SRI-50 scores would meet the definition of improvement by SLEDAI (decrease ≥4).

Results: The Characteristic of 141 patients are represented in table 1.

Sex (F/M)		89.4%/10.6%
Race	Caucasian	57.4%
	Black	16.3%
	Asian	9.9%
	Other	16.3%
Age at diagnosis		29.1 ± 11.4 years
Age at 1st visit in study		29.1 ± 11.4 years
Disease duration at 1st visit in study		15.3 ± 11.2 years
Time between baseline and follow-up visits		3.2 ± 1.4 months
SLEDAI-2K at 1st visit in study		4.79 ± 4.67

Patients were assessed as: worse 14, same 65 and improved 62. SRI-50 scores did not decrease below their presenting SLEDAI-2K score in patients who remained stable or worsened. In patients who improved, the SRI-50 score decreased by a mean of −2.40±3.11 while SLEDAI scores did not decrease (Table 2).

Table 2. Statistical results in patients who changed their disease activity

	Worse (n=14)	Same (n=65)	Improved (n=62)
SLEDAI 0	4.43 ± 3.32	3.15 ± 4.16	6.58 ± 4.84
SLEDAI 1	7.29 ± 4.55	2.97 ± 4.03	4.94 ± 4.47
SRI-50	7.21 ± 4.61	2.76 ± 3.86	4.18 ± 4.06
Δ SLEDAI	2.86 ± 3.76	−0.18 ± 2.64	1.65 ± 2.91
Δ SRI-50	2.79 ± 3.79	−0.39 ± 2.74	−2.40 ± 3.11

Δ SLEDAI=SLEDAI 0 - SLEDAI 1
Δ SRI-50=SLEDAI 0 - SRI-50

SRI-50 scores decreased more in patients with PGA≥6 compared to PGA 4–5 with a decrease of ≥4 (r=0.52; p=0.0001). The decrease in SRI-50 scores compared to the decrease in SLEDAI scores were statistically and clinically more significant in patients with PGA≥6 (p <0.0001) compared to those with PGA 4–5 (p=0.003) (Table 3).

Table 3. Change in SLEDAI and SRI-50 scores in patients who improved in association with the external construct

	Δ SLEDAI	Δ SRI-50
PGA 4 (n=15)	−0.33 ± 1.99	−0.47 ± 2.07
PGA 5 (n=20)	−0.95 ± 2.68	−1.50 ± 2.72
PGA 6 (n=20)	−2.40 ± 2.60	−3.80 ± 2.95
PGA 7 (n=7)	−4.29 ± 4.07	−5.14 ± 3.18
r	0.42	0.52
p	0.0009	0.0001
	Improvement (n=62)	
PGA 4–5	−0.69 ± 2.40	−1.06 ± 2.48
PGA ≥ 6	−2.89 ± 3.09	−4.15 ± 3.01
t-test	0.003	<0.0001

Conclusions: These results show that the SRI-50 has construct validity. SRI-50 is able to demonstrate incomplete improvement which would not have been discerned using SLEDAI-2K.

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The Relative Importance of Current Versus Past Use of Medication in Excess Rates of Adverse Cardiovascular Events among Patients with SLE. Michelle A. Petri[1] and Laurence S. Magder[2]. [1]Timonium, MD, [2]Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, Baltimore, MD

Background: Previous studies have suggested that some of the excess risk of adverse cardiovascular events (CVE) in patients with SLE may be due to treatments such as prednisone. Other studies have suggested that treatment with hydroxychloroquine results in reduced risk. In this study, we investigated whether past or current drug exposures have greater association with CVE.

Methods: We examined CVE rates in a large clinical cohort, in subgroups defined by medication history. CVE was defined as myocardial infarction (MI), stroke, coronary procedure, incident angina, or claudication. The analysis was based a data set which had one record per patient-month of participation in the cohort. Each record contained data regarding the clinical history up until that time, the most recently measured levels of disease activity, medications taken at that time, and whether a CVE occurred during that month. This file was analyzed using pooled logistic regression.

Results: 134 CVE events were observed from among 1874 patients who were followed for 9485 person-years during periods between 1987 to 2010. Events included 65 strokes, 27 MI, 29 cases of angina or coronary procedures, and 13 cases of claudication. The table shows rates of CVE in subgroups defined by current and past medication use.

Table. Rates of CVE in Subgroups defined by Current and Past Medication Use

Subgroup	Number of CVE	Rate of CVE per 1000 person-years	Rate Ratios based on a model that adjusts for age (95% CI)	P-value
Prednisone exposure				
None	22	13.3	1.0 (Ref. Group)	
Past (not current)	23	7.9	0.6 (0.4, 1.2)	.14
Currently taking (any dose)	88	18.2	1.6 (1.0, 2.5)	.057
Currently taking >=20 mg/day	25	35.4	4.0 (2.2, 7.1)	<.0001
Plaquenil Use				
None	46	17.9	1.0 (Ref. Group)	
Past (not current)	20	20.3	1.1 (0.7, 1.9)	.65
Currently used but for <6 consec. mo.	14	16.9	1.0 (0.6, 1.9)	.95
Current use, >6 consec. mo	54	10.6	0.5 (0.4, 0.8)	.0019
NSAID Use				
None	51	12.6	1.0 (Ref. Group)	
Past (not current)	42	15.0	1.0 (0.7, 1.6)	.86
Current	41	15.6	1.1 (0.7, 1.6)	.78
Immunosuppresant Use				
None	56	12.1	1.0 (Ref. Group)	
Past (not current)	3	10.1	0.8 (0.2, 2.5)	.67
Current	75	16.5	1.5 (1.0, 2.5)	.31

In multivariable models, cumulative (past) corticosteroid exposure was not associated with CVE after controlling for current use. Similarly, cumulative exposure to hydroxychloroquine was not protective after controlling for current use. Also, in multivariable models, the association between current corticosteroid use and CVE persisted after controlling for the most recent measure of disease activity.

Conclusion: Current (but not past) use of high-dose corticosteroids was associated with high rates of CVE. Current (but not past) use of hydroxychloroquine for 6 or more months was associated with lower rates of CVE. This study strongly supports long-term use of hydroxychloroquine in SLE.

Disclosure: M. A. Petri: None; **L. S. Magder:** None.

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Validation of CLASI Scale with Lupus Disease Activity, Damage, Body Image and Quality of Life. Meenakshi Jolly[1], Rachel A. Mikolaitis[3], Thomas F. Cash[2] and Joel A. Block[2]. [1]Rush University Medical Center, Chicago, IL, [2]Rush University Medical Center, Chicago, IL, [3]Rush University Medical Center

Purpose: Cutaneous Lupus Erythematosus Disease Area &Severity Index (CLASI) has been developed to assess cutaneous activity & damage in Systemic Lupus Erythematosus (SLE). Its validation against SLE disease activity & damage is not known. Also, its association with body image (BI) and quality of Life (QOL) is not known. Herein, we present the results of correlation between CLASI items, CLASI total activity &CLASI total damage with (a) Physician global assessment (PGA), total SLE disease activity & itemized disease activity, (b) Total SLE disease damage (SDI), itemized SLE damage, (c) BI, and (d) QOL.

Methods: CLASI, BILS (body Image in Lupus Screen), BIQLI (body Image Quality of Life Index) and LupusPRO were administered to 14 consenting SLE patients. SLE disease activity & damage were evaluated using SELENA-SLEDAI and SLICC-SDI. Descriptive statistics & correlation analysis were obtained. A p value of ≤ 0.05 on two tailed test was considered significant.

Results: Mean $\pm$ SD age was 45.1 $\pm$ 12.7 yrs. Ninety three percent of participants were women; 71.4% African American, 14.3% Caucasian and 14.3% Hispanic. Mean $\pm$ SD (Median) PGA & SLEDAI score were 1.1 $\pm$0.7 (1.0) &3.7$\pm$4.6 (2). Mean $\pm$ SD (Median) SDI was 1.8$\pm$1.5 (2). Mean $\pm$ SD (Median) CLASI activity and damage scores were 8.3$\pm$4.2 (7) & 8.6$\pm$5.8 (8.5).

Total CLASI activity score correlated with PGA (r 0.62, p=0.03), SLEDAI- proteinuria (r 0.59, p=0.03). CLASI activity item "Ear Scale" correlated with total SLEDAI (r 0.62, p=0.02). CLASI activity items correlated with SLEDAI "rash" included "chest erythema" (r 0.63, p=0.02), & "arms erythema" (r 0.56, p=0.04). Mucous membrane lesions on CLASI correlated with SLEDAI-mucous membrane lesions (r 0.53, p=0.05). Recent hair loss on CLASI correlated with SLEDAI recent hair loss (r 0.60, p=0.02).

Total CLASI damage score correlated with SDI-extensive skin scarring/panniculum (r 0.60, p=0.05). CLASI "nose dys-pigmentation" correlated with SDI "skin ulceration" (p 0.77,p=0.01). "Arms dys-pigmentation" (r 0.61, p =0.05), "arms scarring" (r 0.63, p=0.04), "hands dys-pigmentation" (r 0.69,p=0.02), "hands scarring" (r 0.73, p=0.01) & 'feet dys-pigmentation" (r 0.62, p=0.04) were associated with SDI "skin extensive scarring/panniculum". CLASI 'scalp scarring" correlated with SDI skin scarring/alopecia (r 0.99, p=0.001).

CLASI "face scale" (r −0.56, p=0.04) and "hand scale" (r −0.46, p =0.09) were associated with BILS. CLASI "nose scale" (r −0.56, p=0.04) & "V area neck erythema" (r −0.52, p=0.06) correlated with BIQLI. Overall QOL was inversely associated with "ear Scale" (r −0.50, p=0.07) & "chest erythema" (r −0.51, p=0.06). Poor coping was associated with "nose scale" (r −0.60, p=0.02), "V area of neck erythema" (r −0.58, p=0.03), "posterior neck-shoulders erythema" (r −0.52, p=0.06). Satisfaction with treatment &"Hands scale" (r −0.59, p=0.03) were related.

Conclusions: This is the first study on performance of CLASI against SLE disease activity & damage. CLASI activity and damage scores do correlate with muco-cutaneous manifestations of SLE activity & damage. Data suggest poor QOL (coping and body image) among SLE Patients with cutaneous manifestations of the disease.

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Validity of the ACR Criteria and SLICC Proposed Criteria for the Diagnosis and Classification of Systemic Lupus Erythematosus. Felipe Rodriguez-García[2], Karina Santana- de Anda[2], Ali Duarte-García[1], Virginia Pascual-Ramos[2], Gabriela Hernández-Medina[2], Tatiana Rodríguez-Reyna[2] and Jorge Sanchez-Guerrero[3]. [1]Instituto Nacional ce Ciencias Medicas y Nutricion Salvador Zubiran, [2]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, [3]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico

Objective: To validate the 2007 ACR and the SLICC proposed criteria for the diagnosis and classification of SLE.

Methods: We included 55 patients (Group A) who were hospitalized in our Institute for the diagnosis of systemic manifestations of recent-onset

(<6months). All the patients were evaluated by 2 physicians with specialty in Internal Medicine and who are in-training in Rheumatology. A complete physical examination was done, and pertinent studies were requested according to the medical condition. In all of them, all the tests necessary to evaluate the ACR and SLICC SLE criteria were done. The final diagnosis was established according to the treating physicians after 6 months of the clinical evaluation in order to have the final reports of all studies performed (laboratories, X-ray, pathology, etc) and looking after the stability of the diagnosis. We also included 51 consecutive patients (Group B), participating in a cohort of patients with SLE of recent-onset (<12 months) according to the 1982/2007ACR criteria. In this group we looked for the fulfillment of the proposed SLICC criteria within 6 months of enrollment into the cohort. Finally, 33 patients participating in cohorts of early inflammatory arthritis and Sjögren's syndrome (Group C) were also included.

The validity of the ACR and SLICC criteria for SLE diagnosis was evaluated among the patients in Group A. and the validity for classification among all the patients in the 3 groups.

Results: Patients in group A had a mean (SD) age of 37.3 (17.7) years, and 40 (73%) were females. The main reasons for hospitalization were: chronic fever 16, nephritic/nephrotic syndrome 9, severe weight loss 8, polyarthritis 4, cytopenias 3, lymphadenopathy 2, others 13. Patients in group B had a mean age of 29.9 (8.8) years, and 43 (84%) were females. Patients in group C had a mean age of 40.4 (14.6) years, and 30 (86%) were females.

In group A, 21 (38%) patients were newly diagnosed as SLE, and the observed agreement between both sets of criteria was 87.3, kappa 74.5. Also, among all the patients in the three groups, the observed agreement for SLE classification was 92.2, kappa 84.3.

No significant differences were observed between both sets of criteria in terms of sensitivity (SN), specificity (SP), positive (PPV) and negative predictive value (NPV) for the diagnosis and the classification of SLE (table). Overall, the efficacy of both sets of criteria was inferior for diagnosis than classification.

	SN (95% C.I.)	SP (95% C.I.)	PPV (95% C.I.)	PPV (95% C.I.)
SLE diagnosis				
Group A (n=55)				
ACR Criteria	85.7 (76–95)	82.4 (72–92)	74.5 (63–86)	90.6 (83–98)
SLICC Criteria	90.5 (82.7–98.3)	76.5 (70.8–82.2)	70.0 (58.0–82.0)	93.0 (88.0–99.7)
SLE classification				
Groups A, B, C (n=141)				
ACR Criteria	94.4 (89.2–99.7)	88.4 (80.9–96.0)	89.5 (82.6–96.3)	93.9 (88.0–99.7)
SLICC Criteria	95.8 (91.2–100)	85.5 (77.2–93.8)	87.3 (80.0–94.7)	95.2 (89.8–100)

Conclusion: The efficacy of the current ACR and the proposed SLICC criteria for the diagnosis and classification of SLE patients is similar; however, their utility for diagnosis is inferior to classification.

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Work Disability, Lost Productivity and Associated Risk Factors in Patients Diagnosed with Systemic Lupus Erythematosus (SLE). Tammy O. Utset[5], Barbara M. Segal[6], Laura Trupin[4], Sarika Ogale[1], Ellen Herberich[2] and Kenneth C. Kalunian[3]. [1]Genentech, [2]Harris Interactive, [3]UCSD School of Medicine, La Jolla, CA, [4]University of California, San Francisco, [5]University of Chicago, Chicago, IL, [6]University of Minnesota, Minneapolis, MN

Purpose: To compare self-reported workplace and household productivity, physical function, and symptoms in SLE patients and healthy controls.

Methods: US-based adult ambulatory SLE patients without co-morbid rheumatoid arthritis (RA) completed a questionnaire. Patients gave a similar survey to two age and gender matched friends. Patient and control surveys included The Health and Work Performance Questionnaire (HPQ), Short Form 12 (SF-12), FACIT-Fatigue, Thinking Scale and the Center for Epidemiologic Studies (CESD) Depression Scale. Rheumatologists completed a survey which included the Mexican SLEDAI and a global rating of disease severity over the previous 12 months. Logistic regression was used to study the association between these measures and being unemployed due to health among SLE patients.

Results: 200 patients, and 221 controls have submitted surveys to date. In SLE patients, disease activity as measured by the Mex-SLEDAI had a mean score of 3.5 (median 1.0). Approximately 40% of lupus patients had no activity by the Mex-SLEDAI.

Mean scores for controls were close to the US population on all SF-12 domains (50 points) and on the FACIT-Fatigue (40 points), indicating that the controls in our study had symptom levels representative of the US population.

Patients reported higher levels of pain, fatigue and depression, and lower levels of physical, cognitive and social function, compared with controls (See table).

	MEAN SCORES		
	Patients	Controls	*p*-value
SF-12 [Health Related Quality of Life] ***(Patient n=200; Control n=221)***			
(Range of expected scores 0–100; higher scores indicate better functioning)			
Physical Functioning	34.8	50.3	$p<.01$
Role Limitations - Physical	34.8	49.6	$p<.01$
Role Limitations - Emotional	36.5	47.7	$p<.01$
Vitality	39.0	52.4	$p<.01$
Mental Health	42.2	50.6	$p<.01$
Social Functioning	36.0	49.4	$p<.01$
Pain	35.7	50.9	$p<.01$
General Health	34.7	50.4	$p<.01$
FACIT-F [Fatigue] ***(Patient n=198; Control n=221)***	22.41	41.14	$p<.01$
(Range of expected scores 0–52, higher scores indicate lower fatigue)			
HPQ [Absenteeism & Presenteeism] (Patient n=68; Control n=138)			
Absolute Absenteeism	8.24 hours	−4.26 hours	$p=.14$
(Higher scores indicate a higher amount of absenteeism]			
Absolute Presenteeism	75.07%	85.70%	$p<.01$
(Higher scores indicate a lower amount of lost performance, 100% indicates ideal performance)			
CESD [Depression] ***(Patient n=199; Control n=220)***	13.70	5.87	$p<.01$
(A score of 10 or greater is considered depressed)			
THINK [Cognitive Functioning] ***(Patient n=200; Control n=220)***	39.72	16.34	$p<.01$
(Range of expected scores 0–100, higher scores indicate worse functioning)			
Pain ***(Patient n=198; Control n=212)***	5.2	2.1	$p<.01$
(Range of expected scores 0–10, higher scores indicate worse pain)			

SLE patients were more likely to not be employed nor looking for work, compared to controls (31% vs 4%) and/or on extended sick leave or disability (34% vs. 5%). Among those not employed, 86% of patients report that they were not employed at least in part due to health, in comparison to 16% of controls.

Average absenteeism (time missed from paid work), suggests that patients worked 8 hours less and controls worked 4 hours more than expected by their employer over a 7 day period. Presenteeism (the level of performance while at work), was 75% for SLE patients and 85% for controls, where 100% indicates ideal performance. On average, patients were unable to do housework for 8 days and controls 1.9 days of the last 28 days due to problems with physical or mental health.

In multivariate logistic regression, pain severity (OR= 1.21; $p=0.009$) and depression (OR=1.07; $p=0.024$) were significantly associated with the odds of being unemployed due to health among SLE patients, but fatigue, SLE duration, global severity score and MEX-SLEDAI were not associated with this outcome.

Conclusions: SLE patients report significantly higher burden from symptoms such as pain, fatigue and depression relative to healthy controls. Despite

low disease activity on the Mex-SLEDAI, work and household productivity is lower in SLE patients compared with healthy controls. Higher levels of pain severity and depression increase the likelihood of health-related unemployment in SLE patients.

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ACR Poster Session C
Sjögren's Syndrome
Wednesday, November 10, 2010, 9:00 AM–6:00 PM

1883

Activation of Innate Immunity and Sjögren's Syndrome Development. Seshagiri Rao Nandula[1], Yogesh M. Scindia[2], Harini Bagavant[1] and Umesh S. Deshmukh[2]. [1]University of Virginia, Charlottesville, VA, [2]University of Virginia

Objectives: Previously our laboratory has demonstrated that activation of innate immunity through toll-like receptor 3 (TLR3) agonist poly IC causes an acute loss of salivary gland function. This study was undertaken to investigate the effects of innate immunity activation through TLR dependent and TLR independent pathways on development of Sjögren's Syndrome (SS) in experimental mouse model systems.

Methods: To determine the role of TLR mediated innate immunity activation in SS, female NZB/W F1 mice were injected with TLR3 agonist, poly IC. To investigate TLR independent pathways, female NZM2758 mice were injected with alum, which activates innate immunity through the inflammasome pathway. Submandibular glands (SMG) were analyzed for sialadenitis and lymphocytic infiltrates were characterized by flow cytometry and immunohistochemistry. Gene expression levels of inflammatory cytokines and chemokines were determined by real time PCR. Mice were monitored for salivary gland hypofunction by checking pilocarpine induced saliva flow.

Results: Within 2 weeks of poly IC treatment, the SMG showed evidence for lymphocytic infiltration. The dominant cell types infiltrating the SMG at early stages were NK cells and dendritic cells, which correlated with the chemokine pattern induced by poly IC. At later time points, T-B cell aggregates were seen within the SMG with significantly higher levels of IL-12A, IL-21 and IL-21R gene expression. Characterization of CD4+ T cells within the infiltrates showed presence of ICOS+CXCR5+ cells indicative of the T follicular helper cell phenotype. SMG from poly IC treated mice showed IgM and IgG deposition. Although the severity of sialadenitis increased with time, it did not correlate with loss of function. In the inflammasome mediated innate immunity activation model, mice showed evidence for loss of glandular function by 8–10 weeks after alum treatment. At this time point no lymphocytic foci were seen in the SMG. By 4–5 months, SMG from alum treated mice showed evidence for sialadenitis. Interestingly, this did not translate in to further worsening of glandular function.

Conclusions: Our data clearly demonstrates that activation of innate immunity accelerates the development of SS. Although the characteristics of disease development vary depending upon the innate stimulus, the models reinforce a lack of correlation between extent of of sialadenitis and severity of glandular dysfunction, as observed in SS patients. The ability of alum to induce SS in genetically susceptible mouse strains suggests that exposure to aluminum compounds can be a novel risk factor for SS.

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1884

Anticentromere Antibodies (ACA)-Positive Systemic Sclerosis (SSc) Patients with Sjögren's Syndrome: A Distintict Subset at High Risk of Lymphoma. Chiara Baldini, Sara Grossi, Alessandra Della Rossa, Nicoletta Luciano, Marica Doveri, Antonio Gaetano Tavoni and Stefano Bombardieri. Rheumatology Unit, Department of Internal Medicine, University of Pisa, Italy

Background: Sjögren's syndrome (SS) has been considerably associated with anticentromere positive (ACA)-limited cutaneous subtype Systemic Sclerosis (SSc). Nonetheless, only a few studies have analysed the pattern of clinical expression and disease evolution in ACA-SSc-SS patients.

Objectives: to compare the disease phenotype and clinical evolution of ACA-SSc-sSS patients with (a) patients with ACA-SSc and no SS (ACA-SSc) and (b) patients with primary SS (pSS), in order to verify whether the concomitant association between SS and SSc influence the patients' clinical presentation and outcome.

Patients and Methods: Seventy-eight ACA-SSc-sSS patients (78 F: 0 M; mean age = 62 ± 12, yrs; mean follow-up = 5.4±6, yrs), 127 ACA-SSc patients without SS (119 F: 8 M; mean age = 60 ± 13, yrs; mean follow-up = 4.9±6, yrs), and 374 patients with primary SS (pSS) (363F: 11M; mean age 58± 14, years; mean follow-up = 7.3±6.6 years) who had attended our Unit between 1989 and 2009 were included in the study. Diagnosis of SSc was based on the ARA criteria, while diagnosis of pSS and sSS on AECG criteria. Categorical data were compared using the chi-square test and continuous variables by the Student t-test.

Results: (a)When compared to ACA-SSc, ACA-SSc-sSS patients presented a higher frequency of arthralgias ($p<0.0001$), peripheral nervous involvement ($p=0.006$), and altered laboratory findings ($p<0.0001$) (i.e leukopenia, hypocomplementemia, hypergammaglobulinemia, anti-Ro/SSA, anti-La/SSB, Rheumatoid Factor), in addition to the expected increase of symptoms suggestive for glandular involvement. They also presented a lower frequency of pulmonary hypertension ($p= 0.02$) and sclerodactyly ($p<0.0001$) with 26/78 ACA-SSc-sSS patients versus 11/127 ACA-SSc patients being classified as "sine scleroderma" ($p<0.0001$). Noteworthy, ACA-SSc-sSS also presented a higher frequency of MALT lymphomas ($p=0.0009$) which occurred after a mean disease duration of 19±11 yrs, and was not correlated to skin sclerosis. (b) When compared to pSS patients, ACA-SSc-sSS patients presented a higher frequency of signs and symptoms belonging to the spectrum of SSc ($p<0.0001$), i.e Raynaud's phenomenon, dysphagia, teleangectasias, heart involvement and pulmonary hypertension, but also an increased prevalence of salivary glands enlargement ($p<0.0001$). Altered laboratory findings were also more frequent in pSS patients while no differences were observed for lymphoproliferative disorders ($p=0.09$)

Conclusions: Patients with ACA-SSc-sSS presented features from both diseases: we observed that the presence of SS in ACA-SSc dramatically increased the risk of lymphoma. A careful work up is thus mandatory in the follow-up of ACA-SSc-sSS patients.

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1885

Association between Lymphotoxin Alpha Genetic Variants and Primary Sjögren's Syndrome in Scandinavian Samples. Anne Isine Bolstad[1], Stephanie Le Hellard[2], Gudlaug Thora Kristjansdottir[4], Gunnel Nordmark[4], Lilian Vasaitis[8], Marika Kvarnström[6], Christopher Sjöwall[13], Svein Joar Auglænd Johnsen[9], Per Eriksson[12], Roald Omdal[10], Johan G. Brun[5], Marie Wahren-Helenius[6], Elke Theander[7], Ann-Christine Syvänen[3], Lars Rönnblom[4] and Roland Jonsson[11]. [1]Department of Clinical Dentistry-Periodontics, University of Bergen, Bergen, Norway, [2]Department of Clinical Medicine, University of Bergen, Center of Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen, Norway, [3]Department of Medical Sciences, Molecular Medicine, Uppsala University, Uppsala, Sweden, [4]Department of Medical Sciences, Section of Rheumatology, Uppsala University, Uppsala, Sweden, [5]Department of Medicine, Section of Rheumatology, University of Bergen, Bergen, Norway, [6]Karolinska Institutet, Stockholm, Sweden, [7]Malmö University Hospital, Malmö, Sweden, [8]Section of Rheumatology, Uppsala University, Uppsala, Sweden, [9]Stavanger University Hospital, Stavanger, Norway, [10]Stavanger University Hospital, Stavanger, Norway [11]The Gade Institute, University of Bergen, Bergen, Norway, [12]University Hospital Linköping, Sweden, Linköping, Sweden, [13]University Hospital, Linköping, Linköping, Sweden

Primary Sjögren′s syndrome (pSS) is an autoimmune chronic inflammatory disease characterized by lymphoid infiltrations of exocrine glands and increased levels of autoantibodies against the ribonucleoproteins Ro/SSA and La/SSB. Microarray studies have demonstrated increased gene expression of lymphotoxin beta (*LTB*) in pSS salivary glands. The aim of the present study was to investigate whether single nucleotide polymorphisms (SNPs) in the lymphotoxin alpha (*LTA), LTB* and tumor necrosis factor (*TNF)* gene clusters are associated with pSS.

A total of 527 pSS patients and 532 controls participated in the study. All

of them were of Caucasian origin from Sweden and Norway. Eleven SNP markers were genotyped and analysed for their association with pSS using single marker logistic regression and for genotypic association with a chi square test. Eight markers showed significant association with pSS. The SNP rs909253 in intron 1 of *LTA* showed the strongest association with pSS in both the Norwegian cohort (P = 1.3E-03) and the Swedish cohort (P = 2.6E-05). Importantly, the strength of the association increased (P = 1.3E-07) when the two cohorts were analysed together, showing an odds ratio (OR) of 1.59 [95% CI: 1.34 – 1.89]. When only pSS patients positive for anti-Ro/SSA -La/SSB (n = 381) were compared with the controls, the association with SNP rs909253 was even stronger (P = 4.2E-10, OR 1.82 95% CI: 1.51–2.20). Some SNPs within this locus were also associated with extraglandular manifestations such as high plasma levels of IgG, hypothyroidism, arthritis and leucopenia in pSS patients. In conclusion, a strong association was found between several SNPs in the *LTA* gene locus and pSS, some of which lead to amino acid changes. Our data together with previously published reports suggest a direct role for lymphotoxin alpha in the development of pSS. The importance of this finding for the inflammatory processes in pSS needs further investigation.

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1886

B-Cell Profiling Using Multi-Color Flow Cytometry as Biomarker of Disease Progression in Primary Sjogren's Syndrome (pSS). Mustimbo Roberts[2], Craig Maguire[3], Alex Rosenberg[3], Andreea Coca[2], Jennifer H. Anolik[1] and Iñaki Sanz[2]. [1]University of Rochester, Rochester, NY, [2]University of Rochester Medical Center, Rochester, NY, [3]University of Rochester Medical Center

Purpose: Current classification criteria for pSS are limited in their ability to conclusively diagnose patients with sub-clinical manifestations of disease. To remedy these limitations, we have initiated exploratory studies to identify candidate biomarkers for pSS. Multi-color flow cytometry was used cross-sectionally to identify a B-cell phenotypic signature of pSS and to determine if altered B-cell homeostasis in pSS is a predictive indicator of disease onset and/or progression. These signatures are currently being evaluated for their predictive value in an ongoing longitudinal analysis of patients with sicca symptoms, of no obvious clinical reason, that do not meet American European Consensus Group (AECG) criteria.

Methods: B cells from pSS (n=20), sicca (n=14) and healthy (HC) patients (n=20) were analyzed by multicolor flow cytometry to identify differential memory and transitional B-cell subsets. Clinical parameters were used to examine the relationship of phenotypic abnormalities to disease status using Spearman Correlation. Complex, multidimensional immunological data were analyzed using reduction techniques including Principal Component Analysis (PCA).

Results: We report decreased frequencies of switched (SM) ($p<=0.0001$) and unswitched (UM) ($p<=0.0001$) memory cells, and increased frequencies of IgD-CD27- switched B cells ($p=0.03$) and naïve B cells ($p<=0.0001$) in pSS compared to HC. Additionally, pSS patients exhibit increased frequencies of T1 and T2 transitional B cells compared to HC ($p=0.005$). The increased frequency of T1 and T2 cells correlated significantly with serum levels of BAFF, the main survival factor for transitional cells, which were significantly increased in pSS ($p=0.05$). Similar to pSS, sicca patients also feature decreased frequencies of SM ($p=0.02$) and UM ($p=0.01$) and increased frequencies of naïve B cells ($p=0.02$). Longitudinally, sicca patients with normal UM frequencies at baseline experience a dramatic permanent decline in frequency at 1 year and 2 years of follow-up that precedes a relative expansion in the CD27- memory and naive populations. Of note the decrease of UM cells correlated significantly with increased serum IgG, ESR, and years with sicca symptoms. Of great interest, UM decline preceded in some patients the presence of anti-Ro/La antibodies and decreased salivary function.

Discussion: We have defined a B cell signature of pSS that allows for clustering/differentiation of Sicca patients that share a similar signature that clearly separates them from healthy controls and sicca patients that do not progress to pSS. Clinical parameters—elevated IgG, ESR and reduced C4 also cluster based on pSS B-cell signatures. The reduction of UM frequencies seem to be the first immunologic and permanent sign that Sicca patients may develop pSS. PCA of the complex multidimensional flow cytometric data identify the decrease in UM and increase in CD27- memory cells as the driving parameters of the B-cell signature in pSS. Further longitudinal examination of the pSS B-cell signature in Sicca patients will confirm the predictive value of peripheral blood multicolor flow cytometry as a diagnostic tool in pSS.

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1887

Best Scintigraphic Measures of Parotid Gland Dysfunction in Sjogren's Syndrome. Anthony Keyes[4], Julius Birnbaum[2], John Petronis[1] and Alan N. Baer3. [1]Johns Holins University School of Medicine, [2]Johns Hopkins University, Baltimore, MD, [3]Johns Hopkins University, Baltimore, MD, [4]Johns Hopkins University School of Medicine

Purpose: Parotid gland scintigraphy is utilized to document the oral component of Sjogren's syndrome (SS); however the best parameters of dysfunction have not been defined. We sought to determine which parameters of parotid gland scintigraphy best differentiate patients with SS from those with suspected, but unconfirmed, SS.

Methods: In a 12-month period, 61 patients with suspected or confirmed SS underwent parotid gland scintigraphy in order to document or quantify parotid gland dysfunction. Following evaluation in our clinic, 23 had a confirmed diagnosis of SS according to the American-European Consensus Classification Criteria (AECC), independent of scintigraphy, and 32 had symptoms and/or signs of dry eyes and dry mouth but did not meet classification criteria ("sicca controls"). Five patients could not be classified further and were not included in subsequent analyses. Following an intravenous injection of pertechnetate, dynamic imaging was performed over 60 minutes. Hard lemon candy was provided after an elapse of 45 minutes to stimulate parotid gland excretion. Quantitative parameters of parotid gland parenchymal function included the net uptake ratio (NUR, ratio of maximum count and the count at 60 seconds) and the maximum count time (MCT, time at which the maximum count was reached). The parameter of parotid gland excretion function was the discharge fraction [DF, (pre-stimulus maximum count-post-stimulus minimum count/pre-stimulus maximum count)].

Results: The 56 patients, 50 women and 6 men, had a mean age of 53 ± 14 yrs (SD). Measurements of NUR, MCT, and DF in the right and left parotid (P) glands showed strong correlations in all patients. NUR in the parotid gland had a negative correlation with the duration of dry mouth symptoms in the SS patients (left gland: $r^2=.27$, $p=0.02$; right gland: $r^2=.1$, $p=0.19$) but not in the sicca control patients. There was no correlation between these symptoms and MCT or DF in either group. The mean NUR and DF values for the right and left glands were each significantly lower in the SS patients compared with those of the sicca controls ($p<0.05$, Mann-Whitney test). The SS patient group could be differentiated from the sicca control group, using specific parotid gland scintigraphic parameters, as shown in the Table.

Parameter	Cutoff value	Sensitivity (%)	Specificity (%)	+LR	−LR
Net uptake ratio (%)	≤2	57	88	4.75	0.49
	≤2.5	83	50	1.66	0.34
	≤3	96	31	1.39	0.13
Maximum count time (min)	≤40	43	62	1.13	0.92
	≤42	57	50	1.14	0.86
Discharge fraction (%)	≤40	36	97	12	0.66
	≤50	50	87	3.85	0.57
	≤55	59	77	2.57	0.53
	≤60	73	71	2.52	0.38
Combination	NUR ≤2.5, DF ≤60	68	84	4.25	0.38

+LR= positive likelihood ratio; −LR=negative likelihood ratio

The best individual parameter was a DF of ≤60%, which identified SS patients with 73% sensitivity and 71% specificity. A DF of ≤60%, when combined with a NUR of ≤ 2.5 % identified SS patients with 68% sensitivity and 84% specificity.

Conclusions: Measures of radiotracer uptake and discharge, indicative of parenchymal and excretion function, are each lower in SS patients. A combination of these two parameters achieves the best balance of

sensitivity and specificity in differentiating SS patients from suspected SS patients with sicca symptoms and/or signs who do not meet AECC diagnostic criteria.

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1888

Clinical and Immunological Profile of Patients with Primary Sjogren Syndrome Who Developed B-Cell Lymphoma. Analysis of 1010 Spanish Patients (The GEMESS Cohort). Manuel Ramos-Casals[3], Roser Solans[11], Jose Rosas[6], Maria Teresa Camps[2], Antonio Gil[9], Javier Del-Pino[10], Carmen Hidalgo[12], Jaime Calvo[4], Maria Luisa Mico[8], Roberto Perez-Alvarez[7], Rafael Belenguer[1] and Lucio Pallares[5]. [1]Hospital 9 d'Octubre, València, Spain, [2]Hospital Carlos Haya, Malaga, Spain, [3]Hospital Clinic, Barcelona, Spain, [4]Hospital de Sierrallana, Torrelavega, Spain, [5]Hospital de Son Dureta, Palma de Mallorca, Spain, [6]Hospital de Vilajoyosa, Alicante, Spain, [7]Hospital do Meixoeiro, Vigo, Spain, [8]Hospital La Fe, Valencia, Spain, [9]Hospital La Paz, Madrid, Spain, [10]Hospital Universitario de Salamanca, Salamanca, Spain, [11]Hospital Vall d'Hebron, Barcelona, Spain, [12]Hospital Virgen de las Nieves, Granada, Spain

Objective: To analyse the epidemiological, clinical and analytical features related to the development of B-cell lymphoma in a large cohort of Spanish patients with primary Sjogren syndrome (SS).

PATIENTS. The GEMESS Study Group was formed in 2005 with the aim of collecting a large series of Spanish patients with primary SS, and included twelve Spanish reference centers with substantial experience in the management of SS patients. By March 2007, the database included 1010 consecutive patients, recruited since 1994.

Results: The cohort consisted of 1010 patients, including 937 (93%) women and 73 (7%) men (female:male ratio, 13:1), with a mean age at diagnosis of 53.0 + 0.48 years (range, 14–88) and of 58.7 + 0.46 years (range, 16–94) at inclusion in the Registry. Twenty-six (2.57%) patients developed B-cell lymphoma. There were 22 (85%) women and 4 (15%) men, with a mean age of 59 years at diagnosis of lymphoma and a length of SS evolution of 6 years from SS diagnosis to lymphoma diagnosis. Patients with B-cell lymphoma had a higher prevalence of vasculitis (23% vs 9%, $p=0.024$), lung involvement (31% vs 11%, $p=0.005$), anemia (38% vs 17%, $p=0.015$), leukopenia (38% vs 15%, $p=0.004$), thrombocytopenia (42% vs 12%, $p<0.001$) and low C3/C4 levels (42% vs 13%, $p=0.001$) in comparison with patients without lymphoma. Multivariate analysis adjusted by age, gender and length of SS evolution identified lung involvement ($p=0.022$), thrombocytopenia ($p<0.001$) and low C3/C4 levels ($p=0.004$) as significant independent variables related to B-cell lymphoma.

Conclusion: We identified a specific clinical and immunological profile (vasculitic and pulmonary involvement, cytopenias and hypocomplementemia) in patients with primary SS who developed B-cell lymphoma. The adjusted multivariate model confirmed the close association with low C3/C4 levels reported in previous series and identified as new factors associated with B-cell lymphoma lung involvement and thrombocytopenia in patients with primary SS.

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1889

Clonal Analysis of Ig-Expressing Cells in Salivary Glands of Primary Sjögren's Syndrome Patients after Anti-CD20 Treatment. Nishath Hamza[3], Hendrika Bootsma[4], Rodney P. E. Pollard[2], Jiska M. Meijer[2], Fred K. L. Spijkervet[2], Arjan Vissink[2], Hans G. M. Burgerhof[5], Frans G. M. Kroese[1], Cees G. M. Kallenberg[4] and Nicolaas A. Bos[1]. [1]Dept. of Cell Biology, Immunology Section, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, [2]Dept. of Oral and Maxillofacial Surgery, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, [3]Dept. of Rheumatology and Clinical Immunology & Dept. of Cell Biology, Immunology Section, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, [4]Dept. of Rheumatology and Clinical Immunology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, [5]University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Background: B cell depletion by anti-CD20 treatment with Rituximab (RTX) has been shown to be clinically effective in patients with primary Sjögren's syndrome (pSS) suggesting a role for B cells in the pathogenesis. The effect of RTX on the B cell repertoire in salivary glands is largely unknown. This study investigated clonal relationships of IgA & IgG expressing cells that are present within salivary glands of patients before and after treatment with RTX.

Methods: Parotid salivary gland biopsies were taken from 7 immunesuppressed naive pSS patients before treatment and at 12 weeks after treatment [5 RTX and 2 placebo (PL)] and at 36 weeks after treatment (for 5 RTX patients only). All RTX patients improved clinically after treatment. Variable immunoglobulin heavy-chain gene (IGHV) cloning and sequence analysis were carried out on RNA extracted from each parotid biopsy, using a primer specific for IGHV-3 genes in combination with constant region primers for IgA and IgG isotypes.

Results: In total 747 unique Ig sequences were analyzed. Clonally related sequences were identified in biopsies of 4/5 RTX patients before and 12 weeks after RTX when there is complete depletion of B cells in the peripheral blood. Even at 36 weeks after RTX when B cells reappeared in the blood, sequences clonally related to the sequences before RTX were found. In one RTX patient a single clone set was found at all time points. Clonally related sets of sequences expressing IgA and/or IgG isotypes at different timepoints were observed. The same pattern was also seen in different biopsies of each patient in the PL-treated patient group.

Strikingly, in 3/5 RTX patients, significantly more non-unique (redundant) sequences were seen at 36 weeks after RTX compared to baseline (Fisher's exact test, $p \leq 0.01$).

The occurrence of Vh3–23 and Vh3–30 genes were found to be quite high at all timepoints in both PL and RTX patients.

Conclusions: In this study we show the presence of clonally related Ig sequences from parotid gland biopsies of pSS patients before and after RTX. These data indicate the persistence of some B cell clones despite RTX treatment. Furthermore, the diversity of the IgA and IgG repertoire becomes progressively more restricted with time after RTX, suggesting selective advantage for certain B cell clones. The high frequency of Vh3–23 and Vh3–30 genes seen in all pSS patients studied here, has also been previously noted in other autoimmune disorders. This study indicates that the selective persistence of particular B cell clones may contribute to the disease relapse and manifestations of the disease after RTX.

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Correlation of Serum BAFF and Markers of B-Cell Activation with Systemic Involvement Assessed by the EULAR Sjögren's Syndrome Disease Activity Index: Results from the ASSESS Prospective Cohort. Jacques-Eric Gottenberg[16], Raphaele Seror[2], Joelle Benessiano[3], Karine Inamo[2], Philippe Dieude[3], Jean-Jacques Dubost[5], Anne-Laure Fauchais[11], Eric Hachulla[10], Claire Larroche[1], Veronique Le Guern[6], Jacques Morel[12], Aleth Perdriger[14], Xavier Puéchal[9], Stéphanie Rist[13], Alain Saraux[4], Damien Sene[7], Jean Sibilia[16], Olivier Vittecoq[15], Charles Zarnitsky[8], Philippe Ravaud[3] and Xavier Mariette[2]. [1]Avicenne Hospital, [2]Bicetre Hospital, [3]Bichat Hospital, [4]Brest Hospital, [5]Clermont-Ferrand Hospital, [6]Cochin Hospital, [7]La Pitié Hospital, [8]Le Havre Hospital, [9]Le Mans Hospital, [10]Lille Hospital, [11]Limoges Hospital, [12]Montpellier Hospital, [13]Orleans Hospital, [14]Rennes Hospital, [15]Rouen Hospital, [16]Strasbourg Hospital

Objectives: In primary Sjögren's syndrome (pSS), systemic disease activity might result from the stimulation of autoreactive B lymphocytes. Thus, markers of B-cell activation could be useful in the clinical assessment of the disease. However, due to the lack of consensual disease activity score and of prospective cohorts, the only available studies are retrospective and evaluated disease activity only by the presence/absence of extraglandular involvement. A multinational consensual disease activity score was recently established, the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI). We therefore investigated the correlation between markers of B-cell activation and the ESSDAI at enrollment in a multicenter prospective cohort of patients with pSS.

Methods: 15 centers of Rheumatology and Internal Medicine have included patients with pSS according to AECG criteria in the "Assessment of Systemic Signs and Evolution of Sjögren's Syndrome" (ASSESS) 5-year prospective cohort since May 2006. At enrollment, clinical data, ESSDAI disease activity and serum are collected and centralized. Serum IgG, A, M,

beta2-microglobulin and kappa and lambda free light chains (FLCs) of immunoglobulins were assessed at enrollment using nephelometry and B-cell activating factor of the TNF family (BAFF) was assessed using ELISA.

Results: In the 349 analyzed patients (women: 93.7%), mean age and disease duration were 60.5 ± 12.6 years and 9 ± 5.9 years (1st quartile: 5 years), respectively. Anti-SSA antibody was detected in 60.2% of patients, anti-SSB in 35.2% of patients. 189 patients (54.9%) had records of systemic involvement at enrollment, including 19 patients (5.4%) with previous lymphoma. Median BAFF and beta2microglobulin at enrollment were higher in patients with a history of lymphoma (1187.7 vs 893.3 pg/ml, P= 0.002 and 2.6 vs 2.1 mg/l, P= 0.01, respectively).

At inclusion, 31.8% of patients had features of systemic involvement. Median ESSDAI at enrollment, analyzed in 324 patients, was 4 (25^{th} –75^{th}: 1–9).

At inclusion, patients with anti-SSA/SSB had a significantly higher ESSDAI (4[2–9] vs 2[0–6.6] in patients without anti-SSA/SSB, P=0.04). The ESSDAI score at enrollment was significantly correlated with total IgG (r=0.11, P= 0.05), kappa FLCs (r=0.22, P<0.0001), beta2-microglobulin (r=0.2, P=0.0003) and BAFF (r=0.14, P=0.015). Patients with an ESSDAI score greater than 4 had significantly more frequently increased levels of BAFF (>908.8 pg/ml, 75^{th} value in the cohort, 31.5% of increased levels vs 18.3% in patients with an ESSDAI≤4, P=0.009), kappa FLC (>19.4 mg/l, 32.7% vs 15.7%, P= 0.0005), and beta2-microglobulin (>2.34 mg/l, 46.8% vs 25.5%, P= 0.0001)

Conclusion: In pSS, disease activity assessed by the ESSDAI is correlated with serum levels of BAFF, a pivotal B-cell activating cytokine, and markers of B-cell activation (anti-SSA/SSB, kappa FLCs, and beta2-microgobulin). Prospective follow-up in the ASSESS cohort will allow to determine whether these markers predict new systemic complications of the disease, including lymphomas.

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Detection of HTLV-1 p19 Protein in Labial Salivary Glands from Patients with Sjögren's Syndrome: A Distinct Clinical Subgroup? Sung-Ji Lee[1], Seong-Rye Seo[1], Tae-Jong Kim[1], Yong-Wook Park[1] and Shin-Seok Lee[2]. [1]Chonnam National University Medical School, [2]Chonnam Natl Univ Med School, Gwangju, Korea, Republic of

Purpose: Etiologically, human T-cell lymphotropic virus type 1 (HTLV-1) is associated with two major diseases: adult T-cell leukemia and HTLV-1-associated myelopathy-tropical spastic paraparesis. Of interest, recent studies have suggested that HTLV-1 is involved in the pathogenesis of Sjögren's syndrome (SS). However, the clinical and serological differences in SS patients with and without this infection are not well characterized. Therefore, we examined whether SS patients could be distinguished based on the expression of HTLV-1 p19 protein and, if so, whether the subgroups differ in their clinical features and serological parameters.

Methods: The polymerase chain reaction was used to amplify viral DNA from peripheral blood mononuclear cells (PBMCs) in 54 patients with SS, using primers from the HTLV-1 p19 region and minor salivary gland (MSG) biopsy specimens from 33 SS patients who were examined for the presence of HTLV-1 p19 genes immunohistochemically. The sociodemographic, glandular, and extraglandular manifestations, and laboratory findings including autoantibodies, complements, and immunoglobulin levels, were analyzed.

Results: The HTLV-1 p19 gene was not detected in PBMC samples from 54 patients, while HTLV-1 p19 protein was expressed immunohistochemically in MSG specimens in 10 out of 33 SS patients (30.3%). On separating the SS patients into two groups based on HTLV-1 p19-positive immunohistochemistry, the p19-positive patients had lower anti-Ro/SS-A titers, rheumatoid factor, and C3 levels, and higher lymphocyte counts than the p19-negative patients (p=0.049, p=0.014, p=0.018, and p<0.001, respectively). The prevalence of glandular and extraglandular manifestations, including dryness of the eyes and mouth, enlargement of the parotid gland, photosensitivity, swollen hands, Raynaud's phenomenon, arthralgia, lymphadenopathy, renal disease, psychosis, interstitial lung disease, peripheral neuropathy, and autoimmune thyroid disease, did not differ between the p19-positive and p19-negative patients.

Conclusions: Our findings suggest that the presence of HTLV-1 p19 in the salivary gland is involved in the pathogenesis of a subpopulation of SS, and HTLV-1-associated SS could have different immunological patterns compared to idiopathic SS, raising the possibility that HTLV-1 p19 is a marker of a pathogenetically distinct form of SS.

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Effect of Rituximab Treatment on BAFF Levels in Patients with Primary Sjögren's Syndrome: A Placebo-Controlled Clinical Trial. Rodney Pollard[2], Wayel Abdulahad[2], Jiska Meijer[2], Frans Kroese[2], Fred Spijkervet[2], Cees Kallenberg[1], Arjan Vissink[2] and Hendrika Bootsma[2]. [1]Univer Med Center Groningen, Groningen, The Netherlands, [2]Univer Med Center Groningen

Objective: To assess the effect of rituximab (anti-CD20) treatment on B-cell activating factor (BAFF) levels in patients with primary Sjögren's syndrome (pSS).

Background: pSS is a systemic autoimmune disease characterized by mononuclear infiltrates of B-and T-cells in exocrine glands eventually leading to destruction of these glands. B-cell activating factor (BAFF), a member of the tumor necrosis factor (TNF)-ligand family, is essential for the control of B-cell maturation and survival.

Methods: In a randomised double-blinded placebo-controlled trial patients were treated on days 1 and 15 with either rituximab (n= 20) or placebo (n= 10). To minimise side effects (infusion reactions, serum sickness), all patients were pre-medicated with methylprednisolone and oral prednisone. Fresh blood samples were collected at various time points (before, 5, 12, 36 and 48 weeks following treatment). In addition, age- and sex-matched blood samples were collected from healthy controls (n=10). BAFF levels were assessed by Enzyme-Linked Immunosorbent Assay (R&D Systems). In addition, percentages and numbers of B-cell subsets were examined by four-color cytometry.

Results: Depletion of B-cells was observed in the rituximab treated group after infusion, while B-cell levels remained unchanged after placebo treatment. B-cells reappeared in the rituximab treated group within 24 to 48 weeks after treatment. Repopulation of the B-cell compartment started with reappearance of transitional B-cells, followed by naïve B-cells, and a relative late recovery of memory B-cells. At baseline, BAFF levels were significantly increased in all pSS-patients in comparison to healthy controls.

Placebo-treated patients showed a slight (0.5 fold, p<0.05), but significant, increase in BAFF levels only at week 5, likely due to methylprednisolone administration.

Strikingly, long-term elevated levels of BAFF (3.0–4.0 fold, p<0.05) were observed during 36 weeks following rituximab-treatment. By week 48, BAFF levels had reached baseline values in rituximab treated group.

Conclusion: These preliminary data show a sharp increase in BAFF levels after rituximab therapy. These levels appear to correlate negatively with the presence of B-cells in the peripheral blood. BAFF could be involved in the pathogenesis of SS, possibly by triggering the activation of self-antigen-driven autoimmune B-cells. Since BAFF levels are much higher after rituximab treatment, this may also have implications for manifestations of the disease, related to therapy. This observation might be important for treatment strategies with biologicals like anti-BAFF and /or B-cell depletion. Extended data are in progress and can be presented at the ACR meeting.

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Efficacy of Rituximab in Primary Sjogren's Syndrome with Peripheral Nervous System Involvement: Results from the French AIR Registry. Arsene Mekinian[6], Eric Hachulla[9], Claire Larroche[2], Jean Leone[11], Bruno Gomberg[7], Mohamed Hamidou[8], Alain G. Cantagrel[5], Christian Marcelli[4], Stephanie Rist[10], Maxime A. Breban[1], Olivier Fain[6], Jacques E. Gottenberg[12] and Xavier Mariette[3]. [1]Courbevoie, France, [2]Avicenne Hospital, [3]Bicetre Hospital/Paris Univ, Le Kremlin Bicetre, France, [4]Caen Hospital, [5]Hopital Purpan, Toulouse, France, [6]Jean Verdier Hospital, [7]La Rochelle Hospital, [8]Nantes Hospital, [9]National Scleroderma Centre, Lille Cedex, France, [10]Orleans Hospital, [11]Reims Hospital, [12]Strasbourg Hospitals, Strasbourg, France

Purpose: To evaluate the efficacy of Rituximab in primary Sjogren'syndrome with peripheral nervous system involvement.

Methods: Prospective data from patients with primary Sjogren's syndrome and peripheral nervous involvement included in the French AutoImmunity and Rituximab (AIR) registry, were analyzed. Peripheral nervous involvement was defined by clinical signs of peripheral neuropathy confirmed by nerve conduction study. Vasculitis was defined by the presence positive neuromuscular biopsy and/or of purpura. Neurological response to Rituximab was defined by the clinician in charge of the patient.

Results: Seventeen patients (median age 63 years [31–82], 14 female sexes) with Sjogren's syndrome and peripheral nervous involvement received treatment by Rituximab. The median duration of Sjogren's syndrome was 10 years [2–26]. Median baseline ESSDAI index was 18 [10–44], joint and cutaneous involvement were present in 7 cases each. Neurological features were sensory neuropathy (n=3), axonal sensory-motor neuropathy (n=12) and multiple mononeuropathy (n=2). Twelve patients have been treated by another immunosuppressor before Rituximab and 10 patients were on corticoids. Other immunosuppressive treatment was associated to Rituximab in 5 cases (methotrexate in 2 cases, mycophénolate mofetil, azathioprine and plasma exchange in 1 case each).

Cryoglobulinemia was present in 9/17 cases (53%) and in these 9 patients neuropathy was considered to be related to the cryoglobulinemia (axonal sensory-motor neuropathy in 7 cases and multiple mononeuropathy in 2 case). Patients with cryoglobulinemia were significantly younger (56 vs 76 years; p=0.02), had more important ESSDAI (24 vs 14; p=0.003), and more profound hypocomplementia (p=0.0001). Vasculitis (defined by biopsy (n=2) or purpura (n=5)) was present in 7/17 patients (41%), and 6/7 (86%) had cryoglobulinemic vasculitis.

Neurological improvement was noted in 11 patients (65%) at 3 months and persisted in 9 cases (53%) at 6 months. Median ESSDAI index was 11 [7–21] at 3 month with joint and skin improvement in 9/12 cases each. Rituximab was effective at 3 month in 9/10 cases (90%) with vasculitis and/or cryoglobulinemia, and in 2/7 cases (29%) in the absence of cryoglobulinemia and vasculitis (p=0.03). Among responders to Rituximab, 4 (36%) experienced a relapse, and 3 of them responded after retreatment with Rituximab.

Conclusion: Rituximab could be effective in peripheral nervous system involvement of patients with primary Sjogren'syndrome, in particular when related to cryoglobulinemia or vasculitis.

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Efficacy of Rituximab in Primary Sjogren's Syndrome with Central Nervous System Involvement: Results from the French AIR Registry. Arsene Mekinian[4], Claire Larroche[1], Eric Hachulla[7], Bruno Gomberg[6], Claire Blanchard-Delaunay[8], Alain G. Cantagrel[3], Olivier Fain[5], Jean Sibilia[9], Jacques E. Gottenberg[10] and Xavier Mariette[2]. [1]Avicenne Hospital, [2]Bicetre Hospital/Paris Univ, Le Kremlin Bicetre, France, [3]Hopital Purpan, Toulouse, France, [4]Jean Verdier Hospital, [5]Jean Verdier Hospital, [6]La Rochelle Hospital, [7]National Scleroderma Centre, Lille Cedex, France, [8]Niort Hospital, [9]Strasbourg Hospital, [10]Strasbourg Hospitals, Strasbourg, France

Purpose: To evaluate the efficacy of Rituximab in primary Sjogren's syndrome with central nervous system (CNS) involvement.

Methods: Prospective data from patients with primary Sjogren's syndrome and CNS involvement included in the French AutoImmunity and Rituximab (AIR) registry were analyzed. CNS involvement was defined by the presence of central nervous impairment associated with diffuse white matter T2-weigted hypersignal in the exclusion of other aetiologies. Neurological response was defined as complete disappearance of neurological impairment, or improvement of subjective and/or clinical signs. Expanding Disability Status Scale (EDSS) was used as previously defined.

Results: Eleven patients (median age 57 years [42–81], 10 female sexes) with Sjogren's syndrome and central nervous involvement received treatment by Rituximab. The median duration of Sjogren's syndrome was 8 years [3–23]. Median baseline ESSDAI index was 17 [5–25]. Articular involvement was present in 4 cases, cutaneous in 2 cases, biological and haematological involvements in 6 and 4 cases respectively. Neurological features were progressive multiple sclerosis-like manifestations in 8 patients, anxiety and depression disorder in 1 patient and cognitive dysfunction in 2 cases. Median EDSS score before Rituximab was 4 [2–6]. Magnetic resonance imaging showed white matter abnormalities in all cases.

Rituximab was indicated for neurological involvement in all cases. Other immunosuppressive treatment was associated with Rituximab in 4 cases (cyclophosphamide in 3 cases and mycophenolate mofetil in 1 case). The median number of post-rituximab visits was 3 [1–5]. No neurological modification was noted in the 7 patients with multiple sclerosis-like symptoms and 2 patients with cognitive dysfunction at 3, 6 and 9 months visits. EDSS score was 3.5 [2–6], 3.3 [2–6.5] and 4.5 [2–6.5] at 3, 6 and 9 months respectively. One patient with depression disclosed subjective improvement. One patient with myelitis which has been treated before Rituximab by cyclophosphamide had improvement of his walk perimeter (160 meters versus 116). Median ESSDAI index was 15 [5–19] at 3 month with articular and cutaneous improvement in all cases.

Conclusion: Rituximab is not effective in CNS progressive multiple sclerosis-like manifestations of patients with primary Sjogren'syndrome.

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Epitope Mapping of the Autoantigen Aquaporin-4 Reveals Linear Epitopes Located in the Intracellular Region of the Molecule. Eleni I. Kabylafka[1], John G. Routsias[1], Haralampos Alexopoulos[1] and Athanasios G. Tzioufas[2]. [1]Department of Pathophysiology, Medical School of Athens, Athens, Greece, [2]Medical School-Univ of Athens, Athens, Greece

Background: Autoantibodies to aquaporin-4 (AQP4), a water channel localized in astrocytic foot processes at the blood-brain barrier, have been shown to correlate with Neuromyelitis Optica (Devic's syndrome), a rare syndrome. The main symptoms of the syndrome are optic neuritis and myelitis. The latter can be found in the context of a systemic autoimmune disease, such as Systemic Lupus Erythematosus (SLE), and primary Sjögren's syndrome (pSS). Despite the fact that anti-AQP4 antibodies have an established role in the pathogenesis of Neuromyelitis Optica, their fine specificity and regulation of their production has not been clarified. The aim of the present study was to identify the B cell linear epitopes of the AQP4 protein, investigate putative similarities with other molecules and evaluate the sensitivity and specificity in detecting anti-AQP4 autoantibodies.

Methods: Sera from 21 patients with Devic's syndrome, all positive for anti-AQP4 antibodies using indirect immunofluorescence in mouse brain tissue, were used. Sera from 23 SLE and 23 pSS patients, without neurologic involvement were utilized as disease controls. 26 healthy individuals were also used. 11 overlapping peptides, spanning the entire intracellular and extracellular domains of the AQP4 molecule, were synthesized (Bio-synthesis Inc, U.S.A.), and all sera were screened by ELISA for the presence of antibodies against the peptides. The cut-off values for each peptide assay were determined using the mean OD plus 2 SD of sera from 26 healthy controls. Specificity was evaluated by homologous inhibition assays.

Results: Reactivity against 3 different peptides spanning the sequences aa1–22 [MSDRPTARRWGKCGPLCTRENI], aa88–113 [FGHISGGHINPAVTVAMVCTRKISIA] and aa252–275 [FCPDVEFKRRFKEAFSKAAQQTKG] was demonstrated in 33%, 24% and 24% of sera from Devic's patients, respectively, while 38% of patients' sera were reactive against at least one of the 3 peptides. All epitopes were localized in the intracellular domains of AQP4. A 73% sequence similarity was observed between the [aa252–275] peptide (amino acids 257–271), and the aa219–233 domain of the Tax-1 HTLV-1 protein, which appears to play a pathogenetic role for spastic paraparesis. None of healthy controls showed any reactivity. Homologous inhibition assays produced high inhibition rates (84.3%, 71.1% and 84% for peptides aa1–22, aa88–113 and aa252–275, respectively). SLE patients tested positive for antibodies against peptides aa1–22, aa88–113 and aa252–275 in 8.6%, 0% and 8.6%, respectively, while pSS patients recognized the above peptides in 8.6%, 4.3% and 8.6%.

Conclusions: This is the first epitope mapping of the autoantigen AQP4. Most of antibodies to AQP4 are directed against conformational epitopes but a significant proportion targets certain linear epitopes, located in the intracellular domains of the molecule. Future studies in our laboratory are aiming to determine the pathogenic relevance of these epitopes.

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EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI): Development of a Consensus Patient Index for Primary Sjögren's Syndrome. Raphaèle Seror[5], Philippe Ravaud[13], Xavier Mariette[4], Hendrika Bootsma[18], Elke Theander[9], Arne Hansen[3], Manel Ramos-Casals[1], Thomas Dörner[3], Stefano Bombardieri[20], Eric Hachulla[11], Johan G. Brun[17], Aike A. Kruize[19], Sonja Praprotnik[14], Matija Tomsic[14], Jacques E. Gottenberg[12], Valerie Devauchelle[6], Salvatore Devita[16], Cristina Vollenweider[8], Thomas Mandl[9], Athanasios G. Tzioufas[10], Steven E. Carsons[22], Alain Saraux[7], Nurhan Sutcliffe[2], Claudio Vitali[21], Simon J. Bowman[15] and The EULAR Sjögren's Task Force. "Josep Font", Hospital Barcelona, [2]Barts & The Royal London Hospital, [3]Berlin Charité, University Hospital, [4]Bicetre Hospital/Paris Univ, Le Kremlin Bicetre, France, [5]Bicetre Hospital/Paris Univ, Le Kremlin Bicetre, France, [6]CHU de la Cavale Blanche, [7]CHU de la Cavale Blanche, Brest Cedex, France, [8]German Hospital, Buenos-Aires, [9]Malmö University Hospital, [10]Medical School-Univ of Athens, Athens, Greece, [11]National Scleroderma Centre, Lille Cedex, France, [12]Strasbourg Hospitals, Strasbourg, France, [13]Université Paris Descartes, [14]University Clinical Centre of Ljubljana, [15]University Hospital Birmingham NHS Foundation, [16]University Hospital of Udine, [17]University Hospital, Bergen, [18]University Medical Center Groningen, [19]University Medical Center Utrecht, [20]University of Pisa, [21]Villamarina Hospital, [22]Winthrop Univ Hospital, Mineola, NY

Background: We previously developed a score to assess disease activity in patients with systemic complications of primary Sjögren's syndrome (SS): the ESSDAI.

Objectives: We now aim to develop a second score a disease-specifi patient-reported outcomes, complementary to ESSDAI, to assess patients' symptoms: the EULAR Sjögren's Syndrome Patient reported Index (ESSPRI).

Methods: Based on studies developing the Sicca Symptoms Inventory (SSI) and the Profile of Fatigue and Discomfort (PROFAD), dryness, limb pain, mental and physical fatigue were selected as the main relevant symptoms for primary SS patients. It was suspected that, compared to these long questionnaires, a single 0–10 numerical scale for each of these 4 domains would be sufficient to assess these symptoms. These 4 scales were gathered to form the ESSPRI. Patients were included in 12 different countries by 21 SS experts participating in this international collaborative project promoted by EULAR. All patients completed the ESSPRI, SSI and PROFAD questionnaires and a 0–10 patient global assessment (PGA). Correlations between domains, dryness features and PGA were obtained. Multiple regression modelling, using PGA as the dependent variable, was used to select domains and estimate their weights, and construct the ESSPRI.

Results: 230 primary SS patients (mean age = 55.9 ± 13.9 yrs, 219 [95.6%] females, mean disease duration = 8.3 ± 5.6 yrs, 184 [80.0%] anti-SSA and/or SSB positive) were included. In univariate analysis, PGA had good correlation with dryness, pain, mental and physical fatigue (rho: 0.50 to 0.58, all $p<0.0001$), but was less correlated with each separate dryness feature (rho: 0.38 to 0.48) except ocular dryness (rho=0.54). In multivariate analysis, dryness, pain and physical fatigue, but not mental fatigue, were significantly associated with PGA; weights derived from the regression coefficients were identical for these 3 domains ($R^2=0.49$). Thus, we redefined ESSPRI as the mean of the 3 scales (dryness, limb pain and physical fatigue). Correlation with PGA (rho) was, 0.70, 0.66 and 0.56 for ESSPRI, PROFAD and SSI, respectively. Last ESSPRI correlated with PROFAD (rho=0.73) and with SSI (rho=0.66).

Conclusion: ESSPRI is a patient index designed to measure patients' symptoms in primary SS. This very simple index has good construct validity when PGA is considered as the gold standard and good correlations with more complicated validated indexes: SSI and PROFAD. ESSPRI and ESSDAI are currently being evaluated for sensitivity to change and validated in order to be used as an outcome measure in clinical trials.

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Evolution of Autoimmune Minor Salivary Gland (MSG) Lesions in Sjögren's Syndrome (SS). Efstathia K. Kapsogeorgou[3], Maria I. Christodoulou[4], Demosthenes B. Panagiotakos[2], Spyros Paikos[1] and Haralampos M. Moutsopoulos[4]. [1]Dental Department, "Laikon" General Hospital of Athens, Athens, Greece, [2]Dietetics and Nutrition Dept, Harokopio University of Athens, [3]Pathophysiology Dept, School of Medicine, National University of Athens, Athens, Attica, Greece, [4]Pathophysiology Dept, School of Medicine, National University of Athens, Athens, Greece

Purpose: The MSG lesions of SS patients extend from mild to severe. The prevalence of certain types of infiltrating mononuclear cells (MNC), including total T cells and their subpopulations, B cells, macrophages (MΦ) and interdigitating dendritic cells (iDC) varies according to lesion severity. MSG lesions are generally thought to develop stepwise, starting from mild infiltrates that progress through time. However, studies of sequential biopsies evaluating this progress are missing. The aim of this study was to evaluate repetitive MSG samples of SS patients and define the evolution of the grade and composition of lesions through time.

Methods: 28 SS patients, which agreed to perform second MSG biopsy, were studied. In 24 patients, the first biopsy had been performed at diagnosis. The median interval (range) between the two sequential biopsies was 55 (30–110) months. The evolution of the grade of MSG lesions was evaluated by the number of lymphocytic foci/4 mm^2 of tissue (biopsy focus score), Tarpley score and the number of total infiltrating MNC/mm^2-tissue. The percentage of total T, $CD4^+$ T, $CD8^+$ T, Treg and B cells, MΦ, iDC, follicular DC (fDC) and natural killer (NK) cells to total infiltrating MNC was analyzed immunohistochemically in the entire tissue. General linear model for repeated measures adjusted for biopsy time interval and non-parametric Wilcoxon test for paired observations were used.

Results: The biopsy focus score was found to change in 4 patients [1^{st} - 2^{nd} biopsy focus score (%-change): 8.2–11.4 (39), 1.8–3.1 (71), 4.0–11.6 (190) and 6.9–2.0 (−71)]; in two of them was followed by a change in Tarpley score (from 3+ to 4+ and 3+ to 2+, respectively). The number of infiltrating MNC/mm^2-tissue was found to increase in 7 patients (% increase: 37, 38, 48, 70, 89, 185 and 204) and reduce in 2 patients (% decrease: 62 and 68). This progression was not found to associate with biopsy time interval, incidence of the various inflammatory cell types, other histological, demographic and clinical features or therapy. Statistical analysis of all SS samples revealed that the biopsy focus score and MNC number/mm^2-tissue did not change significantly between the two sequential biopsies. From the cell populations studied, only the $CD4^+$ T cell incidence changed through time. The percentage of $CD4^+$ T/MNC cells was found significantly decreased in the second biopsy (mean±SD in the 1^{st} *vs* 2^{nd} biopsy: 30.8±7.9 *vs* 26.9±10.2, p:0.038); however, without affecting the $CD4^+/CD8^+$ T cell ratio (2.2±1.03 *vs* 1.4±0.9, p:0.29). Other histological parameters, such as fibrosis, fat infiltration or germinal center formation did not differ between the two sequential biopsies. The biopsy time interval was not found to affect the evolution of the lesion grade or composition. Finally, the histological parameters tested were not found to correlate with any demographic, clinical and therapeutic features of patients.

Conclusions: In the majority of SS patients, the grade and composition of MSG lesions at diagnosis remained mainly unchanged through follow-up. These findings suggest that the MSG autoimmune infiltrates do not significantly progress and accordingly, the progression of SS lesions is a rather slow process.

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Extra-Glandular Manifestations of Primary Sjögren's Syndrome in the SICCA International Sjögren's Syndrome Registry. Arundathi S. Malladi[12], Kenneth E. Sack[8], Stephen Shiboski[10], Caroline Shiboski[10], Alan N. Baer[2], Pekka Helin[7], Bruce Kirkham[4], Hisanori Umehara[3], Frederick B. Vivino[6], Cristina F. Vollenweider[1], Yan Zhao[5], John Greenspan[10], Troy Daniels[9] and Lindsey A. Criswell[11]. [1]German Hospital, Buenos Aires, Argentina, [2]Johns Hopkins University, Baltimore, MD, [3]Kanazawa Medical University, Ishikawa, Japan, [4]King's College London, UK, [5]Peking Union Medical College Hospital, Beijing, China, [6]Penn Presbyt Med Ctr, Philadelphia, PA, [7]Rigshospitalet, Copenhagen, Denmark, [8]UCSF, Tiburon, CA, [9]UCSF, San Francisco, CA, [10]UCSF, [11]UCSF-Box 0500, San Francisco, CA, [12]University of California at San Francisco (UCSF), San Francisco, CA

Purpose: To study the prevalence of extra-glandular manifestations (EGM) in patients with primary Sjögren's Syndrome (pSS) among participants enrolled in the Sjögren's International Collaborative Clinical Alliance (SICCA) cohort.

Methods: We studied 1618 participants (ppts) enrolled in the SICCA cohort. Inclusion required one of the following: symptoms of dry eyes or dry mouth; prior suspicion/diagnosis of SS; positive serum SSA, SSB, RF or ANA; increase in dental caries; parotid gland enlargement; or a possible diagnosis of secondary SS. We excluded ppts with RA, SLE or scleroderma (n=87) from this analysis. Ppts underwent thorough rheumatologic, ocular and oral examinations. Medical questionnaires were completed and ppts were asked about the presence of thyroid, liver, kidney disease or lymphoma. We then confirmed details of these diagnoses from treating physicians, specifically inquiring about the 8 diseases listed below. The frequency of EGM between the cases and each control group were compared using the chi square statistic.

Results: For the 1529 ppts in this analysis, average age at enrollment was 54 years; 92% were female; 47% were Caucasian, 34% Asian/Pacific islander and 11% Hispanic; 84% had complaints of dry eye symptoms and 90% had complaints of dry mouth symptoms. 635 ppts met the 2002 American-European (AmEu) Consensus Group criteria for pSS. Two "control" groups were defined. Group 1 (N=744) consisted of all ppts who did not meet AmEu criteria. Group 2 (N=264), a subset of Group 1, included ppts who had negative labial salivary gland biopsy (FOCUS score <1), negative anti-SSA/SSB *and* negative ocular staining score (OSS<3). Results are summarized in the table.

Characteristic	pSS Number (%)	Control Group 1 Number (%)	Control Group 2 Number (%)	P1	P2
Number	635	744	264	–	–
RF positive	399 (63)	106 (14)	31 (12)	<0.001	<0.001
ANA ≥ 320	426 (67)	130 (18)	29 (11)	<0.001	<0.001
IgG > 2013	200 (32)	19 (3)	1 (0.4)	<0.001	<0.001
IgA > 463	63 (10)	18 (2)	4 (2)	<0.001	<0.001
IgM>368	22 (4)	19 (3)	6 (2)	0.32	0.35
C3 < 90	74 (12)	85 (12)	34 (13)	0.89	0.61
C4 < 16	103 (16)	56 (8)	14 (5)	<0.001	<0.001
Wbc < 3.8	104 (16)	30 (4)	6 (2)	<0.001	<0.001
Hct < 38.5	306 (48)	218 (29)	65 (25)	<0.001	<0.001
Platelet < 140	42 (7)	22 (3)	8 (3)	<0.001	0.032
Graves Disease	12	8	4	0.21	0.7
Hashimoto's	32	38	8	0.95	0.18
Interstitial Nephritis	2	1	0	0.47	0.36
PBC	13	4	0	0.011	0.019
Autoimmune hepatitis	5	4	0	0.57	0.15
RTA	3	1	0	0.25	0.26
Glomerulonephritis	2	5	2	0.35	0.36
Lymphoma	2	2	0	0.87	0.36
Neuro Motor Sx	273 (43)	429 (58)	161 (61)	<0.001	<0.001
Neuro Sensory Sx	337 (53)	484 (65)	187 (71)	<0.001	<0.001
Joint stiffness >1hr	171 (27)	288 (39)	115 (44)	<0.001	<0.001
Joint pain/swelling	314 (50)	481 (65)	178 (68)	<0.001	<0.001
Joint Synovitis on exam	53 (8)	63 (9)	20 (8)	0.93	0.7
Raynaud's	105 (17)	94 (13)	26 (10)	0.041	0.01
Lymphadenopathy	44 (7)	38 (5)	13 (5)	0.15	0.26

P1 compares pSS with Group 1 controls
P2 compares pSS with Group 2 controls
Wbc: white blood cell, Hct: hematocrit, PBC: primary biliary cirrhosis, RTA: renal tubular acidosis. Sx: Symptoms

The frequency of positive RF, ANA titer ≥320, hypergammaglobulinemia (IgG and IgA) and low C4 are significantly higher in the patient group vs. control groups. Hematologic abnormalities (leukopenia, anemia and thrombocytopenia) are also more prevalent in the pSS cases. There was no significant difference in the frequency of the 8 diseases studied, with the exception of PBC. Joint and neurological symptoms were common in all three groups but significantly higher in the control groups.

Conclusions: Our results confirm that primary SS is associated with serum auto-antibodies, hypergammagobulinemia, low C4 levels, and hematologic abnormalities. Furthermore, the prevalence of EGM such as thyroid, liver and kidney disease may be lower than reported in previous, smaller studies. While neurological symptoms may be common in pSS patients, our results suggest that the prevalence of these symptoms may be similarly high in control populations, thereby stressing the importance of controls when evaluating these symptoms in pSS. A limitation of our study is the difficulty in fully characterizing EGM due to the large size and international nature of the SICCA cohort.

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1899

Germinal Center (GC) Formation in Salivary Gland Biopsies at Diagnosis of Primary Sjögren's Syndrome (pSS) Is a New and Strong Predictor of Non-Hodgkin's Lymphoma (NHL) during Follow-Up. Elke Theander[4], Lilian Vasaitis[3], Eva Baecklund[5], Gunnel Nordmark[5], Gunnar Warfvinge[4], Rolf Liedholm[4], Karl Brokstad[1], Roland Jonsson[1] and Malin V. Jonsson[2]. [1]University of Bergen, Bergen, Norway, [2]University of Bergen, Bergen, Norway, [3]University of Lund, Uppsala, Sweden, [4]University of Lund, Malmö, Sweden, [5]University of Uppsala, Uppsala, Sweden

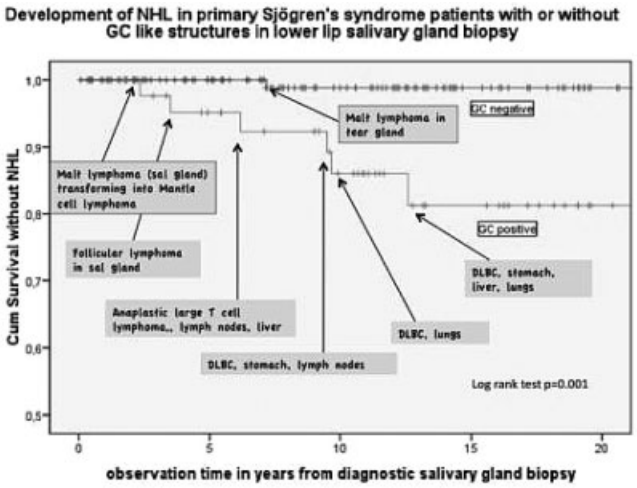
Background: Due to increased risk of NHL in pSS the identification of better markers for lymphoma development is crucial.

Objective: Does GC formation in salivary gland biopsies from the time point of pSS diagnosis predict NHL? Does GC formation correlate with other markers of NHL?

Methods: 174 pSS minor salivary gland biopsies from the Swedish SS centers in Malmoe and Uppsala underwent blind and independent reevaluation by light-microscopy at the Broegelmann Research Laboratory, Bergen, Norway for the presence of GC-like structures.These were determined by a densely packed dark zone and a light zone in biopsies with classical focal infiltration within otherwise normal salivary glands. The presence of NHL was determined by linkage of the local SS registries to the Swedish cancer registry. Observation time was defined as time from the salivary gland biopsy until lymphoma diagnosis, death or end of follow-up. The median (IQ range) time between diagnosing pSS and biopsy was 1 week (0–16). The total observation time was 1859 patient years at risk (range:1 month - 26 yrs).Time between salivary gland biopsy and NHL diagnosis was in median 8 years (range: 2 yrs and 4 months – 12 yrs and 7 months).

Statistics: Risk of developing NHL in patients with or without GC formation was compared by Cox regression analysis and Kaplan Meier statistics/log rank test. Associations between GC formation and other risk variables were determined by χ^2statistics.

Results: In total 136 biopsies showed focal sialadenitis (focus score ≥1) at reevaluation. In 43 (32%) of the biopsies with focal sialadenits GC like structures were detected. Seven patients had developed NHL. Six of the 7 NHL patients (86%) had GC like structures at the time of diagnosing pSS. Patients with GC-like structures had 15 times increased risk of developing NHL compared to those without. Hazard Ratio (HR) 15.4, 95%CI: 1.85–128, p=0.01. Log-rank test: p=0.001. Positive predictive value 16%, negative predictive value 99%.



GC positivity correlated with autoantibodies to SSA/SSB, lymphadenopathy, systemic disease activity (ESSDAI domains), high-risk type of SS (all $p<0.05$).

Conclusion: The presence of GC-like structures in the diagnostic salivary gland biopsies in pSS is highly predictive of lymphoma development with a HR of >15. This marker is an important new prognostic factor in the care of pSS patients. It may be included in guidelines for selection of pSS patients for biological B-cell directed treatment.

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1900

IL-7 Receptor Effector T Cells Are Increased in the Inflamed Salivary Glands of pSS Patients and Correlate with Inflammatory Markers. A. Bikker, A. A. Kruize, M. J. G. Wenting, J. W. J. Bijlsma, F. P. J. G. Lafeber and J. A. G. van Roon. Rheumatology & Clinical Immunology, University Medical Center Utrecht, The Netherlands

Background: In patients with primary Sjögren's syndrome (pSS) local T cell-driven inflammation can contribute to destruction of exocrine glands associated with clinical symptoms of dryness. Recently we documented increased IL-7 in labial salivary glands (LSG) of pSS patients that was capable to induce Th1 and Th17 activity and proinflammatory cytokine secretion. IL-7 mediates its effects by signaling through the high affinity IL7R (IL-7Rα subunit in conjunction with the γc chain). We and others have shown that IL-7R+ CD4 T cells that strongly proliferate upon TCR activation, while IL-7R- CD4 T cells remain anergic and can be regulatory of nature. At the level of the salivary gland this could lead to a heightened and ongoing inflammatory response, especially in the presence of increased local IL-7 expression.

Objective: To identify IL-7R expression in the labial salivary gland of and to examine the phenotypical characteristics of IL-7R+ CD4 T cells between pSS and non-Sjögren's syndrome sicca (nSS) patients. Additionally, to study the capacity of soluble human IL-7R in preventing immune activation.

Methods: The presence of infiltrating immune cells and IL-7R+ cells in inflamed salivary glands of pSS patients (n=14) and non-inflamed LSG of nSS patients (n=7) was studied by immunohistochemistry and FACS analysis upon tissue digestion.

Results: In the LSG of pSS patients significantly increased numbers of IL-7R+ cells were found as compared to nSS (pSS vs nSS; 244.3 $\pm$40.7 vs 12.3 $\pm$4.6 cells/mm^2). IL7R+ T cells were found throughout the tissue but mainly in the CD3-rich lymphocytic areas. In the salivary glands of nSS patients only a few resident CD3+ T cells were detected. IL7R+ T cells strongly correlated with local disease parameters (lymphocytic focus score [LFS]; $p\leq0.001$,$r=0.744$ and % IgA+ cells $p\leq0.005$,$r=-0.658$) as well as with immune cells present in the LSG (CD3 $p\leq0.001$, $r=0.890$; CD20 $p\leq0.005$, $r=0.717$; CD1a $p\leq0.005$, $r=0.660$; CD208 $p\leq0.001$, $r=0.763$).

FACS analysis of isolated cells from patients' LSG confirmed a strongly increased percentage of both CD3 and IL-7R+ CD3 T cells in pSS as compared to nSS (both $p<0.01$). Furthermore, abundant IL-7R expression was detected on high proportions of CD4 and CD8 (on average 66% $\pm$ 5% and 56% $\pm$ 4% respectively). Other CD45+ leucocytes and CD45-tissue cells did not or hardly express the IL-7R. IL-7R+ CD3, CD4, and CD8 T cells as percentage of the total LSG cells showed a significant correlation with the LFS ($p\leq0.05$, $r=0.533$; $p\leq0.01$, $r=0.593$; $p\leq0.01$, $r=0.631$ respectively).

Blockade of IL-7R-mediated signaling by soluble human IL-7R furthermore inhibited lymphocyte proliferation that was induced by ligands for Toll-like receptors 7, 8 and 9 (all $p<0.05$).

Conclusions: The abundant presence of IL-7R+ T cells in the inflamed salivary glands of pSS patients, which correlates to inflammation, suggests that increased IL-7 expression could significantly contribute to glandular inflammation by activation of IL-7R+ effector T cells. Blockade of the IL-7R might be a novel therapeutic strategy for pSS.

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1901

Immunization with Ro60 Peptide Leads to Sjögren's Like Syndrome in Mice with Appropriate Genetic Background. Biji T. Kurien[1], Sima Asfa[3], Anil D'souza[3], Yaser Dorri[3], Skyler P. Dillon[3], Sherry Hubbel[3], Ali W. Khalili[2], Olga Yeliosof, Yun Jong Lee, Shannon Maier[3] and R. Hal Scofield[3]. [1]Oklahoma Medical Research Foundation, [2]University of Oklahoma, [3]University of Oklahoma Health Sciences Center

Purpose: Our previous studies showed that BALB/c mice are amenable as an animal model for Sjögren's syndrome (SS) with (a) diminished salivary flow (b) intramolecular epitope spreading to Ro 60 autoantigen and (c) salivary gland lymphocytic infiltration upon immunization with Ro 274 peptide derived from Ro 60 autoantigen. We hypothesized that there would be a strain dependent susceptibility for SS induction.

Methods: Fourteen mice each from BALB/c, DBA-2, SJL/J, C57Bl/6 and PL/J strains were used. Seven mice from each strain were immunized (day one) with 50 μg of a linear peptide (273–289 amino acid sequence from Ro 60) or saline emulsified in Freund's Complete Adjuvant (FCA). Subsequent boosts were in Freund's Incomplete Adjuvant. The first, second and third boosts were given on day 7, 27 and 60 respectively. Ro 60 multiple antigenic peptide ELISA, Ro 60 ELISA and immunoblots were performed. Epitope spreading, salivary flow (upon induction with pilocarpine and isoproterenol) and histochemical lymphocytic infiltration were determined. Upon sacrifice, salivary glands were excised and a portion was saved for histopathological studies.

Results: Immunization with Ro-274 linear peptide resulted in anti-Ro-274 antibodies as early as the first bleed in BALB/c, DBA-2 and PL/J strain of mice. A milder anti-Ro 274 response was elicited in the B6 strain of mice by the sixth bleed while the SJL/J mice displayed a very poor response throughout the study. In the Ro-274 peptide immunized group 5/5 BALB/c, 1/5 DBA, 3/4 PL/J mice bound Ro 60 antigen by immunoblot. SJL/J and C57Bl/6 mice did not bind. Except for one DBA control mice that bound Ro 60 antigen on immunoblot the remaining control mice did not make antibodies to this antigen. Ro-peptide immunized BALB/c and DBA mice had lymphocytic infiltration of the salivary glands greater than controls However, salivary flow was significantly decreased only in the BALB/c mice compared to controls.

Conclusions: Only BALB/c mice displayed the complete SS-like condition, with diminished salivary flow, anti-Ro 60 antibodies and salivary gland lymphocytic infiltration upon immunization with Ro 274 peptide. DBA mice had significant salivary infiltrates and anti-Ro 60 antibodies but no salivary dysfunction. PL/J mice made antibodies and had epitope spreading but did not have salivary pathology or dysfunction. C57Bl6 bound the peptide but had no further progression in the model while SJL/J never produced antibodies to the immunogen, These data suggest a stepwise, or quantum, genetic control of the response that leads to a Sjögren's-like illness after Ro-peptide immunization.

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1902

Impaired Gastric Emptying in Primary Sjögren's Syndrome. Oskar Hammar, Bodil Ohlsson, Per Wollmer and Thomas Mandl. Skåne University Hospital Malmö, Malmö, Sweden

Purpose: To investigate the prevalence of impaired gastric emptying (IGE) and its relation to autonomic dysfunction (AD), functional bowel syndrome as well as inflammatory and serological variables in patients with primary Sjögren's syndrome (pSS).

Materials: 28 patients with pSS (median age 62 (range 29–65) years, 26 females) according to the American-European Consensus Criteria, without diabetes or other disease affecting autonomic nervous function, were included in the study. The controls consisted of previously investigated healthy individuals, i.e. 50 controls for the octanoate breath test (median age 43 (range 25–59) years, 25 females), 56 controls for the deep-breathing and orthostatic heart rate tests (median age 40 (range 16–59) years, 22 females), 80 controls for the finger-skin blood flow test (median age 43 (range 19–81) years, 37 females), 238 controls for the orthostatic blood pressure test (median age 60 (range 16–96), 106 females) as well as 200 population based controls for the Autonomic Symptom Profile (ASP) questionnaire on autonomic nervous dysfunction symptoms (median age 45 (range 20–69) years, 100 females).

Methods: Gastric emptying was evaluated by the octanoate breath test, from which half time ($t_{½}$) and lag time (t_{lag}) were determined. The results were corrected according to age and gender and expressed as z-scores. AD was evaluated by 5 objective autonomic reflex tests (ART), i.e. the deep-breathing test (expiration/inspiration (E/I)-ratio), the orthostatic heart rate test (acceleration index (AI)), the finger-skin blood flow test (vasoconstrictory (VAC)-index), and the orthostatic blood pressure test (systolic and diastolic blood pressure (SBP & DBP)-ratios). The results were age-corrected and expressed as z-scores by comparison with three previously examined control groups. Patients also filled out the ASP and these results were corrected according to age, gender, height and weight and were mainly expressed as z-scores. Patients were also assessed regarding symptoms of functional bowel syndrome as well as by inflammatory and serological tests. For comparison between groups the Mann-Whitney-U test and Fisher's exact test were used and for correlations the Spearman rank correlation test.

Results: The $t_{½}$ and the t_{lag} were significantly prolonged in patients compared to controls (1.18 (−0.71, 2.06) vs. −0.06 (−0.72, 0.74); p=0.03 and 1.40 (−0.14, 3.11) vs. −0.03 (−0.57, 0.66); p=0.00 respectively). Thus 43% of pSS patients presented signs of IGE whilst 29% fulfilled criteria for gastroparesis. Significant correlations between t_{lag} and increased levels of IgG (p=0.03) and erythrocyte sedimentation rate (ESR) (p=0.02) were found. In addition, rheumatoid factor (RF) seropositives showed objective signs of IGE to a greater extent than RF seronegatives. No associations between IGE, ART variables, ASP variables or functional bowel syndrome were found.

Conclusions: Impaired gastric emptying was common in pSS. Associations with inflammatory and serological features of pSS could imply immunological mechanisms behind the IGE. Objective signs of IGE were not associated with objective or subjective signs of AD nor functional bowel syndrome.

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1903

Increased Numbers of IL-7Rα-CD25+FoxP3+ T Cells in pSS Patients Do Not Prevent Th1 and Th17 Induction by IL-7. A. Bikker, F. M. Moret, A. A. Kruize, J. W. J. Bijlsma, F. P. J. G. Lafeber and J. A. G. van Roon. Rheumatology & Clinical Immunology, University Medical Center Utrecht, The Netherlands

Background: In patients with primary Sjögren's syndrome (pSS) local T cell-driven inflammation can contribute to destruction of exocrine glands associated with clinical symptoms of dryness. Recently we documented increased IL-7 expression in salivary glands of pSS patients that was capable to induce Th1 and Th17 activity and proinflammatory cytokine secretion by mononuclear cells from peripheral blood. Previously, a specific subset of T cells, expressing the receptor for IL-7 (IL-7R; IL-7Rα subunit in conjunction with the γc chain) has been classified as pro-inflammatory responder T cells. These T cells could potentially activate B cells and monocytes and also induce tissue damage. In contrast, T cells lacking the IL-7Rα and expressing CD25 and FoxP3 are said to be regulatory of nature. A shift in the balance between these two opposing subsets could lead to an increase in local inflammation and eventually cause tissue destruction, especially in the presence of increased IL-7 levels.

Objective: To examine the phenotypical characteristics of IL-7Rα+ and IL-7Rα- CD4 T cells and the possible imbalance between these immune cells in pSS patients versus healthy controls (HC) and the functional consequences this has for IL-7R-mediated T cell activation.

Methods: Expression of CD25, and FoxP3 on IL-7Rα (CD127) positive and negative CD4 T cells from 15 pSS patients and 15 HC was assessed using FACS analysis. The functional properties of IL-7Rα+ and IL-7Rα- CD4 T from pSS patients were tested in vitro upon α-CD3 T cell stimulation (n=9). Also, the capacity of IL-7 to activate total CD4 T cells from pSS patients as compared to HC was tested in coculture with monocytes (n=6).

Results: IL-7Rα- and IL-7Rα-CD25+ T cells (both p<0.01) were significantly increased in blood of pSS patients as compared to HC. This was in contrast to T cells defined by CD25 alone. IL-7Rα- and IL-7Rα-CD25+ T cells contained a high % of Foxp3 expressing T cells (70% and 94% resp.), but this did not differ between patients and HC. IL-7Rα+ CD4 T cells strongly proliferated upon activation in vitro TCR triggering (6812 ± 3067 cpm), whereas IL-7Rα-CD25+ T cells were anergic (107 ± 28 cpm). Despite increased numbers IL-7Rα-CD25+FoxP3+ T cells the proliferative capacity of total CD4 T cells to respond strongly to IL-7 was not prevented in pSS patients as compared to HC. Also, IL-7 induced strong expression of IFNg, IL-17 and to a lesser extent IL-4 (on average from 112 ± 52 pg/ml to 1886 ± 477 pg/ml, from 45 ± 17 pg/ml to 512 ± 129 pg/ml, from 103 ± 84 pg/ml to 473 ± 169 pg/ml respectively, all p<0.001) by CD4 T cells which was similar in pSS patients and HC.

Conclusion: This study reveals that IL-7R+ cells are highly proliferating cells that systemically respond strongly to IL-7, despite an increased number of FoxP3-expressing (CD25+)IL-7Rα- T cells. These data suggest that increased IL-7 expression could contribute to glandular inflammation by activation of IL-7Rα+ responder T cells.

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1904

Interferon Type I Signature in Monocytes in Primary Sjögren's Syndrome. Zana Brkic[1], Cornelia G. van Helden-Meeuwsen[1], Joop van der Merwe[1], Hemmo A. Drexhage[1] and Marjan A. Versnel[2]. [1]Dept Immunology, Rotterdam, The Netherlands, [2]Dept Immunology, Erasmus MC, Rotterdam, The Netherlands

Establishment of the diagnosis of primary Sjögren's syndrome (pSS) is difficult due to lack of specific diagnostic biomarkers and the heterogeneity of the disease. If, however, specific diagnostic biomarkers based on pathogenic pathways could be found, this heterogenic group of patients could be divided into different subgroups. This could eventually lead to new options for evidence-based individualized therapies. Using microarray analysis we described an Interferon (IFN) type I induced signature in monocytes of pSS patients (Wildenberg et al., 2008). B-cell activating factor of the tumour necrosis factor family (BAFF) is an IFN type I inducible factor recently found to be involved in the pathogenesis of pSS.

The aim of this study was to determine the prevalence of the IFN type I signature in a large group of pSS patients and relate it to complement levels, immunoglobulin levels, in vivo BAFF expression by monocytes, and the disease activity.

The expression of monocyte RNA profiles was determined by Real time Quantitative Polymerase Chain Reaction (RQ-PCR) in 50 pSS patients and 35 healthy controls. The disease activity of the pSS patients was determined by use of the Sjögren's Syndrome Disease Activity Index (SSDAI). Using Enzyme-Linked Immuno Sorbent Assay (ELISA), complement and immunoglobulin levels were determined.

We found a significant increased expression of the IFN type I inducible genes (IFN type I signature) in 40% of pSS patients compared to healthy controls. A significant positive correlation was found between the IFN type I signature and the expression of BAFF mRNA (r=0.771, p<0.001), IgG level (r=0.288, p=0.045) and disease activity (r=0.476, p=0.034). A significant negative correlation was found between C3 (r=0.450, p=0.016), C4 (r=0.415, p=0.031) and the IFN type I signature.

We conclude that determination of the IFN type I signature in pSS can be used to identify a subgroup of pSS with a high BAFF mRNA expression, high level of IgG, high disease activity and low complement level. This knowledge opens new doors for specific treatment of this subgroup by blocking the IFN type I activity.

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1905

Is Retreatment with Rituximab in Patients with Primary Sjögren's Syndrome Safe and Effective? Petra M. Meiners, Arjan Vissink, Jiska M. Meijer, Fred K. L. Spijkervet, Cees G. M. Kallenberg and Hendrika Bootsma. University Medical Center Groningen, Groningen, The Netherlands

Purpose: To assess the treatment outcome of retreatment with rituximab in patients with primary Sjögren's syndrome (pSS).

Methods: Thirty-seven patients with pSS, all fulfilling the revised European–US criteria, were subjected to repeated rituximab treatments (up to 4 courses, 65 courses in total). Retreatment was started on basis of return of complaints after previous treatment (objective: return of B cells, increase of IgM-rheumatoid factor level (IgM-Rf), decrease of salivary flow and subjective symptoms: e.g. sicca complains, fatigue, and/or extraglandular manifestations). Sixteen patients received 1 course, 16 patients received 2 courses, 3 patients received 3 courses and 2 patients received 4 courses of rituximab.

Safety of rituximab (re)treatment was assessed in all patients. Efficacy was assessed up to 24 weeks after each course. Stimulated whole saliva (SWS) was chosen as primary end-point. Secondary end-points were IgM-Rf and level of general fatigue (Multidimensional Fatigue Inventory; MFI).

Results: *Safety*

The first 8 patients were treated with 4 infusions of rituximab per course (375 mg/m2 per infusion; premedication 25mg prednisolone i.v.); 5 of these patients were retreated. Because of a high occurrence of serum sickness-like disorder in this initial cohort of pSS patients (in 3 out of 13 courses), the treatment schedule was changed; patients were treated with 2 infusions of rituximab per course (1000 mg per infusion; premedication 100 mg prednisolone i.v., 1000 mg oral paracetamol and 2 mg clemastine i.v.). Both courses were accompanied by a tapering dosage of oral prednisone 60-15 mg/day in 5 days afterwards. Serum sickness-like disorder occurred in 2 patients after the schedule had changed (in 2 out of 52 courses).

Efficacy

After initial treatment, a rapid decrease in peripheral B cells occurred in all patients. In rituximab treated pSS patients, SWS stayed at the same or a higher level during follow-up, whereas SWS declined in untreated patients. At 24 weeks after the first course of rituximab, there was still a decrease in IgM-Rf levels and a decrease in general fatigue compared to baseline. Next a gradual return of the various complaints to baseline was observed. Most, but not all, complaints had returned to baseline by the 9th month. Additional treatments with a second, third and fourth course led to results comparable to initial treatment.

Conclusion: Rituximab was shown to be effective for 6–9 months in pSS patients after the first course of rituximab. Additional courses of rituximab resulted in a comparable beneficial effects in pSS patients on functional parameters, serological parameters and fatigue. Higher doses of corticosteroids led to a reduction of the occurrence of serum sickness-like disorder. Based on these interim results, additional courses with rituximab seem to be a safe and effective treatment for pSS.

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1906

Molecular and Cellular Evolution of Functional Tertiary Lymphoid Structures in Salivary Glands of NOD Mice. Elisa Astorri[3], Michele Bombardieri[3], Elisa Corsiero[3], Francesca Barone[1], Gordon Proctor[2] and Costantino Pitzalis[3]. [1]Birmingham University, Birmingham, United Kingdom, [2]King's College, London, London, United Kingdom, [3]Queen Mary University London, London, United Kingdom

Background: Tertiary Lymphoid Structures (TLSs) formation is a common feature of chronic inflammatory diseases including Sjogren's syndrome (SS). We recently showed that these ectopic structures acquire functional properties typical of secondary lymphoid organs and are capable of supporting autoreactive B cell activation and autoantibody production as demonstrated by expression of activation-induced cytidine deaminase (AID) and Ig class switching. Dissecting TLSs dynamics in humans is technically and ethically challenging. Thus, we used the NOD mouse model, a spontaneous model of autoimmune sialoadenitis, to characterize the cellular and molecular basis of autoreactive B cell activation and evolution of functional Ectopic Lymphoid Structures (ELS) in the chronically inflamed NOD salivary glands.

Methods: Submandibolar (SUBM) glands from 110 female NOD mice from 4 to 35 weeks of age were collected. Paired snap-frozen, OCT-embedded samples were analysed by immunohistochemistry (IHC) for T and B lymphocytes (CD3/CD20) in order to evaluate immune cell infiltration and the degree of B/T cell segregation. ELS were detected by staining for FDC-M1 (follicular dendritic cell networks), GL7 (germinal centre B cells) and AID (marker for ELS functionality). Characterization of B cell subsets within the infiltrates was carried out by immunostaining and by FACS analysis with CD19, CD21, CD23, B220, IgD, IgM, CD1d and CXCR5 antibodies. Quantitative TaqMan real-time PCR was performed to investigate the mRNA expression of ELS related genes. The same analysis was performed in sex/age matched Balb/c mice as controls.

Results: NOD infiltrates in SUBM glands displayed progressive features of ELS from week 8, with 75% of mice developing B/T cell segregation, FDC networks and GL7+ ectopic germinal centers (GCs) from week 20. Formation of ectopic GCs was always associated with B/T segregation. Evolution of TLSs was closely associated with mRNA upregulation of genes regulating ectopic lymphoid tissue organization and function such as lymphoid chemokines CXCL13/CCL19 and their specific receptors CXCR5/CCR7, lymphotoxins and B cell survival factors BAFF and APRIL. In agreement with CXCL13/CXCR5 mRNA expression, B cells infiltrating NOD SUBM glands display strong CXCR5 expression and were mostly characterised by a follicular phenotype (B220+/IgD+/IgMlow/CD23+/CD21low) as demonstrated by both IHC and FACS analysis on isolated cells. Finally, functionality of ELS was demonstrated by expression of AID mRNA and protein within FDC networks, which paralleled the detection of circulating SS-related autoantibodies.

Conclusion: This work provided the first in depth characterization of the cellular and molecular mechanisms underlying the evolution of functional TLSs within SUBM infiltrates of NOD mice. These data strongly support the hypothesis that B cells can be activated within TLSs in the target organ and promote an in situ autoantibody response. Overall, these data support the critical importance of ELS formation in chronic autoimmune inflammation and identified NOD mice as a suitable model to test therapeutic strategies aimed at modulating B cell functionality.

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1907

New Classification Criteria for Childhood Sjögren's Syndrome. Naoto Yokogawa[8], Scott M. Lieberman[1], Sharon M. Bout-Tabaku[3], Faizan Alawi[7], Juan P. Palazzo[6], Martha Guttenberg[2], David D. Sherry[5] and Frederick B. Vivino[4]. [1]Children's Hosp of Philadelphia, Philadelphia, PA, [2]Children's Hosp of Philadelphia, [3]Nationwide Children's Hospital, Columbus, OH, [4]Penn Presbyt Med Ctr, Philadelphia, PA, [5]The Children's Hospital of Philadelphia, Philadelphia, PA, [6]Thomas Jefferson Univ., [7]Univ. of Pennsylvania, [8]Univ. of Pennsylvania/Tokyo Metropolitan Tama Medical Center

Purpose: To develop new classification criteria for childhood Sjögren's syndrome (SS).

Background: Adult classification criteria for SS have not been validated in children and currently proposed pediatric criteria lack diagnostic sensitivity.

Methods: Retrospective review of medical records of 41 patients (pts) was performed at Children's Hospital of Philadelphia and the Penn Sjögren Center to identify cases of suspected pediatric SS. Diagnosis by physician global assessment required 1) symptom onset at age <20 yrs, 2) consensus agreement on diagnosis by pediatric and adult rheumatologists, 3) abnormal serologies and/or lip biopsy. Pts with overlapping autoimmune disease were not excluded. Clinical presentation, serologies, objective tests for sicca and histopathology were reviewed. All available salivary gland biopsies were blindly reviewed by oral pathologists to calculate a focus score (FS) and compared to biopsy findings from non-SS pts. Pts were also classified as childhood SS (score:3 or more) or non SS (score 2 or less) using a novel scoring system (maximum = 8) based on a modification of American-European Consensus Group (AECG) criteria (Vitali et al, 2002).

		Point
Sicca symptoms	Dey eye (I) AND dry mouth/parotid swelling (II)*[1]	2
	Dry eye (I) OR dry mouth/parolid swelling (II)	1
	No sicca symptoms	0
Objective findings	Abnormal eye exams (III) AND abnormal salvary flow (V)	2
	Abnormal eye exams (III) OR abnormal salivary flow (V)	1
	Normal eye exams and normal salivary flow	0
Laboratory findings	Positive SSA and/or SSB (VI)	2
	Positive ANA AND Negative SSA/SSB	1
	Negative ANA/SSA/SSB	0
Biopsy findings	Focus score≥ 1 OR characteristic findings of SS*[2]	2
	Presence of focus AND Focus Score<1	1
	Absence of focus	0

Childhood SS: total score≥3 points
*[1]Include parotid enlargement by radiological study
*[2]Parotid biopsy may be sufficient to diagnose SS.

Results: Following global assessment and long term follow-up of the pediatric cohort (41 pts), 35 pts had confirmed childhood SS, 3 pts had suspected but unconfirmed SS, and 3 pts were diagnosed as HIV, sarcoidosis, or IPEX syndrome. Using the novel scoring system, all 35 pts with definite childhood SS were classified as SS and all 3 pts with other final diagnosis were classified as non SS.

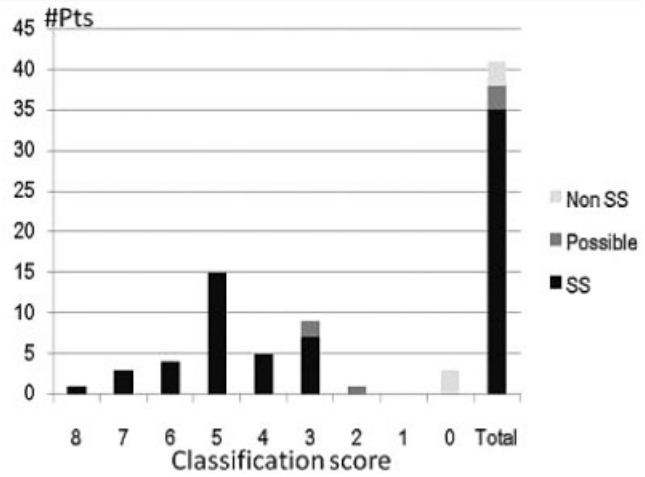

Figure 1.

An expert oral pathologist blindly calculated FS in 21 pts. Among 17 pts with definite childhood SS, FS and Classification Score were positively correlated ($R=0.67$ $p<0.005$) and 8 pts had FS less than 1.

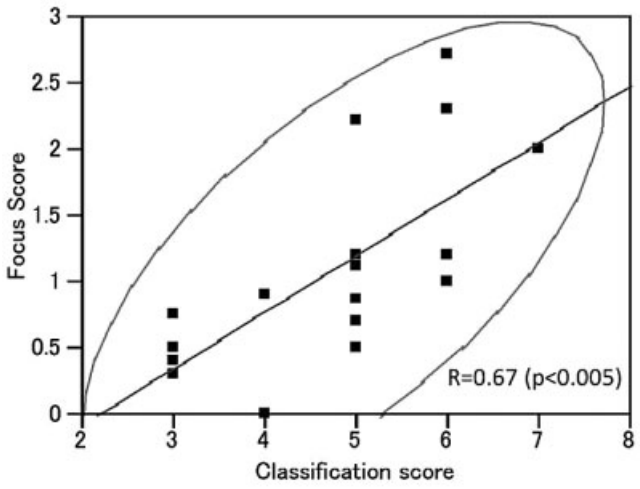

Figure 2.

Conclusions: Inclusion of the presence of ANAs and any focal lymphocytic sialadenitis (both more clinically significant in children than adults) in classification criteria for childhood SS can be used to maximize diagnostic sensitivity in order to facilitate earlier treatment and prevent long-term complications.

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1908

New Insights in Sjögren Syndrome Associated Peripheral Neuropathies: The Small Fibre Neuropathy and Its Clinical, Immunological and Neurophysiological Features from a Moncentre Cohort of 24 Patients. Damien Sène[2], Jean-Pascal Lefaucheur[1], Julien Haroche[2], David Saadoun[2], Baptiste Hervier[2], Jean-Charles Piette[2], Zahir Amoura[2] and Patrice Cacoub[2]. [1]Henri-Mondor Hospital, [2]Pitié-Salpêtrière Hospital

Objective: Primary Sjögren syndrome (pSS) may account for 9 to 30% of causes of sensory small fibre neuropathies (SFN), clinically characterized by sensory painful symptoms mostly associated with normal clinical and electromyographic examinations. Nevertheless, the main features of SFN have never been evaluated in a large cohort of pSS-patients. The aim of this study was to analyze the clinical, immunological and neurophysiological features of pSS-associated SFN.

Patients and Methods: 24 consecutive pSS-patients (according to Americano-European group criteria consensus revised on 2002) presenting a definite SFN were included. The SFN was defined by the presence of sensory painful symptoms with a DN4 score ≥ 4 and the evidence of abnormal nerve small fibre neurophysiological tests, including laser evoked potentials (LEP), quantitative sensory test (QST) and sensory skin reflex (SSR). The 24 included patients were compared to 89 SS-patients without peripheral neuropathy.

Results: the 24 patients included 20 female (83%) and 4 men (17%) with a mean age of 64 ± 10 years. For 21 patients (87.5%), SFN led to pSS diagnosis. SFN involved both upper and lower limbs for 19 patients (79%) and lower limbs alone for 5 patients (21%). The neurophysiological tests abnormalities included altered LEP in 21 patients (87.5%), abnormal QST in 21 patients (87.5%) and abnormal SSR in 13 patients (54.2%).

Compared to the 89 pSS-patients who did not present with a peripheral neuropathy, patients with a pSS-associated SFN were older at the time of pSS diagnosis (63 ± 10.5 vs 48.5 ± 14 years; $P<10^{-4}$), and had more frequently a central nervous system involvement (25% vs 2%; $P<10^{-4}$). They were featured by a lower frequency of serum B cell activation markers, i.e, less often positive ANA (58% vs 90%; $P<10^{-3}$), anti-SSA (37.5% vs 73%; $P=0.001$), anti-SSB (12.5% vs 42%; $P=0.008$) and rheumatoid factor (37.5% vs 68%; $P=0.008$), and lower serum gammaglobulins levels (12.5 ± 5 vs 16 ± 7 mg/L; $P=0.0045$).

Conclusion: Our study reported for the first time the main features of SFN in pSS patients. Our results showed that patients with a pSS-associated SFN are characterized by an older age at SS diagnosis and a more frequent CNS involvement, and a distinctive immunological profile hallmarked by a lower frequency of serum B cell activation markers (ANA, anti-SSA, anti-SSB, rheumatoid factor, and gammaglobulins).

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1909

Novel Lupus Susceptible Gene Polymorphisms in Patients with Sjögren's Syndrome in Japanese Population. Tetsuya Horita[1], Hisako Nakagawa[1], Takashi Kurita[1], Toshio Odani[1], Yuichiro Fujieda[1], Kotaro Otomo[2], Masaru Kato[1], Shinsuke Yasuda[1], Tatsuya Atsumi[1] and Takao Koike[1]. [1]Medicine II, Hokkaido University, Sapporo, Hokkaido, Japan, [2]Medicine II, Hokkaido University

Background: Genetic background of Sjögren's syndrome (SS) is still unknown. SS can occur alone (primary SS) or in conjunction with other autoimmune diseases such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (secondary SS). Several novel lupus susceptible genes were reported in the recent candidate gene approaches and genome wide association studies in Caucasian population. In this study, we analyzed these lupus susceptible gene polymorphisms in patients with SS in Japanese population.

Patients and Methods: This study comprised 190 SS patients and ethnically matched 428 healthy controls. Patients with SLE were excluded. B lymphocyte specific tyrosine kinase (BLK) (rs13277113), B-cell scaffold protein with ankyrin repeats 1 (BANK1) (rs10516487 and rs3733197), signal transducer and activator of transcription 4 (STAT4) (rs7574865), interferon regulatory factor 5 (IRF5) (rs2004640), tumor necrosis factor ligand superfamily member 13 (TNFSF13) (rs11552708), tumor necrosis factor alpha induced protein 3 (TNFAIP3) (rs13192841, rs2230926 and rs6922466), tumor necrosis factor ligand superfamily member 4 (TNFSF4) (rs844644), rs10798269 in 1q25.1 region were evaluated using TaqMan Genotyping Assay. Allele frequencies in each polymorphism were compared using chi-square test and the related risk was approximated by the odds ratios. In addition, stratification analysis by anti-SS-A and anti-SS-B was performed. The genetic risk scores composed of the numbers of risk alleles in SS susceptible genes were also calculated and the scoring system was evaluated.

Results: The allele frequencies of lupus risk in SS were significantly higher in BLK (odds ratio (OR) $=1.61$, 95% confidence interval (CI):1.21–2.15), STAT4 (OR=1.83, 95%CI:1.43–2.36), IRF5 (OR=1.40, 95%CI:1.07–1.82) and rs10798269 in 1q25.1 region (OR=1.62, 95%CI:1.20–2.18), compared with those in healthy controls. No significant associations were found in BANK1, TNFSF13, TNFAIP3 and TNFSF4. In stratification analysis. STAT4 was associated with the presence of both anti-SS-A and anti-SS-B, whereas BLK and SNP (rs10798269) in 1q25.1 region were associated with anti-SS-A and IRF5 was associated with anti-SS-B. In genetic risk scoring system for SS, the presence of five or more risk alleles in 4 common susceptible genes (BLK, STAT4, IRF5 and 1q25.1) was strongly associated with SS (OR=2.79, 95%CI:1.89–4.14).

Conclusions: BLK, STAT4, IRF5 and 1q25.1 region were not only lupus susceptible genes but SS susceptible genes in Japanese population. SS share, in part, common genetic background with SLE.

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1910

Patients' Complaints Depend on Systemic Status in Patient with Primary Sjögren 's Syndrome: Concordant Results from 2 Independant Cohorts. Raphaèle Seror[3], Philippe Ravaud[23], Simon J. Bowman[24], Hendrika Boostma[25], Manel Ramos-Casals[17], Elke Theander[18], Thomas Doerner[1], Eric Hachulla[20], Jacques E. Gottenberg[22], Athanasios G. Tzioufas[19], Alain Saraux[7], Veronique Le Guern[16], Stephanie Rist[10], Claire Larroche[14], Anne Laure Fauchais[8], Aleth Pedriger[12], Jacques Morel[9], Jean Sibilia[21], Jean-Jacques Dubost[6], Olivier Vittecoq[13], Philippe Dieudé[15], Xavier Puechal[5], Damien Sene[11], Charles Zarnitsky[4], Claudio Vitali[26] and Xavier Mariette[2]. [1]Berlin Charite University Hospital, [2]Bicetre Hospital/Paris Univ, Le Kremlin Bicetre, France, [3]Bicetre Hospital/Paris Univ, Le Kremlin Bicetre, France, [4]CH du Havre, [5]CH du Mans, [6]CHU Clermont-Ferrand, [7]CHU de la Cavale Blanche, Brest Cedex, France, [8]CHU Limoges, [9]CHU Montpellier, [10]CHU Orléans, [11]CHU Pitié Salpetriere, [12]CHU Rennes, [13]CHU Rouen, [14]Hopital Avicenne, [15]Hopital Bichat, [16]Hopital Cochin, [17]Josep Font Hospital, Barcelona, [18]Malmö University Hospital, [19]Medical School-Univ of Athens, Athens, Greece, [20]National Scleroderma Centre, Lille Cedex, France, [21]Strasbourg Hospitals, [22]Strasbourg Hospitals, Strasbourg, France, [23]Universite Paris-Rene Descartes, [24]University Hospital Birmingham NHS Foundation Trust, [25]University Medical Center Groningen, [26]Villamarina Hospital Pimobino

Objectives: To determine whether common symptoms of dryness, fatigue and pain differed between patients with or without systemic complications in primary Sjögren's syndrome (SS).

Methods: Data concerning primary SS patients were analyzed from 2 different prospective studies: 1–230 patients included by 21 SS experts participating in an EULAR study for the development of the EULAR Sjögren's Syndrome Patient reported Index (ESSPRI), and 2–354 patients from the French prospective SS cohort (ASSESS). All patients completed the ESSPRI (0–10 numerical scales for pain, fatigue, and dryness features), Sicca Symptoms Inventory (SSI), Profile of Fatigue and Discomfort (PROFAD) questionnaires and a 0–10 patient global assessment (PGA). Severity of each symptom was compared between patients with and without systemic involvement.

Results: 140 (60.9%) of the 230 patients from the EULAR study (mean age = 55.9 ± 13.9 yrs, 219 [95.6%] females, mean disease duration = 8.3 ± 5.6 yrs, 80.0% anti-SSA and/or SSB positive), and 253 (71.5%) 354 patient from the ASSESS cohort (mean age = 57.5 ± 12.9 yrs, 332 [93.8%] females, mean disease duration = 6.6 ± 5.8 yrs, 60.7% anti-SSA and/or SSB positive) had past or present systemic involvement. Systemic involvements included articular (if arthritis), cutaneous, peripheral or central nervous system, pulmonary, muscular (if myositis) involvements or B-cell proliferative disorder.

Patients with past or present systemic complications had higher levels of symptoms severity for fatigue, and limb pain, but not for dryness.

	EULAR Study			ASSESS cohort		
	Systemic N=140	Non-systemic N=90		Systemic N=140	Non-systemic N=90	
Fatigue	6.4 ± 2.7	5.4 ± 3.0	p=0.01	6.2 ± 2.7	5.5 ± 2.6	p=0.04
Pain	5.6 ± 2.9	4.2 ± 3.0	p=0.0009	5.1 ± 2.9	3.9 ± 2.9	p=0.00009
Dryness	6.7 ± 2.3	6.4 ± 2.4	p=0.53	5.4 ± 2.3	5.0 ± 2.3	p=0.20
ESSPRI	6.2 ± 2.1	5.4 ± 2.2	p=0.004	5.6 ± 2.2	4.8 ± 1.9	p=0.03
PROFAD	4.2 ± 2.4	5.1 ± 2.4	p=0.007	4.9 ± 2.2	3.9 ± 1.9	p=0.0008
SSI	5.0 ± 2.2	5.3 ± 2.2	p=0.26	5.3 ± 2.3	4.9 ± 2.0	p=0.18

Similarly, PROFAD and ESSPRI scores were higher in patients with systemic features, but SSI scores were not.

Conclusion: In 2 independent cohorts of primary SS patients, we showed that patients with systemic complications have higher levels of fatigue, pain, but similar levels of dryness, compared to those without. Thus, alterations of common patient reported outcomes, present in most of the patients with pSS, are more intense in patients with systemic complications. This supports the interest of using ESSPRI in both groups of patients with and without systemic complications.

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1911

Primary Sjögren's Syndrome-Associated Non Ataxic Sensory Neuropathies and Sensorimotor Neuropathies Are Characterized by Distinctive Immunological Profiles. Damien Sène[2], Moez Jallouli[2], Jean-Pascal Lefaucheur[1], David Saadoun[2], Thierry Maisonobe[2], Julien Haroche[2], Marie-Claude Diemert[2], Lucile Musset[2], Jean-Charles Piette[2], Zahir Amoura[2] and Patrice Cacoub[2]. [1]Henri-Mondor Hospital, [2]Pitie-Salpetriére Hospital

Objective: To characterize the relationship between primary Sjögren's Syndrome (pSS)-associated peripheral neuropathies (PN) and markers of B cell monoclonal proliferation and chronic activation.

Patients and Methods: 120 consecutive patients presenting with a definite pSS were included. Serum markers of chronic B-cell activation included auto-antibodies and hypergammaglobulinemia. Monoclonal B-cell proliferation markers included mixed cryoglobulin, monoclonal gammopathy, abnormal κ/λ free light chain (FLC) ratio or B-cell non Hodgkin lymphoma (B-NHL).

Results: A definite PN was present in 30 patients (25%) including 7 patients with a sensorimotor neuropathy (23%), 3 patients with an ataxic sensory neuropathy (10%) and 20 patients with a non-ataxic sensory neuropathy (67%). Patients with a sensorimotor neuropathy differed from those without PN by higher rates of monoclonal B-cell proliferation markers, i.e. mixed cryoglobulin (57% vs. 11%; P=0.008), monoclonal gammopathy (71% vs. 17%; P=0.004), higher FLC ratio (2.7±1.5 vs. 1.7±1.8; P=0.024) and B-NHL (57% vs. 3%; P<0.001). Patients with non-ataxic sensory neuropathy were featured by a higher age (57.5±10.7 vs. 48.7±14.3 years; P=0.007), a more frequent CNS involvement (15% vs. 2%; P=0.04) and a lower prevalence of chronic B-cell activation serum markers, i.e., ANA (60% vs. 90%; P=0.003), anti-SSA (Ro) (40% vs. 72%; P=0.009), anti-SSB (La) (15% vs. 41%; P=0.039), RF (37% vs. 67%; P=0.02), and hypergammaglobulinemia (35% vs. 64%; P=0.023). In multivariate analysis, a sensorimotor neuropathy was associated with the presence of B-NHL (OR=39.0; P<0.001), whereas a non-ataxic sensory neuropathy was associated with the presence of a CNS involvement (OR=17.0; P=0.025) and ANA (OR=0.07; P<0.001).

Conclusion: Up to 25% of pSS-patients presented with peripheral neuropathy, which was predominantly a sensory neuropathy. Distinctive immunological profiles were found according to the type of SS-associated neuropathy, as non-ataxic sensory neuropathy was hallmarked by a low prevalence of B-cell activation markers and sensorimotor neuropathy by a high prevalence of B-cell monoclonal proliferation markers

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1912

Prognosis of Non-Hodgkin Lymphomas in Primary Sjogren's Syndrome. Michael Voulgarelis, Panayiotis D. Ziakas, Aristea Papageorgiou, Athanasios G. Tzioufas and Haralampos M. Moutsopoulos. Dept of Pathophysiology, Medical School, University of Athens, Greece

Background: Sjogren's syndrome (SS) has been associated with the development of Non-Hodgkin's lymphomas (NHL).

Methods: Fifty-three consecutive lymphoma cases (51 female/2 male), with a median age of 54 years (range 28 to 90 years) were retrospectively analyzed. Overall survival (OS), event-free survival (EFS) and standardized mortality ratio (SMR) were calculated. An event was defined as relapse, treatment failure, progression, transformation, or death, whichever occured first following lymphoma diagnosis.

Results: Mucosa-associated lymphoid tissue (MALT) lymphomas constituted the majority (59%) of lymphoma subtypes, followed by nodal marginal zone lymphomas (NMZLs) (15%), diffuse large B-cell lymphomas (DLBCLs) (15%) and other histologies (11%).

After a long median follow-up of 40.8 months for the entire lymphoma cohort, 6 patients died. Median survival was not reached, and 3-year OS was 0.96 (95% CI 0.83 to 0.98). Median EFS was 85.3 months. The corresponding

age-sex adjusted SMR of lymphoma compared to the general population was 3.25, suggesting a shorter life expectancy.

In nine localized MALT lymphomas with low International prognostic index(IPI), treatment was withheld. Among these cases, only one transformed to DLCBL. Eight patients with limited stage MALT and extraglandular manifestations were treated with rituximab monotherapy. The remaining MALT cases were treated with combined modality protocols. Treatment resulted in high complete response rates (94%), upon completion of therapy. Overall, 3-year OS and EFS were 0.97 and 0.78 respectively for MALT cases.

Combined immunochemotherapy was the standard therapeutic intervention for DLCBLs, resulting in 100% OS and EFS at 3 years. NMZLs had a disappointing outcome (3-year OS 0.80 and EFS 0.53), warranting the urgent need for a new standard of treatment.

Conclusion: Our results explicitly describe the course and prognosis of SS-associated lymphomas and highlight the need for a risk-stratified treatment approach.

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1913

Risk of Non-Hodgkin's Lymphoma in Primary Sjögren's Syndrome. Svein J A. Johnsen[3], Johan G. Brun[1], Tom B. Johannesen[2], Lasse Gøransson[3], Karstein Haldorsen[1], Roland Jonsson[4] and Roald Omdal[3]. [1]Haukeland University Hospital, [2]Norwegian Cancer Registry, [3]Stavanger University Hospital, [4]University of Bergen

Background: It is well known that patients with primary Sjögrens syndrome (PSS) have an increased risk for developing non-Hodgkin lymphoma (NHL), although the exact risk reported has varied in different studies. Such discrepancies could be due to the use of different criteria applied for PSS diagnosis over time, and the inclusion of more or less biased patient samples. The aim of this study was to assess the risk of NHL and other hematological malignancies in a well-defined population in Western Norway applying the widely accepted American-European Consensus Group criteria for PSS (1).

Methods: All patients with PSS were identified in the two counties Hordaland and Rogaland (896 840 subjects—18.59% of the total population of Norway). A linked registry study between the PSS registry and the Cancer Registry of Norway was performed, and in addition all medical files were screened for ascertainment of diagnoses. The risk of NHL in PSS patients was compared with the risk in the general population based on the Cancer Registry data. Descriptive statistics with mean, SD and ranges were used to present patient demographic data.

Results: As of June 1st 2009, 432 Caucasian PSS-patients were alive, of which 406 (94%) were women and 26 men (6%). Mean age was 62 years, SD 13.2 [range 16–95]. Mean age at diagnosis was 53.8 years, SD 13.5 [range 15–89]. Mean duration of disease PSS was 8.65 years, SD 5.2 [range 1–35]. Total follow-up was 3,722 patient years. Five cases of NHL (1.16%) were identified, all marginal zone lymphomas. Three of these were MALT-lymphomas of the salivary glands, one MALT-lymphoma from the lingual tonsil and one extranodal marginal zone lymphoma located in the bone marrow. In addition, the latter patient presented a monoclonal B-cell population consistent with a κ-positive B-cell chronic lymphocytic, also classified as NHL. No high-grade lymphomas were detected.

Conclusion: PSS patients have an increased risk of developing NHL compared with the risk in the general population ($p<0.001$). The risk, however, seems lower than previously reported.

1. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for sjögren's syndrome: A revised version of the european criteria proposed by the american-european consensus group. Ann Rheum Dis 2002;61:554–8.

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The FMS-Like Tyrosine Kinase3-Ligand (FL) Is a Marker for Lymphoma in Primary Sjögren's Syndrome (SS). Jacques-Olivier Pers[1], Gabriel J. Tobon[1], Jacques E. Gottenberg[7], Raphaèle Seror[4], Valérie Devauchelle[2], Jacques Morel[5], Stéphanie Rist[6], Alain Saraux[3] and Pierre Youinou[1]. [1]Brest University, Brest, France, [2]Brest University, [3]CHU de la Cavale Blanche, Brest Cedex, France, [4]Le Kremlin Bicetre Hospital, [5]Montpellier University, [6]Orleans Hospital, [7]Strasbourg Hospitals, Strasbourg, France

Background: The exocrine glands of patients with primary SS become sites of intense immunological activity and thereby present with tissue damage. Salivary glands exhibit a lymphoproliferative sialadenitis, associates with lymphocyte infiltration and epithelial cell apoptosis. Compared with healthy individuals, patients with SS are at greater risk of developing non-Hodgkin's lymphoma. We recently published that FL, a cytokine implicated in B-cell ontogenesis and malignant proliferation, might unveil primary SS at risk of developing lymphoma (Tobón et al., Arthritis Rheum. 2010).

Methods: In order to confirm this observation, serum levels of FL were measured in 334 patients enrolled in the French cohort of primary SS patients. All fulfilled the European American criteria for SS. Association between FL positivity and: 1- criteria linked to a high risk of lymphoma such as purpura, low C4 levels, enlargement of the parotid glands, monoclonal Ig, cryoglobulinemia; 2- lymphoma development; 3- disease activity according to visual analogic score (VAS) for subjective signs and the EULAR SS Disease Activity Index (ESSDAI).

120 pg/mL of FL was considered as positive (FL+) i.e. 2 SD above the mean of 50 controls. Nevertheless, sensitivity and specificity were calculated at different cut-off values. To compare data FL+ and FL-, we used the chi-square or Fisher exact test for qualitative variables and the Mann-Whitney test for quantitative variables (Statistical Package for the Social Sciences).

Results: Main results are listed in the Table. FL+ patients were younger. The sex ratio, subjective symptoms of dryness and parotidomegaly were not statistically associated to FL. In contrast, purpura and lymphoma, as well as ESSDAI were significantly associated with elevated levels of FL. ROC analysis showed that 175 pg/mL was ideal cut-off to detect the association with lymphoma: sensitivity 44%, specificity 97.5%.

	FL+	FL−
Age (years)	56.59	62.58 ($P<0.0001$)
Sex M/F	5/94	17/240
Parotidomegaly	29/93	90/239
Purpura	16/9	21/235 ($P<0.01$)
History of lymphoma	13/94	5/240 ($P<0.0001$)
VAS sicca	5.12	5.45
VAS pain	4.71	4.82
VAS fatigue	5.94	6.01
ESSDAI	6.68	5.33 ($P<0.05$)

Conclusion: FL is elevated and correlated with history or presence of lymphoma in primary SS 334 patients. The role of FL in B cell proliferation may explain the clinical evolution to B cell lymphoma in some patients and targeting FL open new therapeutic options.

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1915

The Role of Immunostaining Against the Panaxonal Protein PGP 9.5 in the Evaluation of Sjogren's Sensory Neuropathies, and the Increased Frequency of Male Sex and Seronegativity to Anti-La/SS-B Autoantibody with Peripheral Neuropathies. Julius Birnbaum, Alan N. Baer and Michael Polydefkis. Johns Hopkins University, Baltimore, MD

Purpose: The frequency of different subtypes of peripheral neuropathies (PNS) in larger number of Sjogren's patients has not been studied using diagnostic techniques which have been validated for other PNS syndromes. Specifically, the quantification of nerves immunostained against the PGP 9.5 panaxonal protein allows for the diagnosis of a "small-fiber" neuropathy affecting unmyelinated nerves. Therefore, we sought to understand the frequency of different subtypes of neuropathies in Sjogren's patients, and to characterize whether Sjogren's patients with neuropathies may have distinguishing demographic, clinical, and immunologic features.

Methods: We characterized the neuropathy occurring in 186 consecutively evaluated Sjogren's patients, by examination, electrodiagnostic studies, and by skin biopsy when there was suspicion for a small-fiber neuropathy. The diagnosis of small-fiber neuropathy was based on decreased intraepidermal innervation (IENF) of unmyelinated nerves immunostained against the PGP 9.5 panaxonal protein. Logistic regression analysis was performed to determine whether the presence of neuropathies (as the dependent variable), was independently associated with demographic, clinical, and autoantibody covariates.

Results: Forty-seven patients had peripheral neuropathies; of 41 patients with sensory neuropathies, 32 patients had neuropathies affecting the unmyelinated nerves, versus 9 patients with axonal sensory neuropathies and ganglionopathies assessed by electrodiagnostic studies. The association of demographic, clinical, and immunologic covariates with peripheral neuropathies was assessed by logistic regression. Male sex ($p=0.04$) and seronegativity to the anti-La/SS-B autoantibody ($p=0.04$) were respecitvely and independently associated with neuropathies.

Conclusions: The most common subtype of neuropathy in Sjogren's patients is a neuropathy targeting the unmyelinated nerves. The integrity of the smaller-fiber, unmyelinated nerves can be assessed by immunostaining against the PGP 9.5 protein 9.5, cannot be assessed by routine electrodiagnostic studies, and may account for the lower frequency of neuropathies reported in larger cohort studies of Sjogren's patients. The increased frequency of male sex and seronegativity of anti-La/SS-B autoantibodies seen in Sjogren's patients with PNS manifestations suggests discriminating hormonal and immunologic mechanisms.

Disclosure: J. Birnbaum: None; **A. N. Baer:** None; **M. Polydefkis:** None.

1916

The Temporal Appearance of Symptoms and Signs in Primary Sjögren's Syndrome. Chiara Baldini, Nicoletta Luciano, Pasquale Pepe, Rosaria Talarico, Sara Grossi, Antonio Gaetano Tavoni and Stefano Bombardieri. Rheumatology Unit, Department of Internal Medicine, University of Pisa, Italy.

Aims of the Study: (1) to characterise the clinical presentation of primary Sjögren's syndrome (pSS) in a large cohort of patients and to determine whether epidemiological, clinical and analytical features modulate disease expression; (2) to determine possible changes in clinical and immunological patients'profiles over time.

Methods: We reviewed the case records of 515 pSS patients (17 M: 498 F, mean age 57.4 years, mean follow-up 6.5± 6.4 years) who had attended our Unit in the decades between 1989 and 2009. The diagnosis was made according to either the AECG criteria (390/515) or the European Preliminary Criteria for pSS (125/515). Patients' cumulative clinical and immunologic features were collected. The lag time between the onset of the disease and the onset of each pSS clinical and serological manifestation was recorded in order to group the disease features according to their mean periods of appearance. Logistic regression analysis was applied to explore clinical and serological associations.

Results: Demographic, clinical and immunologic features of the patients are summarised in Table 1.

Disease manifestations	Prevalence (%)	Lag time from the disease onset (yrs)	
Dry mouth/Dry eyes	94%/96%	0.3 ± 0.6/0.2 ± 0.6	At the onset
Arthralgia	63%	0.8 ± 2.7	
Fatigue	45%	0.3 ± 0.7	
Raynaud's phenomenon	26%	0.7 ± 2.7	
Dry vagina	19%	0.5 ± 1.8	
Skin involvement	16%	0.7 ± 1.4	
Difficulty in swallowing	14%	0.3 ± 0.7	
Hypocomplementemia	18%	0.3 ± 0.6	
Hypegammaglobulinemia	48%	0.2 ± 0.7	
Antinuclear antibodies	83%	0.2 ± 0.2	
Anti Ro/SSA/anti La/SSB	62%/28%	0.2 ± 0.4	
Salivary gland enlargement	32%	2.2 ± 4.7	Within the first 5 years
Hematological manifestations	25%	2.3 ± 5.4	
Kidney involvement	1%	1 ± 2	
Arthritis	11%	3 ± 4.2	
Lung	7%	5.8 ± 7.0	
Peripheral nervous system	6%	5.1 ± 6.7	
Central nervous system	0.3%	11 ± 1.4	Late disease manifestations
Lymphoma	3%	17.4 ± 10.8	

Glandular manifestations were generally present at the onset of the disease. Among pSS extraglandular manifestations, arthralgias, Raynaud's phenomenon (RP), skin involvement, fatigue and difficulty in swallowing were also mainly observed at the onset of the disease, and significantly correlated with the positivity for anti-Ro/SSA and hypocomplementemia. Parotid enlargement, cytopenias, kidney involvement, peripheral nervous system and lung involvement were more frequent within the first five years of the disease, especially in seropositive patients and in patients with a lower age at diagnosis. Finally, lymphoma was generally a late disease manifestation with the lymphoproliferative risk increasing over time with an exponential function ($p=0.002$). The multivariate analysis identified a disease duration longer than 9 years ($p=0.006$), salivary glands enlargement ($p=0.003$) and hypocomplementemia ($p=0.03$) as independent variables for lymphoma.

Conclusion: This study confirmed that pSS can be considered as a mild, benign chronic disorder, the most severe lymphoproliferative manifestations being usually late complications of the disease. Epidemiological, clinical and serological features have a significant impact on the clinical presentation of pSS influencing the prevalence of extraglandular involvement and the disease outcome.

Disclosure: C. Baldini: None; **N. Luciano:** None; **P. Pepe:** None; **R. Talarico:** None; **S. Grossi:** None; **A. G. Tavoni:** None; **S. Bombardieri:** None.

1917

Vaccination of Patients with Primary Sjogren's Syndrome Induces IL-7 and Skewed B Cell Maturation with Increased Levels of Plasmablasts Resulting in Higher Titers of Vaccine-Specific IgG Antibodies. Susanna R. Brauner[2], Marika Kvarnstrom[2], Sabrina Goergen[2], Karl A. Brokstad[3], Christina Trollmo[2], Lars Klareskog[1], Roland Jonsson[3], Vivianne Malmstrom[2] and Marie Wahren-Herlenius[2]. [1]Karolinska University Hospital, Stockholm, Sweden, [2]Reumatology Unit, Karolinska Institutet, Stockholm, Sweden, [3]University of Bergen, Bergen, Norway

Background: Multiple immune disturbances underlying disease development and progression have been implicated in Sjogren's syndrome, including defects in the B cell compartment. In this study we used vaccination as a tool for in vivo intervention to understand defects in immune regulation by studying the primary immune response of individuals with primary Sjogren's syndrome, and specifically to characterize B cell development and responses.

Methods: Fourteen SSA/Ro positive women with primary Sjogren's syndrome and 18 gender and age matched healthy controls were vaccinated with A H1N1 influenza vaccine and boosted three weeks later. Blood samples were taken at vaccine administrations, as well as one and three weeks after, with a total of five sample points for each subject. At each sampling total Ig and vaccine specific immunity was analyzed by ELISPOT, ELISA and hemagglutination tests, lymphocyte phenotype was characterized by flow cytometry and routine laboratory tests were performed. Cytokine levels were analyzed in serum using a Luminex assay. Clinical parameters and potential adverse reactions of vaccination were monitored with a clinical questionnaire at each of the five visits.

Results: No significant differences in immunoglobulin levels or lymphocyte compartments were observed between patients and controls at the start of the study. After vaccination, all subjects developed protective immunity as determined by hemagglutination assay. However, already one week after the first vaccination the patients had developed significantly fewer class switched CD19+ B cells ($p<0.05$), and more immature B cells (CD19+IgD+IgM+) persisted in circulation ($p<0.05$). This skewed pattern of B cell maturation remained throughout the whole study. Surprisingly, plasmablasts (CD19lowCD138+) still increased, and were detected at a significantly higher level in patients after the second vaccination ($p<0.01$). In accordance, signficantly higher levels of several innate proinflammatory cytokines (IL-6, IL-10, IL-12p40 and TNF-alpha) as well as IL-7 ($p<0.05$), a B cell promoting cytokine, were induced in the patients. Further, the Sjögren's syndrome patients developed significantly higher titers of IgG vaccine specific antibodies ($p<0.02$). Despite this humoral immune activation in the patients, SSA/Ro52 titers remained unaffected throughout the study.

Several commonly reported adverse reactions to the vaccine were observed. Surprisingly controls reported significantly more fever and myalgia as side effects after vaccinations.

Conclusions: Patients with Sjogren's syndrome respond to vaccination and develop protective immunity. However, the induced titers of vaccine specific antibodies are significantly higher than in controls. Analysis of the immune reactions leading to antibody production revealed a skewed B cell maturation and proinflammatory cytokine response, which may reflect the mechanisms allowing high titers of autoantibodies to develop in autoimmune patients.

Disclosure: S. R. Brauner: None; **M. Kvarnstrom:** None; **S. Goergen:** None; **K. A. Brokstad:** None; **C. Trollmo:** None; **L. Klareskog:** None; **R. Jonsson:** None; **V. Malmstrom:** None; **M. Wahren-Herlenius:** None.

1918

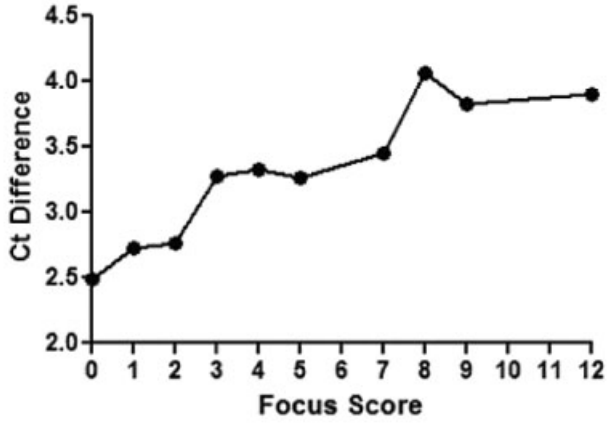
Validation of microRNAs as Biomarkers of Salivary Gland Inflammation in Sjögren's Syndrome. Seyed M. Emamian[1], Ilias Alevizos[1] and Gabor G. Illei[2]. [1]NIDCR, [2]NIDCR, NIH #10 1N114, Bethesda, MD

The diagnosis of Sjögren's syndrome (SS) is based on a number of diagnostic criteria, including the assessment of inflammation (quantified by the focus score) in a minor salivary gland (MSG) biopsy. MicroRNAs (miRNAs) are a group of RNAs, 18–24 nucleotides in length, involved in the regulation of cellular processes. miRNAs are promising as biomarkers as they are resistant to degradation and can be isolated from various sources including formalin-fixed, paraffin-embedded (FFPE) biopsies. In a preliminary study done on frozen MSG biopsies we have demonstrated that the relative expression of two miRNAs showed good association with various degrees of inflammation in a small cohort.

Purpose: To validate hsa-mir-574-3p and hsa-mir-768-3p as biomarkers of inflammation in a larger cohort of subjects.

Methods: the training cohort consisted of 49 subjects 33 with primary Sjögren's patients and 16 non-Sjogren's controls. In the validation cohort 49 subjects had pSS, 26 had sicca symptoms but no SS and 12 were healthy controls. miRNA was isolated from FFPE biopsies from MSGs. The relative expression of hsa-mir-574-3p and hsa-mir-768-3p was determined by calculating the difference of their respective threshold level (ΔCt) from the same quantitative TaqMan Real Time PCR reaction. A one unit difference in the Ct between the two microRNAs represents a two-fold difference of expression between the two microRNAs.

Results: Using a teaching cohort of 49 subjects, we first showed the ΔCt of hsa-mir-574-3p and hsa-mir-768-3p derived from FFPE samples can distinguish samples from Sjögren's from non-Sjögren's MSGs regardless of focus score (p 0.0001, one-way analysis of variance) as well as groups with various degree of inflammation. To validate the applicability of these miRNAs as biomarkers we determined the correlation between individual focus scores and the ΔCt in an independent set of 87 subjects.



A Pearson's correlation analysis showed a significant relationship between ΔCt of hsa-mir-574-3p and hsa-mir-768-3p and focus scores (r=0.85, r2=0.72, p= 0.0001).

Conclusion: The relative expression of hsa-mir-574-3p and hsa-mir-768-3p shows a strong correlation with focus scores in MSGs of Sjögren's patients validating these miRNAs are biomarkers of MSG inflammation and suggesting that they may be used to reduce the subjectivity involved in the diagnosis of SS.

Disclosure: S. M. Emamian: None; **I. Alevizos:** None; **G. G. Illei:** None.

ACR Poster Session C
Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment II
Wednesday, November 10, 2010, 9:00 AM–6:00 PM

1919

Abatacept (ABA) in the Treatment of Psoriatic Arthritis (PsA): 12-Month Results of a Phase II Study. Philip J. Mease[8], Mark C. Genovese[9], Geoffrey S. Gladstein[3], Alan J. Kivitz[2], Christopher T. Ritchlin[11], Paul P. Tak[1], Jurgen Wollenhaupt[7], Jean-Claude P. Becker[4], Sheila M. Kelly[6], Yun Peng[5] and Dafna D. Gladman[10]. [1]Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, [2]Altoona Arthritis & Osteo Ctr, Duncansville, PA, [3]Arthritis Int Med Assoc LLC, Trumbull, CT, [4]Bristol-Myers Squibb, Princeton, NJ, [5]Bristol-Myers Squibb, Pennington, NJ, [6]Bristol-Myers Squibb, Doylestown, PA, [7]Schoen Klinik, Hamburg, Germany, [8]Seattle Rheumatology Associate, Seattle, WA, [9]Stanford University, Sunnyvale, CA, [10]Toronto Western Hospital, Toronto, ON, Canada, [11]University of Rochester Medical Center, Rochester, NY

Purpose: A phase II study evaluating ABA in PsA patients (pts) previously exposed to disease-modifying antirheumatic drugs (DMARDs) including anti-TNF agents demonstrated the efficacy of ABA against both arthritis and psoriasis after 6 months (mos) of double-blind (DB) treatment (Mease P, et al. *Ann Rheum Dis* 2010;69(Suppl3):98. Abstract SAT0288). Here, we assess the efficacy and safety of ABA after pts completed at least 6 mos of an open-label (OL) extension phase.

Methods: In the 6-mo DB study, 170 PsA pts previously exposed to DMARDs, including anti-TNF agents, were randomized (1:1:1:1) to receive placebo (PBO) or ABA 30/10 (2 initial doses of 30 mg/kg, followed by 10 mg/kg), 10 or 3 mg/kg on Days 1, 15, 29, and once every 28 days thereafter. Pts who completed this phase were eligible to continue in an OL study, and received ABA 10 mg/kg every 28 days for at least 6 mos. Endpoints included measures of joint disease (ACR20, DAS28), joint inflammation by magnetic resonance imaging (MRI), skin disease (target lesion [TL] score, Psoriasis Area and Severity Index [PASI]), physical function (Health Assessment Questionnaire-Disability Index [HAQ-DI]), and safety. Data were as-observed and analyzed on a modified intent-to-treat basis.

Results: A total of 147 pts from all 4 DB treatment groups entered the OL phase; baseline characteristics were similar among groups except for more pts being previously exposed to anti-TNF agents in the 30/10 mg/kg group (49%) than other groups (24–37%). Eighty-eight pts were still on treatment with 47 pts discontinuing due to lack of efficacy. Efficacy data are presented by original randomization group [Table 1]. At Day 169 of DB treatment, ABA improved ACR20 and DAS28, HAQ-DI, TL and PASI scores, and also resulted in less joint damage by MRI evaluation, as compared to PBO. Improvements in ACR and DAS28, reduction in joint damage by MRI and improvement in HAQ-DI continued through Day 365 in pts treated with ABA in the OL phase. Improvements in TL and PASI scores also continued through Day 365. Pts on PBO during the DB period achieved comparable improvements in joint and skin disease, joint inflammation and physical function after ABA treatment in the OL phase. Pts treated with ABA 10 mg/kg during the DB period appeared to have achieved the greatest overall improvements. The safety profile during the OL treatment was consistent with that during the DB period. Serious adverse events were numerically higher in the 10 mg/kg group (18%) vs other groups (8–12%); these were single events with no obvious pattern. One serious infection was reported in each group except for 2 cases in the 10 mg/kg group. There was 1 malignancy, a lentigo maligna, in the 3 mg/kg group. There were no autoimmune events or deaths.

Conclusions: The efficacy of ABA in pts with PsA, demonstrated during short-term DB treatment, was sustained throughout 6 mos of OL treatment. No new safety issue was detected.

Table 1. Efficacy of ABA in PsA pts at Days 169 (DB) and 365 (OL)

Response	ABA 30/10 mg/kg N=37	ABA 10 mg/kg N=34	ABA 3 mg/kg N=43	Placebo N=33
ACR20* at Day 169	49 (33, 65)	56 (39, 73)	35 (21, 49)	24 (10, 39)
ACR20* at Day 365	46 (30, 62)	58 (41, 74)	54 (38, 69)	47 (30, 64)
DAS28 (CRP)†* at Day 169	60 (44, 75)	56 (39, 73)	42 (26, 57)	21 (7, 35)
DAS28 (CRP)†* at Day 365	52 (35, 69)	79 (63, 94)	58 (42, 74)	52 (34, 69)
MRI of joints‡ at Day 169				
Erosion	0.9 (3.2)	−0.4 (3.4)	0.8 (2.5)	1.7 (5.1)
Edema	−0.5 (1.6)	−0.8 (3.0)	−0.1 (1.1)	0.6 (3.4)
Synovitis	−0.2 (3.2)	−1.2 (4.0)	0.3 (2.1)	0.4 (3.5)
MRI of joints‡ at Day 365				
Erosion	0.5 (2.6)	0.3 (5.1)	0.6 (2.1)	1.2 (3.8)
Edema	−1.1 (2.0)	−1.7 (2.6)	−0.1 (1.4)	−0.5 (2.5)
Synovitis	−1.8 (3.0)	−2.5 (4.4)	−0.6 (2.1)	−0.7 (3.4)
TL response¶* at Day 169	38 (22, 54)	44 (27, 61)	44 (29, 59)	33 (17, 49)
TL response¶* at Day 365	40 (23, 58)	41 (24, 59)	44 (27, 61)	39 (19, 59)
PASI50* at Day 169	42 (20, 64)	40 (915, 65)	45 (23, 67)	19 (0, 38)
PASI50* at Day 365	31 (9, 54)	54 (27, 81)	47 (21, 72)	40 (10, 70)
HAQ§* at Day 169	41 (25, 56)	53 (36, 70)	38 (23, 53)	24 (10, 39)
HAQ§* at Day 365	40 (23, 58)	57 (39, 76)	53 (36, 70)	52 (32, 73)

Treatment groups represent treatment received the DB period. N indicates the number of pts who completed the DB treatment and who received abatacept 10 mg/kg in the OL phase. *% pts with 95% CI; †Improvement of ≥ 1.2 unit from baseline; ‡Mean (SD) change from baseline; ¶Scoring of target lesions as clear or almost clear; §Improvement of ≥ 0.3 unit from baseline

Disclosure: P. J. Mease: Bristol-Myers Squibb, 2, 5, 8; **M. C. Genovese:** Bristol-Myers Squibb, 2, 5, 8; **G. S. Gladstein:** Bristol-Myers Squibb, 2, 5, 8; **A. J. Kivitz:** Bristol-Myers Squibb, 2, 5, 8; **C. T. Ritchlin:** None; **P. P. Tak:** Bristol-Myers Squibb, 5; **J. Wollenhaupt:** Bristol-Myers Squibb, 9; **J.-C. P. Becker:** Bristol-Myers Squibb, 1, 3; **S. M. Kelly:** Bristol-Myers Squibb, 1, 3; **Y. Peng:** Bristol-Myers Squibb, 1, 3; **D. D. Gladman:** Abbott Laboratories, 2, 5, 8, Amgen Inc., 2, 5, 8, Bristol-Myers Squibb, 2, 5, 8, Pfizer Inc, 2, 5, 8.

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Agreement between Total Joint Count and DAS 28 Joint Count in Psoriatic Arthritis. Jose Luis Fernandez-Sueiro[1], Eugenia Gonzalez Diaz de Rabago[1], J. Pinto-Tasende[1], Sonia Pertega-Diaz[1], J. C. Fernandez-Lopez[1], N. Oreiro-Villar[1], F. Galdo[1] and Francisco J. Blanco[2]. [1]Complejo Hospitalario Universitario La Coruña, La Coruña, Spain, [2]Complejo Hospitalario Universitario La Coruña, A Coruna, Spain

Background: Distal interphalangeal involvement is a characteristic feature of psoriatic arthritis (PsA), in this sense total joint count in PsA can be considered as 78 tender and 76 swollen joints. DAS 28 only evaluates 28 joints, therefore it is not clear whether counting only 28 joints is sufficient to evaluate peripheral joint involvement in PsA.

Objective: to evaluate the agreement between total joint count and DAS 28 joint count in PsA patients.

Patients and Methods: analysis at three consecutive time points (T0, T1 and T2) of a longitudinal observational cohort of PsA patients. In all patients total joint count (78 tender joint count (TJC) and 76 swollen joint count (SJC)) were performed. Analysis of the agreement between total joint count and DAS28 joint count was performed with the Bland-Altman methodology and the Kappa index.

Results: Mean TJC was: T0 total 3.9±6.7 vs DAS28: 2.5±5.0 (p<0,001), T1 2.3±4.5 vs 1.2±2.7 (p<0.001), T2 3.2±7.3 vs 1.8±4.5 (p=0.001). Mean SJC: T0 total 1.3±3.5 versus DAS28 0.9±2.7 (p=0.004), T1 0.6±0.5 vs 0.5±1.5 (p=0.002), T2 0.5±1.5 vs 0.1±0.4 (p=0.021). The mean difference between the number of tender joints (total joint count – DAS 28) was: T0 1.4±3.0, T1 1.3±2.9, T2 1.4±3.7, in swollen joints was T0 0.4±1.7, T1 0.3±1.1, T2 0.3±1.5.

Disagreement in one or more tender joints between the total count and the DAS 28 was found in T0 30.4%, T1 28.8%, T2 28.3% of the patients. In swollen joints, these figures were T0 11.1%, T1 14.4% and T2 13.0%. After categorizing TJC in ≤1 joint and >1 joint, Kappa index for the agreement between the total joint count and DAS28 was T0 0.764, T1 0.722, T2 0.836. For SJC, Kappa index was T0 0.811, T1 0.704, T2 0.378.

Using DAS28 joint count, at T0 51.9% (T1 60.5%, T2 65.5%) of the patients met minimal disease activity criteria. Of these, 7.5% (T1 12.0%, T2 5.1%) would not meet the criteria when using the total joint count (Kappa index=0.923).

Conclusions: At three different time-points, there are differences between total tender and swollen joint count and DAS 28 joint count, however the agreement between total joint count and DAS28 is high. On the other hand the agreement to classify patients with minimal disease activity is fairly good. These data suggest that DAS 28 joint count may be reliable for evaluating peripheral involvement in PsA.

Disclosure: J. L. Fernandez-Sueiro: None; **E. Gonzalez Diaz de Rabago:** None; **J. Pinto-Tasende:** None; **S. Pertega-Diaz:** None; **J. C. Fernandez-Lopez:** None; **N. Oreiro-Villar:** None; **F. Galdo:** None; **F. J. Blanco:** None.

1921

An Initial Diagnosis of Lumbar Disc Herniation Is Associated with a Late Refferral to the Rheumatologist and a Delay in the Diagnosis of Ankylosing Spondylitis. Servet Akar[1], Vedat Gerdan[1], Dilek Solmaz[1], Mehmet Sayarlioglu[4], Mehmet Akif Ozturk[2], Ahmet Mesut Onat[3], Bünyamin Kisacik[3], Mehmet Emin Tezcan[2], Merih Birlik[1], Fatos Onen[1] and Nurullah Akkoc[1]. [1]Rheumatology, Dokuz Eylul Univerisity Faculty of Medicine, Izmir, Turkey, [2]Rheumatology, Gazi University, Ankara, Turkey, [3]Rheumatology, Gaziantep University Faculty of Medcine, Gaziantep, Turkey, [4]Rheumatology, KahramanMaras Sutcu Imam University Faculty of Medicine, KahramanMaras, Turkey

Background: Among all the rheumatologic diseases, AS still remains to be the one with, the longest diagnostic delay mostly due to the slow development of radiographic sacroiliitis. In clinical practice, many patients with AS are diagnosed to have lumbar disk herniation (LDH), which in our opinion might be one of the the possible determinants of diagnostic delay in these patients. In this study we assessed the diagnostic delay in AS patients with an initial diagnosis of LDH compared with those without such diagnosis.

Patients and Methods: 393 patients (258 male [65,6%], mean age 39,3 ± 10,8 years) with AS according to the modified New York criteria from five rheumatology clinics in different cities were included in this analysis. A face to face interview was performed by using a structured questionnaire addressing all the possible factors that may lead to diagnostic delay, including the specialty of the first consulted physician, the initial diagnosis and history for LDH. Total *diagnostic delay was calculated* as the time elapsed from the initial visit to the physician due to back pain until the diagnosis of AS. Factors associated with the diagnostic delay were evaluated by Spearman's correlation and linear regression methods

Results: An initial diagnosis of LDH was reported by 33% of the 300 patients who could answer this question. The diagnostic delay in patients with an initial diagnosis of LDH vs those without such diagnosis was 9.1± 8,5 years and 6,2±7,4, years, respectively (p=0.002). Twenty six patients had undergone operation for LDH and the diagnostic delay in those patients was markedly higher than the patients without LDH surgery (13,3 ± 11,3 vs 6.2 ± years, P=0,023). Referral time to the rheumatologist was also significantly greater in patients with an initial diagnosis of LDH and in patients with a history of LDH surgery compared to the others.

Rheumatologists were seen as the initial physicians by only 4% of the patients whereas, 30% consulted physiatrist, 25% consulted orthopedists and 16% consulted orthopedists at their 1st medical visit due to back pain. The shortest delay in diagnosis was observed when rheumatologists were the first consulted physicians (2,9 ± 5,3 years).The delay period for the physiatrists was shorter (6,3 ± 7,6 years) than the orthopedists (9,6 ± 9,1 years) and neurosurgeons (8,8 ± 6,6 years). However, diagnostic delay was not found to be correlated with sex, family history, HLA-B 27 status and acute phae response. In the linear regression analysis age at spondyloarthritic symptom onset (p=0,013), age at back pain onset (p=0,01), and education level (p=0,003) were also found to be significant predictors of the diagnostic delay.

Conclusion: Our results suggest that prior diagnosis of LDH may lead to late referral of AS patients to rheumatologists resulting in a delay in diagnosis. A relatively high percentage of patients with LDH surgery is of concern, pointing out the necessity of continuous medical education of the specialists who are likely to see patients with AS, on the concept of spondyloarthritis.

Disclosure: S. Akar: None; **V. Gerdan:** None; **D. Solmaz:** None; **M. Sayarlioglu:** None; **M. A. Ozturk:** None; **A. M. Onat:** None; **B. Kisacik:** None; **M. E. Tezcan:** None; **M. Birlik:** None; **F. Onen:** None; **N. Akkoc:** None.

1922

Ankylosing Spondylitis Disease Activity Score (ASDAS): Defining Cut-Off Values for Disease Activity States and Improvement Scores. Pedro Machado[1], Robert Landewe[7], Elisabeth Lie[3], Tore K. Kvien[2], Juergen Braun[6], Daniel G. Baker[5] and Desiree M. Van Der Heijde[4]. [1]Coimbra University Hospital, Coimbra, Portugal; Leiden University Medical Center, Leiden, The Netherlands, [2]Diakonhjemmet Hospital, Oslo, Oslo, Norway, [3]Diakonhjemmet Hospital, Oslo, Norway, [4]Leiden University Medical Center, Meerssen, The Netherlands, [5]Research and Development, Centocor Inc, Malvern, PA, [6]Rheumazentrum Ruhrgebiet, Herne, Germany, [7]Univ Hosp Maastricht, Maastricht, The Netherlands

Purpose: ASDAS is a new composite index to assess disease activity in ankylosing spondylitis (AS). It has high construct and discriminatory validity. Criteria for disease activity states and improvement scores are important for clinical trials and clinical practice and have not been developed so far. Our aim was to determine clinically relevant cut-off values for disease activity states and improvement scores using the ASDAS.

Methods: The ASDAS is calculated using BASDAI questions 2, 3 and 6, patient global assessment (all 0–10cm VAS) and CRP (mg/L). We performed receiver operating characteristic (ROC)-curve analysis against several external criteria (ExCr) and used several approaches to determine the optimal cut-off (fixed 90% specificity, Youden index and closest point to (0,1)). The final choice was made on clinical and statistical grounds, after debate and voting by Assessment in SpondyloArthritis Society (ASAS) members. For the identification of proposed cut-offs we used baseline (BL) and 3-month (M) data of NOR-DMARD (N=295–477), a registry that includes AS patients starting a conventional DMARD or a TNF-blocker. Cross-validation was performed in ASSERT, a database of AS patients participating in a randomized placebo-controlled trial with infliximab.

Results: Four disease activity states were chosen by consensus: inactive disease, moderate-, high- and very high disease activity. The 3 cut-offs for separating them were: 1.3 (ExCr: ASAS partial remission, patient and physician global <1cm), 2.1 (ExCr: patient and physician global <3cm) and 3.5 (ExCr: patient and physician global >6cm). Selected cut-offs for improvement scores were: change ≥1.1 units for clinically important improvement (ExCr: patient reporting as being "better" or "much better" since start of treatment) and change ≥2.0 units for major improvement (ExCr: patient reporting as being "much better" since start of treatment). Results of the cross-validation in ASSERT strongly supported the cut-offs (tables 1 and 2).

Table 1. Disease activity states (%) in ASSERT: Infliximab vs Placebo (Chi^2, p-value)

Time-point	n	ASAS Partial Remission	ASDAS <1.3	1.3 ≤ ASADAS < 2.1	2.1 ≤ ASDAS ≤ 3.5	ASDAS >3.5
BL	166 vs 57	0 vs 0 (NA)	0 vs 0 (NA)	1.2 vs 1.8 (0.1, 0.756)	30.1 vs 26.3 (0.3, 0.586)	68.7 vs 71.9 (0.2, 0.645)
3M	163 vs 56	21.5 vs 1.8 (11.8, 0.001)	25.8 vs 1.8 (15.2, <0.001)	26.4 vs 3.6 (13.3, <0.001)	38.7 vs 39.3 (0.01, 0.933)	9.2 vs 55.4 (53.5, <0.001)
6M	163 vs 56	23.3 vs 1.8 (13.2, <0.001)	31.9 vs 0 (23.4, <0.001)	23.3 vs 12.5 (3.0, 0.084)	32.5 vs 33.9 (0.04, 0.846)	12.3 vs 53.6 (40.6, <0.001)

Table 2. Improvement criteria (%) in ASSERT: Infliximab vs Placebo

Improvement criteria	3 months (n=164 vs 56)	chi-square (p-value)	6 months (n=163 vs 56)	chi^2 (p-value)
Δ ASDAS≥ 1.1	71.3 *vs* 19.6	45.9 (<0.001)	69.3 *vs* 23.2	36.3 (<0.001)
Δ ASDAS≥2.0	43.9 *vs* 3.6	30.4 (<0.001)	50.9 *vs* 5.4	36.3 (<0.001)
Δ BASDAI≥2	60.4 *vs* 23.2	23.1 (<0.001)	62.6 *vs* 19.6	30.8 (<0.001)
BASDA150	50.6 *vs* 10.7	27.6 (<0.001)	51.5 *vs* 12.5	26.1 (<0.001)
ASAS20	64.0 *vs* 25.0	25.6 (<0.001)	63.2 *vs* 21.4	29.2 (<0.001)
ASAS40	50.6 *vs* 16.1	20.5 (<0.001)	47.2 *vs* 14.3	19.1 (<0.001)

Conclusions: Cut-off values for disease activity states and improvement scores using the ASDAS have been developed. They proved to have external validity and a very good performance compared to existing criteria.

Disclosure: P. Machado: Articulum Network, 9; **R. Landewe:** Centocor, Inc., 5; **E. Lie:** None; **T. K. Kvien:** None; **J. Braun:** Centocor, Inc., 5; **D. G. Baker:** Centocor, Inc., 3; **D. M. Van Der Heijde:** Centocor, Inc., 5.

1923

Ankylosing Spondylitis Patient Organisations—Are There Benefits of Membership? In-Ho Song[1], Cornelia Brenneis[1], Ludwig Hammel[2], Ernst Feldtkeller[2], Joachim Listing[3], Joachim Sieper[1] and Martin Rudwaleit[1]. [1]Charite Campus Benjamin-Franklin, Medical Clinic I, Rheumatology, Berlin, Germany, [2]German Ankylosing Spondylitis Society (DVMB), Schweinfurt, Germany, [3]German Rheumatism Research Center, Berlin, Germany

Background: Patient organisations for ankylosing spondylitis (AS) exist in many countries. The aims of these patient organisations are to inform and to educate patients in order to help them better deal and cope with the disease, to organize supervised physiotherapy groups, to support the exchange of experiences, and to represent the interests of patients in society and law (see www.spondylitis-international.org).

Objective: To evaluate differences between AS patients who are members of a patient organisation and AS patients who are not such members.

Methods: The German Ankylosing Spondylitis Society (DVMB) is a large patient organisation with more than 14,000 members in Germany. A cross-sectional survey based on a questionnaire was performed between December 2008 and April 2009. The questionnaire consisted of 82 questions regarding demographics, diagnosis, smoking, acquisition of information about the disease, disease activity, mobility, functional status, patient satisfaction, quality of life, treatment and disability to work and educational level. The questionnaire was distributed to AS patients by rheumatolgists in 51 hospitals and/ or private practices. In addition, the questionnaire was sent to 3400 randomly selected members of the German AS society. Data collection and analysis was done anonymously.

Results: In total, 1273 patients responded (1068 members of the patient organisation and 205 non-members). As DVMB members and non-members were not comparable regarding age (mean 54.9 vs. 46.6 years) and disease duration (mean 30.2 vs. 20.1 years) we performed a 2:1-matching of members to non-members regarding age, disease duration and also sex. In the matched population (n=549), members (n=366, mean age 47.0 years, mean disease duration 21.1 years, 63.9% male, HLA-B27 positive 89.0%) and non-members (n=183, mean age 46.3 years, mean disease duration 20.1 years, 63.9% male, HLA-B27 positive94.6%) differed in the following aspects: members more often felt that they were well informed (62.2% vs. 35.4%, p= < 0.001), more often used the information provided by the patient organisation (58.5% vs. 11.5%, p< 0.001), and more often had a positive family history for AS (34.4% vs. 23.3%, p= 0.004). There were nodifferences regarding disease activity (BASDAI 4.0 vs. 4.2, p= 0.172) or in the percentage of patients taking NSAIDs, DMARDs or anti-TNF-blocking agents.

Members as opposed to non-members had a better functional status (BASFI 3.4 vs. 3.9), p= 0.021), had less work days missed during the last year (15.1 days vs. 31.2 days, p= 0.003), were more often non-smokers (55.9% vs. 71.0%, p= 0.001). However, significantly more members had a higher educational status (e.g. percentage with university diploma 26.0% vs. 12.4%, p< 0.001).

Conclusion: There are numerous benefits associated with the membership in an ankylosing spondylitis patient organisation. AS patients who are members feel better informed about AS, have a better functional status and a healthier life style, and, overall, seem to cope better with the disease than non-members. Whether the educational status and the degree of physically challenging jobs influence the findings needs further examination.

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1924

Anterior Chest Wall Pain in Spondyloarthritis Is a Frequent Manifestation, Appearing Early in the Disease Course, Which May Respond to NSAIDs. Muriel Elhai[1], Simon Paternotte[1], Fanny Roure[1], Eugénie Koumakis[1], Judith Payet[1], Vincent Burki[1], Isabelle Fabreguet[1], Magali Meyer[1], Maxime Dougados[2] and Laure Gossec[1]. [1]Cochin Hospital and Paris Descartes University, Paris, France, [2]Hospital Cochin, Paris, France

Background: Chest pain is a common but little studied feature of spondyloarthritis (SpA).

Objective: To assess the prevalence of anterior chest wall pain (ACWP) among a cohort of patients with SpA in a tertiary care center and to describe clinical characteristics of ACWP.

Method: *Study design*: retrolective single center observational study in

2010 (COSPA). *Patients*: definite SpA (Amor's criteria). Each patient underwent direct interview by a physician. *Data collection*: prevalence of ACWP, according to SpA subtype (axial versus peripheral, enthesitic or extra-articular) and if present, the date of appearance, the localization and nature of the pain, and effectiveness of the different treatments. *Analysis*: descriptive analysis.

Results: To date, 151 consecutive SpA patients were assessed: median age 43 (inter-quartile range 35–55) years, median disease duration 15 (8–25) years, 97 (64%) were men. In all, 56 patients (37%) suffered from SpA-associated ACWP. ACWP appeared before the diagnosis of SpA in 38% (17/45) cases; it was the first symptom of SpA in 5% (3/56) cases, and it appeared during the first 5 years of disease duration in 69% (31/45) cases. ACWP was localized in the sternoclavicular joint (26%), the manubrio-sternal joint (48%), the upper sternocostal joints (67%) and/or the lower sternocostal joints (55%). ACWP was usually acute, with painful flares (76%), with (N=16) or without (N=24) chronic pain. Coronary tests were performed for this pain in 2 cases. Respiratory movements and movements of the arm increased the pain in respectively 78% (40/51) and 55% (26/47) of cases; pain during the night was less frequent (40%, 21/53). Nonsteroidal anti-inflammatory drugs prescribed for this indication were effective in 53 % of cases (17/32), whereas anti-tumor necrosis factor agents were reported as effective in 73 % of cases (19/26).

Conclusion: This study is the largest clinical description of ACWP in SpA. ACWP is a frequent manifestation in SpA (37%); it occurs early in the disease which may be a challenge for diagnosis. ACWP in SpA is usually acute; it does not frequently lead to night pain. NSAIDs may be a useful first line treatment.

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1925

Assessment of Efficacy and Safety of Pamidronate in Undifferentiated Spondyloarthropathy (uSpA): A Placebo Control Trial in a Tertiary Level Centre. Rathindra N. Sarkar[1], Sibaji Phaujdar[2], Sattik Siddhanta[2], Siwalik Banerjee[2], Dibeyendu De[2], Kuntal Bhattacharyya[2] and H. K. Pal[2]. [1]Calcutta Medical College, Kolkata, West Bengal, India, [2]Calcutta Medical College, Kolkata

Background: Undifferentiated spondyloarthropathy (uSpA) represents an incomplete form or early phase of Ankylosing spondylitis (AS) or another distinct type of spondyloarthropathy, whereas nonsteroidal anti-inflammatory drugs (NSAIDs) and disease modifying anti-rheumatic drugs (DMARDs) are still mainstay of treatment, tumour necrosis factor antagonists have shown good results in patients (pts) with severe symptoms or axial involvement but are very expensive and suppresses immunity. Pamidronate, an aminobisphosphonate, has shown anti-tumour necrosis factor properties. We evaluated efficacy and safety of Pamidronate in Indian uSpA pts refractory to NSAIDs therapy.

Methods: Fifty four pts fulfilling the modified Amor criteria for diagnosis of uSpA, having active disease even after 3 month's continuous therapy with two NSAIDs in maximal dose were selected. Active disease was defined as a Visuo-Analogue Scale (VAS) >50 (0–100mm scale) in 3 out of 4 following parameters: pts' global assessment, pain, Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI-morning stiffness). Patients receiving Sulfasalazine, 2–3g orally per day for peripheral arthritis were allowed to continue.

Patients were divided into Pamidronate group (N=40, received 60 mg monthly i.v. infusion in 500 ml Normal saline) and Placebo group (N=14, received Normal saline monthly i.v. infusion). Pts allowed continuing the analgesics. Efficacy assessment at the baseline and at 6-month was done using BASMI, BASFI, BASDAI, Bath Ankylosing Spondylitis Global Score (BAS-G), CRP and ESR. Proportion of pts achieving ASAS-20 and BASDAI-50 were also recorded at 6 months. Pts were observed for any AE. This study has clearance from Institutional Ethics Committee.

Results: Pts with USpA (n=54, M: F: 8:1), mean (SD) age was 46.54 (8.57) years, mean (SD) disease duration was 3.94 (1.14) years. Baseline characteristics and the disease activity in both treatment groups were similar. Changes in the parameters from baseline to 6 months in both groups are as described in Table 1. In Pamidronate group, there was significant reduction in all parameters compared to baseline while 32 pts (80 %) achieved ASAS-20 and 27 pts (67.5 %) achieved BASDAI-50 response, Pts in the placebo group showed increase in all the parameters. Very early feel good response was found in 23 pts (57.5 %) within 36 hours of first Pamidronate infusion. Mild fever, arthralgia, myalgia noted in 7 (17.5%) pts after first dose and in 3 cases (7.5 %) after second dose of Pamidronate.

Table 1. Clinical and laboratory parameters at baseline and 6 months

	Pamidronate (N=40)		Placebo (N=14)	
Parameter	**Baseline**	**6 months**	**Baseline**	**6 months**
BASDAI	7.68 ± 1.33	3.80 ± 1.74*	8.04 ± 1.22	8.31 ± 1.05
BASFI	7.53 ± 0.98	3.67 ± 1.79*	7.53 ± 0.84	7.97 ± 0.87
BAS-G	7.56 ± 0.941	3.14 ± 0.62*	7.57 ± 0.90	7.68 ± 1.22
BASMI	7.33 ± 1.12	3.05 ± 0.71*	7.36 ± 1.01	7.86 ± 0.86
CRP(mg/L)	9.40 ± 3.74	8.83 ± 2.76*	8.83 ± 2.77	9.76 ± 2.81
ESR(mm/h)	78.93 ± 22.05	30.00 ± 5.33*	81.64 ± 19.63	86.21 ± 11.05

All values mean ± SD; *p < 0.0001 compared to baseline

Conclusion: Pamidronate appears to be effective treatment option for pts with uSpA with acceptable safety profile.

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1926

Can Clinical Phenotype Identify Early Psoriatic Arthritis in an Early Arthritis Cohort? Laura C. Coates[3], Philip G. Conaghan[3], Paul Emery[3], Michael J. Green[4], Gamal Ibrahim[1], Helen MakIver[1] and Philip S. Helliwell[2]. [1]Bradford Hospitals NHS Trust, UK, Bradford, United Kingdom, [2]LIMM, Section of Musculoskeletal Disease, University of Leeds, Leeds, UK, [3]LIMM, Section of Musculoskeletal Disease, University of Leeds, UK, [4]York Hospital NHS Trust, York, UK

Background: The classification of psoriatic arthritis (CASPAR) criteria are increasingly used to identify psoriatic arthritis. However the initial stem of the CASPAR criteria states that patients must have inflammatory joint, entheseal or spinal disease. The aim of this study was to assess whether the phenotype of inflammatory disease differed between early PsA and other forms of early inflammatory arthritis.

Methods: Cases of early PsA (less than 24 months symptom duration) and controls with other forms of early inflammatory arthritis who were all disease modifying anti-rheumatic drug naive were recruited. Gold standard diagnosis was confirmed by a consultant rheumatologist. A 66/68 joint count, enthesitis count (Maastricht Ankylosing Spondylitis Enthesitis Score – MASES, Leeds Enthesitis Index – LEI and plantar fascia) and assessment of axial disease were performed to assess presence of inflammatory disease.

Results: 111 early PsA cases and 111 early arthritis controls (RA n=82, undifferentiated arthritis n=13, spondyloarthritis n=9, inflamm OA n=4, crystal arthritis n=3) were recruited. All but one of the controls had arthritis. The pattern of arthritis (oligoarticular vs polyarticular) and the average tender and swollen joint counts did not differ significantly between cases and controls. DIP joint involvement was significantly more common in PsA cases than controls (32% vs 16%, p=0.007). When comparing PsA cases only to controls with RA (n=82), PsA cases had significantly lower joint counts (p<0.008)

Presence of enthesitis was significantly more frequent in the PsA patients compared to controls (67% vs 52%, p=0.029). There was a trend towards higher enthesitis counts in PsA cases compared to control patients but this was not significant. Spondylitis appeared more frequent in the PsA patients but the difference was not significant due to small numbers (5% vs 1%, p=0.055).

	Cases (n=111)	Controls (n=111)	RA controls (n=82)
Proportion with arthritis (%)	100	99	100
Oligoarthritis (%)	30	24	15
Polyarthritis (%)	70	76	85
DIP joint involvement (%)	32	16	18
Median TJC (IQ range)	7 (13)	8 (15)	12 (16)
Median SJC (IQ range)	5 (7)	5 (9)	7 (11)
Proportion with enthesitis (%)	67	52	52
Median enthesitis count (IQ range)	2 (4)	1 (3)	1 (4)
Proportion with spondylitis (%)	5	1	0

Conclusion: Different clinical phenotype cannot be relied upon to identify early psoriatic arthritis. Enthesitis and DIP joint involvement are

more frequent in early PsA compared to other forms of inflammatory arthritis, however a significant proportion of controls (including a significant proportion of patients with RA) also have clinical enthesitis. Spondylitis is likely to be more frequent in PsA than in RA, however it cannot be relied upon to differentiate from other forms of inflammatory arthritis.

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1927

Clinical Improvement with Etanercept Versus Sulfasalazine Treatment in Patients with Ankylosing Spondylitis: Comparative Performance of Various Efficacy Measurements (ASCEND). Desiree M. Van Der Heijde[2], Juergen Braun[7], Maxime Dougados[1], Annette Szumski[4], Ronald Pedersen[6], Bonnie Vlahos[3], Bruce Freundlich[4] and Andrew S. Koenig[5]. [1]Hospital Cochin, Paris, France, [2]Leiden University Medical Center, Meerssen, The Netherlands, [3]Pfizer, Inc., Pottstown, PA, [4]Pfizer, Inc., Collegeville, PA, [5]Pfizer, Inc., Blue Bell, PA, [6]Prizer, Inc., Collegeville, PA, [7]Rheumazentrum Ruhrgebiet, Herne, Germany

Background: Ankylosing spondylitis (AS) is a form of spondyloarthritis characterized by inflammatory back pain, peripheral arthritis, enthesitis, and extra-articular features such as uveitis. The disease frequently has an early onset and can seriously impair patients' quality of life and ability to work. Sulfasalazine (SSZ) is commonly used for the treatment of predominantly peripheral as well as axial symptoms of AS. Etanercept (ETN), a fully human TNF soluble receptor, has demonstrated short- and long-term efficacy in patients with AS. Outcome measures used in clinical trials need to be highly responsive to help detect improvement and discriminate between treatment effects. The ASCEND trial, a randomized, double-blind study that compared the efficacy of ETN and SSZ in subjects with axial and peripheral manifestations of AS, did not include a placebo arm, which hampered assessment of the net benefits of treatment. To gain more insight, we compared the discriminatory capacity of several AS assessments used in the trial.

Methods: In the ASCEND trial, subjects with AS received ETN 50 mg once weekly (n=379) or SSZ titrated to a maximum of 3 g daily (n=187) for 16 weeks. Week-16 adjusted treatment differences and effect sizes of improvement from baseline of several outcomes were used to assess their ability to detect improvement and discriminate between the effects of ETN and SSZ. All randomized subjects who received ≥1 dose of study drug and provided data at baseline and Week 16 were included in this analysis.

Results: The adjusted treatment differences and effect sizes of improvement from baseline between treatment groups for several efficacy outcomes are shown in descending order based on their treatment effect size (Table). All measures detected a greater treatment effect with ETN than with SSZ after 16 weeks of treatment.

Adjusted Week-16 treatment differences and effect sizes of improvement from baseline for ETN vs SSZ

Outcome Measure	Adjusted Treatment Difference* (SD)	Adjusted Effect Size† (95% CI)	Outcome Measure	Adjusted Treatment Difference* (SD)	Adjusted Effect Size† (95% CI)
ASDAS	0.80 (0.88)	0.91 (0.72, 1.09)	BASMI	0.59 (1.33)	0.44 (0.26, 0.63)
CRP	8.61 (11.59)	0.74 (0.56, 0.93)	SF-36 PCS	3.70 (8.55)	0.43 (0.25, 0.61)
Noctumal back pain	16.41 (24.83)	0.66 (0.48, 0.85)	Modified Schober's test	0.49 (1.57)	0.31 (0.13, 0.50)
Back pain	14.73 (24.48)	0.60 (0.42, 0.79)	Swollen joint count (68 joints)	0.40 (2.37)	0.17 (−0.02, 0.36)
Physician Global Assessment of disease activity (0–100 mm VAS)	11.44 (19.35)	0.59 (0.41, 0.78)	Chest expansion	0.18 (3.05)	0.06 (−0.13, 0.25)
BASDAI	12.08 (20.93)	0.58 (0.39, 0.76)	Occiput-to-wall distance	0.28 (4.55)	0.06 (−0.12, 0.25)
BASFI	9.92 (20.89)	0.48 (0.29, 0.66)			

*Difference in improvement between ETN and SSZ, based on an ANCOVA model adjusted for the endpoint's baseline and pooled site.
†Adjusted difference between ETN and SSZ, divided by ANCOVA model-based SD estimate.

Conclusions: In this blinded head-to-head trial conducted in subjects with active AS, the ASDAS showed the best discriminatory capacity followed by the objective measure CRP. Overall, subjective outcome measures, such as nocturnal back pain, back pain, Physician Global Assessment of disease activity, and BASDAI, showed a somewhat lower discriminatory capacity than CRP. Including objective measures either as part of the ASDAS or alone as CRP improved the discriminatory capacity of the outcome assessments.

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Comparison of Comorbid Disease Burden in Psoriasis and Psoriatic Arthritis (PsA). Janice Husted[1], Arane Thavaneswaran[4], Vinod Chandran[4], Lihi Eder[4], Sutha Shanmugarajah[4], Cheryl F. Rosen[2] and Dafna D. Gladman[3]. [1]Department of Health Studies & Gerentology, University of Waterloo, [2]Division of Dermatology, Toronto Western Hospital, [3]Toronto Western Hospital, Toronto, ON, Canada, [4]University of Toronto Psoriatic Arthritis Clinic

Background: The purpose of this study was to determine whether the presence of psoriatic arthritis (PsA) is associated with a higher comorbid disease burden compared to psoriasis without arthritis.

Methods: In 2006, lifetime prevalence of comorbid physical and mental conditions was collected for 449 psoriasis patients (without PsA) and 611 PsA patients who attended clinics affiliated with teaching hospitals. All patients were confirmed to have psoriasis by a dermatologist. Patients classified as psoriasis had PsA excluded after evaluation by a rheumatologist. The information on comorbidities was ascertained by clinic physicians using a standard protocol. Descriptive statistics were used to compare frequency of: sociodemographic and illness characteristics; specific comorbid conditions; and health-related quality of life (HRQOL) between groups. We also calculated the Functional Comorbidity Index (FCI), a summary count of all comorbidities, modified for this study to exclude arthritis. Linear regression models were used to compare FCI scores between psoriasis and PsA, adjusting for age, sex, and psoriasis duration.

Results: PsA patients were significantly older than psoriasis patients (mean age (SD) = 50.0 yrs (13.4) versus 46.6 yrs (13.1), $p < 0.0001$) and experienced a longer psoriasis duration (mean duration (SD) = 22.3 yrs (13.4) versus 16.2 yrs (14.1), $p < 0.0001$). Males comprised 58% of both patient groups. There was no significant difference in psoriasis severity as measured by the body surface area affected by psoriasis and PASI score. PsA patients reported lower HRQOL as measured by both SF-36 and HAQ, but higher HRQOL on the Dermatology Life Quality Index (DLQI). PsA patients, on average, reported a higher number of comorbidities than psoriasis patients (mean FCI score=1.44 (1.4), range=0, 7 versus 0.75 (0.9), range=0, 6, $p < 0.0001$). This difference remained significant after adjusting for covariates (age, sex and psoriasis duration). In PsA 39% of patients reported a history of cardiovascular disease, including hypertension compared to 19.6 % of patients with psoriasis ($p < 0.0001$, adjusted for covariates). Respiratory illnesses, depression, diabetes and cancer were the next leading comorbidities in PsA (22.5%, 27.0%, 17.0%, 12.1% and 8.5% of patients, respectively) and were more frequent than that observed in psoriasis (4.9%, 4.2%, 7.9%, 7.9% and 4.2 % of patients, respectively). With the exception of gastrointestinal disease, diabetes and cancer, these differences were statistically significant ($p < 0.05$). PsA patients had a significantly higher mean BMI than psoriasis patients (31.0 (16.5) versus 27.8 (5.5), p=0.0005, adjusted for covariates). However, the frequency of autoimmune disease was significantly higher in psoriasis than in PsA (6.3% versus 3.0%, $p = 0.0027$, adjusted for covariates). Finally, the observed group differences in HRQOL remained after adjusting for FCI score and covariates.

Conclusion: Patients with PsA have a higher comorbid disease burden (excluding arthritis) than patients with psoriasis without arthritis. This is associated with a reduced quality of life.

Disclosure: J. Husted: None; **A. Thavaneswaran:** None; **V. Chandran:** None; **L. Eder:** None; **S. Shanmugarajah:** None; **C. F. Rosen:** None; **D. D. Gladman:** None.

1929

Continued Efficacy of Infliximab in the Treatment of HLA B27 Positive Very Early Ankylosing Spondylitis Following Its Discontinuation; Clinical and Imaging Results of the 40 Week Follow-Up Study of a Three Month, Randomised, Placebo-Controlled Trial. Nick Barkham[3], Helen Keen[4], Laura Coates[4], Phil O'connor[2], Elizabeth Hensor[4], Dennis McGonagle[4], Helena Marzo-Ortega[4] and Paul Emery[1]. [1]Chapel Allerton Hospital, Leeds, United Kingdom, [2]Leeda University, [3]Leeds University, Leeds, Yorkshire, United Kingdom, [4]Leeds University

Objective: Treatment of early inflammatory back pain (AS in evolution) with infliximab, was shown to be efficacious during a 3 month treatment period. The current report describes the clinical and imaging outcomes following discontinuation of infliximab treatment.

Methods: Following an initial randomised, placebo controlled trial, all patients who had received either infliximab or placebo for 3 months discontinued treatment and were followed up to week 40 or time of clinical flare (BASDAI>4).

MRI scans of the spine and sacroiliac joints were performed at baseline, week 16, and week 40 or time of clinical flare. MRIs were scored by 2 observers blinded to treatment group and order using the Leeds 0–3 MRI grading system.

Results: In the placebo group, 17/19 patients (89.5%) had a high BASDAI at some point between the end of treatment (12 weeks) and the end of observation (40 weeks), compared to 12/19 (60.0%) in the infliximab group (Chi-square=4.44, df=1, P=0.035). Time to BASDAI>4 was shorter in patients who had received placebo [median (IQR) 5.0 weeks (4.0 to 16.0)] than those who had received infliximab [20.0 weeks (7.9 to 28.0), Log-rank Chi-square=5.77, P=0.016]. Between baseline and endpoint (at first BASDAI>=4 or week 40), infliximab patients showed significantly greater improvements in ASQoL(p=0.05), BASFI (p=0.033) and BASDAI (p=0.045).

Considering MRI lesions >= grade 2 (lesions not seen in normal spine MRI scans), in the 10 patients who reached week 40 without clinical flare (8 infliximab treated, 2 placebo), there was only one lesion >= grade 2 present at week 16 and no new lesions developed on the follow-up scan. In the 11 patients who flared between wk 16 and week 40 (6 infliximab 5 placebo) there were 8 grade>1 lesions present at week 16 and 12 new lesions developed.

Conclusions: A short course of infliximab treatment results in prompt suppression of disease activity and improvement in quality of life in early AS, which is sustained on withdrawal of therapy. Fewer patients who had received active therapy flared by week 40, and those who did not flare demonstrated no progression of grade>1 lesions on MRI. This raises the possibility that the "remission induction" approach could work in a subset of patients with early AS. As previously reported for the SIJ, the prognostic value of persistent >=grade 2 lesions is demonstrated, and MRI could allow early identification of patients with subclinical disease prior to the onset of clinical flare.

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1930

Correlation of Disease Activity, but Not Radiographic Progression, with Functional Outcomes in Adalimumab-Treated Patients with Active Psoriatic Arthritis. Arthur Kavanaugh[4], Philip Mease[3], Michele Olds[2] and Frederic Lavie[1]. [1]Abbott Laboratories, Rungis, France, [2]Abbott Laboratories, Abbott Park, IL, [3]Swedish Medical Center and University of Washington, Seattle, WA, [4]University of California San Diego, La Jolla, CA

Background: In patients with rheumatoid arthritis, physical function is correlated with both disease activity and radiographic progression[1]; these relationships are unexplored in patients with Psoriatic Arthritis (PsA).

Objective: To explore the association of disease activity and radiographic progression with physical function in PsA patients treated with adalimumab (ADA).

Methods: ADEPT was a 24-week, randomized, placebo-controlled trial of ADA for the treatment of active PsA[2]. Treatment groups were randomized following stratification of subjects with methotrexate usage (≥3 months duration, 51% of patients) and extent of psoriasis (≥3% BSA, 45% of patients). In this post hoc analysis, DAS28 was used to assess disease activity, physical function was assessed through the Health Assessment Questionnaire (HAQ), and radiographic changes were determined using the modified Total Sharp Score (mTSS). Longitudinal generalized linear modeling was used to characterize the dependence of the HAQ on concurrent DAS28 and mTSS, following adjustment for baseline age and gender, and for concurrent CRP.

Results: Physical function following 48 weeks of treatment with adalimumab was linearly related to DAS28 ($P<0.001$). Increasing disease activity scores were predictive of higher HAQ scores (figure 1).

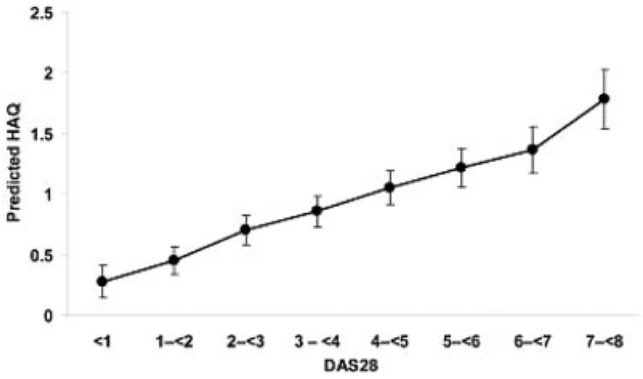

Figure 1.

However, there was no association between radiographic progression and HAQ score in PsA patients treated with adalimumab. The mean change from baseline to week 48 in HAQ score was not significantly different in adalimumab-treated patients with or without radiographic progression (ΔmTSS <0) through week 24. These results were consistent when analyzed by individual mTSS components (JSN and erosions). Radiographic progression measured by mTSS was not significantly associated with HAQ scores ($P=0.14$). However, HAQ scores appear to deteriorate at higher levels of radiographic damage (figure 2).

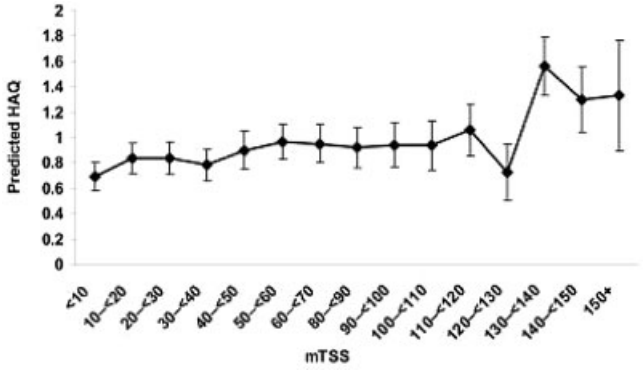

Figure 2.

Conclusion: In psoriatic arthritis patients recently treated with adalimumab, physical function is associated with resolution of disease activity, confirming the close relationship between HAQ and DAS28 early in the disease.[3] HAQ scores appear to relate to radiographic progression in patients with severe radiographic progression, supporting the hypothesis that HAQ is associated with radiographic progression at more advanced stages of the disease.

References:

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[2]Mease PJ, et al. *Ann Rheum Dis* 2009;68:702–9.
[3]Kirwan JR, et al. *J Rheumatol* 2001; 28:881–6.

Disclosure: A. Kavanaugh: Abbott Laboratories, 2; **P. Mease:** Abbott Laboratories, 2, 5, 8, Amgen Inc., 2, 5, 8, Biogen Idec, 2, 5, 8, Bristol-Myers Squibb, 2, 5, 8, Centocor, Inc., 2, 5, 8, Genentech and Biogen IDEC Inc, 2, 5, 8, Pfizer Inc, 2, 5, 8, Roche, 2, 5, UCB, Inc., 2, 5, 8; **M. Olds:** Abbott Laboratories, 1, 3; **F. Lavie:** Abbott Laboratories, 1, 3.

1931

CT Scan Facilitates the Diagnosis of Sacroiliitis in Patients with Suspected Spondyloarthritis, and without Proven Sacroiliitis on Pelvic X-Ray–Results of the ECHOSPA Cohort. Valérie Devauchelle-Pensec[1], Maria-Antonietta d'Agostino[8], Julien Marion[1], Sandrine Jousse-Joulin[2], Marie Lapierre[1], Daniele Colin[1], Isabelle Chary-Valkenaere[6], Christian Marcelli[3], Damien Loeuille[7], Philippe Aegerter[8], Sandrine Guis[5], Philippe Gaudin[4], Maxime Bréban[8] and Alain Saraux[1]. [1]CHU Brest, [2]CHU Brest, [3]CHU Caen, France, [4]CHU Grenoble, [5]CHU Marseille, France, [6]CHU Nancy, [7]CHU Nancy, [8]Hopital Ambroise Paré, France

Objective: To assess the performance of CT-scan for detecting sacroiliitis in patients with suspected spondylarthritis, and without obvious abnormalities of sacroiliac joints on X-ray.

Methods: 489 outpatients with suspected spondyloarthritis were recruited in a multicenter cohort study. At entry, they were submitted to clinical examination, pelvic X-ray, and HLA-B typing. Pelvic CT-scan was performed when rheumatologist was uncertain about the presence of sacroiliitis on X-ray. A set of 100 paired radiograph/CT-scan was read blindly by two radiologists, and the kappa coefficient was used to assess their reliability. One of them read the 173 pairs of X-ray/CT-scan available.

Results: After training, inter-reader reliability was moderate for sacroiliitis staging on X-ray (kappa = 0.52), excellent on CT-scan (kappa = 0.92), and perfect for diagnosing sacroiliitis on X-ray (New York criteria; kappa = 1). Quality was considered as good in 66, and 67 of 100 X-rays (kappa = 0.88), and in 93, and 92 of 100 CT-scans (kappa = 0.93), by readers one and two, respectively. Reliability between X-ray and CT-scan was low for sacroiliitis staging (kappa = 0.08), and diagnosing (kappa = 0.02). Sacroiliitis was retained in 6 (3.5%) patients on X-ray (4 confirmed by CT scan), and in 32 (18.5%) patients on CT-scan. Uveitis was associated with sacroiliitis on both X-rays (P :0.04) and CT-scan (P < 0.0001). Age, sex, HLA B27, arthralgia, enthesitis, rachialgia and buttock pain were not associated to sacroiliitis in our population.

Conclusions: Radiographic sacroiliitis was underestimated on X-ray, whereas CT-scan increased the detection of structural abnormalities leading to a proven diagnosis of sacroiliitis. CT-scan should facilitate the diagnosis of ankylosing spondylitis in patients with suspected spondyloarthritis.

Disclosure: V. Devauchelle-Pensec: None; **M.-A. d'Agostino:** None; **J. Marion:** None; **S. Jousse-Joulin:** None; **M. Lapierre:** None; **D. Colin:** None; **I. Chary-Valkenaere:** None; **C. Marcelli:** None; **D. Loeuille:** None; **P. Aegerter:** None; **S. Guis:** None; **P. Gaudin:** None; **M. Bréban:** None; **A. Saraux:** None.

1932

Dactylitis in Psoriatic Arthritis (PsA): Prevalence and Response to Therapy in the Biologic Era. Olga Ziouzina[2], Arane Thavaneswaran[2], Vinod Chandran[2] and Dafna D. Gladman[1]. [1]Toronto Western Hospital, Toronto, ON, Canada, [2]University of Toronto Psoriatic Arthritis Clinic

Background: Dactylitis is a common feature of PsA and one of the CASPAR criteria for the classification of PsA. It is associated with impaired function and is a marker of disease severity. Randomized clinical trials in PsA have shown remarkable response to treatment with biological agents with improvement in the active joint count, psoriasis, quality of life and function. However, the data on improvement of dactylitis has been sparse. Here we studied the prevalence and response of new acute dactylitis to treatment in a longitudinal PsA cohort.

Methods: Patients with PsA were followed at a PsA clinic January 2000 to January 2010 were included in this study. Patients were followed at 6 and 12 months according to a standard protocol. Acute dactylitis was defined as the presence of painful swelling of an entire digit. Response was defined as either complete resolution of dactylitis or > 50% improvement in the number of dactylitic digits. The prevalence of dactylitis in this cohort was determined. A multivariate generalized estimating equations analysis using a negative binomial model to account for repeated measures was conducted to determine predictors for response to treatment of dactylitis. The variables entered in the model were age, sex, duration of disease, treatment and intra-articular steroid use where treatment was categorized as no treatment, biologics (±DMARDs) and DMARDs.

Results: 294 patients of the 752 seen in clinic during this period had dactylitis at, at least one visit giving a prevalence of (39%). 252 patients (34% females, mean age 47 years, PsA duration 11 years, mean actively inflamed joint count 13.3, and mean damage joints 9.7, PASI score 5.6) with acute dactylitis and data available for response at 6 and 12 months were included in the study on predictors of response to treatment. Multivariate analysis showed only treatment type was a significant predictor of response to dactylitis at 12 months [relative risk 0.528, 95% CI (0.283, 0.985, p= 0.045]. There was a trend showing response at 6 months (p = 0.061). At 6 months, 77.3% of the patients responded to therapy when on biologics in comparison to 51.5% on DMARDs. Similarly, at 12 months, 87.2% of the patients responded to therapy when on biologics in comparison to 69.9% on DMARDs.

Conclusion: The prevalence of dactylitis on at least one visit during the period from January 2000 to January 2010 was 39%. Treatment was associated with improvement of dactylitis. Patients treated with biologics had better response to treatment compared to those treated with DMARDs alone.

Disclosure: O. Ziouzina: None; **A. Thavaneswaran:** None; **V. Chandran:** None; **D. D. Gladman:** None.

1933

Decreased Recurrence Rate of Anterior Uveitis in Ankylosing Spondylitis Treated with Adalimumab—An Interim Analysis. Irene E. van der Horst-Bruinsma[2], J. Christiaan van Denderen[1], Ingrid Visman, Maria S. A. Suttorp-Schulten, Ben A. C. Dijkmans and Michael T. Nurmohamed. [1]Amsterdam, NH, The Netherlands, [2]VU University Medical Centre, Amsterdam, NH, The Netherlands

Introduction: A high percentage (30–40%) of patients with Ankylosing Spondylitis (AS) suffers from acute anterior uveitis (AAU) attacks. Local treatment with corticosteroids is a beneficial treatment and in addition, there are suggestions that TNF blocking agents also decrease the recurrence rate of AAU attacks. However, proper prospective studies investigating the of anti-TNF treatment on the recurrence rate of AAU attacks in AS are lacking.

Objective: To examine whether the use of adalimumab decreases the frequency of attacks of AAU in patients with AS, who receive this treatment due to their spinal disease activity.

Methods: Consecutive AS patients, who were treated with 40 mg of adalimumab every other week according to the international ASAS consensus statement, were enrolled. The number of attacks of AAU before and after treatment were assessed by patient history and ophthalmological controls at baseline and yearly thereafter.

Results: A total of 60 patients was enrolled. After 1 year of treatment 29 patients had their control visit, and follow up data were completed of 6 patients after 2 years. Fourteen out of these 29 (48 %) patients did not have any attacks of uveitis before and after treatment with adalimumab.

Fifteen patients (52 %) suffered from recurrent attacks of uveitis with a mean number of 3.8/year (range 1–12). After one year, the recurrence rate per year in these 15 patients was reduced to none attacks in 11 cases (73%), from 5 attacks to only one attack/year in 2 cases (13%) and remained the same in the other 2 patients (13%, one attack). Interestingly, even the patient with a very high number of attacks of AAU (12 per year) was completely free of attacks after the start of adalimumab, during 2 years of follow up. The recurrence rate decreased significantly (p=0.001) from 15/29 (52%) to 4/29(14%), with a 73% reduction in the recurrence of uveitis.

Conclusions: Our interim analysis revealed a significant reduction of recurrence rate of attacks of acute anterior uveitis during adalimumab treatment, even in patients with a high recurrence rate of the attacks.

Disclosure: I. E. van der Horst-Bruinsma: None; **J. C. van Denderen:** None; **I. Visman:** None; **M. S. A. Suttorp-Schulten:** None; **B. A. C. Dijkmans:** None; **M. T. Nurmohamed:** None.

1934

Direct Imaging Evidence That Adalimumab Induces Resolution of Inflammatory Lesions in AS Patients at Sites of Complete Spinal Ankylosis. Walter P. Maksymowych, Nathalie Morency and Robert G. W. Lambert. University of Alberta, Edmonton, AB, Canada

Purpose: Post-hoc analysis of clinical trial data has demonstrated that AS patients who have extensive spinal ankylosis on radiographs experience clinical improvement with adalimumab that is similar to patients without extensive ankylosis. This benefit has been documented by patient self-report and not objectively using imaging data. We aimed to assess the impact of treatment in AS patients where both radiographs and MR scans were available to analyze the fate of vertebral corner inflammatory lesions (CIL) that demonstrated syndesmophytes and ankylosis on the baseline radiograph.

Methods: MRI scans were performed at baseline, 12, and 52 weeks while radiographs were done at baseline and 104 weeks in 76 AS patients randomized to receive either adalimumab (ADA) 40 mg every other week or placebo (PBO) for 24 weeks in a, double-blind, Phase III study of active AS with an inadequate response to at least one NSAID or DMARD. After the week 12 assessment, patients not achieving an ASAS20 response were eligible for early escape therapy with ADA and after 24 weeks all patients received ADA. The anterior vertebral corners (VC) of the cervical (C2 lower to T1 upper) and lumbar (T12 lower to S1 upper) spine were examined for

syndesmophytes and ankylosis on lateral radiographs of the cervical and lumbar spine by 2 readers scoring independently. Anonymized MR scans were read independently by 2 readers who recorded the presence/absence of both typical CIL (Type A) and complex CIL (dimorphic) at the same anterior VC that were assessed by radiography. The primary analysis was based on concordant radiographic and MRI data. A CIL was defined as being persistent if it was recorded as being present on each MRI scan (baseline, 12, and 52 weeks) and as being completely resolved if either the baseline or 12 week MR scan showed a CIL that was no longer present at the 52 week final MRI examination.

Results: Ankylosis across the disc space was recorded on the baseline radiograph at 248 of 1736 (14.3%) VC that were assessed by both radiography and MRI. A syndesmophyte was recorded in 137 (7.9%) of VC at baseline. A CIL was observed significantly more frequently at VC without either ankylosis or syndesmophytes (212/1351 (15.7%)) as compared to those with ankylosis (13/248 (5.2%), p <0.0001) on baseline radiographs. Over half of CIL at VC with ankylosis at baseline resolved completely (7/13 (53.8%)) as compared to 157/212 (74.1%) of CIL at those VC without syndesmophytes/ankylosis at baseline (P = NS). For VC with baseline ankylosis, complete resolution was observed for almost all Type A CIL (5/6) but in only 2/7 dimorphic CIL.

Conclusion: Our data provide objective evidence for ongoing inflammation at sites of complete spinal ankylosis that can resolve completely with adalimumab, and that complete resolution of inflammation is observed more often in those CIL with a typical configuration than in more complex, dimorphic inflammatory lesions.

Disclosure: W. P. Maksymowych: Abbott Laboratories, 2, 5, Merck Pharmaceuticals, 2, 5, Pfizer Inc, 2, 5; **N. Morency:** None; **R. G. W. Lambert:** Abbott Laboratories, 5.

1935

Disconnect between Radiographic Progression and Clinical Outcomes in Psoriatic Arthritis Patients Treated with Adalimumab. Philip Mease[3], Christopher Ritchlin[4], Michele Olds[2] and Frederic Lavie[1]. [1]Abbott Laboratories, Rungis, France, [2]Abbott Laboratories, Abbott Park, IL, [3]Swedish Medical Center and University of Washington, Seattle, WA, [4]University of Rochester School of Medicine and Dentistry, Rochester, NY

Background: Treatment with adalimumab (ADA) diminishes disease activity and radiographic progression in subjects with active psoriatic arthritis (PsA)[1]. In subjects with rheumatoid arthritis (RA), inhibition of radiographic progression can occur independently of improvements in clinical symptoms following treatment with anti-TNF agents[2]; it is not known if such a disconnect in treatment responses exists in PsA patients.

Objective: To explore the relationship between disease activity and radiographic progression in subjects with active PsA following treatment with ADA or placebo (PBO).

Methods: ADEPT was a 24-week, randomized, placebo-controlled trial of ADA for the treatment of active PsA[1]. Treatment groups were randomized following stratification for methotrexate usage (≥3 months duration, 51% of patients) and extent of psoriasis (≥3% BSA, 45% of patients). In this post hoc analysis, disease activity was monitored by DAS28 and ACR response rates at week 12. The change in modified Total Sharp Score (ΔmTSS) was calculated from X-rays obtained at baseline and week 24; radiographic progression was defined as ΔmTSS >0.25.

Results: Radiographic progression occurred at a lower frequency following treatment with ADA; 84% of ADA-treated subjects were nonprogressors, while 62% of subjects in the PBO group had ΔmTSS ≤0.25 through week 24 ($P<0.001$). ADA-treated subjects were more likely to exhibit lower disease activity and improved ACR responses at week 12 (table). Even in subjects with active clinical symptoms at week 12, treatment with ADA resulted in significantly better radiographic outcomes at week 24 than treatment with PBO; for example, ADA subjects with moderate disease activity (DAS28 ≥3.2 – <5.1) still had reduced bone damage.

Conversely, subjects exhibiting radiographic progression from baseline to week 24 had higher mean DAS28 scores at week 12 in both treatment groups. PBO-treated subjects with ΔmTSS >0.25 had a mean±SD DAS28 of 5.0±1.3, while those showing no progression had a mean DAS28 of 4.3±1.3 at week 12 ($P=0.001$). Subjects treated with ADA with ΔmTSS >0.25 had a mean DAS28 of 3.9±1.6 at week 12, while those without radiographic progression had a mean DAS28 of 3.0±1.2 ($P=0.004$). DAS28 at week 12 showed a mild correlation with ΔmTSS at week 24 in the PBO group (correlation coefficient: 0.36) However, there was a weaker pattern of radiographic progression relative to DAS28 in the ADA group (correlation coefficient: 0.13).

Table. Pattern of radiographic progression (ΔmTSS) relative to disease activity

	PBO		ADA	
Week 12 DAS28	**N**	**ΔmTSS[a]**	**N**	**ΔmTSS[a]**
<2.6	7	0.2 ± 1.9	50	−0.1 ± 0.9
≥2.6–<3.2	23	0.1 ± 0.31	23	−0.2 ± 1.6
≥3.2–<5.1	65	0.5 ± 1.3	42	−0.5 ± 1.6
≥5.1	51	2.2 ± 4.6	14	0.9 ± 1.8
Week 12 ACR				
ACR90	0	n/a	9	−0.2 ± 0.59
ACR70, not ACR90	1	0.0	21	−0.2 ± 0.48
ACR50, not ACR70	5	0.0 ± 0.35	24	−0.7 ± 2.2
ACR20, not ACR50	16	1.1 ± 2.0	32	−0.3 ± 1.3
not ACR20	129	1.1 ± 3.2	54	0.2 ± 1.2

[a]baseline to week 24, mean ± SD.

Conclusions: Radiographic progression is lower in patients with active PsA who are treated with adalimumab compared with placebo, regardless of the treatment response in clinical symptoms. As in RA, it appears that a disconnect in the normal relationship between radiographic progression and disease activity can occur in subjects treated with adalimumab.

References:

[1]Mease PJ, et al. *Ann Rheum Dis* 2009;68:702
[2]Landewé R et al. *Arthritis Rheum* 2006; 54:3119

Disclosure: P. Mease: Abbott Laboratories, 2, 5, 8, Amgen Inc., 2, 5, 8, Biogen Idec, 2, 5, 8, Bristol-Myers Squibb, 2, 5, 8, Centocor, Inc., 2, 5, 8, Genentech and Biogen IDEC Inc, 2, 5, 8, Pfizer Inc, 2, 5, 8, Roche, 2, 5, UCB, Inc., 2, 5, 8; **C. Ritchlin:** Abbott Laboratories, 2, Amgen Inc., 2, Bristol-Myers Squibb, 5, CalciMedica, 5, Centocor, Inc., 2, 5, Pfizer Inc, 2, Schering-Plough, 5; **M. Olds:** Abbott Laboratories, 1, 3; **F. Lavie:** Abbott Laboratories, 1, 3.

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Environmental Risk Factors for Psoriatic Arthritis among Patients with Psoriasis—A Case-Control Study. Lihi Eder[3], Tamryn Loo[3], Vinod Chandran[3], Gideon Kalman-Lamb[3], Sutha Shanmugarajah[3], Richard Cook[1] and Dafna D. Gladman[2]. [1]Department of Statistics and Actuarial Science, University of Waterloo, Waterloo, ON, Canada, [2]Toronto Western Hospital, Toronto, ON, Canada, [3]University of Toronto Psoriatic Arthritis Clinic, Toronto Western Hospital, Toronto, ON, Canada

Aim: To investigate the association between potential environmental exposures and the development of psoriatic arthritis in patients with psoriasis.

Methods: In this case-control study, the cases were patients with recent onset psoriatic arthritis (PsA) of less than 7 years since the diagnosis. The control group was composed of psoriasis patients in whom arthritis was excluded after an evaluation by a rheumatologist. Patients and controls were matched by duration of psoriasis. The occurrence of the following environmental exposures was evaluated by a self administered questionnaire: infections, injuries and fractures, physically demanding occupational tasks, stressful life-events and vaccinations. The patients were asked to report any such event that occurred in the past 10 years and a positive exposure was defined as the occurrence of an event prior to the year of diagnosis. Participants in the control group were assigned a reference year corresponding to the year of PsA diagnosis in the matched case. The association between each exposure to environmental events and disease status were assessed through logistic regression after adjustment for age, sex and duration of psoriasis.

Results: There were 159 subjects in each group. There were no differences in age, sex, ethnicity, and severity of psoriasis as measured by PASI score between the 2 groups. The mean duration of PsA was 3.1 ± 2.2 years. The associations between each of the exposure variables and PsA are presented in Table 1 after adjustment for age, sex and duration of psoriasis.

Table 1. Proportion of environmental exposures

Exposure	Frequency PsA (%)	Frequency Psoriasis (%)	Adjusted P value*
Car accidents that required medical consult	6 (4%)	5 (3%)	0.95
Fractures	16 (10%)	14 (9%)	0.73
Any other injury	34 (21%)	17 (11%)	0.01
Infective diarrhea	20 (13%)	11 (7%)	0.23
Infections that required Ab	53 (34%)	37 (24%)	0.05
Infections that required hospitalization	11 (7%)	0 (0%)	0.0006
Vaccination - Hepatitis A	3 (3%)	4 (4%)	0.58
Vaccination - Hepatitis B	29 (23%)	19 (16%)	0.32
Vaccination - Pneumovax	30 (24%)	20 (17%)	0.35
Vaccination - Flu	59 (42%)	60 (45%)	0.92
Vaccination - Rubella	4 (3%)	5 (4%)	0.81
Vaccination - Tetanus	6 (5%)	4 (4%)	0.97
Death in the family	41 (27%)	44 (29%)	0.91
Divorce	17 (10.9%)	12 (8%)	0.33
Movehouse	74 (50%)	64 (41%)	0.62
Changed job	70 (47%)	56 (40%)	0.62
Becoming unemployed	34 (23%)	35 (23%)	0.80
Treated for anxiety/depression	21 (14%)	26 (17%)	0.55
Occupational risk: Prolonged standing	95 (65%)	85 (58%)	0.31
Squatting	45 (31%)	32 (22%)	0.12
Lifting heavy weights	44 (30%)	19 (13%)	0.0009
Pushing heavy weights	29 (20%)	18 (12%)	0.13
Using vibrating tools	7 (5%)	8 (6%)	0.66
Repetitive hand movement	88 (60%)	85 (58%)	0.96
Forceful gripping	28 (19%)	21 (14%)	0.48
Bending the wrist	65 (45%)	65 (45%)	0.85
Smoking - Current	28 (23%)	38 (35%)	0.05
Past	36 (27%)	51 (42%)	0.03

*Adjusted for age, sex, Ps duration.

The following exposures remained significantly associated with PsA following multivariate logistic regression: lifting cumulative loads of at least 100 pounds/hr (OR 2.9, $p<0.001$), infections that required antibiotics (OR 1.8, $p=0.04$), current smoking (OR 0.5, $p=0.03$) and past smoking (OR 0.5, $p=0.02$). Injury was significantly associated with PsA after adjustment for age, sex and duration of psoriasis, however it was no longer significant after inclusion in the full logistic regression model (OR 1.8, $p=0.07$). No association was found between PsA and vaccination, stressful life events and fractures.

Conclusion: Lifting heavy loads and infections that required antibiotics were associated with the occurrence of arthritis among patients with psoriasis. Smoking and past smoking were negatively associated with PsA. Further studies are necessary to determine whether these and other environmental factors are moderated by predisposing genetic factors.

Disclosure: L. Eder: None; **T. Loo:** None; **V. Chandran:** None; **G. Kalman-Lamb:** None; **S. Shanmugarajah:** None; **R. Cook:** None; **D. D. Gladman:** None.

1937

Estimate of the Prevalence of Psoriatic Arthritis and Improvement with Etanercept Treatment in Moderate-to-Severe Plaque Psoriasis: PASE Results from the PRISTINE Trial. M. Elaine Husni[2], Abrar A. Qureshi[1], Deborah Robertson[4], Ronald Pedersen[4], Bruce Freundlich[4] and Charles T. Molta[3]. [1]Brigham and Women's Hospital, Boston, MA, [2]Cleveland Clinic Foundation, Cleveland, OH, [3]Pfizer, Inc., Paoli, PA, [4]Pfizer, Inc., Collegeville, PA

Background: Psoriatic arthritis (PsA) affects an estimated 30% of patients with psoriasis and may cause irreversible joint damage, underscoring the need for early PsA screening and prompt initiation of therapy. The Psoriatic Arthritis Screening and Evaluation (PASE) questionnaire is a validated tool that can be used to screen for active PsA among individuals with psoriasis and is being evaluated as a measurement of treatment response. We tested the PASE questionnaire in exploratory analyses in a large multinational study of etanercept (ETN), a biological agent approved for the treatment of PsA and psoriasis, to assess whether it is a useful tool for PsA screening and for evaluation of treatment effect in a clinical trial setting.

Methods: The PRISTINE trial evaluated the efficacy and safety of 2 ETN doses for the treatment of psoriasis. The PASE questionnaire was administered during the PRISTINE trial at baseline to estimate the prevalence of PsA using the PASE cutoff scores (absent if <47 or present if ≥ 47) and re-administered at 12 weeks to evaluate changes in PASE score with treatment. Participants were randomized to receive ETN 50 mg once weekly (OW) or 50 mg twice weekly (BIW) for 12 weeks double blind, followed by ETN 50 mg OW open label for 12 weeks in all subjects. Participants were ≥ 18 years old and had stable plaque psoriasis, with BSA $\geq 10\%$ or PASI ≥ 10. At baseline, the number of participants who self reported a history of PsA was assessed by medical history. Within-group p-values for comparison of PASE scores at baseline and week 12 were based on a paired sample T-test.

Results: A total of 273 subjects were enrolled (OW, n=137; BIW, n=136). Subjects were 70% male, and 64% Caucasian; mean age was 44 years, mean PASI was 21, and mean psoriasis duration was 17 years. At baseline, 31% had a self-reported history of physician-diagnosed PsA (mean duration, 8 years). Data from the PASE questionnaire at baseline and week 12 are shown (Table). Approximately 25% of subjects had a PASE total baseline score ≥ 47, meeting criteria for possible active PsA. After 12 weeks of ETN treatment, 13% had a score suggesting the presence of active PsA.

Results from the PASE questionnaire* at baseline and week 12 by treatment group†

PASE variable	ETN 50 mg OW/ETN OW		ETN 50 mg B/W/ETN OW*	
	Baseline	Week 12	Baseline	Week 12
Total score 247, nN (%) (95% CI)	37/136 (27.2%) (19.9%, 35.5%)	15/134 (11.2%) (6.4%, 17.8%)	30/132 (22.7%) (15.9%, 30.8%)	18/130 (13.8%) (8.4%, 21.0%)
Total score				
Mean (SD) (mean change from baseline [SD])	34.4 (15.8)	30.6 (12.7) (−3.8 [13.4])	33.0 (14.7)	29.7 (13.5) (−3.3 [12.4])
Median (min-max) (median change from baseline [min-max])	32.0 (15.0–69.0)	29.0 (15.0–68.0) (−2.0 [−37.0–30.0])	28.5 (15.0–71.0)	26.0 (15.0–75.0) (−2.0 [−52.0–36.0])
Within-group p-value		*0.0009*		*0.0045*
Function score				
Mean (SD) (mean change from baseline [SD])	17.8 (8.8)	15.5 (7.0) (−2.2 [7.7])	16.6 (8.3)	14.8 (7.4) (−1.8 [6.9])
Median (min-max) (median change from baseline [min-max])	16.0 (8.0–38.0)	16.0 (8.0–34.0) (−2.0 [−23.0–16.0])	14.0 (8.0–38.0)	12.0 (8.0–40.0) (0.0 [−26.0–16.0])
Within-group p-value		*0.0007*		*0.0059*
Symptom score				
Mean (SD) (mean change from baseline [SD])	16.7 (7.5)	15.1 (6.3) (−1.6 [6.5])	16.4 (7.0)	14.8 (6.7) (−1.5 [6.5])
Median (min-max) (median change from baseline [min-max])	16.0 (7.0–32.0)	14.0 (7.0–34.0) (−1.0 [−18.0–15.0])	14.5 (7.0–35.0)	14.0 (7.0–35.0) (−1.0 [−26.0–22.0])
Within-group p-value		*0.0051*		*0.0095*

*Includes a total of 15 items, with symptom (7 items) and function (8 items) subscales, possible responses range from 1 (strongly disagree) to 5 (strongly agree). Total scores range from 15 to 75 points, symptoms scores from 7 to 35, and function scores from 8 to 40.
†In the modified intent-to-treat population, based on analysis of last observation carried forward.
‡P=NS, all between-group comparisons.

Conclusions: Consistent with previously published findings, nearly one third of participants in the PRISTINE study reported a physician diagnosis of PsA at baseline. PASE total, function, and symptom scores decreased from baseline to week 12 in both dose regimen groups. These results are generally consistent with clinical improvement with ETN treatment, but further analysis is needed. The findings suggest that PASE may be a useful tool for application in screening psoriasis patients for PsA in clinical trials and evaluating treatment response in a large dermatology setting.

Disclosure: M. E. Husni: Pfizer Inc, 9; **A. A. Qureshi:** Pfizer Inc, 9; **D. Robertson:** Pfizer Inc, 1, 3; **R. Pedersen:** Pfizer Inc, 1, 3; **B. Freundlich:** Pfizer Inc, 1, 3; **C. T. Molta:** Pfizer Inc, 1, 3.

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Evaluation of the New Akylosing Spondylitis Disease Activity Score (ASDAS) To Assess Disease Activity in Patient with Active Non-Radiographic Axial Spondyloarthritis Treated with Adalimumab and Retreated after Interruption of Therapy and Flare. Hildrun Haibel[3], Frank Heldmann[2], Joachim Listing[4], Hartmut Kupper[1], Jürgen Braun[2] and Joachim Sieper[3]. [1]Abbott GmbH & Co. KG, Ludwigshafen, Germany, [2]Centre of Rheumatology Ruhrgebiet, Herne, Germany, [3]Department of Rheumatology, Charité CBF, Berlin, Germany, [4]German Rheumatism Research Centre, Berlin, Germany

Background: The Spondyloarthritis International Society (ASAS) has recently developed a new disease activity score, the ASDAS, which includes

clinical measures and CRP and has a high discriminatory capacity for assessing disease activity in AS. Adalimumab has demonstrated good efficacy for 46 patients with active, non-radiographic, axial SpA during a 12-week, placebo-controlled trial and its 40-week, open-label extension [1].

Objective: To evaluate long-term efficacy after re-treatment with adalimumab for patients whose disease flared after treatment was discontinued at Week 52 using the ASDAS instrument.

Methods: All 46 enrolled patients discontinued therapy at Week 52 and 19 patients with a good response at week 52 had to be retreated because of a flare (defined as not longer reaching ASAS40 response compared to baseline). Patients were treated for up to two additional years (108 weeks of re-treatment). An ASDAS <1.3 was considered as 'inactive', 1.3–2.1 as 'moderate', 2.1–3.5 as 'high' and > 3.5 as very high disease activity. An ASDAS change ≥2 was defined as 'major improvement', as recently proposed.

Results: Of the 19 patients who had to be retreated, 52.6% were male; mean age was 32.5 years [range 24–45]; mean disease duration before treatment was 4 years [range 1–10]; and 74% were HLA-B27+). In these 19 patients, the mean ASDAS decreased from 3.4 at baseline to 1.2 ($p<0.001$) at week 52. At baseline of the retreatment period the mean ASDAS was 2.8 and after 1 and 2 years of retreatment 1.5 ($p=0.001$). For the percentage of patients reaching different disease activity categories see table 1.

Table 1. Percentage of patients (%) reaching different disease activity categories and mean ASDAS and BASDAI during treatment with adalimumab 40 mg eow.

ASDAS	Baseline	Week 52	R-Baseline	R-48	R-108
'Inactive' (%)	0	63.2	0	50	47.1
'Moderate' (%)	10.5	26.3	21.1	22.2	35.3
'High' (%)	47.4	10.5	52.6	22.2	17.6
'Very high' (%)	42.1	0	26.3	5	0
ASAS 40 (%)	NA	100.0	NA	52.6	73.7
ASAS p.R. (%)	NA	57.9	NA	47.4	63.2
ASDAS (Mean)	3.4	1.2	2.8	1.5	1.5
BASDAI (Mean)	6.1	1.4	5.1	2.8	2.4
ASDAS improvement > 1.1 (%)	NA	94.7	NA	50	64.7
ASDAS improvement ≥ 2.0 (%)	NA	36.8	NA	27.8	17.6

R=Retreatment, ASAS40=40% improvement according to the Assessments in SpondyloArthritis Society Criteria, p.R.=partial Remission.

Conclusions: All patients retreated reached a similar level of response as before interruption of adalimumab therapy, as judged by the percentage of patients reaching inactive or moderate ASDAS or ASAS pR. This was not well reflected in the ASAS 40 or ASDAS major improvement rates, probably because the baseline level of activity at retreatment was lower than before. Thus, the ASDAS and its definition of different levels of disease activity performed well in this analysis.

References:

1. Haibel H, et al. Arthritis Rheum. 2008;58:1981–91.

Disclosure: H. Haibel: Abbott Laboratories, 2; **F. Heldmann:** Abbott Laboratories, 2; **J. Listing:** None; **H. Kupper:** Abbott Laboratories, 1, 3; **J. Braun:** Abbott Laboratories, 2, 5, 8; **J. Sieper:** Abbott Laboratories, 2, 5, 8.

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High Prevalence of Psoriatic Arthritis in a Psoriasis Patients Cohort. Majed M. Khraishi[2], Trevor Newhook[1], Ian Landells[3], Jonathan Mong[3] and Kassem Aboushehde. [1]Nexus Clinical Research, St. Johns, NL, Canada, [2]Nexus Clinical Research, St Johns, NL, Canada, [3]Nexus Clinical Research

Objective(s): The prevalence of PsA is reported to range from 5 to 40% in individuals with psoriasis. We set out to detect the prevalence of PsA in psoriasis patients seen in a dermatology practice and define their characteristics utilizing a validated self-administered screening questionnaire, PASQ (the Psoriatic Arthritis Screening Questionnaire)

Method(s): Patients with definite Plaque psoriasis (as determined by the dermatologist) completed the PASQ, a validated screening tool which has an optimal cut-off of 9 in established PsA. To ascertain that all patients with PsA are captured, we chose a lower cutoff point of 7 on the questionnaire. All patients scored 7 and higher on the PASQ were assessed by a rheumatologist to ascertain the diagnosis of PsA according to the CASPAR criteria. Epidemiological, clinical and laboratory parameters were recorded in addition to the score of the PASQ. Statistical analyses were performed utilizing SPSS 17.0.

Result(s): Sixty six patients consecutive patients with confirmed diagnosis of psoriasis who were seen by the dermatologist were enrolled. The mean age (SD) was 45.6 (13.5) years, 30 (45.5%) were females. Average duration of psoriasis was 12.4 (10.1) years. 28 (42.4%) of the patients had baseline PASQ scores of 7 or higher and 17 of those patients were assessed by a rheumatologist where 12 were determined to have definite PsA, three had osteoarthritis, one had undifferentiated synovitis and one had ankylosing spondylitis. Of those 38 patients with a PASQ < 7, five had definite diagnosis of PsA which was reconfirmed by the rheumatologist resulting in 17 patients with PsA in this cohort. Assuming none of the remaining patients were later diagnosed with PsA, the prevalence of psoriatic arthritis in our psoriasis cohort is 25.8%. This would be an underestimate of the true prevalence since 11 of the patients with a PASQ ≥ 7 had not yet been assessed by a rheumatologist yet.

Khraishi et. al.11 determined that when using the PASQ as a screening tool on patients with early PsA (mean symptoms duration of 12 months) a cut-off point of greater or equal to 7 yielded a sensitivity and specificity of 82% and 75%, respectively. If the sensitivity is applied to those 11 patients with a PASQ ≥ 7that were not seen by a rheumatologist, approximately 9 (11*0.82) of these patients should eventually be diagnosed with PsA(assuming they have early PsA). This will result in a total of 26 PsA patients indicating that the estimated prevalence (95% CI) of PsA in patients with psoriasis is 39.4% (27.6%, 51.2%) in a dermatology setting.

Conclusion: Our estimated prevalence of PsA in psoriasis patients from a population of patients drawn from a dermatology practice is larger than most prior estimates. This fact illustrates the importance of screening for PsA in psoriasis patients as this comorbidity may affect the course of treatment and if left untreated may have a profound effect on the disability and quality of life of a large number of psoriasis patients.

Disclosure: M. M. Khraishi: Amgen Inc., 2, Wyeth Pharmaceuticals, 2; **T. Newhook:** None; **I. Landells:** None; **J. Mong:** None; **K. Aboushehde:** None.

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Improved Health-Related Quality of Life (HRQOL) with Apremilast (APR) Treatment in Psoriatic Arthritis (PsA): Results from a Phase 2 Randomized Controlled Study. Vibeke Strand[3], Adele Vessey[1], Angela Hu[2] and Victor S. Sloan[2]. [1]Celgene Corporation, Richlandtown, PA, [2]Celgene Corporation, Basking Ridge, NJ, [3]Stanford University, Portola Valley, CA

Purpose: PsA is a form of inflammatory arthritis with well-established deleterious effects on HRQOL. We evaluated the effect of APR on patient-reported outcomes (PROs) in subjects with PsA.

Methods: A phase 2, multicenter, randomized, double-blind, placebo (PBO)-controlled, efficacy/safety study was conducted in subjects with active PsA (duration >6 mo; ≥3 swollen joints; ≥3 tender joints). Subjects were randomized 1:1:1 to oral APR (40 mg QD or 20 mg BID) or PBO for 12 wk. PROs included Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Health Assessment Questionnaire–Disability Index (HAQ-DI), global and pain visual analog scales (VAS), physical (PCS) and mental (MCS) component summaries and individual domain scores of Short-Form 36-item (SF-36) and Short-Form 6-Dimension (SF-6D) health utilities. Minimum clinically important differences (MCID) are 4.0 points for FACIT-F, −0.22 for HAQ-DI, 10.0 for VAS, 2.5 – 5.0 for PCS and MCS, and 5.0 – 10.0 for SF-36 domain scores. Minimally important differences (MID) for SF-6D are ≥0.041.

Results: 204 subjects were randomized (52.5% M; mean age 50.6 y). At 12 wk, statistically significant ($P<.05$) treatment-associated improvements in mean PCS (2.4) and MCS (3.4) scores that met or exceeded MCID in 20-mg BID group were observed vs PBO (0.8 and −0.8, respectively). Statistically significant ($P<.05$) mean changes in SF-36 domain scores were observed in 7 of 8 domains in the 20-mg BID group: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), social functioning (SF), role emotional (RE), and mental health (MH). These changes were ≥MCID in the PF, BP, SF, RE, and MH domains. Endpoint domain scores in the 20-mg BID group differed from age/gender-matched US normative values by ≈20 points in physical domains, and <10 points in mental domains (except RE), indicating large and clinically meaningful improvements. Mean treatment-associated changes in PCS and MCS in the 40-mg QD group did not meet or exceed MCID and were not statistically significant vs PBO, with the exception of the BP domain ($P=.037$). Treatment-associated improvements in the 20-mg BID and 40-mg QD groups resulted in mean increases of 0.076 and 0.047 in SF-6D scores, respectively, both exceeding MID. More subjects in the 40-mg QD and 20-mg BID groups reported improvements in

HAQ-DI, FACIT-F, and VAS scores ≥MCID vs PBO. Moderate and statistically significant correlations were evident between VAS pain scores and BP, HAQ-DI and PF, and FACIT-F and vitality (VT) domains of SF-36.

Conclusions: Treatment of PsA with APR 20 mg BID was associated with statistically significant and/or clinically meaningful mean improvements vs PBO in PROs including FACIT-F, global/pain VAS, HAQ-DI, SF-36 PCS/MCS, and 7 of 8 domain scores.

Table. Mean Changes From Baseline to Endpoint (Week 12) in SF-36 Domain and SF-6D Scores Across Treatment Groups

	PF	*RP*	*BP*	*GH*	*VT*	*SF*	*RE*	*MH*	*SF-6D*
A/G-matched norms	81.8	81.7	69.7	70.1	59.4	84.4	87.7	75.7	0.821
Placebo									
Wk 12	43.0	43.7	36.6	46.4	41.6	60.5	62.6	60.4	0.520
BL	45.1	42.8	33.9	46.3	38.5	58	68	61.2	0.523
Mean change	*−2.1*	*0.9*	*2.7*	*0.1*	*3.1*	*2.5*	*−5.4*	*−0.8*	*−0.003*
20 mg BID APR									
20 mg BID wk 12	62.5	61.5	50.1	52.1	52.6	75.6	75.1	68.8	0.664
20 mg BID BL	56.3	57.2	38.6	47.3	46	69.2	66.7	63.5	0.588
Mean change	*6.2**	*4.3**	*11.5**	*4.7**	*6.6**	*6.3**	*8.5**	*5.3**	*0.076*
40 mg QD APR									
40 mg QD wk 12	50.5	50.2	46.1	48.0	46.1	65.7	63.3	64.9	0.589
40 mg QD BL	46.7	45.8	38.2	46.2	42.4	61.6	61.2	62	0.542
Mean change	*3.8*	*4.4*	*7.9**	*1.8*	*3.7*	*4.1*	*2.1*	*2.9*	*0.047*

**P*<.05.
A/G=age/gender; APR=apremilast; BL=baseline; BP=bodily pain; GH=general health perceptions; MH=mental health index; PF=physical functioning; RE=role emotional; RP=role physical; SF=social functioning; SF-6D=Short-Form 6-Dimension health questionnaire; VT=vitality.

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Incidence of Tuberculosis in Korean Patients with Ankylosing Spondylitis Treated with Tumor Necrosis Factor Blockers. Eun-Mi Kim[2], Chan-Bum Choi[2], Yoon-Kyoung Sung[2], Wan-Sik Uhm[2], Jae-Bum Jun[2], Tae-Hwan Kim[2], Sang-Cheol Bae[1] and Dae-Hyun Yoo[1]. [1]Hanyang University Hospital for Rheumatic Diseases, Seoul, Korea, Republic of, [2]Hanyang University Hospital for Rheumatic Diseases

Objective: To assess the incidence rate and relative risk of tuberculosis (TB) in patients with ankylosing spondylitis (AS) and in patients with AS treated with tumor necrosis factor (TNF) blockers in Korea.

Methods: Using data from the Korean National Tuberculosis Association(KNTA) as a control and data from a single-center cohort of patients with AS, we conducted an evaluation of 987 patients with AS not exposed to TNF blockers and reviewed medical records of 57, 73 and 208 patients with AS treated with adalimumab, infliximab, etanercept, respectively, between 2002 and 2009.

Results: The mean incidence rate of TB, reported by the KNTA, was 69.8 per 100,000 person years (PS) from 2002 to 2009. In the TNF-blocker-naïve AS cohort, 10 cases of TB developed during 3247PY of followup (308 per 100,000 PY). In the adalimumab-treated AS group, 1 case of TB developed during 204 PY of followup (490 per 100,000 PY). In the infliximab-treated AS group, 2 cases of TB developed during 366 PY of followup (540 per 100,000 PY). In the etanercept-treated AS group, there was no case of TB during 1214 PY of followup. The risk of TB was higher in AS patients not treated with TNF blockers (risk ratio 4.3), in those treated with adalimumab (risk ratio7.0), and in those treated with infliximab (risk ratio 7.7) compared with the general Korean population.

Conclusion: The risk of TB infection is 4.3-fold higher in Korean patients with AS, 7.0-fold higher in AS patients treated with adalimumab and 7.7-fold higher in those treated with infliximab, compared with the general Korean population.

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Long-Term Drug Survival of Anti-TNF Therapy in Ankylosing Spondylitis. Qiang Li[1], Michelle Y. Seah[2], John A. Burgess[3], Shyamali Dharmage[3], Belinda J. Martin[1], Russell Buchanan[1] and Lionel Schachna[1]. [1]Austin Health, Melbourne, Australia, [2]Austin Health, Melbourne, Australia, [3]University of Melbourne, Melbourne, Australia

Background: Unlike rheumatoid arthritis, the long-term efficacy and safety of TNF inhibitor (TNFi) therapy in ankylosing spondylitis (AS) is largely unknown. We examined drug survival (ie, continuation) rates of TNFis among a large cohort of AS patients.

Methods: All biologically-naive patients with active AS commencing TNFi therapy in a single center were followed to March 31, 2010. The effectiveness of treatment was examined by drug survival using life table analysis and multivariate Cox proportional hazards analysis.

Results: We examined 209 consecutive patients who received a total of 326 TNFi courses for active AS over 581.0 patient-years; the median treatment duration was 32.9 months (range: 0.4–68.3). The first TNFi was infliximab in 87 (41.6%), adalimumab in 66 (31.6%) and etanercept in 56 (26.8%). Men constituted 153 (73.2%) of the study sample and the mean age at inclusion was 42.4 (SD 11.9) years with disease duration of 19.1 (SD 11.3) years. At the end of follow-up, 128 (61.2%) remained on their first TNFi while 52 (24.9%) had switched to their second, and 24 (11.5%) to a third TNFi. The reasons for TNFi discontinuation were secondary inefficacy (34.6%), adverse event (24.1%), primary inefficacy (21.1%), convenience (12.0%) and other (8.3%). Treatment discontinuation due to adverse events occurred more commonly for infliximab 19 (17.0%) compared with adalimumab 6 (5.0%) (odds ratio (OR) 3.9, 95CI, 1.4–12.4) and etanercept 7 (7.5%) (OR 2.5, 95CI, 0.9–7.4). Only 13 patients (6.2%) had ceased TNFi therapy entirely (primary inefficacy (3), adverse event (5), planning to conceive (1), other (4)). Drug survival for the first TNFi therapy was 0.82, 0.72, 0.60, 0.53 and 0.43 at 6, 12, 24, 36 and 60 months, respectively. At similar time points, drug survival for the second TNFi was lower only for the first 12 months: 0.74, 0.64. 0.58, 0.52 and 0.44, respectively (p=0.32). For the second course of TNFi, primary inefficacy to the first TNFi was associated with drug survival at 6 months of only 0.50 compared with 0.84 for prior secondary inefficacy and 0.82 for adverse events (p=0.11). Survivor function was equivalent for all TNFis, by log rank test. Predictors for treatment discontinuation in multivariate analysis were absence of HLA-B27 (hazards ratio (HR) 2.0, 95CI, 1.1–3.8) and female sex (HR 2.0, 95CI, 1.3–3.0).

Conclusions: Switching to an alternative TNFi is common in AS but few patients entirely cease treatment. Primary inefficacy to initial TNFi is associated with low continuation rates of a second TNFi.

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Long-Term Radiographic Outcome in Psoriatic Arthritis Patients Treated with Golimumab: 104 Week Results from the GO-REVEAL Study. Arthur Kavanaugh[7], Desiree M. Van Der Heijde[4], Dafna D. Gladman[6], Philip J. Mease[5], Iain B. McInnes[8], Gerald G. Krueger[9], Weichun Xu[3], Neil Goldstein[2] and Anna Beutler[1]. [1]Centocor Research and Development, Inc, Collegeville, PA, [2]Centocor Research and Development, Inc, [3]Centocor Research and Development, Inc., [4]Leiden University Medical Center, Meerssen, The Netherlands, [5]Seattle Rheumatology Associate, Seattle, WA, [6]Toronto Western Hospital, Toronto, ON, Canada, [7]University of California-San Diego, La Jolla, CA, [8]University of Glasgow, Glasgow, United Kingdom, [9]University of Utah Health Sciences Center

Objectives: Golimumab (GLM), a human monoclonal anti-TNFα antibody administered as every 4 weeks subcutaneous injections demonstrated long-term clinical efficacy and acceptable safety through wk104. The effect of GLM on inhibition of progression of structural damage PsA pts has been shown through wk52. Week 104 radiographic results are being reported now.

Methods: Adult PsA pts with ≥3 swollen & ≥3 tender joints (SJC/TJC) were randomized to receive SC placebo (PBO) or GLM 50 mg or 100 mg q4 wks. At wk16, pts with <10% improvement in SJC/TJC's entered early escape (EE) in a double-blinded manner to GLM 50 mg

(PBO pts) or GLM 100 mg (GLM 50 mg pts). All pts randomized to PBO received GLM 50 mg from wk24 through wk104. Pts on GLM 50 mg could be dose-escalated based on the investigator's judgment to GLM 100 mg after unblinding at wk52. Radiographs of the hands and feet were read at wks 0, 52, and 104. Erosions and joint space narrowing were evaluated by two independent readers unaware of treatment and image time sequence using the van der Heijde-Sharp (vdH-S) method modified for PsA. Data was analyzed based on randomized groups. Due to lack of adequate control arm, no statistical comparisons were performed at wk52 or wk104.

Results: 405 pts were enrolled. Mean age was 46–48 yrs, median SJC/TJC's were 12–14/22–24, HAQ scores were 1.0–1.1, CRP levels were 0.6 mg/dL, and mean (median) total vdH-S scores were 16.34–22.99 (9.00–10.50).

Conclusions: GLM 50 mg and 100 mg treated patients with active PsA showed no to minimal evidence of radiographic disease progression through wk104.

	PBO*	GLM 50 mg**	GLM 100 mg***
Change from baseline to wk52 in total score[a]			
N	87	116	128
Mean ± SD	0.10 ± 1.88	−0.30 ± 1.65	−0.35 ± 1.70
Median (IQR)	0.00 (0.00, 0.50)	0.00 (−0.50, 0.00)	0.00 (0.00, 0.00)
Change from wk52 to wk104 in total score[b]			
N	87	116	127
Mean ± SD	−0.03 ± 1.59	−0.10 ± 0.10	0.02 ± 0.71
Median (IQR)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Change from baseline to wk104 in total score[a]			
N	87	117	128
Mean ± SD	0.08 ± 3.19	−0.39 ± 2.04	−0.32 ± 1.873
Median (IQR)	0.00 (−0.50, 0.50)	0.00 (−0.90, 0.00)	0.00 (−0.50, 0.00)

*Includes pts who qualified for EE, crossed-over to GLM 50 mg and pts were dose-escalated from GLM 50 mg to GLM 100 mg, **Includes pts who qualified for EE and pts who were dose-escalated to GLM 100 mg,
***Includes pts who qualified for EE, [a]Includes pts with baseline and 1 post wk52 score, [b]Includes pts with wk52 and 1 post wk52 score.

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Low Doses of Etanercept Can Be Effective in Ankylosing Spondylitis Patients Who Achieve Remission of the Disease. Victoria Navarro Compán, Rafael Ariza Ariza, Carmen Vargas Lebrón, Blanca Hernández Cruz, Virginia Moreira Navarrete and Federico Navarro Sarabia. Hospital Universitario Virgen Macarena

Background: There is no evidence other than symptoms control to maintain the antiTNF therapy in patients with ankylosing spondylitis (AS). In this regard, low dose regimens could be considered in patients whose disease is clinically controlled. Moreover, the economic implications of this strategy can be important. However, although dose reduction can be common in clinical practice, the available data about it are scarce.

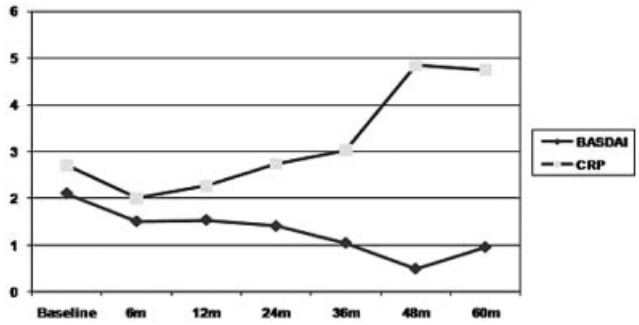
Objective: to explore the effectiveness of low dose of etanercept (ETN) in patients with ankylosing spondylitis (AS) who achieves a good control of their disease in daily clinical practice.

Methods: case series of AS patients treated with ETN. According to the judgment of the treating rheumatologist and patient′s preferences, a dose reduction was done in those patients who achieved a good control of their disease defined by BASDAI < 5 and C-reactive protein normal values. Descriptive statistics were calculated with mean, mode, median, ranges percents and lower and upper quartiles.

Results: 51 AS patients treated with ETN were identified and 16 of them (32%) were on dose reduction regimen.]

Group	Patients with low doses of Etanercept*	All
	n=16, 32%	n=51, 100%
Male n, %	14 (94%)	45 (91%)
HLA-B27 + n, %	14 (87%)	43 (84%)
Peripheral arthritis	3 (19%)	36 (71%)
Uveitis n, %	5 (31%)	41 (80%)
Sacroilitis n, %	4 (25%) II	12 (24%) II
	10 (62.5%) III	20 (39%) III
	2 (12.5%) IV	19 (37%) III
Previous DMARD treatment n, %	6 (31%)	34 (67%)
	Median (range)	Median (range)
Age, years	42.5 (30.5–57)	44 (32.53)
Disease duration, years	8 (3.5–14.7)	10 (6.5–18)
BASDAI	5.8 (4.5–7.7)	6.2 (4.7–7.9)
BASFI	5.9 (4.2–6.9)	6.5 (5–8.1)
ESR	34 (16–72)	29 (14–72)
CRP (mg/L)	17.9 (9.1–33.0)	18 (10–39)
PGA	55 (47–84)	62 (50–87)

Several regimens of dose reduction were used. Mean time receiving ETN before adjusting the dose was 17 ± 12 months. Mean follow up after dose change was 2 1±21 months. At this point all the patients in whom dose reduction was done remained in the low dose regimen. Median BASDAI (range) at starting the low dose regimen and 6 months later were 1.6 (0.9–2.4), and 1.4 (0.3–3.2), respectively. Median CRP values (range) at starting the low dose regimen and 6 months later were 1mg/l (0.1–2.8), and 1.3 mg/l (0.3–4.1), respectively. Other disease-related variables also remained unchanged. Patients with follow up at 12 and 24 months and longer remained in clinical remission with BASDAI values <2 and normal CRP values.



Conclusions: our data suggest that AS patients in clinical remission can use low doses of ETN without increasing disease activity. So, it can be a promising strategy but additional studies are needed to prove it.

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1945

Methotrexate Does Not Influence Infliximab Pharmacokinetics and Concentration-Effect Relationship in Ankylosing Spondylitis. Emilie Ducourau[2], David Ternant[2], Francine Lauféron[2], Denis Mulleman[2], Daniel Wendling[1], Gilles Paintaud[2] and Philippe Goupille[2]. [1]Universite de Franche-Comte, Besançon, France, [2]Universite François Rabelais de Tours, Tours, France

Introduction: Methotrexate (MTX) was shown to modify IFX pharmacokinetics in rheumatoid arthritis (1). However, its combination with infliximab in the treatment of ankylosing spondylitis (AS) is not recommended. The objective of this study was to investigate the influence of MTX on IFX pharmacokinetics and pharmacokinetic-pharmacodynamics (PK-PD) in axial AS patients.

Methods: Patients with axial AS were randomized to receive infliximab alone (infusions of 5 mg/kg at week 0, 2, 6, 12 and 18) or infliximab combined with MTX (10 mg/week). A clinical and laboratory evaluation was performed at each visit. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was the primary endpoint of clinical response. The pharmacokinetics of IFX was described using a two-compartment model with

first order distribution and elimination constants. The relationship between IFX concentration and BASDAI score was described using an indirect response model with inhibition of BASDAI 'input'. A population approach was used and models were run simultaneously. The influence of MTX was tested as a covariate on each pharmacokinetic and PK-PD parameter.

Results: Twenty six patients were included (14 with MTX, 12 without MTX). A total of 507 blood samples were available for measurement of serum infliximab (2). The PK analysis showed an influence of body size and history of a previous anti-TNF failure on the distribution volume of the central compartment but did not identify any influence of MTX on the estimated parameters (3). The evolution of BASDAI, clinical measurements and biomarkers of inflammation were no different in both groups. Main pharmacodynamic parameters were the maximum inhibition of BASDAI input (Em) = 46%, (59%) and the concentration leading to 50% of Em (C50) = 6.3 mg/L. MTX did not influence any of pharmacokinetic or PK-PD parameters.

Conclusion: MTX influenced neither pharmacokinetics nor PK-PD of IFX. Our study does not support the combination of methotrexate with infliximab in axial AS.

clinicaltrials.gov as NCT00507403

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Disclosure: E. Ducourau: None; **D. Ternant:** None; **F. Lauféron:** None; **D. Mulleman:** Abbott Laboratories, 2; **D. Wendling:** None; **G. Paintaud:** Roche, 5, Schering-Plough, 5, Wyeth Pharmaceuticals, 5; **P. Goupille:** Abbott Laboratories, 5, Bristol-Myers Squibb, 5, Roche, 5, Schering-Plough, 5, Wyeth Pharmaceuticals, 5.

1946

Nonsteroidal Anti-Inflammatory (NSAIDs) Drug-Sparing Effect and Sustained Clinical Improvement of Etanercept in Advanced Ankylosing Spondylitis. Results of an Open Label Extension Following a Randomized Double Blind Placebo-Controlled Study (SPINE). Maxime Dougados[2], Jürgen Braun[5], Sandor Szanto[6], Bernard Combe[1], Pal Geher[4], Veronique Leblanc[3] and Isabelle Logeart[3]. [1]Lapeyronie Hospital, Montpellier, France, [2]Paris-Descartes Univ, Cochin Hospital, Paris, France, [3]Pfizer France, Paris La Défense, France, [4]Polyclinic of the Hospitaller Brothers of St. John of God, Budapest, Hungary, [5]Ruhrgebiet Univ, Herne, Germany, [6]Univ of Debrecen, Debrecen, Hungary

Background: Etanercept (ETN) was showed to significantly improve rheumatic signs, symptoms and pulmonary function in patients with advanced ankylosing spondylitis during the randomized placebo-controlled trial (RCT) phase of SPINE study (1). A pre-planned open label extension (OLE) was aimed at assessing the sustained rheumatic effects of ETN for 3 additionnal months. In contrast to the RCT phase, the NSAID intake was at the discretion of the patients during this OLE phase. The purpose was to evaluate whether ETN therapy could be maintained with a concomitant NSAID treatment reduction.

Methods: *Patients*: Definite AS patients (modified New York criteria) with active (BASDAI ≥40), refractory (at least 2 NSAIDs), severe (at least 2, 3 or 2 inter-vertebral radiological consecutive bridges at the lumbar, thoracic or cervical level respectively), anti-TNF naive. *Study design*: Multicenter, double blind, RCT vs placebo of 12-week duration followed by a 12-week OLE. Patients who completed RCT phase entered the OLE and received etanercept (ETN). *Study drugs*: ETN 50 mg OW and identical placebo (PBO) during RCT phase and ETN 50 mg OW during the OLE phase. *Outcome measures*: BASDAI, BASFI, BASMI, and intake of NSAIDs using the ASAS-NSAIDs scoring system (2).

Results: Of the 82 randomized patients, 77 (males: 92%, age: 47.5±10.5 y, disease duration (since AS diagnosis): 16±10.7 y, B27 positive: 83.1%) entered the OLE phase (original ETN group: n=38; original PBO group, n=39). At baseline, patients had an active (BASDAI: 61.5±13.2, CRP: 20.5±26.1 mg/l) and severe (BASMI: 5.7±1.4, mSASSS: 37±20.2) disease and 83.1% of patients were receiving one NSAID at least at baseline. During the 12 weeks of the OLE trial, 3 patients discontinued the treatment (1 in the original PBO arm [due to withdrawal of consent] and 2 in the original ETN arm [due to withdrawal of consent: 1; due to lost to follow-up:1]). The mean change in BASDAI from baseline showed a sustained improvement reaching −15±20 and −27.4±23.8 at Week 12 and −28.6±24.3 and −37.6±22.4 at Week 24 in the original PBO group and ETN group, respectively.

Whatever the original group, the concomitant intake of NSAIDs significantly decreased during OLE phase in comparison to RCT phase: mean absolute change in ASAS-NSAID equivalent score between OLE and RCT was – 39.5 (−36%), p=0.005 and −20.9 (−17%), p=0.0005 in the original ETN and placebo group, respectively.

Conclusion: This prospective study conducted in advanced AS patients confirms the sustained symptomatic efficacy of ETN. Despite a relevant decrease in NSAIDs intake, such findings might be beneficial for the patients, not only in terms of long term symptomatic status but also in terms of prevention of long term NSAIDs toxicity.

This study was sponsored by Wyeth Pharmaceuticals France (Wyeth has been acquired by Pfizer in October 2009)

[1]Dougados M et al. *Arthritis & Rheumatism* 2009;60 (suppl 10): S194(Abstract 524).
[2]Dougados M et al. *Annals Rheum Dis*. 2010;abstract FRI0364.

Disclosure: M. Dougados: Pfizer Inc, 5, 8; **J. Braun:** Pfizer Inc, 5; **S. Szanto:** Pfizer Inc, 5; **B. Combe:** Pfizer Inc, 2, 5, 8, Schering, 2, 5, 8, UCB, Inc., 2, 5; **P. Geher:** Abbott Laboratories, 5, Pfizer Inc, 5, Schering-Plough, 5; **V. Leblanc:** Pfizer Inc, 3; **I. Logeart:** Pfizer Inc, 3.

1947

Periarticular Bone Changes in Psoriatic and Rheumatoid Arthritis Patients Following Anti-TNF-alpha Therapy. Agnes Szentpetery[2], Phil Gallagher[2], Susan Van der Kamp[2], Malachi J. McKenna[1], Douglas J. Veale[2] and Oliver FitzGerald[2]. [1]St. Vincent's University Hospital, Department of Endocrinology, Dublin, Ireland, [2]St. Vincent's University Hospital, Department of Rheumatology, Dublin, Ireland

Purpose: to examine the effect of anti-TNF-alpha therapy on periarticular bone mineral density (BMD) in patients with psoriatic arthritis (PsA) and rheumatoid arthritis (RA) prior to and 3 months, 1 and 3 years after receiving biologic treatment. Further, to explore associations between hand BMD and clinical responses in PsA and RA.

Methods: PsA and RA patients with active disease were selected following a decision to commence anti-TNF-alpha therapy. Global hand dual-energy × ray absorptiometry (DXA) including all hand bones distal to the wrist joint and 7 sub-regions of interests (ROI) were analysed at baseline, 3 months, 1 and 3 years. These included the carpus (R1) and the periarticular regions of 2nd (R2), 3rd (R3) and 4th (R4) MCPs and the 2nd (R5), 3rd (R6) and 4th (R7) PIPs. Clinical assessments including ESR, CRP, DAS28-CRP and HAQ were recorded at all time points.

Results: 62 patients (27 PsA, 35 RA) were recruited. Patients' median disease duration was 7 years (0.16–40). At baseline, global hand BMD (g/cm^2) was significantly greater in PsA than RA (0.349 v.0.327 p=0.025) and remained higher at all time points. BMD was higher in PsA than in RA in each ROI at all time points except in R2 at 3 years. BMD was significantly higher in PsA than in RA at baseline and at 3 months in R5 (0.316 v. 0. 292 p=0.035 and 0.316 v. 0.279 p=0.028) and R6 (0.331 v. 0.302 p=0.042 and 0.329 v. 0.293 p=0.04).

ESR remained significantly lower in PsA than in RA at all time points ($p<0.05$). In PsA CRP was lower at baseline and at 3 month whilst DAS28-CRP at 3 months and 12 months compared with RA ($p<0.05$). SJC, DAS28-CRP and HAQ remained lower in PsA during the study period.

In PsA, there were significant negative correlations between ESR and global hand BMD at 1 year (r = −0.6; p=0.028) and at 3 years (r = −0.6; p=0.008) and in RA between DAS28-CRP and global BMD at 3 years (r = −0.4; p= 0.025).

Conclusions: Periarticular bone density was higher in PsA at all time points but increased with anti-TNF-alpha treatment in both diseases. Higher periarticular bone density was associated with lower inflammatory activity in both diseases but earlier in PsA. Anti-TNF-alpha therapy reduces periarticular bone loss in patients with inflammatory arthritis.

Disclosure: A. Szentpetery: None; **P. Gallagher:** None; **S. Van der Kamp:** None; **M. J. McKenna:** None; **D. J. Veale:** Abbott Immunology Pharmaceuticals, 2, 5, 8, Centocor, Inc., 5, 8, GlaxoSmithKline, 2, 5, 8, Mundipharma Medical GmbH, 2, 8, Opsona Therapeutics, 2, 8, Pfizer Inc, 5, 8, Schering-Plough, 5, 8, Wyeth Pharmaceuticals, 2, 5, 8; **O. FitzGerald:** Abbott Immunology Pharmaceuticals, 2, 5, 8, Bristol-Myers Squibb, 2, Pfizer Inc, 5, 8.

1948

Prediction of Early Response to Anti-TNF Therapy and Disease Activity State Using the Ankylosing Spondylitis Disease Activity Score (ASDAS). Nathan Vastesaeger[5], Yanxin Wang[6], Robert D. Inman[9], Atul A. Deodhar[7], Benjamin L. Hsu[1], Mahboob U. Rahman[2], B. A. C. Dijkmans[11], Juergen Braun[8], Piet P. Geusens[10], Joachim Sieper[3] and Desiree M. Van Der Heijde[4]. [1]Centocor Research and Development, Inc./Univ. of Pennsylvania School of Medicine, Wynnewood, PA, [2]Centocor Research and Development, Inc./ Univ. of Pennsylvania School of Medicine, Malvern, PA, [3]Charite Campus Benjamin Frankl, Berlin, Germany, [4]Leiden University Medical Center, Meerssen, The Netherlands, [5]Merck and Co., Inc., Whitehouse Station, NJ, [6]Merck and Co., Inc., [7]Oregon Health Sciences University, Portland, OR, [8]Rheumazentrum Ruhrgebiet, Herne, Germany, [9]Toronto Western Hospital, Toronto, ON, Canada, [10]University Hasselt, Genk, Belgium, [11]VU Medical Centre, Amsterdam, The Netherlands

Objectives: We previously reported that in the ASSERT and GO-RAISE studies, BASDAI50 response can be accurately predicted with a combination of baseline characteristics. This analysis compares the accuracy of predicted response rates and disease activity as measured by different assessments, including the ASDAS.

Methods: The ASSERT and GO-RAISE trial data were combined and baseline characteristics were used to predict the probability for achieving week 12 ASAS20, BASDAI50 and ASDAS major response and BASDAI and ASDAS scores at week 12. Univariate analyses identified baseline predictors for response. Variable associations were explored using Spearman correlation analysis. A stepwise selection procedure using logistic regression, ROC and correlation analyses was used to select a final set of predictors. Logistic regression was used to calculate the predicted week 12 BASDAI and ASDAS scores and the probability of week 12 response to anti-TNF or placebo respective to combined selected predictors at baseline. The accuracy of prediction between the different assessments was compared using ROC analyses and R-square.

Results: 479 AS patients (NY modified criteria) treated with anti-TNF and 156 patients treated with placebo with continued conventional therapy, with BASDAI and spinal pain assessment ≥ 4 were included. Age (mean 39.5; SD 11.3 yrs), BASFI, (mean 5.4; SD 2.2 cm), Berlin enthesitis-score (mean 2.4; SD 2.9), therapy (anti-TNF or placebo), CRP (mean 2.1; SD 2.4 mg/dL) and HLA-B27 genotype [(+) or (−)] were retained as final predictors of response. The area under the ROC curve of the model which included the six selected predictors (log transfer of CRP values) and interactions between predictors was 0.85, 0.79 and 0.75 and the R-square was 0.43, 0.33 and 0.24 for week 12 ASDAS major response, BASDAI50 response and ASAS20 response, respectively. This indicates good accuracy for prediction of BASDAI50 and ASDAS major response and fair accuracy for ASAS20 response. The R-squares of 0.49 and 0.27 for ASDAS and BASDAI scores respectively, indicate that the week 12 disease activity measured by ASDAS could be more reliably predicted. The figure shows the predicted change in ASDAS from baseline to week 12 versus actual changes.

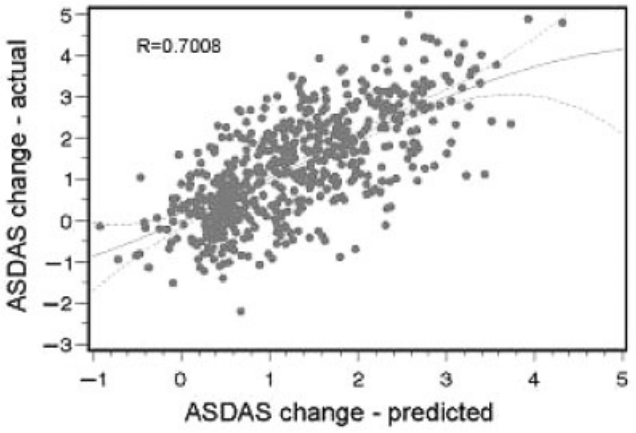

Figure. Change from baseline to week12 in ASDAS score.

Conclusion: Elevated CRP, lower age, lower enthesitis score, lower BASFI, and presence of HLA-B27 genotype are associated with a better treatment response at week 12 in ASSERT and GO-RAISE. The values of these characteristics at baseline allow calculating the predicted response rates and future disease activity of an individual patient. The accuracy of predicting ASDAS and ASDAS response is good and higher than that of other assessments.

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1949

Predictors of Radiographic Progression in Adalimumab-Treated Patients with Ankylosing Spondylitis. Walter Maksymowych[5], Desiree van der Heijde[3], Robert Landewe[4], Aileen Pangan[2], Steve Brown[2] and Frederic Lavie[1]. [1]Abbott Laboratories, Rungis, France, [2]Abbott Laboratories, Abbott Park, IL, [3]Leiden University Medical Center, Leiden, The Netherlands, [4]Maastricht University Medical Center, Maastricht, The Netherlands, [5]University of Alberta, Alberta, BC, Canada

Objective: To identify factors contributing to radiographic progression over 2 years in patients with Ankylosing Spondylitis (AS) who are treated with adalimumab (ADA).

Methods: The ATLAS trial randomized AS patients to treatment with ADA or placebo for a 24-wk double-blind period, followed by an open-label extension with ADA. Two independent blinded readers scored X-rays obtained at baseline and year 2 using the mSASSS method. Dependent variables were: 1) change in mSASSS ≥2 and ≥4 (severe progression) from baseline through 2 years, and 2) development of new syndesmophytes at year 2. Independent variables were age, disease duration, spinal mobility (cervical rotation and lateral lumbar flexion), area under the curve (AUC) from baseline to 2 years for CRP and ASDAS, and baseline ASDAS and mSASSS. Categorical variables were also included: HLA-B27, sex, peripheral synovitis at baseline (SJC>0), peripheral enthesitis at baseline (MASES>0), presence of baseline syndesmophytes, and history of uveitis. Associations were tested univariately; significantly associated variables were entered as explanatory variables in a multivariate analysis.

Results: This analysis includes 275 subjects with 2 years of exposure to ADA; at baseline, subjects had mean disease duration of 10.8 years, mean ASDAS of 3.7, and mean mSASSS of 20.3; syndesmophytes were present in 85% of patients at baseline. Radiographic progression (ΔmSASSS ≥2) was found in 61 subjects (22%), and severe radiographic progression (ΔmSASSS ≥4) was observed in 22 subjects (8%). New syndesmophytes were found by either reader in 106 subjects (39%).

Univariate analysis identified significant associations for age, mobility, and baseline bone damage with radiographic progression (Table). Linear regression revealed similar findings. Sex, HLA-B27, uveitis, peripheral synovitis or enthesitis, disease duration, baseline ASDAS, and CRP levels were not predictive in any analysis.

Table. Logistic regression for factors associated with radiographic progression

Variable	Odds Ratio (95% CI)		
	ΔmSASSS ≥2	ΔmSASSS ≥4	new syndesmophytes[a]
Age	1.04 (1.009, 1.062)†	1.04 (1.003, 1.084)†	1.02 (0.996, 1.040)
Syndesmophytes (BL)	3.87 (1.126, 13.301)*	n/a	6.45 (2.165, 19.200)*
mSASSS (BL)	1.03 (1.011, 1.039)*	1.03 (1.009, 1.049)*	1.01 (1.002, 1.026)†
Cervical rotation (BL)	0.98 (0.968, 0.995)*	0.99 (0.966, 1.006)	0.99 (0.974, 0.996)*
Lateral lumbar flexion (BL)	0.98 (0.890, 1.067)	0.64 (0.476, 0.859)*	0.91 (0.842, 0.992)†
ASDAS AUC (BL to 2 yr)	1.00 (0.997, 1.003)	1.01 (1.001, 1.009)†	1.00 (0.998, 1.003)

[a]identified by either Reader 1 or Reader 2; BL: baseline; n/a: not a valid logistic regression model; *$P \leq 0.01$; †$P < 0.05$.

Multivariate analysis was conducted using significant factors from univariate analysis, with the exception of mobility scores, which are intermediate variables. Only baseline mSASSS was consistently identified as a significant contributor to radiographic progression (ΔmSASSS ≥2 and ≥4, OR [95% CI]: 1.02 [1.005, 1.036], $P<0.01$ and 1.02 [1.001, 1.046], $P=0.04$) and only baseline syndesmophytes were predictive of the development of new syndesmophytes (OR [95%CI]: 7.63 [2.381, 24.476], $P<0.01$).

Conclusion: Clinical measures of disease activity were not related to radiographic progression. Only the presence of radiographic damage at initiation of therapy was consistently associated with the formation of new syndesmophytes through 2 years in AS patients treated with adalimumab. These results support previous studies suggesting a disconnect between disease activity and bone formation in patients with long-standing AS.

Disclosure: W. Maksymowych: Abbott Laboratories, 2, 5, Merck Pharmaceuticals, 2, 5, Pfizer Inc, 2, 5; **D. van der Heijde:** Abbott Laboratories, 5, Amgen Inc., 5, Bristol-Myers Squibb, 5, Centocor, Inc., 5, Chugai, 5, Merck Pharmaceuticals, 5, Novartis Pharmaceuticals Corporation, 5, Pfizer Inc, 5, Roche, 5, sanofi-aventis, 5, Schering-Plough; **R. Landewe:** Abbott Laboratories, 2, 5, 8, Amgen Inc., 2, 5, 8, Bristol-Myers Squibb, 2, 5, 8, Centocor, Inc., 2, 5, 8, Pfizer Inc, 2, 5, 8, UCB, Inc., 2, 5, 8; **A. Pangan:** Abbott Laboratories, 1, 3; **S. Brown:** Abbott Laboratories, 1, 3; **F. Lavie:** Abbott Laboratories, 1, 3.

1950

Prevalence of Psoriatic Arthritis in Thai Psoriasis at Ramathibodi Hospital. Bodin Butthum[4], Suphaneewan Jaovisidha[1], Pintip Ngamjanyaporn[3], Surachai Nithiketkul[2] and Suchela Janwityanujit[2]. [1]Department of Radiology Faculty of Medicine, Ramathibodi Hospital, Mahidol University, [2]Division of Allergy Immunology and Rheumatology, Department of Medicine Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, [3]Division of Allergy Immunology and Rheumatology, Department of Medicine Faculty of Medicine, Ramathibodi Hospital, Mahidol University, [4]Naresuan University, Department of Medicine, Phitsanulok, Thailand

Objective: To determine the prevalence as well as the clinical features of psoriatic arthritis (PsA) in Thai patients with psoriasis. Factors highly associated with the diagnosis of PsA will also be identified.

Methods: Psoriatic patients who visited the dermatology clinic at Ramathibodi hospital during July 1 to December 31, 2009 were prospectively studied. A standard clinical protocol for PsA was used to assess patients for the actively inflamed joint count, dactylitis, enthesitis, nail change, range of body movement and the presence of back disease. X-ray films of the hands, feet, whole spine and the sacroiliac (SI) joints were taken. Based on the clinical and radiological information, the diagnosis of psoriatic arthritis was classified by CASPAR Classification Criteria for Psoriatic Arthritis (1) and the five clinical subsets defined by Moll and Wright (2) were assigned to each patient. Clinical variables indicative of PsA were also collected.

Results: Three hundred and two psoriatic patients (149 males and 153 females) who had complete X-ray studies as defined in the protocol were analyzed. The prevalence of PsA in psoriatic patients was 43.05% (130/302; 73 males and 57 females). Mean age, mean duration of disease and male to female ratio in patients with PsA were 51.3 years old, 12.2 years and 1.3:1 respectively, not differed from those with psoriasis alone. Spondylitis was the most common pattern of PsA (83.1%) followed by polyarthritis, oligoarthritis, DIP involvement and arthritis mutilans in our group of PsA patients. Interestingly, more than half of our psoriatic patients (150/179) had radiographic abnormalities without clinical criteria for PsA.

Conclusion: Radiological assessment gives additional arthritic findings not gained by clinical examination alone. Nail change, morning stiffness more than 1 hour, buttock pain and history of joint inflammation are suggestive of PsA in psoriatic patient.

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Disclosure: B. Butthum: None; **S. Jaovisidha:** None; **P. Ngamjanyaporn:** None; **S. Nithiketkul:** None; **S. Janwityanujit:** None.

1951

Psoriatic Arthritis and Onycholysis—Results from a Study of 1116 Patients with Psoriasis, and Follow-Up of Those with Psoriatic Arthritis over 1–6 Years. Thorvardur J. Love[2], Johann E. Gudjonsson[4], Helgi Valdimarsson[1] and Bjorn Gudbjornsson[3]. [1]Landspitali University Hospital, [2]Landspitali University Hospital, Boston, MA, [3]Landspitali University Hospital, Center for Rheumatology Research, [4]University of Michigan, Department of Dermatology

Psoriatic arthritis is an arthritis associated with the skin disease psoriasis. It is associated with nail changes, and small joint disease is associated with onycholysis. While 15% - 50% of patients with psoriasis have nail changes, up to 85% of patients with psoriatic arthritis do. However, subtypes of nail changes are rarely reported on. We studied the subtypes of nail changes in psoriasis patients and their associations with psoriatic arthritis, as well as the progression of nail changes over 1–6 years.

Methods: We performed a cross sectional analysis of the association between psoriasis and psoriatic arthritis and nail changes. We then followed those patients reporting psoriatic arthritis 1–6 years later, and re-evaluated their fingernails. Psoriasis cases were located from community sources, primarily a local psoriasis patient group, and only those cases with skin disease present, and 18 years of age or older, were included. Location and pattern of skin and nail involvement was recorded. Most patients had their HLA-C type determined. All patients were asked if they had been diagnosed with psoriatic arthritis by a rheumatologist. One to six years later, those patients who had reported psoriatic arthritis were asked to participate in a second study where they were evaluated for skin, nail and joint disease. We tested the location and pattern of skin findings, type of nail changes, and HLA-Cw06 status when available for an association with psoriatic arthritis using the chi-square test and univariate logistic regression. Those variables that were significantly associated with psoriatic arthritis on univariate analysis at a p value of 0.05 or less were further analyzed in a multivariate logistic regression model. Age and gender were included as covariates in all multivariate analyses.

Results: We recruited 1116 patients age 18 or older with active psoriatic lesions on physical examination. The mean age of onset of psoriasis SD was 20.8 +/− SD 12.5 and 56% were women. Chronic plaque psoriasis was present in 94%, with arms, scalp, and legs involved in 85%, 77%, and 71%, respectively. Nails were involved in 36% of patients, and the most common nail change was onycholysis. 183 patients or 16% reported having psoriatic arthritis. Onycholysis, subungual hyperkeratosis, and pitting were all associated with psoriatic arthritis on univariate analysis. Multiple logistic regression showed that onycholysis remained strongly associated with psoriatic arthritis with an OR of 2.02 while the other two types of nail changes no longer showed statistically significantly associations. On follow-up 122 of the 183 patients were evaluated again. All types of nail changes had increased in prevalence, with the overall prevalence of nail changes rising from 36% to 80%. Less than 4% of patients had all nail changes disappear from the first to the second visit.

Conclusions: Psoriatic arthritis is strongly associated with nail changes. Onycholysis may be more associated with arthritis than pitting or subungual hyperkeratosis. Nail changes tend to progress and rarely remit. More studies looking at the subtypes of nail changes in psoriasis and psoriatic arthritis are needed to confirm these findings.

Disclosure: T. J. Love: None; **J. E. Gudjonsson:** None; **H. Valdimarsson:** None; **B. Gudbjornsson:** None.

1952

Psoriatic Arthritis: Oligoarticular or Polyarticular Presentation? Carlotta Nannini[1], Laura Niccoli[2], Emanuele Cassarà[2], Olga Kaloudi[2] and Fabrizio Cantini[2]. [1]Rheumatology Unit, Hospital of Prato, Prato, Italy, [2]Rheumatology Unit, Hospital of Prato, Italy

Background: Polyarthritis has been reported as the most frequent pattern in patients (p.) with Psoriatic Arthritis (PsA), with an estimated frequency of 60%.

Objectives: To determine the occurrence of the different PsA subgroups in a cohort of p. with early PsA selected using the CASPAR criteria.

Methods: We evaluated a cohort of 242 new consecutive outpatients with PsA observed between January 2000 and December 2009 at a secondary referral center. As controls 184 new consecutive early rheumatoid arthritis (RA) outpatients were used. Demographic, clinical, laboratory and radiological data were collected and stored in a computed database. In PsA p. the following clinical patterns were considered: peripheral (oligoarthritis $\leq$4 and polyarthritis $\geq$5 involved joints), axial (Calin's criteria for inflammatory spinal pain, radiologic or MRI evidence of sacroiliitis), mixed (concomitant axial and peripheral features). Involved joints were counted separately without grouping hand and foot small joints.

Results: Female gender (137/242; 57%) was significantly lower in PsA compared to RA (140/184; 78.2%) ($p<0.001$). Mean age was 50.33 $\pm$ 11.7 ys in PsA and 57.2 $\pm$ 13.55 years in RA ($p<0.001$). Mean disease duration of symptoms was 9.38 $\pm$ 2.0 mo. in PsA cohort and 10.1 $\pm$ 1.75 mo. in PsA cohort. At diagnosis, the total number of involved joints was significantly lower in PsA compared to RA ($p<0.001$). Table 1 summarizes the comparison between the demographic and clinical features of early PsA and early RA.

Table 1.

	PsA total	RA	P value
Total N of patients	242	184	-
Age at PsA or RA Dx (yrs)	50.3 ± 11.7	57.2 ± 13.55	<0.001
Female N(%)	137 (57%)	140 (78.2%)	<0.001
Duration of sympthoms (mo)	9.38 ± 2.0	10.1 ± 1.75	NS 0.8
Total N of involved joints at Dx	3 ± 3.5	16.2 ± 7.98	<0.001
ESR at Dx (mm1h)	31 ± 18	56.2 ± 25.03	<0.001
CRP at Dx (mg/dl)	1.83 ± 2.28	3.3 ± 3.37	<0.001
Low back pain N(%)	117 (48%)	NA	
Dactylitis N(%)	62 (26%)	NA	
Enthesitis N(%)	79 (33%)	NA	
Tenosinovitis N(%)	55 (23%)	NA	
Peripheral involvement N(%)	132 (51%)	NA	
Back involvement N(%)	41 (17%)	NA	
Mix involvement N(%)	69 (28%)	NA	
Sacroileitis N(%)	105 (43%)	NA	
Monolateral sacroileitis N(%)	41 (17%)	NA	
Bilateral sacroileitis N(%)	60 (25%)	NA	
HLA B27 N(%)	30 (12.4%)	NA	
HLA CW6 N(%)	58 (24%)	NA	
HLA B39 N(%)	9 (4%)	NA	

As shown in table 2, polyarthritis was present in 54 (22%) PsA p. and 164 (89.3%) RA p. (p<0.001), oligoarticular and monoarticular involvement in PsA was present in 188 patients (78%).

Table 2.

	PsA			
	PsA polyart	Non Polyart	RA polyart	P value
Total N of patients	54 (22%)	188 (78%)	164 (89.3%)	<0.001
Age at PsA or RA Dx (yrs)	54.1 ± 13.49	49.3 ± 11.07	57.2 ± 13.76	<0.001
Female N (%)	25 (54.3%)	88 (55.3%)	86 (78.9%)	<0.001
Duration of sympthoms (mo)	6 ± 5.12	10.0 ± 1.62	9.9 ± 1.74	NS 0.74
Total N of involved joints at Dx	6 ± 4.84	1.6 ± 1.54	17.6 ± 7.12	<0.001
ESR at Dx (mm1h)	33 ± 19.36	29.2 ± 18.62	39.3 ± 33.77	0.005
CRP at Dx (mg/dl)	1.7 ± 2.26	1.7 ± 2.31	2.0 ± 2.35	NA 0.48
Low back pain N (%)	12 (26.1%)	93 (58.5%)	NA	<0.001
Dactylitis N(%)	7 (15.2%)	47 (29.6%)	NA	NS 0.08
Enthesitis N(%)	4 (12.5%)	7 (6.4%)	NA	NS 0.25
Tenosinovitis N(%)	10 (21.7%)	44 (27.7%)	NA	NS 0.42

Conclusion: Differently from other reports we found oligoarthritis as the most frequent pattern of early PsA with a significant lower number of involved joints compared to RA. This may reflect possible selection biases due to the lack of validated criteria before CASPAR set availability and the referral of p. with more severe disease to tertiary centres.

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1953

Radiographic Progression Is Associated with Resolution of Systemic Inflammation in Patients with Axial Spondyloarthritis Treated with TNFα Inhibitors. Susanne Juhl Pedersen[8], Inge Juul Sørensen[13], Kay-Geert Hermann[4], Patrick Garnero[17], Julia S. Johansen[1], Ole Rintek Madsen[9], Annette Hansen[15], Michael Sejer Hansen[10], Gorm Thamsborg[9], Lis Smedegaard Andersen[18], Ole Majgaard[14], Anne Gitte Loft[16], Jon Erlendsson[11], Karsten Asmussen[7], Anne Grethe Jurik[3], Jakob Møller[5], Maria Hasselquist[5], Dorrit Mikkelsen[2], Thomas Skjødt[6] and Mikkel Østergaard[12]. [1]Dep. of Internal Medicine, Herlev Hospital, Copenhagen, Denmark, [2]Dep. of Radiology, Aabenraa Hospital, Aabenraa, Denmark, [3]Dep. of Radiology, Aarhus University Hospitals, Aarhus, Denmark, [4]Dep. of Radiology, Charité University Hospital, Berlin, Germany, [5]Dep. of Radiology, Herlev University Hospital, Copenhagen, Denmark, [6]Dep. of Radiology, Vejle Hospital, Vejle, Denmark, [7]Dep. of Rheumatology, Bispebjerg Hospital, Copenhagen, Denmark, [8]Dep. of Rheumatology, Gentofte and Herlev Hospitals, Copenhagen, Denmark, [9]Dep. of Rheumatology, Gentofte Hospital, Copenhagen, Denmark, [10]Dep. of Rheumatology, Herlev Hospital, Copenhagen, Denmark, [11]Dep. of Rheumatology, Horsens Hospital, Denmark, [12]Dep. of Rheumatology, Hvidovre and Glostrup Hospitals, Copenhagen, Denmark, [13]Dep. of Rheumatology, Hvidovre and Glostrup Hospitals and DANBIO, Copenhagen, Denmark, [14]Dep. of Rheumatology, Hvidovre Hospital, Copenhagen, Denmark, [15]Dep. of Rheumatology, Rigshospitalet, Copenhagen, Denmark, [16]Dep. of Rheumatology, Vejle Hospital, Denmark, [17]INSERM Unit 664, Lyon, and Cisbio Bioassays Bagnols/Cèze, France, [18]Rheumatism Hospital, University of Southern Denmark, Graasten, Denmark

Objectives: To explore the relation between radiographic progression and biomarkers of inflammation (C-reactive protein (CRP), interleukin-6 (IL-6), YKL-40), angiogenesis (vascular endothelial growth factor (VEGF)), cartilage turnover (CTX-II, matrix metalloproteinase 3 (MMP3), total aggrecan, cartilage oligomeric matrix protein (COMP)) and bone turnover (CTX-I, total osteocalcin) and MRI inflammation in patients with axial spondyloarthritis (SpA) treated with TNFα inhibitor.

Methods: Thirty-six patients (27 men, 9 women; median age 40 yrs (range 21–62); disease duration 15 yrs (1–45)) initiated treatment with TNFα inhibitors (infliximab (n=28), etanercept (n=7) and adalimumab (n=1)) and were followed for 46 weeks. Radiographs were evaluated according to the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) at baseline and week 46. Patients developing new syndesmophytes (0 vs. ≥1) or increased in mSASSS (0 vs. ≥1 unit) were compared with those who did not, regarding biomarker levels and MRI inflammation scores of the sacroiliac joints and lumbar spine (Berlin scores) and with biomarker levels of healthy subjects.

Results: The patients increased in mSASSS from median 13 (IQR: 6–24) at baseline to 15 (6–24) (p=0.005) at week 46 (p=0.005). Eighteen (50%) patients increased in mSASSS (i.e. progressed) and 11 (30%) developed new syndesmophytes. mSASSS and biomarkers did not correlate. Compared to mSASSS non-progressors, mSASSS progressors had higher pretreatment total aggrecan (666 ng/ml (537–820) vs. 507 (401–646), p=0.007) and higher time-integrated mean concentrations of total aggrecan from baseline to week 22 (743 ng/ml (612–849) vs. 602 (446–707), p=0.02) and 46 (746 ng/ml (636–895) vs. 638 (450–735), p=0.02). Patients developing new syndesmophytes also had higher time-integrated mean concentration of total aggrecan from baseline to week 22 and 46 as compared to patients without new syndesmophytes (results like above). Development of new syndesmophytes was associated with larger percentage decreases in CRP (−90% (−96;−78) vs. −58 (−88;−25), p=0.007) and IL-6 (−81% (−93;−75) vs. −67 (−89;−16), p=0.02) and increases in osteocalcin (20% (9;36) vs. 9% (−10;25), p=0.049). Radiographic progression was associated with normalization of CRP and IL-6 at week 22 (i.e. CRP ≤8 mg/l and IL-6≤3.3 ng/l) and decrease in MRI inflammation. Radiographic non-progression was associated with persistent systemic inflammation and unchanged/increased MRI inflammation scores (Table 1).

Conclusion: Radiographic progression in patients with axial SpA during treatment with TNFα inhibitors was associated with resolution of systemic inflammation and reduction in MRI inflammation but not with baseline inflammation.

Table 1. Changes in inflammatory parameters (CRP, IL-6 and MRI) versus radiographic progression

	Radiographic progression week 0–46					
	New syndesmophyte (≥1)			mSASSS progression (≥1)		
Changes from baseline to week 0–22	No N=25	Yes N=11	p-value	No N=18	Yes N=18	p-value
CRP decreased to ≤8 mg/l	11 (52)	10 (48)		7 (33)	14 (67)	
CRP remained >8 mg/l	7 (100)	0 (0)	0.03†	6 (86)	1 (14)	0.03†
CRP remained ≤8 mg/l	7 (87)	1 (13)	NS§	5 (63)	3 (38)	NS§
IL-6 decreased to ≤3.3 ng/l	10 (50)	10 (50)		7 (65)	13 (35)	
IL-6 remained >3.3 ng/l	7 (100)	0 (0)	0.03†	7 (100)	0 (0)	0.006†
IL-6 remained ≤3.3 ng/l	8 (89)	1 (11)	NS§	5 (55)	4 (45)	NS§
Change in MRI SIJ IS <0	7 (47)	8 (53)		6 (40)	9 (60)	
Change in MRI SIJ IS ≥1	10 (91)	1 (9)	0.04†	6 (55)	5 (45)	NS
MRI SIJ IS=0 at week 0	6 (86)	1 (14)	NS§	5 (71)	2 (29)	NS

Number (%). Chi² test and Fisher's Exact test. †Normalization vs. persistently increased biomarker levels. §Normalization vs. normal levels at baseline.

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1954

Reliability of Radiographic Scoring Methods in Axial Psoriatic Arthritis. Vinod Chandran[3], Bradley Biagioni[3], Richard Cook[1], Lihi Eder[3], Anupam Wakhlu[3], Michael Li[3], Hua Shen[1] and Dafna D. Gladman[2]. [1]Department of Statistics and Actuarial Science, University of Waterloo, [2]Toronto Western Hospital, Toronto, ON, Canada, [3]University of Toronto Psoriatic Arthritis Clinic, Toronto Western Hospital

Background: More than a third of patients with psoriatic arthritis (PsA) have axial arthritis. Although there are similarities, important differences exist between axial PsA (AxPsA) and Ankylosing Spondylitis (AS). The Bath AS Radiology Index (BASRI), modified Stokes AS Spinal Score (mSASSS) and Radiographic AS Spinal Score (RASSS) were developed to score AS, and Psoriatic Arthritis Spondylitis Radiology Index (PASRI) to score AxPsA. Our aim was to determine the reliability of these scoring systems in AxPsA.

Methods: A computerized scoring module that facilitated scoring radiographic features of axial arthritis on vertebrae, sacroiliac and cervical facet joints, and calculated total scores for all the available scoring methods for AS and AxPsA was developed. Four assessors all rheumatologists blinded to patient information were provided with an e-handbook and one hour training session. Spinal radiographs of 18 patients with AS (satisfying modified NY criteria) and 40 patients with AxPsA (defined as at least unilateral grade 2 sacroiliitis and/or inflammatory back pain and/or restricted spinal mobility) were duplicated, patient identifiers removed, and order randomized. Radiographs were read by the four assessors individually, data entered into the module and scores obtained. Intraclass correlation coefficient (ICC) estimates of the inter- and intra-assessor reliability of scores for each method were obtained. A consensus score for AxPsA patients was also obtained.

Results: The intra-and inter- assessor reliability for the radiographic scoring methods in AS are given in table 1.

Table 1. Inter-class and intra-class correlation coefficients and 95% confidence intervals of radiographic scores in AS (N=18).

Scoring System	Reliability	ICC	95% CI
Sacroiliitis grade (NY criteria)	Between Assessor	0.795	0.646, 0.905
	Within Assessor	0.908	0.837, 0.957
BASRI-spine	Between Assessor	0.861	0.746, 0.938
	Within Assessor	0.955	0.917, 0.98
mSASSS	Between Assessor	0.857	0.735, 0.938
	Within Assessor	0.982	0.967, 0.992
RASSS	Between Assessor	0.748	0.562, 0.888
	Within Assessor	0.961	0.929, 0.983
PASRI	Between Assessor	0.926	0.858, 0.968
	Within Assessor	0.985	0.971, 0.993

All methods had excellent inter- and intra- assessor reliability in AS. Scoring was completed by the assessors within an average duration of 7 minutes. The 40 patients with AxPsA (24 males, age 54 years, disease duration 18 years, mean cervical rotation of 61 degrees, Occiput to wall distance of 2.3 cm, Schober's test of 4.7 cm, Domjan lumbar lateral flexion of 15.5 cm, actively inflamed joint count of 5 and damaged joint count of 16 at the time of radiographic assessment) by consensus read had mean (± standard deviation) BASRI-spine score of 3.98 (2.38), mSASSS of 8 (13.4), RASSS 6.54 (14.1) and PASRI score of 12 (12.3) units. The intra- and inter- assessor reliability for the radiographic scoring methods in AxPsA are given in table 2.

Table 2. Inter-class and intra-class correlation coefficients and 95% confidence intervals of radiographic scores in AxPsA (N=40).

Scoring System	Reliability	ICC	95% CI
Sacroiliitis grade (NY criteria)	Between Assessor	0.67	0.544, 0.785
	Within Assessor	0.807	0.726, 0.875
BASRI-spine	Between Assessor	0.521	0.375, 0.669
	Within Assessor	0.771	0.688, 0.845
mSASSS	Between Assessor	0.652	0.488, 0.798
	Within Assessor	0.911	0.862, 0.949
RASSS	Between Assessor	0.68	0.513, 0.823
	Within Assessor	0.902	0.845, 0.946
PASRI	Between Assessor	0.88	0.817, 0.927
	Within Assessor	0.917	0.874, 0.95

Only PASRI had excellent intra- and inter-rater reliability in AxPsA.

Conclusions: Available radiographic scoring systems have at least moderate inter- and intrarater reliability when applied to AxPsA. The PASRI has the highest reliability in AxPsA and performs well in AS.

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1955

Rituximab in Psoriatic Arthritis Provides Modest Clinical Improvement and Reduces Expression of Inflammatory Biomarkers in Skin Lesions. Philip Mease[2], Arthur Kavanaugh[3], Mark Genovese[1], Chris Ritchlin[4], Sanna Rosengren[3], Alex Quistberg[5] and David Boyle[3]. [1]Stanford Univ, [2]Swedish Medical Ctr, Univ. of Washington, [3]U of Calif San Diego, [4]Univ. of Rochester, [5]Univ. of Washington

Purpose: To determine the effect of rituximab (RTX) on clinical measures and inflammatory biomarkers in biopsies of psoriatic skin lesions compared to non-lesional skin before and after therapy with RTX in PsA patients (pts).

Methods: In this open-label study, 21 PsA pts received 1000 mg RTX + 100 mg solu-medrol on days 0 and 15. The primary clinical endpoint was ACR20 at week 24 and secondary endpoints included ACR50/70 and Psoriasis Area and Severity Index (PASI) 50/75 response. Lesional and non-lesional skin biopsies were collected from select patients pre-treatment and at week 8 for gene expression studies. mRNA levels were determined by quantitative PCR analysis and relative expression was determined using cell-based standard. Expression is reported as geometric mean and 95% confidence interval in relative expression units (REU). Paired t-tests were performed on log-transformed data.

Results: Sixty-four percent of patients were female and mean age was 52.7. Baseline tender and swollen joint count were 28.7 and 15.1. Fourteen of 21 subjects had been on anti-TNF previously. Of 21, 9 were on concomitant MTX, which did not have a significant impact on outcomes. Percent(%) ACR20/50/70 responders, by non-responder imputation (NRI) at 24 weeks, were 30/20/5. Percent PASI50/75 responders were 30/15. Subanalysis of response in anti-TNF inhibitor(i) naïve vs. experienced pts showed % ACR20 response by LOCF to be 50/29 and by NRI to be 33/29 and % PASI50 response by LOCF to be 67/36 and by NRI to be 67/14. One SAE occurred after 24 weeks, death due to pulmonary embolus, considered unrelated to investigational therapy.

Of 21 patients, 5 had evaluable pre and 8 week post-treatment skin biopsies. Few CD19 positive B cells were detected in pre and post lesional or non-lesional skin biopsies. However, IL1β, IL8, and Interferon γ (Table) were significantly elevated in lesional compared to adjacent non-lesional skin. These markers were all significantly reduced by rtx. Surprisingly, TNF expression was indistinguishable between non-lesional and pre and post lesional skin. IL6 trended higher in lesional and lower post treatment.

	Non-lesional skin: baseline*	Psoriasis lesion: baseline*	Psoriasis lesion: week 8*	P value†
IL1β	0.436 (0.112–1.69)	17.9 (5.74–55.8)	2.74 (1.33–5.65)	0.0019
IL6	0.109 (0.0505–0.236)	0.171 (0.0545–0.537)	0.0844 (0.0352–0.202)	NS
IL8	0.0886 (0.0600–0.131)	88.8 (38.4–205)	2.54 (0.327–19.8)	0.015
Interferon γ	1.11 (0.554–2.22)	17.2 (11.5–25.6)	7.22 (3.10–16.9)	0.0001
TNFi	14.0 (5.37–36.5)	27.8 (16.4–47.2)	30.7 (20.0–47.0)	NS

Conclusion: In this open label trial of 21 PsA pts treated with RTX, modest improvement in arthritis and psoriasis skin lesions was demonstrated, especially in anti-TNFi naïve pts. Therapy was well tolerated. Few B cells were found in lesional skin, however RTX significantly inhibited expression of certain cytokines, including T cells cytokines such as interferon γ. Skin TNF expression was not elevated in lesions nor was it affected by RTX. These data are consistent with a model wherein skin lesional pathobiology may be influenced by immunological activity in other sites.

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1956

Smoking Is Negatively Associated with Development of Psoriatic Arthritis among Psoriasis Patients. Lihi Eder[3], Sutha Shanmugarajah[3], Arane Thavaneswaran[3], Vinod Chandran[3], Richard Cook[1] and Dafna D. Gladman[2]. [1]Department of Biostatistics and Actuarial Science, University of Waterloo, Waterloo, ON, Canada, [2]Toronto Western Hospital, Toronto, ON, Canada, [3]University of Toronto Psoriatic Arthritis Clinic, Toronto Western Hospital, Toronto, ON, Canada

Background: Smoking is a strong risk factor for seropositive rheumatoid arthritis. Smoking has also been associated with higher risk of psoriasis especially in patients with HLA-Cw6. There is no clear documentation of an association between smoking and PsA.

Aim: To determine whether smoking is associated with development of PsA among patients with psoriasis.

Methods: Data collected from two prospective cohorts, PsA and psoriasis uncomplicated with arthritis, was analyzed. In the psoriasis cohort, the presence of clinical inflammatory arthritis was ruled out by rheumatologic assessment. Smoking status was determined at the time of the diagnosis for PsA patients and at the first visit to the clinic for the psoriasis patients. Smoking status was defined as current or past smoker and lifetime non-smoker. A logistic regression model was constructed to determine the association between smoking status and PsA after adjusting for age, sex and duration of psoriasis. The prevalence of current smokers in each group was compared with data of smoking status in the general population from Statistics Canada through standardized prevalence ratios (SPRs).

Results: 791 PsA and 404 psoriasis patients were included in the study. The mean age and duration of psoriasis were: 46.3±13.1 and 16.1±14.1 years, respectively, for the PsA group and 36.7±13 and 8.5±10.2 years, respectively, for the psoriasis group. The proportions of females in the PsA and psoriasis groups were similar (41.6% vs. 43.8%, respectively). The proportion of lifetime non-smokers was higher compared to current smokers in the PsA group (54.7% vs. 43%, $p<0.001$), the proportion of past smokers was higher in the psoriasis group (30.2% vs. 23.4%, $p=0.001$). The number of pack years was similar in the psoriasis and the PsA patients (11.7±14 and 11.3±12.1 pack years respectively). On multivariate analysis after adjusting for age, sex and duration of psoriasis, current smoker status vs. lifetime non-smoker remained negatively associated with PsA (Odds Ratio (OR) 0.6, 95% Confidence Intervals (CI) 0.5–0.8, $p=0.003$), while past smoker vs. lifetime non-smoker status was no longer significantly associated with PsA (OR 0.8, 95% CI 0.6–1.1, $p=0.2$). The SPRs for current smoking for males with psoriasis and PsA were 1.12 (95% CI 1.00–1.26) and 1.0 (95% CI 0.91–1.11), respectively, while the SPRs for females with psoriasis and PsA were 1.29 (95% CI 1.12–1.47) and 1.18 (95% CI 1.13–1.23), respectively.

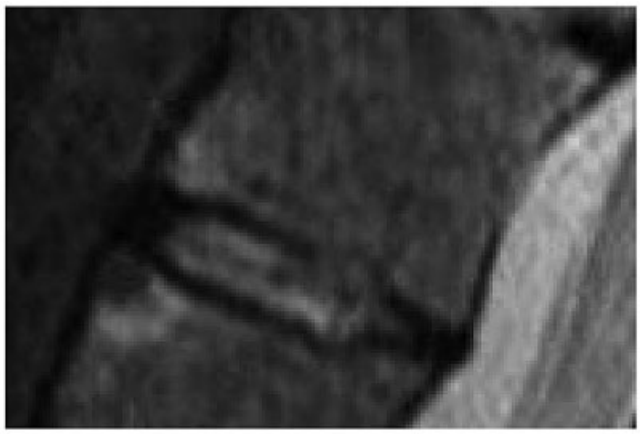
Conclusion: Active smoking is negatively associated with PsA among psoriasis patients. The prevalence of active smoking is higher in females with psoriasis and PsA compared to the general population.

Disclosure: L. Eder: None; **S. Shanmugarajah:** None; **A. Thavaneswaran:** None; **V. Chandran:** None; **R. Cook:** None; **D. D. Gladman:** None.

1957

The Dimorphic Vertebral Corner Inflammatory Lesion (CIL): A Magnetic Resonance Imaging Biomarker Associated with New Bone Formation in Patients with Ankylosing Spondylitis. Walter P. Maksymowych, Nathalie Morency and Robert G. W. Lambert. University of Alberta, Edmonton, AB, Canada

Purpose: One hypothesis proposed to explain the lack of impact of TNF blockers on radiographic progression in established AS is the activation of bone forming pathways in spinal lesions that have advanced from acute inflammation to more complex lesions. The latter may be visible on spinal MRI as a dimorphic corner inflammatory lesion (CIL) where the inflammatory signal at the vertebral corner (VC) on the STIR sequence does not itself extend all the way to the VC as in a typical CIL (Type A) but surrounds an area of decreased signal intensity at the VC which, on the T1 weighted images, may appear to be due to fat infiltration or erosion/bone sclerosis. It is proposed that the overall development of new bone during TNF blocker therapy may depend on the balance between the number of early and more mature inflammatory lesions. We tested the relative association between dimorphic or Type A CIL (lower and upper anterior VC in figure, respectively) and the subsequent development of new bone at the VC.



Method: MRI scans were performed at baseline, 12, and 52 weeks while radiographs were done at baseline and 104 weeks in 76 AS patients randomized to receive either adalimumab (ADA) 40 mg every other week or placebo (PBO) for 24 weeks in a, double-blind, Phase III study of active AS. After the week 12 assessment, patients not achieving an ASAS20 response were eligible for early escape therapy with ADA and after 24 weeks all patients received ADA. The anterior VC of the cervical (C2 lower to T1 upper) and lumbar (T12 lower to S1 upper) spine were examined for new syndesmophytes and ankylosis (baseline, 104 weeks) on lateral radiographs of the cervical and lumbar spine by 2 readers scoring independently. Anonymized MR scans were read independently by 2 readers who recorded the presence/absence of Type A and dimorphic CIL at the same anterior VC that were assessed by radiography. The primary analysis was based on concordant radiographic and MRI data and compared proportions developing new bone using the Pearson's chi square.

Results: Type A and dimorphic CIL were recorded in 155 (11.5%) and 56 (4.1%), respectively, of the 1351 VC analyzed both on MR and radiography. New syndesmophytes and/or ankylosis (from normal VC) was recorded in 45 (3.3%) of all VC. New bone developed significantly more frequently from VC that demonstrated dimorphic CIL (8 of 56 (14.3%)) as compared to Type A CIL (5 of 155 (3.2%), $p = 0.007$) or no CIL (32 of 1118 (2.9%), $p = 0.0004$) on the baseline MRI. This was also noted irrespective of whether the dimorphic CIL resolved or persisted at the 52 week follow up MRI.

Conclusion: Our data confirm previous studies that inflammation at VC on baseline MRI is associated with subsequent new bone formation in established AS. More importantly, we show that this entirely reflects the presence of more complex inflammatory lesions, visualized as dimorphic CIL on MRI, where the process of bone formation may be autonomous from inflammation.

Disclosure: W. P. Maksymowych: Abbott Immunology Pharmaceuticals, 2, 5, Merck Pharmaceuticals, 2, 5, Pfizer Inc, 2, 5; **N. Morency:** None; **R. G. W. Lambert:** Abbott Immunology Pharmaceuticals, 5.

1958

The Impact of Anti-TNF Therapy on Erosive Structural Changes in the Spine of Patients with Ankylosing Spondylitis. Xenofon Baraliakos[4], Joachim Listing[2], Martin Rudwaleit, Joachim Sieper[1] and Juergen Braun[3]. [1]Charite Campus Benjamin Frankl, Berlin, Germany, [2]German Rheumatism Research Center, [3]Rheumazentrum Ruhrgebiet, Herne, Germany, [4]Rheumazentrum Ruhrgebiet Herne

Background: Axial inflammation, potentially leading to osteodestructive and/or osteoproliferative bony changes is visualized by magnetic resonance imaging (MRI). The role of erosions, known to be important in RA, has not been extensively studied in AS to date, especially not in patients receiving anti-TNF therapy.

Objective: To study the course of osteodestructive changes and their relationship to spinal inflammation in AS by MRI.

Methods: T1 and STIR MR images of patients with active AS patients at baseline (BL, n=42), after 3 months (n=38) of therapy with TNF blockers or placebo and after 2 years (n=21) of continuous treatment with TNF blockers were analyzed by the ASspiMRI-a ('S1', scores inflammation and erosion) and its modification, the Berlin score ('S2', scores only inflammation), both scoring vertebral units (VU). Only patients with complete sets of images of BL and 3 months or 2 years of anti-TNF treatment were included in the study.

Results: At BL, 7.8% and 3.5% of the VUs showed active and inactive erosions, respectively, while 29% had signs of inflammation without erosions. In comparison, osteoproliferative changes were seen in 20% of all available VUs. On the patient level at BL, spinal inflammation was seen in 95% and active erosions in 73%, while inactive erosions were found in 38% of patients at BL.

At 3 months, the percentage of inflammed VUs decreased in the anti-TNF treated patients from 27.4% to 14.6%: inflammatory lesions without erosions decreased from 21.5% to 10% and with erosions from 5.9% to 4.6% of all VUs. In the placebo group, inflamed VUs decreased from 30% to 23.5%: without erosions from 22% to 15.5%, while inflammatory lesions with erosions (8%) did not show any change. There was similar improvement after anti-TNF with both scoring systems (56.7% for S1 and 54.7% for S2, both, $p<0.001$ as compared to BL) after 3 months, while inflammation changed by 13% with either system in the placebo group.

After 2 years of anti-TNF treatment, inflammatory lesions decreased from to 33.7% to 11.2% of all VUs: in VUs with inflammation only from 24.8% to 9.5% and in VUs with active erosions from 8.9% to 1.7%. On a patient basis, spinal inflammation was seen in all patients at baseline and in 76% after 2 years, while active erosions were found in 81% at BL and in 31% after 2 years. In contrast, the percentage of inactive erosions in all availble VUs increased from 3.5% at BL to 4.1% after 2 years. Overall 38% patients at BL and 52% at after 2 years had at

least 1 inactive erosion. There were no differences in the occurrence of erosions between the 3 spinal segments.

Conclusions: Erosions occur in the majority of AS patients but in less than 10% of the spinal structures analysed. The percentage of inflammatory lesions and active erosions was clearly reduced after 2 years of anti-TNF therapy. However, many patients still had spinal inflammation (76%) and about 30% still had active erosions. This suggests that the anti-inflammatory efficacy of anti-TNF treatment is not sufficient to completely eliminate inflammation. The Berlin MRI scoring system is sufficient for differentiation between different treatment strategies in the assessment of inflammatory activity in AS patients.

Disclosure: X. Baraliakos: None; **J. Listing:** None; **M. Rudwaleit:** None; **J. Sieper:** None; **J. Braun:** None.

1959

TNF Blocking Agents Promote Resolution of Vertebral Erosions in Patients with Spondyloarthritis. Walter P. Maksymowych[2], Praveena Chiowchanwisawakit[1] and Robert Lambert[2]. [1]Mahidol University, Bangkok, Thailand, [2]University of Alberta, Edmonton, AB, Canada

Purpose: While the impact of anti-TNF agents on new bone formation remains unclear their impact on other structural lesions such as erosions has not yet been studied in SpA because these lesions are not commonly observed in the spine on radiography. Bone erosion is readily discerned on T1-weighted (T1W) MRI at vertebral corners (VC) and affecting the vertebral endplate. MRI can reliably detect these lesions and systematic study has demonstrated erosions in the majority of patients. It is possible that such lesions could be a secondary cause of symptoms in SpA. We aimed to assess the impact of both TNF blocking agents and standard treatment on the evolution of bone erosions using MRI.

Method: MRI scans were performed at baseline and 2 years in 61 AS patients of whom 28 received TNF blocking agents in open label follow up of clinical trials while 33 received either TNF blocking agents (n = 16) or standard therapy (n = 17) in an observational cohort. A bone erosion on MRI was defined as full-thickness loss of the dark appearance of cortical bone at its anticipated location and loss of the normal bright appearance of adjacent bone marrow on T1W MRI. Via televideoconference, reference images were developed in which erosions were assigned by consensus amongst an international MRI working group. Lesions were independently recorded dichotomously (present/absent) from lower C2 to the upper sacrum of the spine at both anterior and posterior vertebral corners and at each vertebral endplate. Anonymized MRI scans were assessed independently by 2 readers who were blinded to treatment and time point. The primary analysis compared the resolution of lesions according to treatment and was based on concordant data indicating agreement on resolution of erosions. Improvement or complete resolution was defined on the basis of ≥ 50% and complete restoration, respectively, towards a normal vertebral contour. Proportions were compared by Fisher's exact test.

Results: Analysis was based on concordant reads for 2801 VC and vertebral endplate sites. Complete resolution of VC erosions was recorded significantly more frequently in the TNF blocker treatment group (11 of 13 erosions (84.6%) whereas this was not observed in a single erosion in patients on standard therapy (p = 0.0002). Similar differences between treatments were noted for individual readers. Vertebral endplate erosions were more frequent than corner erosions but showed minimal resolution after 2 years regardless of treatment.

Table. Number (percentage) of vertebral erosions resolving.

	VC Erosion			Vertebral Endplate Erosion		
Treatment	**Resolved**	**Improved**	**No change**	**Resolved**	**Improved**	**No change**
Anti-TNF						
Concordant	11 (84.6)	0	2 (15.4)	2 (4.8)	2 (4.8)	40 (90.4)
Reader 1	26 (74.3)	2 (5.7)	7 (20)	8 (9.4)	23 (27.1)	54 (63.5)
Reader 2	19 (59)	0	11 (41)	17 (15.7)	3 (2.8)	88 (81.5)
Standard						
Concordant	0	0	8 (100)	0	0	17 (100)
Reader 1	1 (7.7)	4 (30.8)	8 (61.5)	0	6 (22.2)	21 (77.8)
Reader 2	7 (31.8)	4 (18.2)	11 (50)	4 (11.4)	4 (11.4)	27 (77.2)

Conclusion: Our preliminary data supports a beneficial effect of TNF blocker treatment on the resolution of vertebral erosions. The lack of impact on vertebral endplate erosions may reflect greater time dependence due to larger size and/or differences in etiology.

Disclosure: W. P. Maksymowych: Abbott Laboratories, 2, 5, Merck Pharmaceuticals, 2, 5, Pfizer Inc, 2, 5; **P. Chiowchanwisawakit:** None; **R. Lambert:** None.

1960

TNF Switching in PsA Patients. Eliza F. Chakravarty[1], George Reed[5], Dennis Decktor[3], Susan Bolge[3], Rebecca Bolce[3], Michael Ingham[3], Raphael J. DeHoratius[2], Ying Shan[5] and Mark C. Genovese[4]. [1]Mountain View, CA, [2]Centocor Ortho-Biotech, Horsham, PA, [3]Centocor Ortho-Biotech, [4]Stanford University, Sunnyvale, CA, [5]University of Massachusetts Medical School

Purpose: To examine patterns of Anti-TNF switching in psoriatic arthritis (PsA) patients and patient factors associated with switching.

Methods: We identified biologic naïve PsA patients cared for by US rheumatologists participating in the CORRONA registry that initiated their first anti-TNF (Etanercept, Infliximab, Adalimumab) and followed for 2 years. Maintainers were defined as patients with no change of anti-TNF over two years. Switchers were defined as patients who discontinued and started another biologic within 6 months of discontinuation. Discontinuers were defined as patients who discontinued and did not initiate another biologic within 6 months. We defined early switchers as patients who switched within the first year and late switchers as patients who switched between 12 and 24 months. Maintainers were compared to switchers at time of switch using a comparable follow-up time point. Multivariable logistic regression estimated associations of characteristics with switching in early and late switchers.

Results: There were 139 biologic naive PsA patients who initiated an anti-TNF and had ≥2 years of follow up. Of these, 91 (65%) were maintainers, 18 (13%) were discontinuers, and 30 (22%) were switchers. Distribution of maintainers and switchers were significantly different between IV anti-TNF and subcutaneous (SC) anti-TNF with 85% maintainers, 9% discontinuers, 6% switchers in IV vs. 59% maintainers, 14% discontinuers and 27% switchers in SC anti-TNF (p=0.012). Among those patients who switched from any of the anti-TNFs the proportion achieving a Modified ACR 20 at 6 and 12 months was 23%, and 29%.

Table 1 compares characteristics among the patient groups. At initiation, switchers and discontinuers had higher disease activity as measured by patient pain, patient global and physician globas assessments. Switchers were more likely to be female, younger, have higher BMI and a shorter duration of disease. At the time of the switch, switchers and discontinuers had higher disease activity compared to maintainers.

In the multivariable analyses, Physician Global Assessment (OR=1.6 95%CI:[1.05, 2.41]) and duration of disease (OR=0.81 [0.67, 0.98]) were the best predictors for early switchers. In late switchers, Patient Global Assessment (OR=1.54 [1.14, 2.09]), Age (OR=0.92 [0.85, 0.98]), and being female (OR=10.7 [2.2, 52.5]) were the best predictors of switching.

Conclusions: Over a two year period the majority of patients started on a TNF inhibitor for PSA will remain on their original treatment. Fewer patients discontinued IV TNF inhibition (Infliximab) than SC TNF inhibition (Etanercept, Adalimumab), however the factors associated with this are unknown. In those who remained on initial therapy benefit appeared to be maintained, in those who switched there was a mild likelihood of improvement. A number of factors were associated with either early or late switch.

Table 1. Patient Characteristics (Mean ± SD)

	Maintainers n=91	**Discontinuers n=18**	**Switchers n=30**	**p-value**
Female	41%	61%	73%	0.005
Age	52 ± 10.6	52 ± 9.1	47 ± 14.2	0.095
BMI	31.0 ± 5.5	33.2 ± 5.7	34.3 ± 8.2	0.029
Duration PsA	10.5 ± 10.4	7.8 ± 7.7	6.3 ± 7.8	0.092
At Initiation				
Pt pain (0–100)	34.4 ± 22	51.4 ± 22.0	47.7 ± 19.9	<0.001
MD global (0–100)	25.3 ± 20.0	29.2 ± 22.3	34.1 ± 19.3	0.112
Pt global (0–100)	35.1 ± 25.0	46.3 ± 23.1	44.2 ± 17.8	0.068
At time of Switch Discontinuation*				
Pt pain (0–100)	27.8 ± 23.2	45.0 ± 29.0	40.1 ± 24.7	<0.001
MD global (0–100)	13.5 ± 14.7	21.7 ± 19.6	22.9 ± 16.9	0.008
Pt global (0–100)	24.4 ± 22	33.8 ± 27.7	44.4 ± 19.9	<0.001

* use comparable time after initiation in Maintainers.

Disclosure: E. F. Chakravarty: None; **G. Reed:** Corrona, 5; **D. Decktor:** Ortho Biotech Products L.P., 1, 3; **S. Bolge:** Johnson & Johnson, 1, 3; **R. Bolce:** Ortho Biotech Products L.P., 3; **M. Ingham:** Johnson & Johnson, 1, Ortho Biotech Products L.P., 3; **R. J. DeHoratius:** Ortho Biotech Products L.P., 1, 3; **Y. Shan:** None; **M. C. Genovese:** Abbott Laboratories, 2, 5, Amgen Inc., 2, 5, Ortho Biotech Products L.P., 2, 5, Pfizer Inc, 2, 5.

1961

Treatment of Active Ankylosing Spondylitis with Abatacept—An Open Label 24-Week Study. In-Ho Song[2], Frank Heldmann[1], Martin Rudwaleit[3], Hildrun Haibel[2], Anja Weiss[4], Jurgen Braun[1] and Joachim Sieper[2]. [1]Centre of Rheumatology, Herne, Germany, [2]Charite Campus Benjamin-Franklin, Medical Clinic I, Rheumatology, Berlin, Germany, [3]Charite Campus Benjamin-Franklin, Medical Clinic I, Rheumatology, Berlin, Germany, [4]German Rheumatism Research Center, Berlin, Germany

Background: An immunotherapy targeting T cells in ankylosing spondylitis (AS) might be of interest, given histological studies have shown T-cell clusters in facette joints and antigen-specific T cell response has been described in AS [1]. There is still an unmet medical need as some patients with AS may even not respond to anti-TNF agents.

Objective: To explore prospectively the short term efficacy and safety of abatacept in patients either naïve or with an inadequate response (IR) to anti-TNF agents.

Methods: In this open label (OL) pilot study, abatacept (10mg/kg) was administered intravenously on days 1, 15, 29 and every 28 days thereafter up to week 24 in 15 anti-TNF-naive patients (group 1) and 15 patients with IR to anti-TNF (group 2) with active AS. The primary end point was the proportion of patients with assessment of SpondyloArthritis international Society criteria (ASAS 40) in both groups at week 24 for which the likelihood of targeted minimum true response rates of 30% was investigated by estimating the 95% confidence interval [95% CI] of the observed response rates. Disease activity was assessed using ASAS and BASDAI responses, pain and CRP levels in the intent to treat population using LOCF analysis. Safety was assessed in patients who received at least 1 dose of OL abatacept.

Results: Of 15 patients enrolled in group 1 and group 2 respectively, each 12 completed 24 weeks (withdrawals for inefficacy each 2 in group 1 and 2) and SAE (each 1 in group1 and 2). In group 1 and 2, baseline characteristics were: 60% and 73% of males, mean disease duration of 14.5 (SD 10.3) and 20.5 (SD 10.8) years; 100% and 93% HLA-B27 positive and mean age of 38.0 (SD 7.2) and 45.3 years (SD 9.8), respectively.

At week 24, 13.3% [2.4%; 38.4%] of patients in group1 and 0% [0%; 21.3%] of group 2 achieved ASAS 40 (Table). The upper limit of the 95% CI in group 1 but not in group 2 exceeded the pre-specified minimum true response rates of 30%. We found no change of T cell function in regards of interferon-gamma (IFN-gamma) (% of IFN-gamma positive cells out of CD4 positive cells after stimulation with phorbol myristate acetate (PMA) ionomycin 14.8% at screening and 13.1% at week 24) or interleukin-17 secretion (% of IL-17 positive cells out of CD4 positive cells after stimulation with PMA ionomycin 1.5% at screening and 0.9% at week 24) supporting that T cell function is not suppressed but only modulated. Overall, abatacept was well-tolerated with 5 serious events (SAEs), including 1 gastroenteritis. Three mild to moderate acute infusion reactions were reported. There was no death, opportunistic infection, malignancy or TB reported.

Conclusions: In this pilot AS study, Abatacept was well tolerated. A major response was not observed in our study, but an efficacy cannot be excluded based on the limited sample size. Its short term therapeutic potential needs to be further evaluated.

Table: ASAS20/40/partial remission (PR) and BASDAI20/50 response rates in TNF-blocker naive and TNF-blocker failure patients at week 24

	TNF-blocker-naive patients (n=15)	TNF-blocker failure patients (n=15)
ASAS20	26.7%	20.0%
ASAS40	13.3%	0%
ASAS PR	6.7%	0%
BASDAI20	33.3%	20.0%
BASDAI50	6.7%	0%

References:

1. Appel H et al. Arthritis Res Ther 2006;8(5):R143.

Disclosure: I.-H. Song: Abbott Immunology Pharmaceuticals, 5, Schering-Plough, 5; **F. Heldmann:** Schering-Plough, 5; **M. Rudwaleit:** Abbott Immunology Pharmaceuticals, 5, Schering-Plough, 5, Wyeth Pharmaceuticals, 5; **H. Haibel:** Abbott Immunology Pharmaceuticals, 5, Schering-Plough, 5, Wyeth Pharmaceuticals, 5; **A. Weiss:** None; **J. Braun:** Abbott Immunology Pharmaceuticals, 5, Schering-Plough, 5, Wyeth Pharmaceuticals, 5; **J. Sieper:** Abbott Immunology Pharmaceuticals, 5, Bristol-Myers Squibb, 5, Schering-Plough, 5, Wyeth Pharmaceuticals, 5.

1962

Ultrasound (US) and × Rays (XR) Entheseal, Synovial and Sacroiliac Abnormalities in Early Psoriatic Arthritis (ePsA). Francesca Bandinelli[5], Diletta Bonciani[3], Francesca Prignano[3], Leonardo Giovannini[6], Giuliana Salvadorini[6], Ledio Collaku[1], Antonio Candelieri[4], Francesca Bartoli[6], Torello Lotti[2] and Marco Matucci Cerinic[6]. [1]Department of Internal Medicine of University of Tirana, Faculty of Medicine, Albania, [2]Dermatology Unit, University of Florence, Italy, [3]Dermatology Unit, University of Florence, Italy, [4]Laboratory of Decision Engineering for Health Care Delivery, Department of Electronics, Informatics and Systems, University of Cosenza Italy, [5]Rheumatology Division, University of Florence, Department of Biomedicine, Florence, Italy, [6]Rheumatology Division, University of Florence, Department of Biomedicine, Florence, Italy

Objective: To investigate entheseal/synovial and sacroiliac abnormalities in ePsA respectively with ultrasound (US) and traditional × rays (XR) and the correlation with ePsA features (familiarity, psoriasis, inflammatory markers, HLA) useful for diagnosis.

Methods: 92 ePsA patients (51±15 years old, 51 female and 41 male,), with duration of symthoms < 1 year, diagnosed according to CASPAR criteria (1) were consecutively studied with US (My Lab 70 XVG US Esaote 7–18 MHz linear array transducer) of entheses (Achilles, quadriceps, patellar and plantar fascia) and joints (radiocarpal, intercarpal, hands MCP, IFP and IFD, tibio-tarsal, feet MTP and IP) joints and with radiography (XR) of sacroiliac joints. Patients were scored respectively for entheses with Glasgow Ultrasound Enthesitis Scoring System (GUESS) (2) and Power Doppler signal (PD) (semiquantitative system, score 0–3), for peripheral joints with presence/absence of PD active synovitis, for sacroiliac joints with New York score (NYS) (3). We studied the correlation between GUESS and PD of entheses, active synovitis, NYS of sacroiliac joints with familiarity (for psoriasis and spondiloarthropathies), psoriasis area and severity Index (PASI), distribution -hand, feet, lower limbs- and characteristics -vulgaris, eritrodermic, pustulosus, guttata-, nail involvement, ESR, CRP, HLA aplotypes (B27, B35, B38, B39, CW6, CW7, DR4) were investigated.

Results: Abnormalities are present in high percentage: in entheses (GUESS>1:100%, PD 40,2%), in peripheral joints (40,2% PD active synovitis), in sacroiliac joints (NYS>1: 25%). GUESS and PD of entheses correlated with the presence of lower limb psoriasis (respectively $p<0,02$, $p<0,05$, Mann Whitney test) but not with PASI and entheses PD with ESR ($p<0,005$) (linear correlation Pearson). GUESS was higher ($p<0,05$ Mann Whitney test) in CW6 positive patients (29,6%) but not other significant difference were found in other aplotypes. Synovitis and sacroileitis didn't correlate with familiarity, psoriasis, ESR/CRP, HLA.

Conclusions: In ePsA patients, entheseal and synovial US and sacroiliac XR modifications are present in high percentage. Our data clearly indicate that a thorough US and XR investigations must be always perform in early phase.

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1963

Validation of the ASAS Definition of a Positive MRI in a Cohort of Patients with Early SpA Followed for Eight Years. Helena Marzo-Ortega[2], Alexander N. Bennett[2], Dennis McGonagle[2], Paul Emery[2] and Walter P. Maksymowych[1]. [1]University of Alberta, [2]University of Leeds, United Kingdom

Background: The Assessment of SpondyloArthritis International Society (ASAS) recently proposed a definition of a positive MRI for sacroiliitis based on the finding of bone marrow edema (BME) on STIR in subchondral or periarticular bone marrow of the sacroiliac joint (SIJ). MRI is considered positive for SpA if there are two BME lesions on the same coronal slice through the SIJ or a single BME lesion present on two consecutive slices. This

proposal requires validation, preferably in prospective cohorts to evaluate development of radiographic changes of sacroiliitis.

Objective: To compare the diagnostic utility of global assessment of MR scans versus the ASAS definition using a standardized approach to evaluation of the SIJ in an early SpA cohort followed over 8 years.

Method: Four rheumatologists blinded to patient and diagnosis independently assessed MRI scans (T1W and STIR) from 37 patients with SpA according to ESSG criteria (median symptom duration 24 weeks); 13 developed radiographic sacroiliitis after 8 years, 11 controls mechanical low back pain (mLBP), 11 healthy controls. Semi-coronal slices through the SIJ were read systematically according to a standardized online training module. BME, fat infiltration, erosions, and ankylosis was recorded using an online data entry system. Schematics of the SIJ divided into quadrants allowed recording of these lesions (yes/no) in each quadrant of each coronal slice. The ASAS definition was defined as met when BME was recorded in 2 SIJ quadrants on the same slice or when a single lesion in one SIJ quadrant was present in 2 consecutive slices. Readers also answered (yes/no) whether this SIJ scan confirmed the presence of SpA. Sensitivity, specificity, and LRs for individual and concordant data (at least 2 readers) were calculated according to clinical diagnosis at baseline and according to the development of radiographic sacroiliitis.

Results: MRI had high diagnostic utility for SpA according to global assessment by individual readers (mean for 4 readers (range) sensitivity/specificity: 66.9% (61.8–70.6)/94.4% (88.9–100), LR+ 11.9, LR- 0.2) as well as concordant data (sensitivity/specificity: 67.6%/94.4%, LR+ 12.1, LR- 0.3). By comparison, sensitivity for SpA of the ASAS definition was higher but there was reduction in specificity with 11.1% of control scans (3 mLBP) meeting the ASAS definition so that diagnostic utility was lower than for global assessment. Diagnostic utility of baseline MRI for radiographic sacroiliitis after 8 years follow up was even higher: global assessment (sensitivity/specificity: 100%/94.4%, LR+17, LR- not calculable (nc), ASAS definition (sensitivity/specificity: 100%/88.9%, LR+ 9, LR- nc).

Conclusion: The diagnostic utility of the ASAS definition resembles global evaluation by expert readers, the principle limitation being the finding of BME in patients with mLBP.

Global Assessment ASAS Definition

	Sensitivity	Specificity	LR+	LR−	Sensitivity	Specificity	LR+	LR−
R1	70.6	54.4	12.6	0.3	75.5	88.9	6.4	0.3
R2	70.6	94.4	12.6	0.3	70.4	88.9	6.4	0.1
R3	64.7	88.9	5.8	0.3	67.4	77.8	1.7	0.2
R4	61.8	100	na	0.3	58.8	100	na	0.4
Concordant*	67.6	94.4	12.1	0.3	79.4	88.9	7.2	0.2

Disclosure: H. Marzo-Ortega: None; **A. N. Bennett:** None; **D. McGonagle:** Schering-Plough, 5; **P. Emery:** Abbott Laboratories, 5, Bristol-Myers Squibb, 5, Pfizer Inc, 5, Roche, 5, Schering-Plough, 5; **W. P. Maksymowych:** None.

1964

Which Clinical Variables Predict Radiographic Progression in Spondyloarthritis? An Analysis of the Spondyloarthritis Research Consortium of Canada (SPARCC) Cohort. Walter P. Maksymowych[4], Nigil Haroon[6], Nathalie Morency[5], Richard Cook[7], Hua Shen[7], Proton Rahman[1], Dafna D. Gladman[2] and Robert D. Inman[3]. [1]Memorial University Newfoundland, St. Johns, NL, Canada, [2]Toronto Western Hospital, Toronto, ON, Canada, [3]Toronto Western Hospital, Toronto, ON, Canada, [4]University of Alberta, Edmonton, AB, Canada, [5]University of Alberta, Edmonton, Canada, [6]University of Toronto, Toronto, Canada, [7]University of Waterloo

Purpose: About a third of patients with SpA have been shown to exhibit radiographic progression over 2 years. There is limited prospective data on the factors that predict progression, even amongst clinical variables assessed in routine practice. Baseline radiographic score, measured with the modified Stoke AS Spine Score (mSASSS) method, and serum metalloproteinase 3 have been shown to predict progression but no evidence has yet implicated clinical measures of disease activity. We aimed to identify clinical variables contributing to radiographic progression over 2 years in patients with Ankylosing Spondylitis (AS).

Methods: The SPARCC cohort comprises patients with SpA followed prospectively with clinical and radiographic outcomes. Two readers scored X-rays obtained at baseline and year 2 using the mSASSS method. Dependent variables were: 1) raw change in mSASSS and >2 units from baseline through 2 years, 2) development of new syndesmophytes at year 2. Independent variables were age, sex, baseline Bath AS Disease Activity Index (BASDAI) and C-reactive protein (CRP), and baseline mSASSS score. Variables that associated significantly with the dependent variables in univariate analysis were also tested as explanatory variables in multivariate logistic and linear regression analyses.

Results: Baseline and 2-year radiographs were available on 279 patients with AS according to the modified New York criteria. At baseline there were 227 (81.7%) males, mean (SD) age 41.6 (13.3) years, mean (SD) age at onset of back pain 23.7 (8.4) years, mean (SD) BASDAI 4.8 (2.3), mean CRP 14.6 mg/L (20.8), and mean (SD)/median mSASSS 18.7 units (21.2)/8.0. Mean (SD) change in mSASSS over 2 years was 1.7 units (3.3) and 62 (22.2%) of patients had progression >2 mSASSS units. A new syndesmophyte was recorded in 27.7%. Uni- and multivariate logistic regression analysis where the dependent variable was mSASSS change >2 units showed that only baseline CRP was significantly associated with progression.

Baseline Covariates	Univariate Model OR	95%CI	P value	Multivariate Full Model OR	95%CI	P value	Multivariate Reduced Model OR	95%CI	P value
mSASSS	1.00	0.98, 1.02	0.90	1.00	0.98, 1.02	0.81			
CRP	1.02	1.00, 1.03	0.01	1.02	1.00, 1.03	0.02	1.02	1.00, 1.03	0.01
BASDAI	1.06	0.92, 1.22	0.45	1.01	0.87, 1.17	0.88			

Conclusion: Our data support the importance of inflammation, as reflected by CRP, as a factor influencing radiographic progression in SpA.

Disclosure: W. P. Maksymowych: None; **N. Haroon:** None; **N. Morency:** None; **R. Cook:** None; **H. Shen:** None; **P. Rahman:** None; **D. D. Gladman:** None; **R. D. Inman:** None.

ACR Poster Session C
Poster Spondylarthritis and Psoriatic Arthritis - Pathogenesis, Etiology, and Animal Models
Wednesday, November 10, 2010, 9:00 AM–6:00 PM

1965

Ankylosing Spondylitis Macrophages Produce Greater IL-23 in Response to Lipopolysaccharide without Significant Unfolded Protein Response Induction. Ling Zeng, Mary Lindstrom and Judith Smith. University of Wisconsin

Purpose: Inflamed tissue from Ankylosing Spondylitis (AS) patients display a preponderance of macrophages. Previous work from an HLA-B27 transgenic rat model suggests that macrophages from arthritic animals develop an intracellular stress response called the Unfolded Protein Response (UPR) and as a result, secrete increased cytokines in response to Toll like receptor agonists such as lipopolysaccharide (LPS). Our objective was to determine if macrophages from AS patients undergo a UPR and secrete increased cytokines/chemokines in response to LPS.

Methods: Peripheral blood monocytes were isolated from 10 AS patients (median age 46.5y, 90% male, 70%HLA-B27+ and 2ND) and 10 controls (HC, median age 45y, 90%male, all HLA-B27-), and differentiated in vitro with M-CSF for 5 days. Select samples were then treated with 1000U/mL IFN-γ for 24h to up-regulate MHC class I prior to stimulation with LPS for 3h (for RNA collection), or 8–24h (supernatants). UPR induction was assessed by up-regulation of ERdj4, BiP and CHOP mRNA detected by quantitative PCR. Supernatants were analyzed for cytokine/chemokine production by ELISA or Luminex. Statistical analysis involved 2-sample Wilcoxon tests for cytokine data, and a linear mixed effect model following log transformation of gene expression data.

Results: In response to LPS alone, AS macrophages secreted more CXCL9, IL-10, IL-12p70, IL-23, and TNFα than HC macrophages ($p< \text{or} = 0.02$). We did not detect significant differences between AS and HC for IL-6, IL-8, CXCL10, IL-1β, IFN-β or MCP-1. IFN pre-treatment tended to minimize differences between AS and HC for all cytokines/chemokines except IL-12p70. The most striking difference between AS and HC macrophages was for IL-23 production (median HC 9pg/mL vs. AS 265 pg/mL at 24h, $p=0.0007$). 3h LPS treatment had no effect on UPR gene expression. Although IFN treatment up-regulated HLA-B expression by 2–3 fold, it did not enhance BiP or CHOP expression. ERdj4 expression weakly increased (2-fold, $p=0.03$–0.06) in IFN+LPS AS samples only.

Conclusions: Gene association studies and animal models have implicated the IL-23/Th17 pathway in pathogenesis. These results showing greater IL-23 production by AS patient macrophages in response to LPS further support the development of IL23-directed therapy. Since we were unable to detect significant UPR induction in AS macrophages, the relationship between UPR and inflammatory cytokine production remains unclear.

Disclosure: L. Zeng: None; **M. Lindstrom:** None; **J. Smith:** None.

1966

Association between Killer-Cell Immunoglobulin-Like Receptor (KIR) Gene Polymorphisms and Psoriatic Arthritis (PsA). Vinod Chandran[2], Fawnda Pellett[2], Renise Ayearst[2], Remy Pollock[2] and Dafna D. Gladman[1]. [1]Toronto Western Hospital, Toronto, ON, Canada, [2]University of Toronto Psoriatic Arthritis Clinic, Toronto Western Hospital

Background: KIR genes within the leukocyte receptor complex on chromosome 19q are associated with PsA. We sought to further characterize this association and determine whether the associations are independent of HLA allele associations.

Methods: 685 cases of European ethnicity (295 females, mean age 43 years, PsA duration 7 years, psoriasis duration 15 years, actively inflamed joint count 11, PASI score 5.2) with PsA and 706 ethnically matched controls (273 females, mean age 53 years) were recruited for the study. Genotyping for 15 KIR genes was performed on genomic DNA obtained from peripheral blood using PCR-SSP and that for HLA-B, and -C alleles was performed using PCR-SSO reverse line blot. Phenotype frequencies (frequencies of individuals positive for each gene or allele) were calculated and differences between cases and controls determined using Fisher's exact test using a dominant model. Multivariate logistic regressions were performed, including all KIR genes present in <95% of cases or controls, and HLA alleles present in >5% of cases and controls and significant in univariate analyses. Association of KIR2DS1 and KIR2DS2 with PsA in the presence/absence of HLA-Cgrp2 (HLA-C*02, C*04, C*05, C*06) and Cgrp1 (HLA-C*01, C*03, C*07, C*08) ligands for their corresponding inhibitory KIRs (KIR2DL1 and KIR2DL2/2DL3 respectively) was also investigated using chi- square test and evidence of trend with combined risk genotypes determined using Mantel-Haenszel trend test.

Results: In univariate analyses, KIR2DS2 (Odds ratio 1.13 p = 0.028), KIR2DL2 (OR 1.13, p = 0.031), HLA-B*07 (OR 0.56, p<0.0001), B*13 (OR 1.73, p = 0.016), B*27 (OR 3.04, p <0.0001), B38 (OR 7.24, p <0.0001), B39 (OR 2.04, p = 0.008), B51 (OR 0.45, p <0.0001), B*57 (OR 1.81, p <0.0001), B*60 (OR 0.58, p =0.008), C*01 (OR 1.89, p =0.002), C*02 (OR 1.98, p <0.0001), C*03 (OR 0.64, p =0.002), C*04 (OR 0.74, p =0.027), C*06 (OR 1.65, p <0.0001), C*07 (OR 0.66, p<0.0001), C*12 (OR 2.38, p <0.0001) and C*15 (OR 0.48, P=0.005) were significantly associated with PsA. The results of the multivariate analysis using logistic regression with backward selection are given in Table 1.

Table 1. Results of multivariate logistic regression analyses using HLA alleles found significant in the univariate analyses as well as KIR genes present in <95% of the population as explanatory variables.

Allele/Genotype	Odds Ratio	95% Confidence Interval	P value
HLA-B*07	0.71	0.54, 0.94	0.0169
HLA-B*13	2.14	1.35, 3.4	0.0012
HLA-B*27	3.52	2.46, 5.03	<0.0001
HLA-B*38	8.22	4.66, 14.51	<0.0001
HLA-B*39	2.54	1.49, 4.34	0.0006
HLA-B*51	0.53	0.34, 0.81	0.0038
HLA-B857	2.30	1.61, 3.3	<0.0001
HLA-C*03	0.74	0.56, 0.99	0.0457
KIR2DS2	1.31	1.04, 1.64	0.0205

HLA-B*13, B*27, B*38, B*39 and B*57 were found to increase PsA risk whereas HLA-B*07, B*51 and C*03 were protective. Among the KIR genes only KIR2DS2 was found to significantly increase risk for PsA after adjusting for HLA-B and -C associations. Association between PsA and combined KIR2DS2 and HLA-Cgrp1 risk genotypes was demonstrated (trend p= 0.024). Although, chi square test using combined KIR2DS1 and HLA-Cgrp2 genotypes showed evidence of association (p = 0.025), no evidence of a trend could be demonstrated (trend p = 0.81).

Conclusions: KIR2DS2 is associated with PsA independent of HLA alleles. The risk for PsA increases with the presence of KIR2DS2 in the absence of ligands for KIR2DL2/2DL3 with risk being highest when KIR2DS2 is present in the absence of HLA-Cgrp1 alleles.

Disclosure: V. Chandran: None; **F. Pellett:** None; **R. Ayearst:** None; **R. Pollock:** None; **D. D. Gladman:** None.

1967

Decreased TH17 Cells in the Peripheral Blood of Patients with Early Spondyloarthritis (ESpA). María Belén Bautista-Caro[2], Irene Arroyo-Villa[2], Concepcion Castillo-Gallego[2], Eugenio de Miguel-Mendieta[2], Emilio Martín-Mola[2] and María Eugenia Miranda-Carus[1]. [1]Hospital La Paz, Madrid, Spain, [2]Hospital La Paz

Background: Th17 cells may be implicated in the pathogenesis of Spondyloarthritides (SpA). Previous data regarding the percentage of Th17 cells in the peripheral blood of Early SpA (ESpA) patients are limited and contradictory.

Objective: To determine the frequency and phenotype of Th17 cells in the peripheral blood of patients with ESpA.

Patients: We studied 22 healthy controls and 22 patients with ESpA (who met ESSG or other accepted SpA Classification Criteria) from the "Esperanza" programme of the Spanish Rheumatology Foundation. The inclusion criteria were inflammatory back pain or asymmetric peripheral arthritis, duration of disease of three to 24 months and age of 18 to 45 years. At baseline visit, medical history, physical examination, ESR, CRP, HLAB27 and pelvis conventional x-Ray were recorded.

Methods: CD4 T cells were magnetically sorted from freshly isolated peripheral blood and cultured overnight in the presence of PMA and ionomycin. IL-17 was determined by ELISA of culture supernatants and by flow cytometry of monensin-treated cells. In addition the expression of CCR6, IL-23R and RORγT were examined by flow cytometry.

Results: ESpA patients were 7 females, 15 males. Age was (mean ± SD) 36 ± 7 years, duration of disease 17 ± 10 months. BASDAI index was 3.7 ± 2.2 (median 3.55, range 1.2–8.3) and BASFI was 1.82 ± 1.69 (median 1.65, range 0.3–6.1). CD4 T cells of ESpA patients secreted signficantly lower amounts of IL-17 into the culture medium (1134.9 ± 488.6, median 687.97, range 99.02–3156.33) when compared with controls (2059.3 ± 664.6 pg/ml, median 1719.67, range 448.11–6243.9), p<0.05. Likewise, the percentage of IL-17 producing CD4 T cells (Th17 cells) was significantly lower in ESpA patients: 0.93 ± 0.26, median 0.84, range 0.22–2.15 in patients vs 1.50 ± 0.56,median1.13, range 0.66–3.92 in controls, p< 0.05. Th17 cells expressed CCR6, RORγT and IL-23R. Disease activity as assesed by BASDAI index was negatively correlated with IL-17 concentration and with the percentage of Th17 cells. Likewise, BASFI function index showed a negative correlation with soluble IL-17 and with the percentage of Th17 cells.

Conclusion: Peripheral blood CD4 T cells from ESpA patients demonstrate a decreased secretion capacity of IL-17 together with decreased percentage of Th17 cells, that are related with disease activity as assessed by BASDAI index and with the functional index BASFI.

Disclosure: M. B. Bautista-Caro: None; **I. Arroyo-Villa:** None; **C. Castillo-Gallego:** None; **E. de Miguel-Mendieta:** None; **E. Martín-Mola:** None; **M. E. Miranda-Carus:** None.

1968

Distinctive Patterns of Gene Expression Post-Infliximab Therapy in Psoriasis, Rheumatoid and Psoriatic Arthritis. Christopher T. Ritchlin[3], Yahui Grace Chiu[2], Alexander Rosenberg[2], Darren Tabechian[2], Sharon Moorehead[2], Rick Barrett[2], Hangtao Fan[1], Fred Baribaud[1], H. Liu[1], Nancy Peffer[1], David Shealy[1] and Edward S. Schwarz[2]. [1]Centocor R&D, [2]University of Rochester Medical Center, [3]University of Rochester Medical Center, Rochester, NY

Background: Despite divergent phenotypes, psoriasis (Ps), rheumatoid (RA) and psoriatic arthritis (Ps) often improve after anti-Tumor Necrosis Factor (TNF) therapy but the comparative effect of TNF inhibition on gene expression in circulating CD14+ monocytes, synovium and skin in these disorders is not well understood.

Objectives: To compare gene expression profiles in RA and PsA monocytes and synovium and Ps monocytes and skin plaques following infliximab (IFX) therapy.

Methods: Microarray analyses with Affymetrix hg U133 plus 2.0 PM

(HT) chips were performed on CD14+ monocytes isolated from 10 Ps, 9 RA and 12 PsA patients (pts) at baseline and 10 weeks and plaque biopsies from 5 Ps pts at baseline and week 2 after IFX treatment. Synovial biopsies from RA (3) and PsA (5) pts were also analyzed at baseline and 10 weeks. Pathway characterization and analysis of functional annotation enrichments for genes with a significant change in expression at 2 (skin) or 10 weeks post-infliximab ($p<0.05$) were performed using DAVID 6.7 (NIAID/NIH web-based tool).

Results: A significant decline in the DAS28score was noted in the RA (5.9 to 4.1; $p<.005$) and PsA pts (4.6 to 3.3; $p<.001$) following IFX. In the Ps pts, a significant decrease in the PASI score (5.3 to 2.3; $p<.00008$) was observed 2 weeks after IFX. IFX was well tolerated in all pts. The number of genes that significantly changed expression from baseline to 10 weeks (either up or down) in CD14+ monocytes, skin and synovial tissues from Ps, RA and PsA pts differed between the 3 groups (shown in table).

	Ps	RA	PsA
CD14+ cells	141	104	267
Skin/synovium	1260	819	255

Number of genes that demonstrated a significant change in expression post-IFX treatment.

Only a single gene, GTP binding protein (GBP4), changed significantly in monocytes from all 3 groups. Based on gene-annotation enrichment analysis, the most significant changes in Ps monocytes were noted in immunoglobulin (Ig), antigen binding and immune response genes similar to RA monocytes in which both immune response and Ig genes showed the greatest change. In PsA monocytes, genes related to phosphoproteins, cell motion and migration and Sh2 domains showed the greatest change. In Ps plaques, genes associated with the cell cycle, cell division, the immune response and leucocyte activation showed the greatest change compared to RA synovium where genes that control cell adhesion, Wnt and G-protein signaling were most highly affected. Lastly, PsA synovium showed significant changes in gene expression associated with protein kinase A (PKA) and the following signaling pathways: IL-6, IL-17, IL-27 and JAK-STAT following treatment with IFX.

Conclusion: IFX was highly effective for skin and joint inflammation in this cohort yet the impact of TNF inhibition on gene expression was surprisingly distinctive in the 3 disorders. These data suggest the presence of unique pathophysiologic mechanisms in immune mediated disorders downstream of TNF. If so, disease biomarkers in Ps, RA, and PsA are likely to be disease-specific.

Disclosure: C. T. Ritchlin: Centocor, Inc., 2, 5; **Y. G. Chiu:** None; **A. Rosenberg:** None; **D. Tabechian:** None; **S. Moorehead:** None; **R. Barrett:** None; **H. Fan:** Centocor Ortho Biotech Inc., 9; **F. Baribaud:** Centocor Ortho Biotech Inc., 9; **H. Liu:** Centocor Ortho Biotech Inc., 9; **N. Peffer:** Centocor Ortho Biotech Inc., 9; **D. Shealy:** Centocor Ortho Biotech Inc., 9; **E. S. Schwarz:** None.

1969

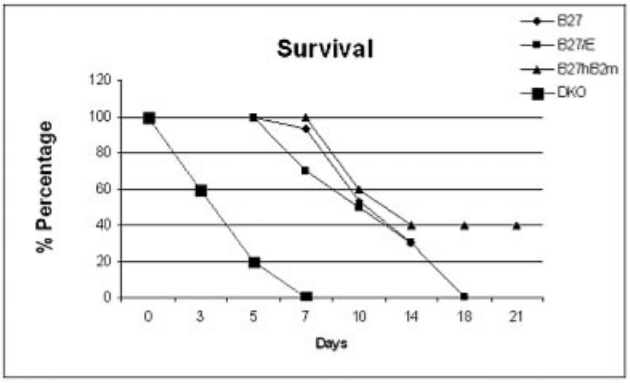
Endoplasmic Reticulum Aminopeptidase (ERAP) Deficiency Alters IL-17 Production and Host Response Following Yersinia Gastrointestinal Infection in B27-Transgenic Mice. Robert D. Inman[1] and Fei Zhu[2]. [1]Toronto Western Hospital, Toronto, ON, Canada, [2]University of Toronto, Toronto, ON, Canada

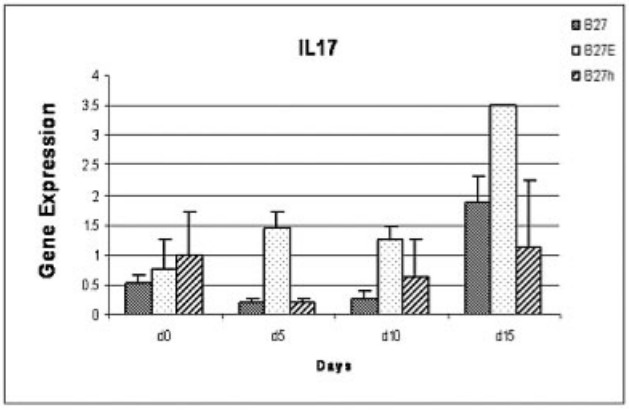
Objective: Recent genetic studies have demonstrated that polymorphisms in ERAP are strongly associated with spondyloarthritis. But the mechanism of this interaction has not been resolved. In the present study we examine the host immune response to Yersinia enterocolitica (Ye) using mice with genetic alteration of class I MHC or ERAP.

Methods: The following mice (all on a B6 background) were compared: (i) deficient in endogenous class I MHC (DKO) (ii) transgenic for HLA B*2705 (B27) (iii) transgenic for B*2705/human β_2M (B27/β_2M) (iii) transgenic for HLA B*2705 *and* deficient in ERAP (B27/ERAP−/−). Mice were challenged intragastrically with 10^7 Yersinia enterocolitica 0:8. Survival curves were generated and cytokine responses were assessed by quantitative PCR on mesenteric lymph nodes and liver.

Results: Survival curve (figure1) indicated the following ranking: B27/β_2M> B27/ERAP−/− > B27> DKO. Only DKO showed significant effects (<3 days) on early survival, confirming that ERAP effects on host immune responses implicate adaptive immunity not innate immunity. With respect to cytokine profiles, the clearest differential was an elevated expression of IL-17 in B27/ERAP−/− mice, which coincided with the temporal course of mortality. There was no consistent impact of ERAP deficiency on IL-4, IL-23, IFN-γ, TGF-β, or TNF-α after Yersinia infection.

Conclusions: ERAP deficiency was associated with enhanced IL-17 production after gastrointestinal infection with Yersinia (figure2). These findings suggest that polymorphisms which affect ERAP function might play a deleterious role in IL-17-mediated immune responses to arthritogenic pathogens.





Disclosure: R. D. Inman: None; **F. Zhu:** None.

1970

Evaluation of T Helper 17 Axis in Ankylosing Spondylitis. Ali Taylan, Ismail Sari, Didem Kozaci, Arif Yuksel, Safak Bilge, Yasar Yildiz, Gulten Sop, ISIL Coker, Necati Gunay and Nurullah AKKOC. Izmir Tepecik Training and Research Hospital, Department of Internal Medicine, Izmir, Turkey

Background: Ankylosing spondylitis (AS) is a chronic inflammatory disorder which primarily affects the axial skeleton. Although the etiology of AS is unknown, available data strongly suggests the importance of genetic factors in the susceptibility to the disease. Recent studies suggest that interleukin-23 receptor (IL-23R) is one of the major generic factors involved in susceptibility to AS. In accordance with this observation, recent studies focused on the T helper 17 (Th17) axis in patients who have AS or spondylarthropathy (SpA).

Objectives: To evaluate T helper 17 (Th17) axis and its relation with tumor necrosis factor (TNF) alpha blockage and disease activity in ankylosing spondylitis (AS).

Methods: 127 AS patients (100M/27F) and 38 (27M/11F) controls were studied. Spinal mobility was assessed by the Bath Ankylosing Spondylitis Metrology Index (BASMI). Patients were also evaluated with the Bath Ankylosing Spondylitis Functional Index (BASFI) and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Serum sample measurement of cytokines including IL-6, IL-12, IL-17A and IL-23 were performed by using commercially available ELISA kits.

Results: Age, and sex distributions were similar between patients and controls ($p>0.05$). Cytokines including IL-6, IL-12, IL-17, and IL-23 were significantly higher in the AS patients than the controls ($p<0.05$; 3.06 [0.73–339,4] vs.1.42 [0.74–4]pg/mL, 4.65 [3,4–41,1] vs. 4.27 [3.47–57,8] pg/mL, 0.72 [0–31,6] vs. 0.15 [0–3.85]pg/mL, 98 (38–206) vs. 57 (36–160) pg/mL respectively).

Comparison of the patients who were on anti-TNF and conventional therapy revealed Th-17 related Cytokines were not different between the groups ($p>0.05$). Cytokines also were similar between the active vs. inactive patients' groups ($p>0.05$).

On correlation analysis, IL-17 was correlated with IL-23 and IL-12 ($p<0.05$). IL-23 showed correlations with IL-17, IL-12 and BASMI ($p<0.05$). Other correlations ($p<0.05$) were as follows:IL-6 with CRP, IL-12 with IL-17 and IL-23.

Table 1. Clinical and laboratory characteristics of the patients and controls

	AS Patients (n=127)	Controls (n=38)	P value
Age (years)	38 (16–64)	38 (23–56)	0.94
Sex (M/F)	100/27	27/11	0.38
BMI (kg/m2)	25.9 (16,3–36,7)	25,3 (18,2–34,3)	0.28
Disease duration (years)	10 (1–35)		
BASFI	3.6 (0–9,5)		
BASDAI	4.4 (0–9,2)		
BASMI	2 (1–9)		
CRP (mg/L)	7.5 (0.27–119,1)	1.15 (0.19–6,4)	<0.001
IL-6 (pg/mL)	3.06 (0.73–339,4)	1.42 (0.74–4)	<0.001
IL-12 (pg/mL)	4.65 (3,4–41,1)	4.27 (3.47–57,8)	0.04
IL-17 (pg/mL)	0.72 (0–31,6)	0.15 (0–3.85)	<0.001
IL-23 (pg/mL)	98 (38–206)	57 (36–160)	0.001
TGF-β (pg/mL)	26.4 (5.2–87)	22.1 (0,4–39)	0.01

Conclusions: In this study we found serum levels of Th-17 axis related cytokines to be significantly increased in the sera of AS patients. Disease activity, treatment type and history of peripheral arthritis(not shown) seem no effect on these cytokines. Targeting the cytokines related with the Th-17 axis may be a reasonable approach in AS patients who don't respond anti-TNF therapies.

Disclosure: A. Taylan: None; **I. Sari:** None; **D. Kozaci:** None; **A. Yuksel:** None; **S. Bilge:** None; **Y. Yildiz:** None; **G. Sop:** None; **I. Coker:** None; **N. Gunay:** None; **N. AKKOC:** None.

1971

Functional Significance of mTor in FLS Proliferation and Its Role in the Pathogenesis of Psoriatic Arthritis. Siba P. Raychaudhuri[2], Ankit Saxena[1] and Smriti K. Raychaudhuri[3]. [1]UC Davis, [2]UC Davis/VAMC Sacramento, Davis, CA, [3]UC Davis/VAMC Sacramento

Purpose: Hyperproliferation and impaired apoptosis of resident synoviocytes (FLS) are critical pathologic events in the pathogenesis of autoimmune inflammatory arthritis like in rheumatoid arthritis (RA) and psoriatic arthritis (PsA). Synovial hyperplasia leads to cartilage and bone damage in the inflamed joints. Increasing evidence places mammalian target of rapamycin (mTOR) as a central regulator of both cell growth (size) and proliferation, this is achieved in part by regulation of translation initiation. We hypothesize that mTOR signaling cascade proteins are upregulated in the FLS obtained from PsA patients and thus maintains proliferation and survival of these cells causing disease pathology. The aim of this study was to investigate the association of mTOR signaling proteins in regulating the proliferation and survival of these synoviocytes of psoriatic arthritis.

Methods: FLS were isolated and prepared from the synovial tissue collected from PsA patients (n=5). FLS obtained from OA (n=5) were used as control. Cell lysates were prepared from these FLS. By western blot assay denovo expression of mTOR and its phosphorylated downstream signaling protein p-mTOR was determined. Also effect of mTOR inhibitors were observed on the proliferation and survival of these FLS. FLS were cultured with rapamycin (10nM) and NVP-BEZ235 (50nM) for 3–5 days at 37°C in 5% CO_2. FACS based CFSE dilution and MTT assays were used for proliferation studies.

Results: We found enhanced expression of mTOR (relative intensity (R.I.)= 1.9 ± 0.1) and its downstream activated signaling protein p-mTOR (R.I.= $0.73\ \pm0.02$) in FLS obtained from PsA in comparison to the non inflammatory OA FLS (R.I.= $0.9\ \pm\ 0.05$; p-mTOR R.I.= 0.26 ± 0.05). The difference of mTOR and p-mTOR was found to be significant at $p<0.01$. Also the FLS proliferation was found to be significantly reduced when cultured in presence of rapamycin [proliferation index (PI)=$.35\pm0.04$) and NVP-BEZ 235 (PI=$0.28\pm\ 0.02$), in comparison to untreated cells (1.2 ± 0.035), data were found to be significantly different between treated and untreated groups at $p<0.01$.

Conclusions: We observed high expression of mTOR signaling cascade proteins in the FLS obtained from PsA in comparison to noninflammatory OA cells. We used FLS from RA patients as positive controls and observations were similar to that of FLS of PsA. Further inhibition of proliferation of these cells in presence of mTOR inhibitors rapamycin and NVP-BEZ235 substantiates the role of mTOR signaling pathway in regulating the proliferation of FLS cell. Proliferating FLS is the major component of the invading pannus in inflammatory arthritis. The novel observations described herein provide new insights for the molecular mechanism of FLS proliferation as well as provides new avenues for treatment of psoriatic disease and RA.

Disclosure: S. P. Raychaudhuri: None; **A. Saxena:** None; **S. K. Raychaudhuri:** None.

1972

Genetic Studies of Ankylosing Spondylitis in Korean Confirm Associations with ERAP1 and 2p15 Reported in Caucasian Cases. So-Young Bang[5], Tae-Hwan Kim[5], Bitnara Lee[5], Eunji Kwon[5], Sang Hyun Choi[6], Ki Soo Lee[1], Seung Cheol Shim[2], Angela Pope[8], Proton Rahman[3], John D. Reveille[7] and Robert D. Inman[4]. [1]Cornell University, Republic of Korea, [2]Eulji University, Republic of Korea, [3]FRCPC, Memorial University of Newfoundland, [4]FRCPC, Toronto Western Hospital, University of Toronto, [5]Hanyang University Hospital for Rheumatic Diseases, Republic of Korea, [6]Korean Minjok Leadership Academy, Republic of Korea, [7]Rheumatology and Clinical Immunogenetics, University of Texas Health Science Center at Houston, [8]Senior Scientist, Newfound Genomics

Objective: Ankylosing spondylitis (AS) is a chronic disabling disorder and pathogenesis is not understood. Multiple genetic factors are thought to be important contributors to disease susceptibility and MHC, IL23R, ERAP1, 2p15 and 21q22 are known to be associated with AS. TASC investigators have recently reported additional genes associated with AS susceptibility including IL1R2, ANTXR2, and gene deserts at 2p15 and 21q22. We evaluated these new candidate genes in a large cohort of Korean AS cases.

Methods: A total of 1164 AS cases and 752 ethnically matched, healthy controls who are native Koreans were enrolled for this study. 8 SNPs were analyzed to define genetic association with Korean AS. The MassARRAY® system (Sequenom, San Diego, CA) was used to genotype each study participant in a two-well reaction designed using Assay Designer 3.1.

Results: Significant positive associations of AS with ERAP1 SNPs, rs27037 ($p = 1.31\times10^{-4}$) and rs27434 ($p = 4.59\times10^{-6}$), were observed. The SNP rs10865331 of gene desert at 2p15 also showed a significant association with AS ($p = 4.63\times10^{-5}$).

Table 1. Genotype and allele frequency of 8 SNPs in Korean AS cohort*

Chromosomal band	SNP	Gene	Allele 1	Allele 2	Cases (n=1164) Genotypes 11	12	22	MAF	Controls (n=752) Genotypes 11	12	22	MAF	OR (95%CI)	P
2p15	rs4672495	-	T	G	939	197	12	0.096	563	155	11	0.121	0.77 (0.63-0.95)	0.01
2p15	rs10865331	-	G	A	410	539	200	0.409	315	325	87	0.342	1.53 (1.16-1.52)	4.63×10^{-5}
2q11.2	rs2310173	IL1R2	C	T	605	515	125	0.334	353	301	72	0.306	1.14 (0.99-1.31)	0.05
4q21.21	rs4333130	ANTXR2	T	C	1039	113	2	0.051	666	77	5	0.059	-	-
5q15	rs27037	ERAP1	C	T	409	678	142	0.384	343	280	89	0.322	1.31 (1.14-1.51)	1.31×10^{-4}
5q15	rs27434	ERAP1	G	A	126	626	295	0.543	215	336	167	0.466	1.36 (1.19-1.56)	4.59×10^{-6}
6p22.2	rs3734523	-	C	T	1144	13	0	0.006	725	13	1	0.010	-	-
21q22.2	rs2836754	-	G	A	346	575	230	0.450	219	336	171	0.457	0.93 (0.82-1.06)	0.30

* 1016 subjects were genotyped (1164 cases and 752 controls) for SNPs with missing values. The rs3734523 SNP was rare and rs3734523 SNP was not common. Odds ratio (OR) and 95% confidence interval (95% CI) were calculated using chi-square test. SNP = single nucleotide polymorphism, MAF = minor allele frequency.

Conclusions: This is the first confirmation in a non-Caucasian population that genetic polymorphisms of rs27037, rs27434 and rs10865331 are associated with AS, implicating common pathogenetic mechanisms in Korean and Caucasian AS.

Disclosure: S.-Y. Bang: None; **T.-H. Kim:** None; **B. Lee:** None; **E. Kwon:** None; **S. H. Choi:** None; **K. S. Lee:** None; **S. Shim:** None; **A. Pope:** None; **P. Rahman:** None; **J. D. Reveille:** None; **R. D. Inman:** None.

1973

HD6: A Novel Antibody That Recognises Cell Surface HLA-B27 Homodimers. Kirsty McHugh[3], Sravan K. Payeli[1], Simon Kollnberger[2], Markus Thiel[1], Jacqueline Shaw[2], Sascha Kleber[1], Andreas Wadle[1], Christoph Renner[1] and Paul Bowness[2]. [1]Department of Oncology, University of Zurich, [2]MRC Human Immunology Unit, Weatherall Institute of Molecular Medicine, Oxford, [3]MRC Human Immunology Unit, Weatherall Institute of Molecular Medicine, Oxford, Oxfordshire, United Kingdom

Background: Possession of HLA-B27 is strongly associated with development of the spondyloarthropathies, including Ankylosing Spondylitis (AS). The mechanism by which HLA-B27 confers this susceptibility is unclear. HLA-B27 forms both heterotrimers (B27) associated with peptide and beta-2-microglobulin, and also heavy chain homodimers (B272). A pathogenic role for these homodimers has been proposed. However, determination of the extent, distribution and triggers of B272 expression have been hampered by the lack of a specific detection reagent. In order to investigate the role of homodimers in AS, we generated an antibody to B272 using phage display technology.

Methods: Phage display technology was used to generate monoclonal antibodies specific for B272. Biotinylated recombinant B272 complexes were used for positive selection and heterotrimeric B27 for negative selection of a phage Fab library. One clone selected for further characterisation, HD6, was then sub-cloned to generate a chimeric antibody comprising human Fab2 and murine IgG1 Fc. ELISA was used to confirm its specificity for B272 complexes. For recognition of cell-expressed B272, human B cell lines transfected with HLA-B27 or control HLAs, and AS patient and control peripheral blood mononuclear cells were used and results analysed by FACS. Inhibition of the interaction of B272 with the immunoreceptors KIR3DL1, KIR3DL2 and LILRB2 was determined using transfected and FACS-sorted cell lines.

Results: 1) In ELISA, HD6 specifically recognised recombinant B272 but not HLA-A2, B7 or B27 heterotrimers. 2) HD6 bound in FACS to LBL721.220 cells transfected with HLA-B27, which express B272 cell surface homodimers, but not to LBL721.220 B7 or to B27 with Cys 67 mutated to serine (which do not express B272). HD6 also bound the C1R human B cell line transfected with HLA-B27 but not with HLA-A2. 3) Cell surface HD6-reactive HLA-B27 molecules were sensitive to treatment with papain (in 3 independent experiments). 4) HD6 bound in FACS to peripheral blood monocytes from AS patients but not controls. B272 expression on monocytes from AS patients ($n=7$) was significantly higher when compared to monocytes from B27+ ($p=0.01$, $n=4$) or B27- ($p=0.06$, $n=7$) healthy individuals, respectively. Low level binding to B27+ B but not T lymphocytes was also observed. 5) HD6 inhibited the binding of the immunoreceptors KIR3DL1, KIR3DL2 and LILRB2 to B272.

Conclusions: A novel phage display-derived monoclonal antibody recognises both recombinant and cell-expressed B272. HD6 stains monocytes from AS patients, implicating these cells in AS pathogenesis. HD6 will be a powerful tool to address the potential pathogenic role of B272 in SpA and may additionally have therapeutic potential.

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1974

HLA- B*27 and Cw*06 Are Risk Alleles for Psoriatic Arthritis among Psoriasis Patients. Lihi Eder[2], Fawnda Pellett[2], Vinod Chandran[2], Sutha Shanmugarajah[2] and Dafna D. Gladman[1]. [1]Toronto Western Hospital, Toronto, ON, Canada, [2]Toronto Western Hospital, Centre for Prognosis Studies in the Rheumatic Diseases, Toronto, ON, Canada

Aim: Genes that differentiate patients with Psoriatic Arthritis (PsA) from those with psoriasis alone serve as markers for the development of PsA in patients with psoriasis. We aimed to identify HLA alleles that are associated with PsA among psoriasis patients.

Methods: In this population based association study, we performed HLA typing in 3 groups: PsA, psoriasis without arthritis and healthy controls. The PsA group included adult patients satisfying the CASPAR criteria that were part of a large prospective PsA cohort. The psoriasis patients were recruited from a recently established psoriasis cohort that was confirmed by a dermatologist. These patients were examined annually by a rheumatologist to rule out the presence of inflammatory arthritis. Control DNA was from healthy Caucasian volunteers, cadaveric organ donors from laboratories of the University Health Network and from a commercial biobank. Extracted genomic DNA was amplified by PCR using locus specific primers for each of the HLA-A, -B, -C, -DR and DQ loci. PCR amplicons were identified by Sequence Specific Oligonucleotide probes using a reverse line blot technique. Caucasian subjects from the PsA and psoriasis cohorts were combined into a "Psoriatic disease" group that was compared to the healthy controls. The differences in allelic distributions for each of the HLA loci were compared using chi square test and Fisher exact test. Bonferroni corrected p values were calculated to adjust for multiple testing. A logistic regression analysis was performed to account for the strong linkage disequilibrium between the HLA alleles.

Results: 804 PsA patients, 412 psoriasis patients without arthritis and 719 healthy controls were included in the study. The mean ages for the psoriasis, PsA and control subjects were: 45.7 ± 13.1, 42.3 ± 12.6 and 43.6 ± 17.2 years respectively. The proportions of females were: 41.9%, 43.5% and 49.3% respectively. The following HLA alleles were found to be significantly different between the psoriatic disease group and healthy controls: A*03 (20% vs. 27.3%, Odds Ratio (OR) 0.6, $p=0.05$), B*07 (16.3% vs. 25.8%, OR 0.6, $p= 4*10^{-4}$), B*13 (9.7% vs. 4.7%, OR 2.2, $p=0.01$), B*27 (14.1% vs. 7.2%, OR 2.1, $3*10^{-4}$), B*38 (11.9% vs. 2.5%, OR 5.3, $p= 10^{-10}$), B*51 (5.7% vs. 10.7%, OR 0.5, $p= 3*10^{-5}$), Cw*03 (15.9% vs. 22.5%, OR 0.7, $p=0.05$), Cw*06 (32.8% vs. 18.1%, OR2.2, $p= 8*10^{-10}$), Cw*07 (44.2% vs. 56.6%, OR 0.61, $p= 4*10^{-5}$), Cw*12 (19.4% vs 10.2%, OR 2.1, $p= 2*10^{-5}$), DRB1*15 (19.2% vs. 26.5%, OR 0.7, $p=0.03$), DQB1*0602 (17% vs. 24.7%, OR 0.6, $p=0.009$). When the PsA group was compared to the psoriasis alone group the only HLA alleles that were found to be significantly different were: B*27 (17.7% vs. 4.1%, OR 5, $p= 4*10^{-9}$), Cw*02 (11.6% vs. 4.8%, OR 2.7, $p=0.01$) and Cw*06 (26.9% vs. 42.1%, OR 0.5, $p= 8*10^{-6}$). On logistic regression analysis only HLA B*27 (OR 4.6, 95% Confidence interval (CI) 2.5–8.3) and Cw*06 (OR 0.5, 95% CI 0.4–0.7) remained significantly associated with PsA compared to psoriasis.

Conclusions: HLA*B27 is a risk allele for PsA among psoriasis patients, while HLA-Cw*06 is a protective allele.

Disclosure: L. Eder: None; **F. Pellett:** None; **V. Chandran:** None; **S. Shanmugarajah:** None; **D. D. Gladman:** None.

1975

HLA-Bw4 Alleles and HLA-C Alleles That Have High Cell-Surface Expression Are Associated with Susceptibility to Psoriatic Arthritis (PsA). Vinod Chandran[3], Fawnda Pellett[2], Renise Ayearst[2], Remy Pollock[3] and Dafna D. Gladman[1]. [1]Toronto Western Hospital, Toronto, ON, Canada, [2]University of Toronto Psoriatic Arthritis Clinic, Toronto Western Hospital, Toronto, ON, Canada, [3]University of Toronto Psoriatic Arthritis Clinic, Toronto Western Hospital

Background: Natural-Killer (NK) cells and NK-T cells are important in the pathogenesis of PsA. The killer-cell immunoglobulin-like receptors (KIRs) on NK cells regulate the inhibition and activation of NK-cell responses through recognition of HLA class I molecules on target cells. It was previously shown that individuals with KIR3DS1 and HLA-B alleles with the serological Bw4 epitope and amino acid isoleucine at position 80 (HLA Bw4 80Ile-B*1513, 1516, 1517, 1524, 2702, 3801, 4901, 51, 5201, 5301, 5302, 57, 58), as well as those with expressing HLA-C alleles that have high cell-surface expression (HLA-C Hi- C* 02, 05, 06, 08, 12, 15, 16) progress more slowly to AIDS. Given the important epidemiological relationship between PsA and AIDS we sought to determine whether these genotypes are associated with susceptibility to PsA.

Methods: 685 cases of European ethnicity (295 females, mean age 43 years, PsA duration 7 years, psoriasis duration 15 years, actively inflamed joint count 11, PASI score 5.2) with PsA and 706 ethnically matched controls (273 females, mean age 53 years) were recruited for the study. Genotyping for HLA-B, and -C alleles was performed using PCR-SSO reverse line blot and that for KIR genes was performed

using PCR-SSP on genomic DNA obtained from peripheral blood. Association between genotypes and PsA was investigated using chi square, Mantel-Haenszel trend test and logistic regression.

Results: HLA-Bw4 80Ile was associated with PsA with risk being higher in subjects with two Bw4 80Ile alleles compared to those with one or no alleles [Bw4 80Ile 2 copies vs. none OR = 1.91, p = 0.03; 1 copy vs. none OR = 1.61, p<0.0001, trend p <0.0001] independent of HLA-B*27. KIR3DS1 was not associated with PsA in univariate analysis (p=0.82), although in a multivariate logistic regression analysis including all KIR genes, KIR3DS1 was protective (OR=O.54, p = 0.038). Analysis for association of Bw4 80Ile and/or KIR3DS1 with PsA where the hierarchy of putative biological effects, namely, Bw4 80Ile absence and KIR3DS1 presence < absence of both Bw4 80Ile and KIR3DS1 < Bw4 80Ile presence and KIR3DS1 absence < presence of Bw4 80Ile and KIR3DS1 (highest risk group) was taken into account showed that the combined genotype was associated with PsA (p trend < 0.0003). HLA-C Hi alleles also were associated with PsA with risk being higher in subjects with two HLA-C Hi alleles compared to those with one or no alleles (C Hi two copies vs. none OR = 2.56, p <0.0001; 1 copy vs. none OR = 1.49, p=0.0012, trend p <0.0001) independent of HLA-C*06, KIR2DS1 and KIR2DS2. Multivariate regression analysis including both Bw4 80Ile and C Hi alleles in a logistic model revealed that both HLA-Bw4 80Ile and HLA-C Hi are independently associated with susceptibility to PsA.

Conclusions: HLA and KIR genes that are associated with better control of HIV/AIDS are independently associated with increased susceptibility to PsA.

Disclosure: V. Chandran: None; **F. Pellett:** None; **R. Ayearst:** None; **R. Pollock:** None; **D. D. Gladman:** None.

1976

IL-17 Receptor and Its Functional Significance in Psoriatic Arthritis. Siba P. Raychaudhuri[2], Ankit Saxena[1] and Smriti K. Raychaudhuri[1]. [1]UC Davis, [2]UC Davis/VAMC Sacramento, Davis, CA

Purpose: The infiltration of T lymphocytes into the synovium involves a dynamic interaction between the subintimal endothelial cells and the fibroblast-like-synovial cells (FLS) in autoimmune arthritis. Overproduction of the pro-inflammatory cytokine, IL-17 has been reported in the rheumatoid arthritis(RA), psoriatic arthritis (PsA) synovium compared to osteoarthritis (OA) patients. Increased levels of IL-17 induce a multitude of factors contributing to the degradation of the articular cartilage and erosion of the underlying bone. In contrast to the restricted site of synthesis of IL-17, the IL- 17 receptor (IL-17R) is expressed ubiquitously. The IL-17R is a type-I membrane protein with no homologue to any of the known family of cytokine receptors. There is no study available about the IL-17R in PsA. To gain knowledge about the expression and function of IL-17R in patients with PsA we analyzed FLS from patients with PsA, RA and OA.

Method: FLS were isolated from the synovium of RA (n=5), PsA (n=5) and OA (n=5) patients. IL-17R expression in FLS was identified by western blotting (WB) and flowcytometry. We also measured IL-17 levels in the synovial fluid (SF) of PsA, RA and OA by ELISA. T lymphocytes derived from synovial fluid (SF) of these patients were studied to identify and phenotype the Th17 cells. Further we determined the functional significance IL-17R in respect to the production of proinflammatory cytokines and endopeptidase.

Results: We observed by flowcytometry that IL-17R expressing cells in FLS obtained from the synovium of RA, PsA and OA were 16.5%±5.37, 12.5%± 3.04, 0.3%±0.9 respectively. WB analyses showed that relative intenstity (RI) of IL-17R protein were higher in RA and PsA compared to OA. RI of IL-17R for RA, PsA and OA were 0.74±.034, 0.68± 0.02, 0.044±.01 respectively.The difference between the groups was found to be significant at p<0.01. The IL-17 level in SF was highest in the PsA group (288.5 pg/ml ± 85.2; n=12). In RA (n=12) and OA (n=12) the level of IL-17 were 225 pg/ml ± 55 and 52 pg/ml±16 respectively. A significant enrichment of IL-17-producing CD4+T cells (10%±3.2) was noticed in the SF of the PsA patients compared to the OA (p<.001). Compared to OA, recombinant IL-17 induced higher levels of IL-6, IL-8, and MMP-3 in PsA derived FLS. Further blockade of the IL-17 R inhibits production of IL-6, IL-8, and MMP-3.

Conclusion: This is the first report to demonstrate the functional significance of IL-17R in PsA. High expression of IL-17R in PsA correlates with the inflammatory outcome of the disease. Our results support the hypothesis that IL17/IL-17R interaction may contribute to an unbalanced production of cytokines and likely to play a significant role in the pathogenesis of PsA. Further our study provides evidence that IL-17R blocking agents/monoclonal antibodies likely to be effective in psoriatic arthritis.

Disclosure: S. P. Raychaudhuri: None; **A. Saxena:** None; **S. K. Raychaudhuri:** None.

1977

Increase of CD5+ 'Innate' B Lymphocytes with Regulatory Capacities in Spondyloarthritis. Tineke Cantaert, Gabriela FrancoSalinas, Jacky Paramarta, Yvonne Tiersma, Christine Teitsma, Paul P. Tak and Dominique Baeten. Academic Medical Center/University of Amsterdam

Background: B lymphocytes play a pivotal role in many autoimmune diseases by terminal differentiation to autoantibody-producing plasma cells, by antigen presentation to T cells, and by cytokine production. However, innate-like CD5+ B cells have recently been shown to down-regulate inflammation by IL-10 production in several colitis models. Considering the relationship between gut and joint inflammation as well as the unknown role of B cells in spondyloarthritis (SpA), we aimed to characterize the presence and function of CD5+ B cells in this seronegative disease.

Materials and Methods: Peripheral blood B cells were analyzed and sorted by flow cytometry in patients with SpA as well as in healthy controls (HC) and patients with rheumatoid arthritis (RA). Sorted cells were stimulated in vitro with either anti-IgM and CD40L or with CpG. Production of cytokines was measured by real-time PCR and ELISA. Synovial biopsies were obtained from actively inflamed joints by needle arthroscopy and were analyzed by double immunohistochemistry.

Results: B cell phenotyping revealed no alterations in naïve, memory, and extra-follicular B cells as well as plasmablasts in SpA. However, there was a significant increase of CD5+ B cells in SpA compared to HC in all B cell subsets (p<0.05). This was not due to increased B cell activation in SpA as the early activation marker CD69 was not increased and both HLA-DR (p<0.01) and CD40 (p=0.013) expression were even decreased on SpA versus HC B cells. Moreover, activation in vitro did not result in an upregulation of CD5. The increase of CD5+ B cells was also specific for SpA and not due to preferential migration of CD5- B cells to the inflamed target tissues as there was no increase in CD5+ B cells in RA peripheral blood and as CD5+ CD19+ B cells were detected in the inflamed synovial tissue. As to the function of the CD5+ B cells in SpA, they displayed not only lower levels of HLA-DR and CD40 but also lower expression of CD80 and CD86 when analyzed directly ex vivo as well as after in vivo activation, suggesting a decreased ability to fully activate T cells. Moreover, the CD5+ B cells produced increased levels of IL-10 but lower levels of IL-6 after BCR stimulation in vitro. This was not the case after innate immune activation by CpG.

Conclusion: CD5+ innate-like B cells are specifically increased in SpA. Their reduced expression of molecules involved in antigen-specific cross-talk with T lymphocytes as well as their ability to produce IL-10 indicate that this B cells subset has regulatory capacities. These data warrant further investigation of their potential contribution to the pathophysiology of SpA in vivo.

Disclosure: T. Cantaert: None; **G. FrancoSalinas:** None; **J. Paramarta:** None; **Y. Tiersma:** None; **C. Teitsma:** None; **P. P. Tak:** None; **D. Baeten:** None.

1978

Increased Expression of Carbonic Anhydrase I in the Synovium of Patients with Ankylosing Spondylitis. Xiaotian Chang[2], Yan Zhao, Xinfeng Yan and Yunzhong Zhang[1]. [1]China, [2]Shandong Acedemy of Medicinal Sciences, China

Background: The most distinctive features of ankylosing spondylitis (AS) is new bone formation and bone resorption at sites of chronic inflammation. Previous studies have indicated that the hyperplasia and inflammation of synovial tissues are significantly related to the pathogenic

process of AS. The present study applied a proteomics approach to identify novel AS-specific proteins by simultaneously comparing the expression profiles of synovial membranes from patients with AS, rheumatoid arthritis (RA) and osteoarthritis (OA).

Methods: Proteins extracted from synovial tissues (n=10 for each disease) were separated by 2-D electrophoresis, and the proteins with significantly increased expression in the AS samples were subjected to MALDI-TOF/TOF-MS analysis. The results were verified using western blotting and immunohistochemistry. The levels of candidate proteins in synovial fluids (n=40 for each disease) were measured using ELISA.

Results: Compared with RA and OA tissue samples, the proteomics approach revealed significantly increased expression of carbonic anhydrase I (CA1) in the synovial membrane of patients with AS. Immunohistochemistry and western blotting analysis confirmed the above finding.

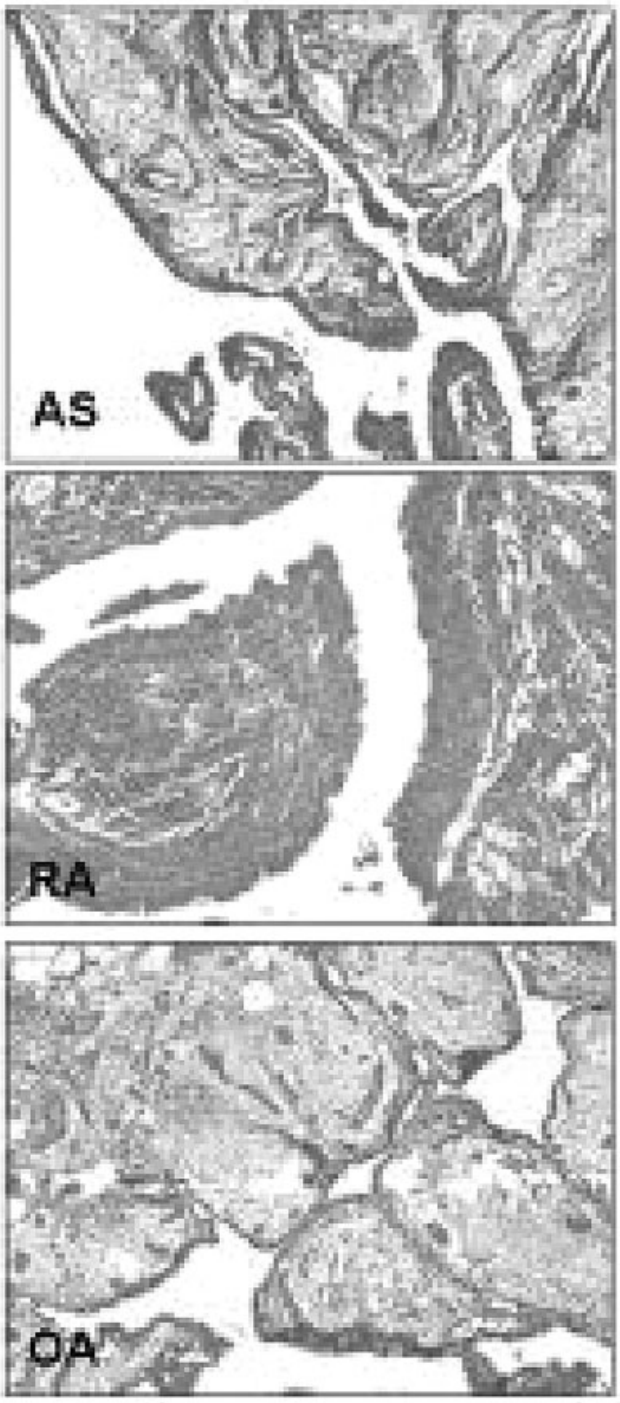

Figure 1.

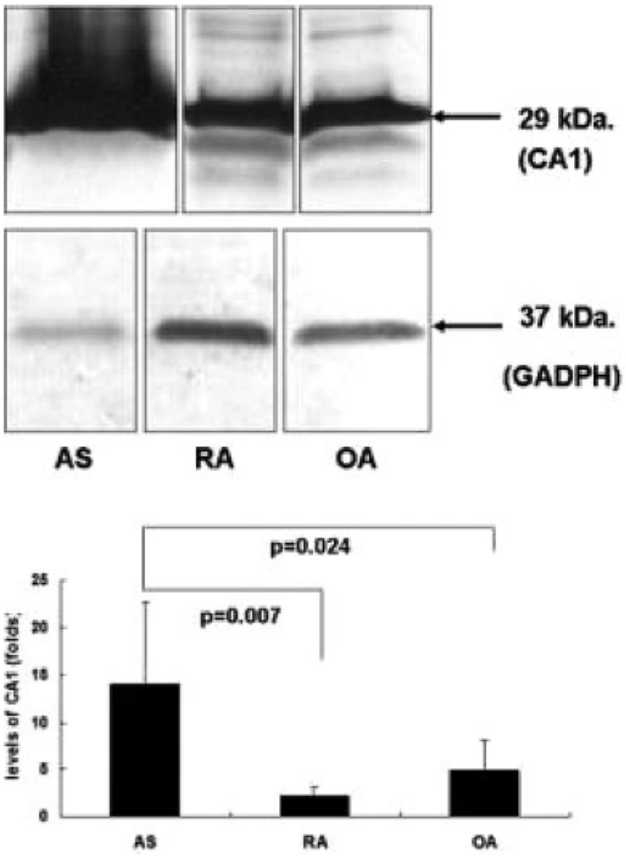

Figure 2.

ELISA detected a higher level of CA1 in synovial fluids from patients with AS than in RA and OA samples. The study also detected increased expression of alpha-1-antitrypsin in the synovial tissues from AS patients, which corresponds to other reports.

Conclusion: *In vitro* experiments by other groups indicated that CA1 catalyzes the generation of HCO_3^- through hydration of CO_2, which then combines with Ca^{2+} to form a precipitation of $CaCO_3$. Many evidences indicated that carbonic anhydrase also stimulates bone resorption. Hence, over-expression of CA1 in synovium of AS may promote improper calcification and bone resorption in AS.

Disclosure: X. Chang: None; **Y. Zhao:** None; **X. Yan:** None; **Y. Zhang:** None.

1979

MICA*016 Allele Differentiates Skin and Joint Manifestations of Psoriatic Disease. Vinod Chandran[3], Remy Pollock[3], Jessica Barrett[1], Lihi Eder[3], Fawnda Pellett[3], Christopher Yao[3], Marsel Lino[3], Sutha Shanmugarajah[3], Vernon Farewell[1] and Dafna D. Gladman[2]. [1]MRC Biostatistics Unit, University of Cambridge Institute of Public Health, Cambridge, UK, [2]Toronto Western Hospital, Toronto, ON, Canada, [3]University of Toronto Psoriatic Arthritis Clinic, Toronto Western Hospital

Background: The Major Histocompatibility Complex Class 1 Chain-Related Gene A (*MICA*) is a multiallelic locus in the MHC region that encodes a 43 kDa cell-surface protein that functions to activate pathways in innate and adaptive immunity. Previous studies have shown associations between psoriatic arthritis (PsA) and MICA-A9 corresponding to MICA*00201 and MICA*017, and MICA-A4, corresponding to MICA*001, MICA*00701, and MICA*018, when compared to healthy controls. However, it is not clear whether the associations are with psoriasis or with PsA, and if the associations are independent of HLA alleles. Our purpose was to delineate the contributions of MICA alleles to susceptibility to skin and joint manifestations of psoriatic disease.

Methods: 249 unrelated Caucasian subjects with PsA (96 females, mean age 41 years, PsA duration 7 years, psoriasis duration 14 years, actively inflamed joint count 10, PASI score 5.3), 243 with psoriasis (100 females,

mean age 47 years, psoriasis duration 17 years, PASI score 5) and 248 healthy controls (141 females, mean age 49 years) were recruited for this study. Genotyping for 55 MICA alleles was done by PCR-SSP and for HLA-B, and -C alleles by PCR-SSO reverse line blot. Allele frequencies were calculated and univariate and multivariate logistic regressions performed, adjusting for HLA-B and C alleles previously shown to be associated with psoriasis and/or PsA.

Results: In univariate analyses MICA*00201/020, MICA*016 frequencies were significantly increased in psoriatic disease (PsA and psoriasis combined) compared to controls, while MICA*00801, MICA*018 and MICA*049 frequencies were decreased. MICA*00201/020 and MICA*00701/026 were increased in PsA compared to controls and MICA*004, MICA*00801 and MICA*018 were decreased. MICA*00201/020, MICA*016 and MICA*017 frequencies were significantly increased in psoriasis compared to controls, while MICA*00801 was decreased. Finally, MICA*00701/026 was increased in PsA compared to psoriasis, and MICA*016 was decreased. There was a significant effect of homozygosity for the allele MICA*00801. Results of the multivariate analyses are provided in the table.

Table. Results of multivariate logistic regression analyses using *MICA* alleles found significant in the univariate analyses as explanatory variables, as well as the results after the inclusion of HLA alleles that were found to be at least marginally significant in univariate analyses.

			After Adjustment for HLA	
Allele	**OR**	**P Value**	**OR**	**P Value**
Psoriatic Disease vs. Controls				
MICA*00201/020	1.694	0.012	1.505	0.078
MICA*00801	0.686	0.03	0.788	0.211
MICA*016	3.022	0.044	*3.628*	*0.021*
MICA*018	0.451	0.017	*0.494*	*0.041*
MICA*049	0.126	0.06	0.176	0.115
PsA vs. Controls				
MICA*00201/020	1.824	0.014	1.462	0.174
MICA*004	0.528	0.028	0.681	0.204
MICA*00701/026	2.602	0.002	0.333	0.115
MICA*00801	0.764	0.209	0.846	0.480
MICA*018	0.437	0.051	0.448	0.067
Psoriasis vs. Controls				
MICA*00201/020	1.836	0.011	1.473	0.135
MICA*00801	0.686	0.062	*0.638*	*0.036*
MICA*016	4.461	0.009	*4.388*	*0.011*
MICA*017	1.875	0.019	1.218	0.619
PsA vs. Psoriasis				
MICA*00701/026	5.074	<0.001	1.026	0.969
MICA*00801†	1.173	0.449	1.294	0.265
MICA*016	0.608	0.243	0.597	0.245

After adjusting for HLA-B*13, −27, −38, −57 and HLA-Cw*01, −02, −06, −12 alleles, no MICA alleles were associated with PsA, but MICA*016 remained significantly associated with psoriasis [Odds Ratio (OR) = 4.4, p = 0.011] and MICA*00801 remained protective [OR = 0.69, p = 0.036]. MICA*00801 homozygosity significantly increased susceptibility to PsA for patients with psoriasis.

Conclusions: MICA allele associations with psoriasis and PsA are dependent on linkage disequilibrium with HLA-B and HLA-C risk alleles. Independent of HLA, only MICA*016 and MICA*00801 influence the risk of developing psoriasis without arthritis, and homozygosity for MICA*00801 increases the risk of developing PsA.

Disclosure: V. Chandran: None; **R. Pollock:** None; **J. Barrett:** None; **L. Eder:** None; **F. Pellett:** None; **C. Yao:** None; **M. Lino:** None; **S. Shanmugarajah:** None; **V. Farewell:** None; **D. D. Gladman:** None.

1980

Peripheral Joint Ankylosis in the Spontaneous Model of Arthritis in DBA/1 Mice Is Associated with a Locus on Chromosome 3 That Contains the BMP Receptor Type 1b. Rik Lories[2], Inge Derese[3], Shea Carter[3], Kirsten Braem[3], Ana Valdes[1] and Frank P. Luyten[2]. [1]King's College, [2]KU Leuven, Leuven, Belgium, [3]KU Leuven

Background: Progression of ankylosis in patients with ankylosing spondylitis is highly variable. Diseases such as diffuse idiopathic skeletal hyperostosis (DISH) and fibrodysplasia ossificans progressiva (FOP), show new bone formation with striking similarities to AS both at the histomorphological and molecular level. This suggests that ankylosis is at least partially due to genetic factors. We used the ankylosing enthesits model in DBA/1 mice to search for associated regions and genes.

Methods: Male DBA/1 were crossed with female BALB/c mice. Male F2 mice from different litters were studied by histomorphology at 26 weeks. 159 markers with sequence-length polymorphisms on the autosomes were selected. Median spacing between the markers was 6.9 cM. 162 F2 male mice were studied. Genes in regions of interests were linked to skeletal development, bone morphogenetic protein (BMP) and Wnt signaling pathways with the Gene Ontology database. The association was evaluated by Chi-square tests with a False Discovery Rate (FDR) algorithm.

Results: Incidence of ankylosing enthesitis was lower in the F2 generation as compared to wild-type DBA/1 males (42% vs. 72%; $p<0.0001$). When applying the FDR algorithm for 159 markers, associations with *D3MIT199* and *D3MIT160* were significant ($p<0.016$). Adjacent markers were additionally genotyped. In the associated region between markers *D3MIT42* and *D3MIT129*, 162 genes were found among which *Bmpr1b, Cxxc4, Lef1, Papss1, Pitx2*, and *Ube2d3*. Only BMP receptor type 1b (*BMPr1b*) was specifically upregulated in mice with spontaneous arthritis as demonstrated by quantitative RT-PCR.

Conclusion: By using F2 mouse genetics in the analysis of a specific phenotype of joint ankylosis, we identified a locus on chromosome 3 that shows association. Within this locus, several genes could play a role in ankylosis but the expression profile suggests that BMP receptor 1b is involved, further supporting a critical role for BMPs in this process.

Disclosure: R. Lories: None; **I. Derese:** None; **S. Carter:** None; **K. Braem:** None; **A. Valdes:** None; **F. P. Luyten:** None.

1981

Phenotypic, Functional and Transcriptomic Analysis of Monocyte-Derived Dendritic Cells from SpA Patients Revealed Their Hypo-Stimulatory Capacity and Specific Molecular Response to LPS Compared to Healthy Controls. Maxime Breban[1], Nelly Bonilla[2], Badredine Mohand Oumoussa[2], Alice Talpin[2], Henri-Jean Garchon[2] and Gilles Chiocchia[2]. [1]AP-HP, [2]Inserm

Purpose: DCs from B27 transgenic rats have a diminished ability to interact with CD4+ T cells and to stimulate a proliferative response, as compared to control DCs. Such results raised the hypothesis that an altered interaction between antigen-presenting cells and CD4+ T lymphocytes might be critical in AS pathogenesis. Nevertheless, we need data in the human disease. Thus, it is of first importance to analyse the expression of HLA molecules and to evaluate the function and genes expression profiling of DCs in AS patients.

Objectives: To study HLA and accessory molecules expression in monocyte-derived DCs (MD-DC), to examine the functional capacity of MD-DC from patients compared to normal controls and the genes expression profiling in monocytes and their derived dendritic cells before and after stimulation.

Method: AS patients (11 HLA-B27+; mean age 44+12 years; BASDAI = 38+22; BASFI = 19+21) and 10 healthy controls were studied. Multi-colours FACS analysis of in vitro MD-DCs was used to compare the expression level of HLA-DR and a full set of cell markers: CD4, CD8, CD11c, CD14, CD40, CD80, CD83, CD86. In vitro derived DCs were obtained from purified CD14+ population cultured for 7 days in the presence of IL-4 and GM-CSF. HuGene 1.0 microarrays were used for genes expression profiling of both monocytes and their derived dendritic cells.

Results: The expression of HLA-DR was higher in AS patients than in controls ($p=0.009$) on monocyte-derived DCs obtained after 7 days of culture and activated with LPSWe observed that like it was reported in rat, the monocytes-derived DCs from AS patients exhibited a weaker stimulatory efficiency of CD4+ T cells than DCs from controls both on autologous and heterologous stimulation conditions. The analysis of genes differentiellyexpressed between CD14+ monocytes from AS patients and controls showed that inflammatory mediators genes transcrits such as CCL2 chemokine, IL-1b and IL-6 cytokines were significiently overexpressed on AS patients CD14+ cells. We also observed a specific molecular signature response to LPS by MD-DC from AS patients compared to controls.

Conclusions: Our findings revealed consistent differences in HLA expression on DCs from AS patients, as compared to healthy controls. We bring evidence that DC from SpA patients have a lower ability to stimulate CD4+ T cell proliferation, as compared to control DC. Transcriptomic analysis of monocytes CD14+ from patients compared with healthy controls showed an inflammatory signature in which genes of inflammatory mediators are significantly overexpressed in SpA. Furthermore, transcriptomic analysis of MD-DCs stimulated with LPS revealed a difference in molecular signature between patients and healthy controls.

Disclosure: M. Breban: None; **N. Bonilla:** None; **B. Mohand Oumoussa:** None; **A. Talpin:** None; **H.-J. Garchon:** None; **G. Chiocchia:** None.

1982

Plasma Cytokine Profles in Ankylosing Spondylitis. Brock E. Harper[4], Michael H. Weisman[1], Pravitt Gourh[5], Shervin Assassi[4], Laura A. Diekman[4], Michael M. Ward[2], John D. Reveille[3] and Sandeep K. Agarwal[4]. [1]Cedars-Sinai Medical Center, Los Angeles, CA, [2]NIH, NIAMS, IRP, Bethesda, MD, [3]Univ Texas Health Sci Ctr, Houston, TX, [4]Univ. of Texas Health Science Center Houston, Houston, TX, [5]Univ. of Texas Health Science Center Houston

Background: Ankylosing spondylitis (AS) is commonly treated with TNFα inhibitors (TNFi) with success; however, our understanding of the immunology of AS is limited. Identification of the genetic association of *IL23R* with AS susceptibility implicates involvement of the Th17 pathway in the pathogenesis of AS. This study aims to investigate the possible effects of TNFi use and patterns of lymphocyte activation in AS.

Methods: Plasma from 128 AS patients and 144 nonautoimmune controls were obtained from patients seen at the University of Texas Health Science Center at Houston Rheumatology Division within the PSOAS cohort. Levels of 13 cytokines were evaluated by electrochemiluminescent multiplex assays.

Results: AS patients had higher levels of IL-23 ($p=0.004$), IL-4 ($p=0.0007$), IL-6 ($p<0.0001$) and lower levels of IL-1β ($p=0.002$) and IL-8 ($p<0.0001$) compared to controls after adjustment for age and gender. Results of analysis of TNFi subsets are shown in Table 1. No differences were seen between either subset of AS patients and controls for IFNγ, IL-5, IL-12, IL-13 or IL-10.

Table 1. Comparison of Cytokine Levels in Patients On and Off TNF inhibitors. Cytokine values are listed as mean±SD in pg/mL. P-values are of data after log-transformation and adjustment for age and gender.

	Control (N=144)	AS Off TNFi (N=92)	AS On TNFi (N=36)	Adjusted P value Ctl vs Off	Adjusted P value Ctl vs On	Adjusted P value On vs Off
IL 17	1.85 ± 2.27	2.28 ± 2.66	0.61 ± 0	NS	<0.0001	<0.0001
IL 23	4.67 ± 12.38	7.65 ± 20.4	10.86 ± 36.97	0.003	NS	NS
IL 2	1.80 ± 6.98	1.40 ± 2.88	0.74 ± 0.56	NS	NS	0.008
IL 4	1.69 ± 3.08	3.30 ± 4.21	2.40 ± 3.47	<0.0001	0.08	0.05
IL 1β	4.93 ± 11.97	1.05 ± 1.98	1.05 ± 1.59	0.006	0.08	NS
IL 6	6.19 ± 11.79	15.06 ± 22.27	4.27 ± 7.38	<0.0001	NS	<0.0001
IL 8	76.99 ± 343.32	2.82 ± 8.10	4.19 ± 12.00	<0.0001	0.02	NS
TNFα	9.73 ± 7.00	11.45 ± 22.48	31.54 ± 31.66	0.0006	<0.0001	<0.0001

Significant correlations with clinical parameters were found with IL-6 and higher BASDAI, ESR, CRP and limited spinal movement. IL-2 and IL-4 were also associatied with higher BASDAI. IL-17, IL-23, IL-2, IL-4, IL-1β, IL-8 were associated with ESR and CRP.

Conclusions: Plasma cytokines differences between controls and patients with AS particularly with respect to TNFi use support the potential role of dysregulation of the Th17 pathway in AS.

Disclosure: B. E. Harper: None; **M. H. Weisman:** None; **P. Gourh:** None; **S. Assassi:** None; **L. A. Diekman:** None; **M. M. Ward:** None; **J. D. Reveille:** None; **S. K. Agarwal:** None.

1983

Stromal Cell Derived Mediators of Bone Remodeling in Psoriatic Arthritis: Implications for Disordered Osteoclastogenesis and Bone Erosion. Nicola Dalbeth[1], Bregina Pool, Timothy Smith, Karon Callon, Maria Lobo, William J. Taylor, Peter B. Jones, Jillian Cornish and Fiona M. McQueen[2]. [1]Univ Auckland, Auckland, New Zealand, [2]Univ of Auckland Sch of Med, Auckland, New Zealand

Background: Diverse bone pathologies are observed in patients with psoriatic arthritis (PsA). Uncoupling of bone remodeling with disordered osteoclastogenesis has been implicated in the pathogenesis of bone resorption in PsA. The aim of this study was to examine the role of stromal cell derived mediators of bone remodeling in PsA.

Methods: Patients with PsA (n=38), with psoriasis (n=10) and healthy controls (n=12) were studied. Serum was obtained for testing of Dikkopf-1 (Dkk-1), macrophage-colony stimulating factor (M-CSF), osteoprotegerin (OPG) and receptor activator of nuclear factor-κB ligand (RANKL) by ELISA. These stromal cell derived mediators were selected as all have been definitively implicated in bone remodelling in models of inflammatory arthritis. Patients with PsA also had bone densitometry, plain radiographs of the hands and feet, and assessment of peripheral blood osteoclast precursors. Radiographs were scored for erosion and joint space narrowing using the Sharp-van der Heijde (SvdH) method modified for PsA, and for the number of joints with new bone formation.

Results: Compared with psoriasis and healthy controls, patients with PsA had higher circulating concentrations of Dkk-1 and M-CSF (Figure). In patients with PsA, the SvdH radiographic scores correlated with M-CSF concentrations ($r=0.52$, $p<0.01$) and RANKL concentrations ($r=0.36$, $p<0.05$), but not Dkk-1 concentrations ($r=0.15$, $p>0.05$). Circulating mediators of bone remodeling did not correlate with the number of joints with new bone formation or with total hip bone mineral density. The radiographic SvdH scores correlated with the percentage of peripheral blood osteoclast precursors ($r=0.38$, $p<0.05$), the number of osteoclast-like cells ($r=0.37$, $p<0.05$) and resorptive pits ($r=0.47$, $p<0.01$) following culture with RANKL and M-CSF. Circulating M-CSF concentrations correlated with the percentage of peripheral blood osteoclast precursors ($r=0.40$, $p<0.05$).

Conclusions: Systemic expression of stromal cell derived factors that promote osteoclastogenesis and bone loss is disordered in patients with PsA. The data do not support a role for these factors in other bone pathologies of PsA, such as new bone formation.

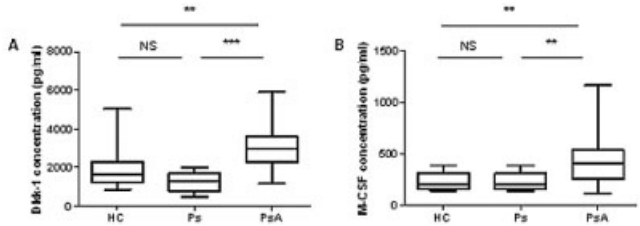

Figure. Stromal cell derived mediators of bone remodeling. Box and whisker plots showing concentrations of A. Dkk-1, and B. M-CSF in healthy controls (HC), patients with psoriasis (Ps) and patients with PsA. **p<0.01, ***p<0.001, one-way analysis of variance with Dunn's multiple comparison test.

Disclosure: N. Dalbeth: None; **B. Pool:** None; **T. Smith:** None; **K. Callon:** None; **M. Lobo:** None; **W. J. Taylor:** None; **P. B. Jones:** None; **J. Cornish:** None; **F. M. McQueen:** Novartis Pharmaceuticals Corporation, 2.

1984

The Association of IL-13 Polymorphism with Psoriatic Arthritis among Psoriasis Patients. Lihi Eder[2], Vinod Chandran[2], Fawnda Pellett[2], Remy Pollock[2], Sutha Shanmugarajah[2] and Dafna D. Gladman[1]. [1]Toronto Western Hospital, Toronto, ON, Canada, [2]Toronto Western Hospital, Centre for Prognosis Studies in the Rheumatic Diseases, Toronto, ON, Canada

Aim: The IL-13 cytokine is involved in T helper type 2 signaling pathway. IL-13 polymorphisms confer a risk for Asthma. Recently, these were found to be associated with a reduced risk for Psoriatic Arthritis (PsA) but not with psoriasis. Smoking was found to abrogate this effect. We aimed to study the association of IL-13 polymorphisms with PsA and psoriasis and their combined effect with smoking.

Methods: We genotyped three groups of Caucasian individuals: patients with PsA, patients with psoriasis without arthritis and healthy controls, for the following Single Nucleotide Polymorphisms (SNPs): rs20541 and rs848, an additional SNP, rs1800925, was genotyped only in the PsA and psoriasis groups. The PsA patients were recruited from a large prospective PsA cohort and satisfied the CASPAR criteria. The psoriasis patients were assessed by a rheumatologist to rule out inflammatory arthritis. The control DNA was from healthy volunteers, cadaveric organ donors from laboratories of the University Health Network and from a commercial bio-bank. Smoking status was defined as smoker ever for smokers and lifetime non-smoker. SNP genotyp-

ing was performed using TaqMan allelic discrimination assays and SDS 2.2.2 software was used for data collection and allele calling.

The differences in allelic distributions were compared by chi square test using PLINK software. The combined effect of genotype and smoking was tested by comparing the proportions of PsA and psoriasis patients and the different combination groups of rs1800925*CT/TT status and smoking status.

Results: 555 PsA patients, 342 psoriasis patients without arthritis and 216 healthy controls were included in the study. Smoking was negatively associated with PsA (258/492 (47.6%) in the PsA group and 139/342 (59.4%) in the psoriasis alone, $p<0.0008$). The minor alleles of rs20541*A and rs848*A were protective for PsA compared to controls (Odds Ratio (OR) 0.61, $p=0.0005$, OR 0.62, $p=0.0007$, respectively). The same alleles were not found to be associated with psoriasis alone (OR 0.75, $p=0.06$, OR 0.79, $p=0.11$, respectively). When PsA patients were compared to those with psoriasis alone, the minor alleles of rs1800925*T (OR 0.78, $p=0.04$) and rs848*A (OR 0.77, $p=0.05$) were found to be protective. A stronger protection was found with the rs1800925*T/ rs20541*A haplotype (OR 0.64, $p=0.007$). The combined effect of rs1800925*CT/TT status and smoking status is presented in Table 1. The combination of smoking and the protective genotype rs1800925*CT/TT was the most protective for PsA. Among non-smokers rs1800925*CT/TT was no longer associated with PsA.

Table 1. The combined effect of smoking status and rs1800925*CT/TT genotype status on the prevalence of PsA

rs1800925 - genotype	Smoking	PsA	Psoriasis	OR*	95% CI**	p value
CT/TT	Yes	82 (48.5%)	87 (51.5%)	0.49	0.33–0.73	0.0003
CC	Yes	146 (55.7%)	116 (44.3%)	0.66	0.46–0.93	0.02
CT/TT	No	69 (61.1%)	44 (38.9%)	0.82	0.52–1.29	0.39
CC	No	196 (60.7%)	127 (39.3%)	Ref.	Ref.	Ref.

*Odds ratio
**Confidence interval.

Conclusions: An IL-13 polymorphism is protective for PsA among psoriasis patients. This effect was not significant among non-smokers.

Disclosure: L. Eder: None; **V. Chandran:** None; **F. Pellett:** None; **R. Pollock:** None; **S. Shanmugarajah:** None; **D. D. Gladman:** None.

1985

The Relationship of Biomarkers and Radiographic Progression in Patients with Ankylosing Spondylitis. X. Baraliakos[5], R. Landewe[4], D. Van Der Heijde[3], J. Listing[2], D. Baker[1], H. Benjamin[1] and J. Braun[6]. [1]Centocor Inc, R&D, [2]German Rheumatism Research Center, [3]LeidenUniversity Medical Center, Meerssen, The Netherlands, [4]Maastricht University Medical Center, Maastricht, The Netherlands, [5]Rheumazentrum Ruhrgebiet Herne, [6]Rheumazentrum Ruhrgebiet, Herne, Herne, Germany

Background: Structural damage in patients with ankylosing spondylitis (AS) is characterized by the development of syndesmophytes. How this is influenced by inflammation and bone metabolism is not entirely clear, and the role of biomarkers associated with new bone formation in this scenario remains to be clarified.

Objective: To determine the level of different biomarkers, analyse their relevance in correlation to clinical, MRI and radiographic measurements and define their role in the prediction of syndesmophyte formation in AS patients under anti-TNF treatment.

Methods: Data of AS patients who participated in ASSERT were retrospectively analyzed. Complete data from radiographs and of the following biomarkers (measured by ELISA) were available at baseline and after 2 years: interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), transforming growth factor-β (TGFβ) for inflammation and osteocalcin (OC), bone alkaline phosphatase (BAP), C Telopeptide 1 (CTX), N Telopeptide (NTX), osteopro¬te¬gerin (OPG) and cartilage oligomeric matrix protein (COMP) for bone turnover.

Assessment of disease activity (BASDAI), function (BASFI), metrology (BASMI), laboratory parameters (CRP, ESR), radiographs and MRIs were available at baseline and after 2 yrs. Analyses were performed based on 'severe radiographic progression' (SRP, increase of $\geq$3 mSASSS units/year) and/or the development of new syndesmophytes at the 2-year follow-up.

Summary statistics were used for the baseline data, and linear and logistic regression to test for the association of serum markers with MRI activity, mSASSS scores, clinical indices and the development of new syndesmophytes. ROC analysis was used for cut-point determination.

Results: Data of 148 patients could be analyzed, 15% of those showed SRP and 19% syndesmophyte formation. Baseline characteristics and the mean serum levels of biomarkers were not significantly different in patients with and without syndesmophytes/radiographic baseline damage. By logistic regression analysis, only OPG serum levels correlated significantly with SRP. The best cut-off for OPG in discriminating between patients with and without SRP was 3.1 units (OR (95%CI): 8.0 (2.6–24), $p=0.001$), sensitivity 67%, specificity 71% (AUC 0.66, LR+: 1.7, LR−: 0.54). Furthermore, baseline radiographic damage (OR (95%CI): 31 (3.2–298), $p=0.003$) and female gender (OR 0.17 (0.033–0.77), $p=0.032$) were also predictive of SRP. HLA-B27 could not be investigated due to low prevalence of HLA-B27 negativity. No correlations with the development of syndesmophytes were found. Among the markers for inflammation, only IL-6 showed a trend towards higher levels for patients with (mean (SD): 14.7 (18.2)) vs. without (13.3 (23.6)) SRP.

Conclusion: Increased levels of OPG, an osteoclastogenesis inhibitory factor, were predictive of severe radiographic progression over 2 years on the group level only. In contrast to previous studies with AS patients and patients with active RA or OA, none of the biomarkers indicative of bone degradation or hyperproliferation were predictive of radiographic progression.

Disclosure: X. Baraliakos: None; **R. Landewe:** None; **D. Van Der Heijde:** None; **J. Listing:** None; **D. Baker:** Centocor, Inc., 3; **H. Benjamin:** Centocor, Inc., 3; **J. Braun:** None.

1986

Whole Blood Transcriptional Profiling in Ankylosing Spondylitis Identifies Novel Putative Candidate Genes for Both the Inflammatory and Tissue-Destructive Aspects of the Disease. Fernando Manuel Pimentel-Santos[2], Dario Ligeiro[3], Mafalda Matos[10], Ana F. Mourão[2], José Costa[4], Helena Santos[9], Elsa Sousa[1], Anabela Barcelos[7], Fátima Godinho[6], João E. Fonseca[1], Henrique Gueds-Pinto[8], Jaime C. Branco[2], Matthew A. Brown[5] and Gethin Thomas[5]. [1](IMM), Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal, [2]CEDOC, Faculdade de Ciências Médicas da Universidade Nova de Lisboa, Lisboa, Portugal, [3]Centro de Histocompatibilidade do Sul, Lisboa, Portugal, [4]Centro Hospitalar do Alto Minho (CHAM), Hospital de Ponte de Lima, Ponte de Lima, [5]Diamantina Institute for Cancer, Immunology and Metabolic Medicine, Princess Alexandra Hospital, University of Queensland, Brisbane, Australia, [6]Hospital Garcia de Orta, Almada, Portugal, [7]Hospital Infante D. Pedro, Aveiro, Portugal, [8]Instituto de Biotecnologia e Bioengenharia, Centro de Genética e Biotecnologia, da Universidade de Trás-os-Montes e Alto Douro (IBB/CGB–UTAD), Vila Real, Portugal, [9]Instituto Português de Reumatologia (IPR), Lisboa, Portugal, [10]UTAD, Universidade de Tás-os-Montes e Alto Douro, Vila Real, Portugal

Background: The aetiopathology of ankylosing spondylitis (AS) is poorly understood. A number of genetic-association studies have identified genes contributing to AS susceptibility but such approaches provide little information as to the gene activity changes occurring during the disease process. Transcriptional profiling generates a "snapshot" of the sampled cells activity and thus can provide insights into the molecular processes driving the disease process. Several recent studies have defined transcriptional profiles generated from peripheral blood mononuclear cells (PBMCs) however PBMC isolation is not viable in multicentre studies and limits the viability of such an approach. An alternate approach is to use whole blood samples collected using PAXgene technology which preserves integrity of the RNA.

Objective: We undertook a whole-genome microarray approach to identify candidate genes associated with AS and validated these gene-expression changes in a larger sample cohort.

Methods: 18 active AS patients, classified according to the New York criteria. and 18 gender-and age-matched controls were profiled using Illumina HT-12 Whole-Genome Expression BeadChips which carry cDNAs for 48000 genes and transcripts. Class comparison analysis identified a number of differentially expressed candidate genes. These candidate genes were then validated in a larger cohort using qPCR-based TaqMan Low Density Arrays (TLDAs).

Results: 239 probes corresponding to 221 genes were identified as being significantly different between patients and controls with a p-value <0.0005 (80% confidence level of false discovery rate). Forty eight genes were then selected for validation studies, using the TLDAs. Thirteen of these genes were validated in the second patient cohort with 12 down-regulated (1.3–2-fold) and only 1 upregulated (1.6-fold).

	Array		TLDA	
Gene symbol	Parametric p-value	Fold-change	Parametric p-value	Fold-change
DNMT1	6,46E-05	0,71	1,30E-06	0,46
CDC25B	0,0002	0,67	2,50E-06	0,5
BCL11B	0,000588	0,70	2,90E-06	0,45
DOCK10	0,000173	0,70	1,81E-05	0,54
CLSTN1	0,000453	0,68	1,94E-05	0,52
SPOCK2	0,000307	0,65	0,000522	0,57
ITGB7	0,000563	0,68	0,001209	0,58
MCM3	0,000424	0,73	0,001398	0,61
PTPN1	1,50E-06	0,69	0,002644	0,67
EP300	0,000126	0,70	0,003489	0,68
PPP2R1A	0,000173	0,71	0,012503	0,71
CLEC4D	0,000347	1,52	0,018409	1,61
CX3CR1	0,000345	0,58	0,020676	0,66

A number of these genes, have well-documented inflammatory roles with PTPN1 and DOCK10 both involved in mediating IL4 action. Of specific interest to AS progression are the established roles of SPOCK2 (osteonectin) and EP300 in cartilage. DNMT1 and EP300 both mediate STAT3 functionality which has also been associated in genetic studies with AS.

Conclusion: We have validated a gene expression signature for AS from whole blood and identified strong candidate genes that may play roles in both the inflammatory and joint destruction aspects of the disease.

Disclosure: F. M. Pimentel-Santos: None; **D. Ligeiro:** None; **M. Matos:** None; **A. F. Mourão:** None; **J. Costa:** None; **H. Santos:** None; **E. Sousa:** None; **A. Barcelos:** None; **F. Godinho:** None; **J. E. Fonseca:** None; **H. Gueds-Pinto:** None; **J. C. Branco:** None; **M. A. Brown:** None; **G. Thomas:** None.

ACR Poster Session C
Systemic Sclerosis, Fibrosing Syndromes and Raynaud's-Pathogenesis and Genetics II
Wednesday, November 10, 2010, 9:00 AM–6:00 PM

1987

Association of the Functional CD226 307Ser Variant with Systemic Sclerosis (SSc): Evidence for the Contribution of Co-Stimulation Pathways in the SSc Pathogenesis. Philippe Dieudé[10], Mickaël Guedj[6], Marie-Elise Truchetet[4], Gabriela Riemekasten[3], Marco Matucci-Cerinic[2], Inga Melchers[1], Eric Hachulla[8], Paolo Airo[7], Carlo Chizzolini[5], Catherine Boileau[11], Yannick Allanore[9] and the GENESYS Consortium. [1]Clinical Research Unit for Rheumatology, University Medical Center, Freiburg, Germany, [2]Department of Biomedicine, Section of Rheumatology, Florence, Italy, [3]Department of Rheumatology and Clinical Immunology, Charité University Hospital, Berlin, Germany, [4]Immunology and Allergy, Geneva University Hospital and School of Medicine, Geneva, Switzerland, [5]Immunology and Allergy, Geneva University Hospital and School of Medicine, Geneva, Switzerland, [6]Laboratoire Statistique et Génome, UMR CNRS-8071/INRA-1152/Université d'Evry Val d'Essonne, France, [7]Rheumatology and Clinical Immunology, Spedali Civili, Brescia, Italy, [8]Université Lille II, Médecine Interne, Lille, France, [9]Université Paris Descartes, Service de Rhumatologie A, Hôpital Cochin, Paris, France, [10]Université Paris Diderot, Service de Rhumatologie, Hôpital Bichat Claude Bernard, APHP, Paris, France, [11]Université Versailles Saint Quentin Yvelines, Laboratoire de Biochimie Hormonale et Génétique, Hôpital Ambroise Paré, AP-HP, Boulogne, France

Background: The non-synonymous polymorphism rs763361 of the CD226 gene, which encodes the DNAX accessory molecule 1, involved in T cell co-stimulation pathways, has recently been identified as a genetic risk factor for autoimmunity.

Objective: To test for association the CD226 rs763361 polymorphism with systemic sclerosis (SSc) in European Caucasian populations.

Methods: CD226 rs763361 was genotyped in 3645 individuals comprising a discovery set (991 SSc patients and 1008 controls) and a replication set (999 SSc patients and 634 controls), all individuals being of European Caucasian origin.

Results: The CD226 rs763361 T allele was found to be associated with SSc in both discovery and replication samples providing the following results in the combined populations: OR 1.22 95%CI [1.10–1.34], $P=5.69\times10^{-5}$. The CD226 T allele was also associated with various SSc subsets highlighting a potential contribution in disease severity. The most remarkable associations of the CD226 TT risk genotype were observed with diffuse cutaneous subtype, anti-topoisomerase I antibodies positive and SSc-related fibrosing alveolitis subsets: OR 1.86 95%CI [1.42–2.43], $P=5.15\times10^{-6}$, OR 1.82 95%CI [1.38–2.40], $P=2.16\times10^{-6}$ and OR 1.61 95%CI [1.25–2.08], $P=2.73\times10^{-4}$, respectively.

	TT (%)	TC (%)	CC (%)	T (%)		P*	P†	OR (95% CI)
				Discovery set				
SSc n = 991	22.8	50.8	26.4	48.2	T	*0.023*	*NS*	1.15 [1.02–1.31]
					TT	*0.016*	*NS*	1.37 [1.06–1.77]
					TC	*0.49*	*NS*	1.07 [0.87–1.32]
Controls n = 1008	18.4	52.3	29.3	44.6				
				Replication set				
SSc n = 996	27.9	51.0	21.1	53.4	T	*0.0018*	*0.018*	1.25 [1.09–1.44]
					TT	*0.0017*	*0.017*	1.56 [1.15–2.06]
					TC	*0.0025*	*0.025*	1.45 [1.14–1.85]
Controls n = 650	24.1	47.4	28.5	47.4				
				Combined populations				
SSc n = 1987	25.4	50.9	23.7	50.8	T	2.67×10^{5}	—	1.22 [1.11–1.34]
					TT	2.47×10^{3}	—	1.49 [1.24–1.80]
					TC	*0.0091*	—	1.23 [1.05–1.44]
Controls n = 1658	20.7	50.4	28.9	45.9				

*By chi-square test or Fisher's exact test.
† *P*-value < 0.05 adjusted after Bonferroni's corrections for multiple comparison. NS: not statistically significant.

Conclusions: Our results establish CD226 as a new SSc genetic susceptibility factor.

Disclosure: P. Dieudé: None; **M. Guedj:** None; **M.-E. Truchetet:** None; **G. Riemekasten:** None; **M. Matucci-Cerinic:** None; **I. Melchers:** None; **E. Hachulla:** None; **P. Airo:** None; **C. Chizzolini:** None; **C. Boileau:** None; **Y. Allanore:** None; **and the GENESYS Consortium:** None.

1988

Characterization of Single Histone Deacetylase Isoforms in Endothelial Cells Derived from Progenitors in Systemic Sclerosis. Hossein Hemmatazad[1], Britta Maurer[1], Beat A. Michel[1], Renate E. Gay[1], Gay Steffen[1], Jèrome Avouac[2], Oliver Distler[1], Yannick Allanore[2] and Astrid Jüngel[1]. [1]Center of Experimental Rheumatology, University Hospital and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland, [2]Department of Rheumatology A, Cochin Hospital, Universitè Paris Descartes, INSERM U781, Paris, France

Background and Objectives: Microvascular damage is a major concern in the pathogenesis of SSc with outcome depending on the extent and severity of vascular lesions. Considering reports which indicate a key role of specific histone deacetylase (HDAC) isoforms in angiogenesis, we investigate here the expression patterns of HDACs in endothelial cells derived from circulating progenitors (EPCs) from patients with SSc and from normal healthy controls, under basal and under hypoxic conditions.

Methods: Late outgrowth EPC-derived cells were obtained from the peripheral blood of 11 patients with SSc and 6 healthy individuals according to the EUSTAR recommendations on endothelial precursor cells in SSc. All patients fulfilled the ACR classification criteria for SSc. Gene expression patterns of HDACs (1–11) and HoxA9, the key transcription factor for endothelial cells, were analyzed under basal conditions and under hypoxic (1% oxygen for 6h) conditions by TaqMan Real-time PCR using 18S for normalization. To assess the expression on protein level, antibodies against HDAC1 and HoxA9 were used for western blot.

Results: Under basal conditions, the mRNA levels of HDAC1, 2 and 5 were significantly up regulated in endothelial cells from SSc patients by 4.33 ± 1.75, 7.40 ± 3.40 and 1.51 ± 0.54 (x-fold ± SD, $p<0.05$) respectively, as compared to normal healthy cells. Moreover, the expression of HDAC6 and HDAC10 were reduced by 44 ± 15 and 31 ± 20 (% ± SD, $p<0.05$) in SSc vs. healthy EPCs. After 6h of hypoxia, we observed a notable increase in the expression of mRNA levels for HDAC1 and 2 by 2.47 ± 0.92 and 3.08 ± 1.27 (x-fold ± SD, $p<0.05$) in SSc cells as compared to healthy controls. In contrast, the expression levels of HDAC6 and 7 were down regulated by 31 ± 20 and 36 ± 19 (% ± SD, $p<0.05$). It is known that HDAC1 activity is required for the expression of HoxA9 which regulates important genes in vascular formation. We observed a significant down regulation of HoxA9 mRNA by 95 ± 3 % in SSc endothelial cells vs. healthy cells. Using western blot we confirmed this data on protein level. Of interest, the protein expression of HDAC1 was in contrast to the mRNA level reduced

in SSc (n=3) as compared to healthy controls under basal conditions. It has been reported that some microRNAs regulate Hox genes. Therefore, we hypothesize that microRNAs prevent the transcription of HDAC1 mRNA and regulate thereby the expression of HoxA9.

Conclusions: We conclude that vasculopathy in SSc might be related to the different expression of HDACs in endothelial cells. Altered expression of HDACs could possibly regulate the expression of important genes involved in vascular formation via transcription factors like HoxA9 and contribute to altered angiogenesis in SSc.

Disclosure: H. Hemmatazad: None; **B. Maurer:** None; **B. A. Michel:** None; **R. E. Gay:** None; **G. Steffen:** None; **J. Avouac:** None; **O. Distler:** None; **Y. Allanore:** None; **A. Jüngel:** None.

1989

Circulating T Cell Polarization Is Associated with Respiratory Decline in Scleroderma Patients with Active Interstitial Lung Disease.

Francesco Boin[1], Fredrick Wigley[2], Robert Wise[2] and Antony Rosen[2]. [1]Johns Hopkins University, Baltimore, MD, [2]Johns Hopkins University

Purpose: Immune activation plays a role in the pathogenesis of systemic sclerosis (SSc) and may be relevant for the initiation and propagation of target tissue injury. In particular, development of interstitial lung disease (ILD) is associated with lung inflammation. The presence of neutrophilia and/or eosinophilia (alveolitis) in the bronchoalveolar lavage (BAL) fluid of SSc patients has been considered indicative of active ILD. However, this measure has not consistently provided reliable prediction of lung disease outcomes. A pro-fibrotic type 2 (Th2/Tc2) T cell response has been detected in the periphery of SSc patients with ILD. In this study we investigated whether an abnormal distribution of polarized T cell subsets in the periphery or the bronchoalveolar lavage (BAL) fluid of SSc patients is associated with the presence of active ILD.

Methods: Peripheral blood and BAL were simultaneously obtained from 22 SSc patients undergoing bronchoscopy for suspected active ILD based on increasing respiratory symptoms, worsening lung volumes or abnormal imaging studies. Decline of the forced vital capacity (FVC) >10% of predicted within 6–10 months prior to the procedure was considered as significant for active ILD. The presence of active BAL alveolitis was defined as neutrophils >3% and/or eosinophils >2.2% on differential cell count. T cell subsets were characterized by flow cytometry using CD3, CD4, CD8, chemokine receptor CCR5 (Th1/Tc1 specific) and CRTH2 (Th2/Tc2 specific) surface markers. CCR5/CRTH2 ratio was used to determine polarization of the immune response towards a type 1 (high ratio) or type 2 (low ratio) phenotype.

Results: Active ILD (FVC decline >10%) was identified in 12 patients and was significantly associated with a relative Th2/Tc2 polarization in the peripheral blood based on a lower CD3+CCR5/CRTH2 ratio (3.9 vs. 11, $p<0.001$). This finding was mostly determined by a lower number of circulating CCR5+ T cells in active vs. non-active ILD patients (CD3 8.6% vs. 24.8%, $p<0.001$; CD4 7.7% vs. 19.4%, $p=0.005$; CD8 14.9% vs. 40%, $p<0.001$). Conversely, the presence of BAL alveolitis was not significantly associated with declining FVC volumes, nor it was correlated with any absolute or relative difference among polarized T cell subsets in the peripheral blood or BAL fluid.

Conclusions: Distinct polarized T cell subsets in the peripheral blood of SSc patients are associated with declining respiratory function and should be prospectively explored as a novel biomarkers to measure disease activity and predict outcomes in ILD and other clinical manifestations of scleroderma.

Disclosure: F. Boin: None; **F. Wigley:** None; **R. Wise:** None; **A. Rosen:** None.

1990

Does Treatment with Imatinib Modify Gene Expression in the Skin and Peripheral Blood Mononuclear Cells of Patient with Systemic Sclerosis?

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Background: Patients with Systemic Sclerosis (SSc) have been shown to have distinct patterns of gene expression in the skin and peripheral blood. In the skin these patterns correspond to clinical involvement. It is not known whether gene expression patterns in the skin correlate with those in the blood or if treatment leads to modulation of gene expression. We hypothesized that imatinib treatment would modulate gene expression in the skin and peripheral blood mononuclear cells (PBMC) of treated patients with diffuse cutaneous (dc)SSc.

Methods: We performed gene expression profiling with microarray on RNA from skin biopsy and PBMC samples of 8 patients with dcSSc from the Imatinib clinical trial at our center. Patients selected had improvements of ≥ 5 points in their Modified Rodnan Skin Scores (MRSS) over 12 months. RNA was hybridized to Affymetrix Human U133 2.0 gene chips. Paired t-tests were performed using Genespring GX11 and Ingenuity Pathways was used to evaluate pathways of interest.

Results: Patient characteristics: 63% female; median age: 44 [18, 71]; median disease duration: 1.8 years [0.3 to 8]; and median change in MRSS: −9 [−5 to −12]. In the skin treatment led to the differential expression of 433 genes at a p-value of 0.05 and a fold-change cut-off of 1.5 without multiple testing correction. In PBMC treatment led to differential expression of 534 genes at the same cut-off. In PBMC unsupervised hierarchical clustering demonstrated a primary separation of groups based on treatment status.

In both skin and blood we observed down-regulation of PI3K signaling with treatment. This included down-regulation of AKT2, PIK3R1, PIK3C2A, EEAl, and ITPRIPL2 in skin and down-regulation of AKT2, INPP4A, HIPK1, LIMK1, MAK, MAP2K6, and PTEN in blood. We were interested especially looking for changes in TGF-β and PDGFR signaling. In the skin there was down regulation of smad2 and AKT2, and in PBMC there was decreased expression the TGF-β Receptor 1, egr2 transcription factor, WNK1 and AKT2. In the skin there was increased expression of PDGFRL.

Other entities differentially regulated include in the skin down-regulation of NCOA3, ADAM10, ADAM17, vitamin D receptor, dihydrofolate reductase, Cxcl3, and integrin β1 as well as up-regulation for col1a1, col6a2, MAPK12, ADAMTS2, and the chemokines CCL 18, 26, 22, 13. In PBMC there was differential expression of the angiogenic mediators VEGFA (up) and flt1 (down.) There was also increased expression of thrombospondin1.

Conclusions: Treatment with imatinib may lead to modulation of gene expression in skin and PBMC. Hierarchical clustering in PBMC is supportive of a treatment effect. One common pathway affected in skin and blood is PI3K signal transduction which was not expected but which may be pathogenically relevant in the transdifferentiation of myofibroblasts. It is important to note that the changes seen are modest and do not stand up to statistical correction for multiple testing in this small number of patients. We plan to analyze this data in the context of several controls – treated patients without clinical improvement, longitudinal disease controls, and healthy controls. Validation of this microarray data by qPCR is planned.

Disclosure: J. K. Gordon: None; **R. Spiera:** Bristol-Myers Squibb, 2, Novartis Pharmaceuticals Corporation, 2, United Therapeutics, 2; **J. N. Mersten:** None; **H. F. Wildman:** None; **Z. Taimeh:** None; **N. Hackett:** None; **S. Vukelic:** None; **K. A. Kirou:** NovoNordisk, 2; **M. K. Crow:** None.

1991

Enhanced Expression of Ephrins and Thrombospondins in the Dermis of Patients with Early Diffuse Systemic Sclerosis: Potential Contribution to Perturbed Angiogenesis and Fibrosis.

Jerome Avouac[6], Maud Clemessy[2], Jorg H. W. Distler[8], Jean Marie Gasc[2], Barbara Ruiz[1], Marie Cecile Vacher-Lavenu[3], Julien Wipff[6], Andre Kahan[4], Catherine Boileau[7], Pierre Corvol[2] and Yannick Allanore[5]. [1]INSERM U781, Necker Hospital, Paris, France, [2]INSERM U833 and Collège de France, Paris, France, [3]Paris Descartes University, Pathophysiology Department, Cochin Hospital, Paris, France, [4]Paris Descartes University, Rheumatology A Department, Cochin Hospital, APHP, Paris, France, [5]Paris Descartes University, Rheumatology A Department, Cochin Hospital, APHP, Paris and INSERM U781, Necker Hospital, Paris, France, [6]Paris Descartes University, Rheumatology A Department, Cochin Hospital, APHP, Paris and INSERM U781, Necker Hospital, Paris, France, [7]U.V.S.Q University, Biochemistry, Hormonology and Molecular Genetics Department, Ambroise Paré Hospital, AP-HP, Boulogne, France, [8]University of Erlangen, Erlangen, Germany

Objective: Ephrins have emerged as essential regulators of angiogenesis and thrombospondins are inhibitors of angiogenesis and strong promoters of fibrosis that are both involved in systemic sclerosis (SSc). Our aim was to investigate whether ephrins and thrombospondins contribute to the dysregulation of angiogenic homeostasis related to systemic sclerosis (SSc) and to the pathologic activation of SSc dermal fibroblasts.

Methods: Skin biopsies were obtained from 8 patients with early diffuse cutaneous subset and from 4 healthy volunteers, matched for age and sex with SSc patients. SSc Skin biopsies were taken from both clinically involved and

non-involved skin. Dermal fibroblasts were cultured from control and clinically involved and non-involved SSc skin. Ephrin (EphB4 and EphrinB2) and thrombospondin (TSP-1 and 2) mRNA and protein levels were analyzed in skin tissue respectively by in situ hybridization and immunohistochemistry. EphB4/EphrinB2 and TSP-1/2 mRNA and protein levels were assessed in SSc and control dermal fibroblasts in basal conditions and after stimulation by TGFβ or 6 hours of hypoxic exposure. Ephrin and thrombospondin expression was also determined in SSc and control dermal fibroblasts cultured with a pan-specific TGFβ blocking antibody.

Results: Increased mRNA and protein levels of EphrinB2 and EphB4 were detected in clinically involved skin of SSc patients. EphrinB2, but not EphB4, was also upregulated in clinically non-involved skin. The expression of Ephrins was restricted to the vessels. Low levels of EphrinB2 and EPhB4 were detected in control and SSc cultured dermal fibroblasts, in basal conditions or after stimulation by TGFβ or hypoxia, suggesting that fibroblasts do not produce ephrins. TSP-1 and 2 were upregulated in SSc skin biopsies taken from both involved and non-involved skin. Their expression was mainly detected in the extracellular matrix located at the periphery of vessels. The overactivation of TSP-1 and TSP-2 persisted in cultured SSc dermal fibroblasts issued from involved and non-involved skin, and might contribute to the activated phenotype of SSc fibroblasts. Culture with TGFβ blocking antibody markedly reduced the upregulated expression of TSP-1 and TSP-2 in SSc dermal fibroblasts, but had little effect on healthy fibroblasts. Moreover, stimulation of healthy dermal fibroblasts with TGFβ, but not with hypoxic exposure, led to TSP-1 and TSP-2 activation.

Conclusion: We investigated for the first time the expression of EphB4/EphrinB2 and TSP-1/TSP-2 expression in the skin and in dermal fibroblasts of patients affected by SSc. EphB4 and EphrinB2 are upregulated in clinically involved skin of SSc patients, suggesting their participation in SSc perturbed angiogenesis. TSP-1 and 2 are upregulated in both clinically involved and non-involved SSc skin and are constitutively activated in a TGFβ dependent/hypoxia independent manner in SSc dermal fibroblasts. Further studies are now warranted to assess the role of TSP-1 and TSP-2 respectively in the early activation of TGFβ and in the assembly of extracellular matrix proteins accumulated under the overproduction of TGFβ.

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1992

Enhanced IL-17A and IL-22 Production by Peripheral Blood Mononuclear Cells Distinguish Systemic Sclerosis from Healthy Individuals. Nicolò C. Brembilla[1], Marie-Elise Truchetet[2], Elisa Montanari[1], Yannick Allanore[3] and Carlo Chizzolini[1]. [1]Immunology & Allergy, Geneva University Hospital, Geneva, Switzerland, [2]Immunology Allergy, Geneva University Hospital, Geneva, Switzerland, [3]Rheumatology, Cochin Hospital, Paris, Paris, France

In systemic sclerosis (SSc) inappropriate T cell responses are thought to participate in initiating events ultimately leading to excessive extracellular matrix deposition and fibrosis. The pattern of cytokine produced distinguish T cell subsets with distinct functional capabilities and the pattern of chemokine receptor expressed at the surface of T cells participate to the code used for homing in peripheral tissues, including the skin. Aim of the present work was to assess whether T cells present in the peripheral blood (PB) of SSc patients could be distinguished from those of healthy controls in terms of cytokine production and whether the chemokine receptor expression on T cells could further predict their functional subset and homing capability.

PB mononuclear cells and clinical characteristics were obtained from 19 immunosuppressant agents naive SSc and 18 healthy controls (Ctrl) upon informed consent and approval by the ethical committee. Multiparameter cytofluorimetric analysis was performed to assess the surface expression of CD4, CD45RA, CCR4, CCR6, CCR10, CXCR3, and CD161 as well the intracellular accumulation of IL-17A, IL-22, IFN-gamma, and IL-4 upon activation by CD3/CD28 crosslinking in PB mononuclear cells at time 0 and after 7 days of culture. The results were stratified according to the presence of SSc, limited (lSSc) or diffuse disease (dSSc). The results of the various patient populations were compared using the Mann Whitney U test and correlations between variables computed using the Spearman r test.

SSc individuals had higher frequencies of CD4+ T cells and higher frequencies of IL-17A and IL-22 producing CD4+ T cells both at time 0 and upon 7 days of culture when compared to Ctrl. A significant increase in IL-4 production was observed only in the dSSc subset. The intracellular levels of IL-17A and IL-22 with the exclusion of IFN-gamma were tightly correlated indicating co-production by the same CD4+ T cell in SSc and not in Ctrl. When the expression level of various chemokine receptors on CD4+ T cells was taken into account, the production level of IL-17A was positively correlated with the lack of CXCR3 expression ($p = 0.0009$) and particularly so in the CXCR3-CCR6+ subset ($p = 0.0006$). Furthermore, the frequency of CD161+ CD4+ T cells was higher in SSc than in Ctrl.

Our results for the first time show that increased IL-17A is accompanied by IL-22 but not IFN-gamma production in SSc CD4+ T cells, thus stressing a preferential Th17 cell expansion in SSc. Furthermore, the production of these cytokines correlates with the expression levels of chemokine receptors important for skin homing, strongly indicating that they may participate to dysregulated matrix deposition at least in this target organ. These results provide a rationale for targeting IL-17 and the Th17 differentiation pathway as novel approaches to harness the clinical course of SSc.

Disclosure: N. C. Brembilla: None; **M.-E. Truchetet:** None; **E. Montanari:** None; **Y. Allanore:** None; **C. Chizzolini:** None.

1993

Gd Compounds Signaling through Toll-Like Receptors 4 and 7 in Normal Human Macrophages: Establishment of a Proinflammatory Phenotype and Implications for the Pathogenesis of Nephrogenic Systemic Fibrosis. Peter J. Wermuth[1] and Sergio A. Jimenez[2]. [1]Jefferson Institute of Molecular Medicine and Division of Connective Tissue Diseases, Thomas Jefferson University, Philadelphia, PA, [2]Thomas Jefferson Univ, Philadelphia, PA

Purpose: Nephrogenic Systemic Fibrosis (NSF) is a progressive and generalized disorder occurring in some patients with renal insufficiency following exposure to Gd based contrast agents (GdBCA). Previous studies showed that GdBCA induced, normal human macrophages to secrete increased levels of profibrotic and proinflammatory cytokines but the mechanisms involved are not known. Increased production of proinflammatory cytokines by macrophages is often triggered via signaling through Toll-like receptors (TLRs) or Nod-like receptors (NLRs), which recognize bacterial and viral components based on common molecular shapes. Here, we examined the hypothesis that GdBCAs can signal through one or more TLRs or NLRs.

Methods: Normal human differentiated macrophages were exposed to 50 mM Omniscan® or saline. RNA was isolated and examined employing Affymetrix human U133 2.0 Plus Microarrays and the data was analyzed by Volcano Plot and pathway analysis (DAVID; NIH). Human embryonic kidney 293 (HEK293) cells engineered to express one of seven different human TLRs (TLR2, 3, 4, 5, 7, 8 and 9) or two human NODs (NOD1 and 2) were exposed for 24 h to varying concentrations of Gd compounds Gd-DTPA, Dotarem®, MultiHance®, ProHance®, OptiMark®, Omniscan®, gadodiamide, Gd-EDTA or Gd-Citrate or to caldiamide, the chelate molecule present in Omniscan®. The signaling activity of each compound was evaluated on its ability to activate expression of a reporter gene under control of an NFκB promoter. Macrophages were pretreated with inhibitory and control peptides targeting the TLR downstream effector NFκB followed by exposure to Omniscan®. RNA was isolated and proinflammatory cytokine expression measured by real-time PCR.

Results: Pathway analysis of differential gene expression of normal differentiated human macrophages exposed to Omniscan® suggested the involvement of TLR signaling. Studies using engineered HEK293 cells each expressing one of a panel of human TLRs or NODs identified TLRs 4 and 7 mediating activation of the NFκB dependent reporter gene following exposure to 5 mM Omniscan® or gadodiamide. Subsequent testing in HEK293 cells expressing either TLR4 or TLR7 showed that Omniscan® and gadodiamide strongly activated TLR4 and TLR7-mediated reporter gene expression in a concentration dependent manner. No or miminal activity was observed for Gd-DTPA, Dotarem®, MultiHance®, ProHance®, OptiMark®, Gd-EDTA and Gd-citrate. Inhibition of activation of the TLR downstream effector molecule NFκB with specific inhibitory peptides in normal differentiated human macrophages strongly blocked Omniscan®-induced expression of proinflammatory cytokines.

Conclusions: We demonstrate that Omniscan® and gadodiamide induce expression of an NFκB dependent reporter via TLRs 4 and 7. Further, we demonstrate that blocking the TLR effector molecule NFκB greatly reduces the Omniscan® dependent expression of proinflammatory molecules in normal human macrophages. The ability of GdBCA to signal via TLRs resulting in increased production of proinflammatory/profibrotic cytokine and growth factor expression by normal human macrophages may be an important component in the pathogenesis of NSF.

Disclosure: P. J. Wermuth: GE Healthcare, 2; **S. A. Jimenez:** GE Healthcare, 2.

1994

Genome-Wide Association Study in Systemic Sclerosis. Yannick Allanore[5], Mohammad Saad[2], Philippe Dieudé[4], Catherine Boileau[1], Maria Martinez[3] and GENESYS Consortium. [1]Biochimie A. Paré Hospital, Université VSQ, Boulogne, France, [2]INSERM U563 Université Paul Sabatier, Toulouse, France, [3]NSERM U563 Université Paul Sabatier, Toulouse, France, [4]Rhumatologie, Inserm u699, Bichat, Paris Diderot Universite, France, [5]Université Paris Descarte, Rhumatologie A, INSERM U781, Paris, Paris, France

Systemic sclerosis (SSc) is an orphan multi-organ disease affecting the immune system, the microvascular network and the connective tissue. SSc leads to major disability and premature death. Epidemiological data suggest a complex genetic etiology.

To dissect genetic susceptibility to SSc we have performed a genome-wide association study in 654 SSc patients of French Caucasian origin from the GENESYS study, and 2,543 French controls (subjects without SSc from GENESYS project and neurologically healthy subjects from the Three-City cohort- Lambert et al, Nat Genet. 2009;41:1094–9). Subjects were genotyped using the Illumina Human 610 QUAD bead chip. The final post-QC discovery (stage-1) sample comprised 564 SSc cases and 2,466 controls, and a total of 489,814 SNPs passed quality control criteria. Association was tested using logistic regression assuming additive genetic effects and adjusted for the two principal components to account for population substructure. The genome-wide association results revealed a number of SNPs with strong evidence ($P<10-5$) of association. Interestingly, in our discovery sample, stronger signals were detected for 6 non-HLA SNPs that spanned 5 distinct genomic loci. Two SNPs belong to a candidate gene previously reported associated to other autoimmune disease of high relevance with regards to SSc pathogenesis. Furthermore, the remaining 4 SNPs are located on 3 previously unreported putative SSc loci. 2 SNPs are close to genes coding for neuro-mediators and 1 SNP is close to a metabolic gene recently showed to deeply contribute to extra-cellular matrix remodeling. Follow-up and replication analysis (stage-2) of these promising and new association signals are under way in a second French/Italian/German/Eastern case-control sample (>1,750 SSc cases and 3,200 controls). Our preliminary GWAS results identified a tractable number of novel candidate genes for SSc that warrant further investigation. All top best associated SNPs will be reported in the meeting.

This work was supported by French, German and Italian research networks on systemic sclerosis and by ANR grant (Projet R08160KS), Association des Sclérodermies de France, Research grants from Institut Servier and Sanofi Aventis, France.

Disclosure: Y. Allanore: None; **M. Saad:** None; **P. Dieudé:** None; **C. Boileau:** None; **M. Martinez:** None; **GENESYS Consortium:** None.

1995

High Resolution Magnetic Resonance Imaging for the Assessment of Dermal Fibrosis in a Pre-Clinical Model of Scleroderma. Helen Jones[1], Emma Derrett-Smith[1], Chris P. Denton[1], David Abraham[1], George Bou-Gharios[2] and Po-Wah So[3]. [1]Centre for Rheumatology, UCL Medical School, [2]Kennedy Institute of Rheumatology, Imperial College London, [3]Pre-clinical Imaging Unit, Institute of Psychiatry, King's College London

Introduction: Scleroderma (Systemic Sclerosis, Ssc) is a heterogeneous chronic multisystem rheumatological disorder. A hallmark of the disease is excessive dermal and organ scarring. Dermal biopsies have been extensively used to evaluate the degree of scarring and development of fibrosis. This invasive technique only allows a 'snapshot' of one region of the skin. Here we used a pre-clinical model of scleroderma to assess the potential for applying non-invasive magnetic resonance imaging for the analysis of dermal fibrosis. We analysed structural changes in the skin of mice harbouring mutations which resulted in modulation of the TGFβ signalling pathways ($T\beta RII\Delta k^{fib}$ mice) by histological staining and high resolution magnetic resonance imaging (MRI) scans to detect and compare changes in skin architecture and composition.

Methods: Full-thickness dermal biopsies were taken from the dorsal region of adult mice and fixed in formalin. Samples were placed within a customised holder containing Fomblin Perfluorosolv PFS-1, positioned within a quadrature volume coil, and MRI performed on a 7 Tesla VMRIS scanner using a gradient echo MRI sequence with the following parameters: repetition time, 250ms; echo time, 2.5ms; field of view, 10 × 10mm; matrix size, 128 × 128; 40° flip angle and 14 consecutive transverse, 1mm thick slices (in plane resolution 78μm). Thickness of the dermis and panniculus adiposus were measured using Image J with 7 measurements, distributed across the image, for each sample. After scanning, samples were embedded in paraffin and serial sections (3 microns) were stained with H&E for routine histology and an extracellular matrix stain for the degree of fibrosis (Picrosirius red). Images were captured at 10x magnification. Thickness of the dermis and panniculus adiposus were measured using Axioskop software with at least 30 measurements, distributed across the length, for each sample.

Results: Histological staining allows easy identification of the dermal and hypodermal compartments, namely the dermis, panniculus adiposus, panniculus carnosus, subcutaneous loose connective tissue, and subcutaneous muscle. Comparison with the MRI images showed that high resolution MRI can also distinguish between dermis, panniculus adiposus, panniculus carnosus, subcutaneous loose connective tissue, and subcutaneous muscle. By gradient echo MRI dermis, panniculus carnosus, and muscle have higher signal intensities than panniculus adiposus and loose connective tissue.

Thickness measurements of dermis and panniculus adiposus are consistent between histological and MRI images, however a better correspondence is observed for dermis than panniculus adiposus. $T\beta RII\Delta k^{fib}$ mutant mice were found to have thicker dermis than wildtype mice ($p<0.01$), which is consistent with the known increase in collagen in the skin of the mutant mice. Interestingly, thickening of the dermis is also accompanied by a thickening of the underlying panniculus adiposus ($p<0.01$).

Conclusion: High resolution MRI scanning is a promising non-invasive technique for assessing dermal fibrosis that warrants further optimisation in pre-clinical models prior to translation into a clinical setting.

Disclosure: H. Jones: None; **E. Derrett-Smith:** None; **C. P. Denton:** None; **D. Abraham:** None; **G. Bou-Gharios:** None; **P.-W. So:** None.

1996

IL-6 Overexpression in Early dcSSc Associates with Poor Clinical Outcome and May Drive Fibrotic Response. Korsa Khan[1], Shiwen Xu[1], Christopher P. Denton[2] and Voon Ong[1]. [1]Center for Rheumatology and Connective Tissue Diseases, UCL Medical School, Royal Free Hospital, London, United Kingdom, [2]Royal Free Hospital, London, United Kingdom

Introduction: We previously reported that thrombocytosis may identify a subgroup of diffuse SSc with elevated IL-6 and a high modified Rodnan skin score (mRSS). In this study, we explore the predictive value of IL-6 overexpression in dcSSc and its potential role in driving fibrosis.

Method: Expression levels of IL-6 were examined with immunohistochemistry and Western blot analysis. Skin biopsies from patients with early dcSSc and thrombocytosis (n=10, mean platelet count: 472×10^9/L, mean disease duration, Mean ± SEM: 35 ± 9.5 months), established dcSSc (n=8, mean platelet count:293×10^9/L, mean disease duration:128 ± 22) and healthy controls (n=12) were used in this study. IL-6 ligand and receptor levels were measured in the supernatant from cultured SSc fibroblasts and their effect on collagen production was studied in normal fibroblasts stimulated with recombinant IL-6.

To explore the potential link between IL-6 levels and clinical outcome in dcSSc, serum IL-6 from 39 patients (74 % female) was quantified by ELISA. The cases were categorised into high IL-6 (≥10pg/ml) and low (<10pg/ml) cohorts. Association between IL-6 levels at presentation and mRSS at 36 month from disease onset was determined by Pearson's correlation. Mean difference of mRSS between the cohorts of IL-6 expression over the 36 month period was compared by Student t-test. Difference in survival between cohorts was examined using Kaplan-Meier methods.

Results: There was significantly greater dermal IL-6 expression in patients with early dcSSc and thrombocytosis than patients with established dcSSc. Prominent staining for IL-6 was associated with dermal vascular structures and mononuclear inflammatory infiltrate in 8/10 (80%) patients with early dcSSc and with fibroblastic staining. Moderate vascular expression for IL-6 was observed in 4/12(33%) controls. Similar expression pattern was observed in 2/8 (25%) patients with established dcSSc with faint staining for IL-6 in some dermal fibroblasts and inflammatory infiltrates.

IL-6 ligand and receptor levels were elevated in supernatant from SSc fibroblasts (n=3) by 17-fold and 13-fold (Densitometric Image Unit, DIU $p<0.05$) respectively. Collagen was upregulated by at least 7-fold in SSc fibroblasts and similar induction by recombinant IL-6 (20 ng/ml) was observed in normal fibroblasts (17.94 ± 3.41 vs 2.18 ± 1.85 DIU control, $p<0.05$). This was partially abrogated with neutralising antibody against IL-6 receptor (4.26 ± 2.07 DIU, $p<0.05$).

Interestingly, serum IL-6 level at presentation positively correlated with mRSS at 36 months follow-up in dcSSc cases with available data ($r=0.81$, $p<0.01$, n=16). There was a significant difference in mean mRSS between the two groups based upon IL-6 expression (10.9, 95% Confidence interval, 3.8, 18.2, $p<0.01$). Kaplan-Meier analysis showed that the 5-year survival was 93% and 81% in the group with low and high IL-6 levels respectively ($p=0.02$, log rank test).

Conclusions: These results confirm overexpression of IL-6 in selected

cases of dcSSc and support the utility of IL-6 as a surrogate marker for outcome. Our study also provides strong support for the potential benefit of targeting the IL-6 axis in some cases of early dcSSc.

Disclosure: K. Khan: None; **S. Xu:** None; **C. P. Denton:** None; **V. Ong:** None.

1997

Imatinib Mesylate and Rottlerin Abrogate Transforming Growth Factor-β Induction of Endothelial-to-Mesenchymal Transition in Primary Lung Endothelial Cells. Zhaodong Li and Sergio A. Jimenez. Jefferson Institute of Molecular Medicine, Thomas Jefferson Univ, Philadelphia, PA

Purpose: Tissue fibrosis, most prominent in the skin, lungs, and microvasculature, is the pathological hallmark of systemic sclerosis (SSc). The origin of the mesenchymal cells responsible for the tissue and vascular fibrosis in SSc has not been fully identified. Recent studies have shown that transdifferentiation of endothelial cells into myofibroblasts via endothelial-to-mesenchymal transition (EndoMT) may participate in the development of tissue fibrosis in various fibrotic diseases. Here we used small molecule kinase inhibitors to investigate the signaling pathways involved in TGF-β-induced EndoMT in murine pulmonary endothelial cells (EC) to identify potential therapeutic targets for the fibroproliferative vasculopathy characteristic of SSc.

Methods: Primary mouse pulmonary EC were isolated by immunomagnetic methods employing sequential anti-CD34 and anti-CD102 antibody selection. The induction of EndoMT was assessed by immunofluorescence and Western blot for α-smooth muscle actin (α-SMA) expression. Expression of the transcriptional repressor Snail-1 was examined by RT-PCR, Western blot of cell lysates and immunofluorescence staining of cultured cells. The signaling pathways involved were examined employing small molecule kinase inhibitors.

Results: 1) TGF-β1 induced α-SMA and type I collagen expression in primary pulmonary EC. The induction of α-SMA in pulmonary EC by TGF-β was mediated by a marked increase in Snail-1 expression, evidenced both at mRNA and protein levels. 2) The TGF-β-induced α-SMA and Snail-1 expression was abolished by treatment with either the c-Abl kinase inhibitor, imatinib mesylate or the PKC-δ inhibitor, rottlerin. Imatinib mesylate also inhibited Snail-1 mRNA expression (Figure) and α-SMA stress fiber organization. 3) The effects of imatinib mesylate and rottlerin were not mediated by PI-3 kinase or Smad-2 phosphorylation but were mediated by inhibition of GSK-3β serine 9 phosphorylation. 4) Inhibition of GSK-3β activity employing a potent and specific inhibitor (BIO) caused marked increase in α-SMA and Snail expression.

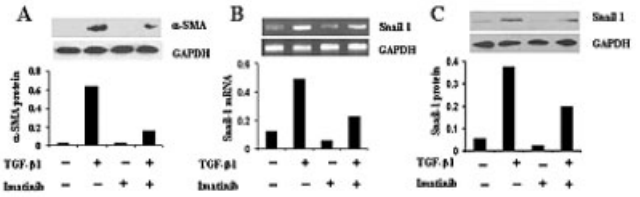

Figure. Inhibition of α-SMA and Snail-1 expression by imatinib mesylate.

Conclusion: These results indicate that c-Abl and PKC-δ participate in TGF-β-induced EndoMT in pulmonary EC. These effects are PI-3 kinase- and Smad2-ndependent and are mediated by GSK-3β. The results suggest that imatinib mesylate and rottlerin or similar inhibitor molecules may be effective therapeutic agents for SSc-associated tissue and vascular fibrosis and may also be effective in other fibroproliferative vasculopathies. Supported by NIH Grant RO1 AR055660 to SAJ.

Disclosure: Z. Li: None; **S. A. Jimenez:** None.

1998

In Systemic Sclerosis, Cooperation between B-Cells and Skin Fibroblasts Promotes Fibrogenic Cytokines and Collagen Production. Antoine Francois[3], Dominique Wachsmann[3], Jean Sibilia[1] and Jacques E. Gottenberg[2]. [1]Strasbourg Hospitals, Illkirch Graffenstaden, France, [2]Strasbourg Hospitals, Strasbourg, France, [3]Universite de Strasbourg, Illkirch Graffenstaden, France

Background: B-cells might play a role in the induction of skin and pulmonary fibrosis in systemic sclerosis. BAFF and APRIL, key cytokines for B-cell activation, are increased in serum and skin from patients with systemic sclerosis. The role of B-cells in fibrosis has been demonstrated in several studies (Novobrantseva, 2005, Komura, 2008) but the mechanisms implicated in B-cells and fibroblasts collaboration as well as the role of BAFF remains unclear. We therefore cocultivate B-cells and fibroblasts and assessed the release of soluble collagen and fibrogenic cytokines.

Methods: We performed cocultures of blood B cells and SSc skin fibroblasts stimulated with BAFF. IL-6, IL1β, TGF-β1, and CCL2 mRNA expression was determined by quantitative RT-PCR. Cytokine release was evaluated by ELISA. We also analysed the release of soluble collagen in cell culture supernatants using the Sircol Collagen Dye.

Summary of the Results: Coculture of skin fibroblasts isolated from SSc patients with blood B-cells induced IL-6 (35ng/mL), TGF-β1 (2000pg/mL) and CCL2 (6300pg/mL) release in culture supernatants. IL1β, which is a strong inducer of collagen, was not detected. Interestingly, BAFF stimulation increased IL-6 (315ng/mL) and CCL2 (17ng/mL) release in cell culture supernatants but TGF-β1 was not modified. We also showed that coculture of SSc fibroblasts with B-cells increased the production of soluble collagen by fibroblasts (from 25μg/mL for fibroblasts alone to 113μg/mL with B-cells) but this effect was not enhanced in presence of BAFF.

Conclusion: Taken together, these data suggest that interaction of B-cells with SSc fibroblasts promotes the production of fibrogenic cytokines and soluble collagen. We found that BAFF enhanced the release of cytokines but had no direct effect on collagen synthesis.

Disclosure: A. Francois: None; **D. Wachsmann:** None; **J. Sibilia:** None; **J. E. Gottenberg:** None.

1999

Inhibition of Glycogen Synthase Kinase (GSK)-3β Downregulates Collagen I Gene Expression in Normal and Scleroderma Fibroblasts and Abrogates the Profibrotic Effects of Transforming Growth Factor β (TGF-β). Jolanta Fertala and Sergio A. Jimenez. Jefferson Institute of Molecular Medicine, Thomas Jefferson University, Philadelphia, PA

Background and Purpose: GSK-3β is a ubiquitously expressed, highly conserved serine/threonine protein kinase which phosphorylates numerous substrates including enzymes and transcription factors and it is a core component of many important cell signaling pathways. Recently, GSK-3 has emerged as an important participant in wound healing and fibrosis. In particular, it has been shown that mice harboring a fibroblast-specific deletion of GSK-3β displayed accelerated wound closure, increased fibrogenesis, and excessive scarring. Fibroblasts isolated from those mice showed increased expression of a-smooth muscle actin and contraction of extracellular matrix. Thus, these results suggested that the presence of the active GSK-3 played a crucial role in maintaining physiological levels of extracellular matrix proteins and normal wound healing. The specific way in which GSK-3 participates in regulation of fibrosis is currently not well understood. Here, we studied the effects of GSK-3β activity modulation on the expression of COL1A1 in human dermal fibroblasts derived from patients with systemic sclerosis (SSc). Thus, the fundamental purpose of this study was to define whether GSK-3 should be considered a target to treat SSc and other fibrotic disorders.

Methods: Normal and SSc dermal fibroblasts were treated with various concentrations of two different GSK-3β inhibitors: (i) Inhibitor XV (EMD4 Biosciences) and (ii) inhibitor IX (BIO, Cayman Chemical). In addition, normal dermal fibroblasts treated with TGF-β were also analyzed. Following treatment with the GSK-3 inhibitors the expression of collagen I at protein and mRNA levels was analyzed by Western blot assays and RT-PCR, respectively.

Results: Quantitative Western blot assays demonstrated that, in comparison to non-treated cells, both normal and SSc dermal fibroblasts cultured in the presence of either GSK-3β inhibitor produced significantly less collagen I. Furthermore, GSK-3 inhibitors also abrogated the stimulation of COL1A1 expression induced by TGF-β. A similar decrease was also observed at the level of expression of COL1A1.

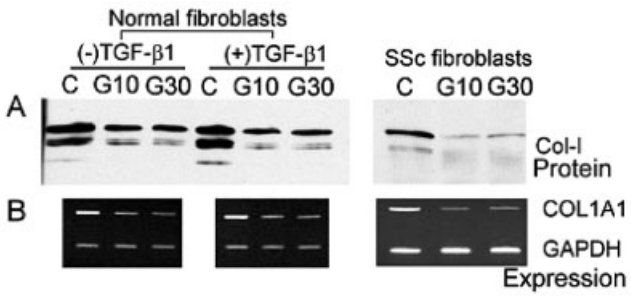

Figure. Analysis of expression of collagen I in normal and scleroderma fibroblasts treated with a GSK-3 inhibitor.

Conclusion: These data demonstrate that inhibition of GSK-3β activity results in a significant decrease in the expression and production of collagen I. These data are in contrast with the previously published study demonstrating that conditional GSK-3 knock-out in mice was associated with accelerated fibrosis. Our observation that inhibiting GSK-3 activity in SSc fibroblasts is associated with a substantial decrease of production of collagen I suggests that this enzyme may be a potential target for treatment of SSc and other fibrotic disorders.

Disclosure: J. Fertala: None; **S. A. Jimenez:** None.

2000

Insights into the Pathogenesis of Systemic Sclerosis Vasculopathy Based on Gene Expression Profile of Endothelial Cells Issued from Progenitors. Jerome Avouac[5], Nicolas Cagnard[1], Jorg H. W. Distler[6], Yoland Schoindre[2], Barbara Ruiz[2], Catherine Boileau[2], Gilles Chiocchia[3] and Yannick Allanore[4]. [1]INSERM U567, Cochin Hospital, APHP, Paris, France, [2]INSERM U781, Necker Hospital, Paris, France, [3]NSERM U567, Cochin Hospital, APHP, Paris, France, [4]Paris Descartes University, Rheumatology A Department, Cochin Hospital, APHP, Paris and INSERM U781, Necker Hospital, Paris, France, [5]Paris Descartes University, Rheumatology ADdepartment, Cochin Hospital, APHP, Paris and INSERM U781, Necker Hospital, [6]University of Erlangen, Erlangen, Germany

Objective: To determine the pattern of gene expression in endothelial cells (ECs) derived from late outgrowth endothelial progenitor cells (EPCs), in basal conditions and after hypoxic exposure, in patients with systemic sclerosis (SSc).

Methods: Late outgrowth EPCs were isolated from the peripheral blood of 10 SSc patients (5 limited and 5 diffuse cutaneous subset) and 5 healthy controls matched for age and sex. Total RNA was extracted and amplified from these cells in basal conditions and after 6 hours of hypoxic exposure. Affymetrix Human Genome HGU133 plus 2.0 Array microarray were used. The data were analyzed in the GeneSpring program, and potential pathways were identified with the Ingenuity software. Validation of genes of interest was performed by quantitative RT-PCR. Protein expression of identified mediators was then assessed in SSc and control skin sections by immunohistochemistry.

Results: Signals from 92 probe sets (33 known genes) were different from controls in basal conditions. The largest group of transcripts included 9 genes related to cell-to-cell interaction. Within this group, was identified in SSc-EPC-derived cells a downregulation of tumor necrosis factor ligand superfamily member 10 (TNFSF10, odds ratio, OR: 0.5, $p=0.04$), which prevents the interaction between PBMCs and ECs. Signals from 188 probe sets (53 known genes) were different from controls after hypoxic exposure. The largest group of transcripts included 5 genes involved in the regulation of vascular remodeling. Within this group, was identified in SSc-EPC-derived cells a downregulation of homeobox gene HOXA9 (OR: 0.5, $p=0.02$), which play a role in the activation of ECs. A respective 2 and 1.5-fold downregulation of TNFSF10 mRNA levels in basal conditions and HOXA9 mRNA levels after hypoxic exposure in SSc-EPC-derived cells further validated these observations. In SSc and control skin sections, no differential expression of TNFSF10 and HOXA9 was found.

Signals from 221 and 307 probe sets (75 and 79 known genes) were different between patients with the diffuse and the limited cutaneous subset, in basal conditions and after hypoxic exposure respectively. Included among these were transcripts for a group related to inflammatory response. In particular, was identified after hypoxic exposure, in EPC-derived cells from patients with diffuse SSc, an upregulation of tumor necrosis factor alpha-induced protein-3 (TNFAIP3, OR:1.5 $p=0.04$) and prostaglandin-endoperoxide synthase-2 (PTGS2, OR:1.75, $p=0.02$). Quantitative RT-PCR analysis confirmed the upregulation of these two genes (respectively 1.5 and 2-fold). TNFAIP3 and PTGS2 were also overexpressed in the skin of patients with the diffuse cutaneous subset.

Conclusion: Our data reveal important gene expression changes in EPC-derived cells from SSc patients, characterized by a proadhesive and activated profile. Our results also support a proinflammatory profile of these cells in the diffuse cutaneous subset. These results emphasize the presence of an endothelial signature in SSc and point to novel mediators in this disease that warrant more in-depth exploration to increase the understanding of the pathogenesis of this incurable disease.

Disclosure: J. Avouac: None; **N. Cagnard:** None; **J. H. W. Distler:** None; **Y. Schoindre:** None; **B. Ruiz:** None; **C. Boileau:** None; **G. Chiocchia:** None; **Y. Allanore:** None.

2001

PDGF Receptor as Therapeutic and Diagnostic Target in Systemic Sclerosis. Gianluca Moroncini[4], Antonella Grieco[5], Chiara Paolini[5], Giulia Nacci[3], Massimiliano Cuccioloni[2], Matteo Mozzicafreddo[2], Cecilia Tonnini[5], Katarzyna Pozniak[5], Silvia Svegliati[5], Mauro Angeletti[2], Enrico Avvedimento[1], Ada Funaro[3] and Armando Gabrielli[5]. [1]Dipartimento di Biologia e Patologia Molecolare e Cellulare, Università Federico II, Napoli, Italy, [2]Dipartimento di Biologia Molecolare, Cellulare e Animale, Università di Camerino, Italy, [3]Dipartimento di Genetica, Biologia e Biochimica, Università di Torino, Italy, [4]Dipartimento di Scienze Mediche e Chirurgiche, Clinica Medica, Università Politecnica delle Marche, Ancona, Italy, [5]Dipartimento di Scienze Mediche e Chirurgiche, Clinica Medica, Università Politecnica delle Marche, Ancona, Italy

Background: Systemic sclerosis or scleroderma (SSc) is a disease characterized by fibrosis of skin and visceral organs. We have provided evidence that the serum of SSc patients contains stimulatory auto-antibodies (auto-abs) directed to the PDGF receptor (PDGFR) that elicit Ha Ras-ERK 1/2 signaling and collagen production in normal human fibroblasts *in vitro* (Baroni SS et al, NEJM 2006). A recent study (Olson LE, Soriano P, Dev Cell 2009) has confirmed the central role of increased PDGFR activation and signaling in driving systemic fibrosis *in vivo* in transgenic mice.

Objectives: To identify the epitopes of PDGFR extracellular domains bound by stimulatory auto-abs. This information will be used to generate i) PDGFR selective inhibitors and ii) binding assays for detection of functional auto-abs in serum.

Methods and Results: IgG-positive memory B cells obtained from peripheral blood of SSc patients were immortalized by EBV infection. Supernatants of individual lymphocyte clones were screened by immunofluorescence and flow cytometry for the ability to react selectively with F alpha cells (mouse fibroblasts expressing the human PDGFR alpha), but not with F−/− cells (mock-transfected mouse fibroblasts). Positive clones were further screened for the production of antibodies stimulating reactive oxygen species (ROS) generation in normal human fibroblasts *in vitro*. Positive clones were expanded in serum-free medium, IgG were purified from supernatants and tested to confirm both binding and biological activity on fibroblasts. mRNA was obtained from such positive B cell clones for sequencing and cloning of antibody variable regions into a human IgG expression vector. Human IgG constructs were expressed in CHO cells, recombinant (rec.) monoclonal antibodies (mAbs) were purified from medium and tested by immunoprecipitation and stimulation experiments. These rec. monoclonal human IgG showed different extents of PDGFR binding and stimulation. Few mAbs displayed the properties identified in total IgG pools purified from serum of SSc patients, since they bound to PDGFR and induced ROS, p-ERK and type I collagen gene expression in normal human fibroblasts. Molecular docking simulation indicated that the PDGFR epitopes bound by stimulatory mAbs differ from those of non-biologically active mAbs. Epitope mapping was confirmed by binding competition experiments using a rec. PDGFR immobilized onto a biosensor. A peptide library is under construction to further define the map of PDGFR epitopes targeted by the different mAbs.

Conclusions: We identified the specific epitopes bound by functional PDGFR auto-abs that trigger PDGFR signaling. This information is shedding light on the structure of active PDGFR domains, on SSc pathogenesis, and can be used to devise new therapeutic strategies to block PDGFR signaling and, specifically, the progression of SSc. Moreover, synthetic polypeptides corresponding to these functional PDGFR domains will be employed to selectively detect stimulatory auto-abs in serum, possibly implicated in the early phases of SSc pathogenesis.

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2002

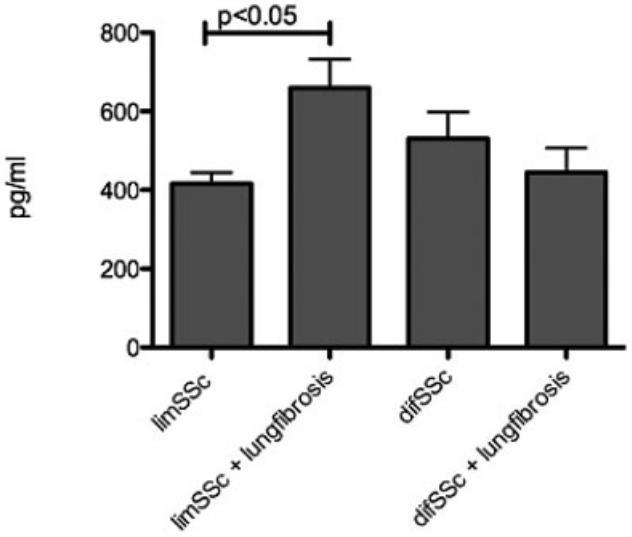
Proteomic Analysis of Systemic Sclerosis Serum Identifies the Toll-Like Receptor Agonists S100A8/A9 as a Novel Possible Pathogenic Marker. Lenny van Bon[3], Arnoud Loof[3], Helmut Wittkowski[1], Waander van Heerde[3], Madelon Vonk[3], Johannes Roth[1], Wim B. Van Den Berg[2], Peter van Lent[3] and Timothy Radstake[3]. [1]Interdisciplinary Centre for Clinical Research University of Muenster, [2]Radboud Univ Nijmegen Med Cntr, Nijmegen, The Netherlands, [3]Radboud University Medical Centre Nijmegen, The Netherlands

Background: Systemic sclerosis (SSc) is an autoimmune disease characterized by fibrosis of the skin and the internal organs. The etiology is still unknown but prominent features are vascular injury and chronic inflammation resulting in fibrosis. Except for anticentromere and anti-topoisomerase I antibodies there are no markers available that predict SSc susceptibility and/or prognosis. This study is the first study that exploits a proteome-wide profiling to identify new targets in the pathogenesis of SSc.

Method: 40 SSc patients were included for initial proteomic identification. Patients were stratified as having diffuse SSc (dSSc) (n= 19) or limited SSc (lSSc) (n=21) according to the extent of skin involvement. As controls 20 healthy donors were included. Blood was drawn and serum was stored before analyzing with the SELDI-TOF-MS. In the first run 10 difSSc patients, 10 limSSc patients and 10 healthy controls were measured as a training set. The rest of the samples were then use as a validation of the training results. SELDI-TOF-MS technology consists of three major components: the ProteinChip array, a mass spectrometer and the data analysis software. For replication a cohort compromising 30 difSSc patients and 60 limSSc was available.

Results: Analysis revealed a list of 29 masspeaks of interest of which 21 could be predicted using Tagident. Six peaks were increased in difSSc and three peaks in limSSc, 18 peaks were increased in both disease subtypes. One of the main significant peaks was S100A8. Since accumulating evidence points to a crucial role of toll like receptors in SSc, and S100A8 is reported to ne an endogenous TLR ligand, we next aimed to replicate the increased expression of S100A8. Further stratification for SSc disease phenotype reveals it to be increased solely in limSSc patients with lungfibrosis. This finding is replicated with an ELISA in 60 limSSc patients S100A8/A9 being 415 pg/ml in limSSc without lungfibrosis and 659 pg/ml in limSSc with lungfibrosis ($p<0.05$) (fig 1). Futhermore we show an increased presence of S100A8 in SSc skin sections.

Conclusion: This is the first study identifying new targets in SSc using proteome wide profiling in serum. S100A8 revealed to be increased in limSSc patients with lungfibrosis specifically. As S100A8 is an important protein in inflammatory processes it is interesting to further investigate its contribution to the pathogenesis of SSc and more specifically lung fibrosis.



Disclosure: L. van Bon: None; **A. Loof:** None; **H. Wittkowski:** None; **W. van Heerde:** None; **M. Vonk:** None; **J. Roth:** None; **W. B. Van Den Berg:** None; **P. van Lent:** None; **T. Radstake:** None.

2003

Role of Agonistic Autoantibodies Directed to the Angiotensin II Type 1 and the Endothelin-1 Type A Receptors in Systemic Sclerosis. Angela Kill[2], Jeannine Günther[2], Mike Oliver Becker[1], Gerd-Rüdiger Burmester[1] and Gabriela Riemekasten[1]. [1]Charité Berlin, Berlin, Germany, [2]Charité/DRFZ, Berlin, Germany

Background: In addition to their vasoconstrictive functions, angiotensin II and endothelin-1 have been shown to play an important role in vascular inflammation. We have identified autoantibodies against the angiotensin II type 1 receptor (anti-AT_1R- autoantibodies) and the endothelin-1 type A receptor (anti-ET_AR-autoantibodies) in patients with systemic sclerosis (SSc). The presence of these autoantibodies is predictive for a higher degree of pulmonary and cutaneous fibrosis as well as for a higher degree of mortality and the development of pulmonary arterial hypertension (PAH) in SSc.

Objectives: To analyze the role of anti-AT_1R- and anti-ET_AR-autoantibodies on the regulation of the pro-inflammatory mediator interleukin-8 (IL-8) in endothelial cells and collagen-1 production in human fibroblasts.

Methods: Using the human endothelial cell line human microvascular endothelial cells-1 (HMEC-1), we analyzed *in vitro* the effect of anti-AT_1R- and anti-ET_AR-autoantibodies on RNA and protein expression levels of IL-8. Collagen-1 production was measured using immunocytochemistry on human dermal fibroblasts of healthy donors. Cells were treated with immunoglobulin G (IgG) containing anti-AT_1R- and anti-ET_AR-autoantibodies. In some experiments receptors were blocked prior to treatment and IgG of healthy donors served as a negative control.

Results: IgG from patients with SSc upregulated the expression of IL-8 in endothelial cells compared to negative control on the RNA level and expression of IL-8 was verified by analysis on protein level expression using sandwich ELISA. These effects were partly blocked through specific antagonism of the angiotensin II type 1 receptor and/or the endothelin-1 type A receptor. Collagen-1 production was elevated as shown by immunocytochemistry compared to negative control treatment and receptor antagonism.

Conclusions: Our findings suggest a role of the anti-AT_1R- and anti-ET_AR-autoantibodies in the regulation of the inflammatory chemokine IL-8 mediated by the angiotensin II type 1 receptor and the endothelin-1 type A receptor. Furthermore the production of collagen-1 is regulated upon treatment of fibroblasts with anti-AT_1R- and anti-ET_AR-autoantibodies. Anti-AT_1R- and anti-ET_AR-autoantibodies thus might play a role in vascular inflammation and fibrosis of SSc.

Disclosure: A. Kill: None; **J. Günther:** None; **M. O. Becker:** None; **G.-R. Burmester:** None; **G. Riemekasten:** None.

2004

Skewed X-Chromosomal Inactivation Impacts T Regulatory Cell Function in Systemic Sclerosis. Jasper Broen[4], Ingrid Wolvers-Tettero[2], Lenny Geurts-van Bon[4], Madelon Vonk[4], Marieke Coenen[3], Robert A. Lafyatis[1], Timothy Radstake[4] and Anton Langerak[2]. [1]Boston University School of Medicine, Arlington, MA, [2]Department of Immunology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands, [3]Radboud University Medical Center, Dept. of Human Genetics, Nijmegen, Netherlands, [4]Radboud University Medical Center, Dept. of Rheumatology, Nijmegen, Netherlands

Objectives: To investigate the role of × chromosomal inactivation (XCI) in systemic sclerosis and its effects on Foxp3 expression in T regulatory cells.

Methods: A total of 217 female SSc patients and 107 female healthy controls were included. From these subjects DNA was isolated from total PBMCs, plasmacytoid dendritic cells, T cells, B cells, myeloid dendritic cells and monocytes after magnetic bead separation. All samples were assessed for skewed XCI patterns with the HUMARA assay. Outcome was assessed with linear regression. Next, CD4+CD25+ cells were isolated and intracellular Foxp3 expression was assessed by flowcytometry.

Results: Skewing is not associated with increased age in SSc, in contrast to the controlpopulation ($r=0.45$, $P<0.0001$). Taking this into account, we found a significantly higher frequency of skewed XCI in SSc patients ($P=0.001$) compared to controls. No difference in skewing was observed between the immune cell subsets. In addition, we found a higher concentration of Foxp3+ cells, exhibiting a lower Foxp3 MFI in the SSc patients with profound XCI skewing (both $P<0.001$), associated with less efficient suppressive activity ($P=0.012$).

Conclusions: Skewed XCI plays a role in susceptibility to SSc, is not restricted and influences Foxp3 expression and suppressive capacity of Tregs.

Disclosure: J. Broen: None; **I. Wolvers-Tettero:** None; **L. Geurts-van Bon:** None; **M. Vonk:** None; **M. Coenen:** None; **R. A. Lafyatis:** None; **T. Radstake:** None; **A. Langerak:** None.

2005

Structural and Vasomotor Dysfunction in the Thoracic and Pulmonary Vessels of the Tight-Skin 1 (Tsk-1/$^+$) Mouse: Role of Endogenous Nitric Oxide. Audrey Dooley[1], Emma C. Derrett-Smith[1], Xu Shiwen[1], Nelson N. Orie[2], Korsa Khan[1], Christopher P. Denton[4], Lucie Clapp[2], Richard Bruckdorfer[3] and David Abraham[5]. [1]Center for Rheumatology and Connective Tissue Diseases, UCL Medical School, London, United Kingdom, [2]Centre for Pharmacology, UCL Medical School, Rayne Institute, London, United Kingdom, [3]Institute of Structural and Molecular Biology, UCL Medical School, London, United Kingdom, [4]Royal Free Hospital, London, United Kingdom, [5]University College London, London, United Kingdom

Background: Systemic sclerosis (SSc) is a disease that features excessive collagen overproduction, fibrosis, as well as large and small vessel dysfunction. Previously we have shown that nitric oxide (NO), an important physiological signalling molecule and vasodilator, has abnormal metabolism in the skin of SSc patients and in the scleroderma-like syndrome of the tight-skin 1 (Tsk-1/$^+$) mouse, an experimental model predisposed to the development of a connective tissue disease (CTD). The present study investigates contractile function and also the role of NO, in the thoracic aorta and pulmonary artery of the Tsk-1/$^+$ mouse.

Methods: Thoracic aortae and pulmonary arteries from heterozygous TSK-1/$^+$ mice (age: 4, 8, 12 months) were compared with pallid littermates as control. Histology was used to stain sections for collagen or elastin expression. Vessel wall structure was further assessed by EM microscopy, and soluble collagen quantified by Sircol assay. Vascular isometric tension measurements of contractile function were studied using an organ bath or small vessel myograph. Potassium chloride (KCL; 30 mM and 80 mM) or phenylephrine (PE; 1 nM–50 μM) agonists were used to induce vasoconstriction in endothelium-dependant or independent vascular rings. Vascular rings were also pre-incubated with L-NAME (100 μM), a non-specific NO synthase (NOS) inhibitor, or 1400W (5 μM), a specific inducible NOS inhibitor. The NO donor sodium nitroprusside (SNP; 1 nM–50 μM) was used to assess endothelial-independent relaxation.

Results: In Tsk-1/$^+$ thoracic aorta, using histological staining and EM microscopy we observed thickening of the aortic arch wall, disruption of the elastic fiber architecture, and elevated levels of collagen in the aortic adventitia. Aortic soluble collagen content was greater in the Tsk-1/$^+$ group compared to controls. Isometric tension measurement revealed that both KCL and PE-induced contractions were reduced in aortic Tsk-1/$^+$ vessels at all ages studied. PE-induced maximal responses (E_{max}) at 4 months were (Tsk-1/$^+$ 217.2 $\pm$ 6.3 mg; control 411.0 $\pm$ 10.1 mg), at 8 months (Tsk-1/$^+$ 322.5 $\pm$ 32.4 mg; control 618.1 $\pm$ 17.9 mg), and at 12 months (Tsk-1/$^+$ 319.4 $\pm$ 44.7 mg; control 576.2 $\pm$ 31.0 mg). Similarly, at 4 months in pulmonary Tsk-1/$^+$ vessels, PE-induced maximal responses were reduced. Inhibition of endogenous NO production in aortic control vessels, by either pre-treatment with L-NAME or removal of the endothelium, increased PE-induced contractions by 61% but had no significant effect in the aortic Tsk-1/$^+$ group, indicating reduced basal NO bioavailability. Pre-treatment with 1400W had no significant effect on either group. SNP-induced endothelium-independent relaxations, completely dilated PE-induced contraction of both control and Tsk-1/$^+$ aortas, indicating no difference in smooth muscle sensitivity to NO.

Conclusion: The pathogenesis of the Tsk-1/$^+$ mouse model of CTD exhibits vasomotor dysfunction of the thoracic aorta that could be associated with increased collagen deposition and reduced NO bioavailability.

Disclosure: A. Dooley: None; **E. C. Derrett-Smith:** None; **X. Shiwen:** None; **N. N. Orie:** None; **K. Khan:** None; **C. P. Denton:** None; **L. Clapp:** None; **R. Bruckdorfer:** None; **D. Abraham:** None.

2006

Th1 and Th17 Cytokine Signatures in Early Pediatric Localized Scleroderma. Kathryn S. Torok[3], Thaschawee Arkachaisri[1], Thomas A. Medsger[2] and Carol A. Feghali-Bostwick[4]. [1]KK Women's and Children's Hosp, Singapore, Singapore, [2]Univ of Pittsburgh, Pittsburgh, PA, [3]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [4]University of Pittsburgh, Pittsburgh, PA

Purpose: Pediatric localized scleroderma (LS) is an autoimmune disease characterized by fibrosis of skin and underlying tissues, including subcutaneous tissue, tendons, and muscles. Infiltration of the skin with T cells is a key feature in both LS and systemic sclerosis (SSc). Specifically, T-helper (Th) cell subsets and their associated cytokines have been identified as contributing to the pathogenesis of scleroderma. Previous studies in both SSc and LS support a primary Th2 response, but more recent reports implicate the Th17 subset and associated cytokines. This study was designed to evaluate serum cytokines representative of all three Th cell lineages (Th1, Th2, Th17) in active pediatric LS.

Methods: Serum samples from 71 pediatric LS patients and 49 healthy pediatric controls were obtained. All of the LS patients had active disease, defined as having new lesion(s), expanding lesion(s) and/or erythematous skin lesion(s), and were naive to systemic medications. Two independent luminex assays were performed to evaluate the Th1, Th2, and Th17 serum cytokine profiles. Statistical analysis was completed using Wilcoxon-rank sum tests and chi-square tests with a p-value <0.05 as significant.

Results: The ranks of the individual cytokines were not significantly different between LS patients and controls using Wilcoxon-rank sum tests. However, the p-value did trend toward significance ($p = 0.05 – 0.30$) with higher serum concentrations in the LS group for IL-1β, IL-6, IL-12p70, IL-17F, IL-22 and IFN-γ. Among LS patients with a greater than 10-fold increase in one or more cytokine compared with the upper IQR level for that cytokine in healthy controls, there were correlations between individual cytokines and disease duration. High levels of IL-12p70, IFN-γ, IL-1β, and IL-6 were significantly more frequently detected in LS patients with short disease duration (<24 months) compared with intermediate duration (24–48 months), who had elevated IL-17F and IL-22 levels, and those with long duration (>48 months), who had no elevated cytokine levels ($p<0.05$). Higher cytokine levels correlated with the presence of linear scleroderma, positive ANA, anti-ssDNA and anti-histone antibodies ($p<0.05$).

Conclusions: Th1 and Th17 related cytokines were elevated in the sera of pediatric LS patients with active disease with short to intermediate duration. Th1 associated cytokines appeared early and Th17 associated cytokines appeared later in disease course. Patients with greater elevations of these cytokines more often had linear LS, ss-DNA and anti-histone antibodies, all previously recognized predictors of more severe disease. Understanding and targeting the immune elements involved in the active early stages of LS is critical to designing novel therapies to prevent long-term complications such as thick fibrotic skin, loss of adipose tissue, joint contractures and limb-length discrepancies, which are associated with physical and psychological morbidity.

Disclosure: K. S. Torok: None; **T. Arkachaisri:** None; **T. A. Medsger:** None; **C. A. Feghali-Bostwick:** None.

2007

The Effect of Oxidative Stress on Protein Tyrosine Phosphatase 1B in Scleroderma Fibroblasts. Pei-Suen Tsou[5], Nadin N. Talia[6], Sonsoles Piera[2], Sergio A. Jimenez[1], James R. Seibold[3], Kristine Phillips[4] and Alisa E. Koch[7]. [1]Thomas Jefferson Univ, Philadelphia, PA, [2]Thomas Jefferson University, Philadelphia, PA, [3]University of Connecticut Health Center, Farmington, CT, [4]University of Michigan, Ann Arbor, MI, [5]University of Michigan Medical School, Ann Arbor, MI, [6]University of Michigan Medical School, [7]Unversity of Michigan, Ann Arbor, MI

Purpose: Skin fibrosis is a main characteristic of systemic sclerosis (SSc). Platelet-derived growth factor (PDGF) and its receptor (PDGFR) have been shown to play key roles in promoting fibrosis in SSc. Upon PDGF stimulation, the PDGFR is phosphorylated, and its downstream signaling pathways, including ERK1/2, are activated. The PDGFR is dephosphorylated by phosphatases, including protein tyrosine phosphatase 1B (PTP1B), and the signaling cascade is hence terminated. In addition, increased superoxide production is observed in SSc dermal fibroblasts compared to normal fibroblasts (NL). In this study we sought to determine whether the thiol-sensitive PTP1B is affected by oxidative stress in these cells, enhancing the ERK1/2 signaling pathway of PDGFR. The effect of the thiol antioxidant n-acetylcysteine (NAC) on PTP1B activity was also investigated.

Methods: SSc and NL fibroblasts were isolated from skin biopsies. Cells were stimulated with 30 ng/ml PDGF and phosphorylation of ERK1/2 as well as PTP1B levels were measured by Western blotting. A phosphate release assay was used to determine PTP1B activity. Superoxide was measured by dihydroethidium.

Results: Activation of PDGFR by PDGF resulted in phosphorylation of ERK1/2. In NL fibroblasts, ERK1/2 phosphorylation was maximal at 45 min (3 fold increase vs. unstimulated [US], $p<0.05$, $n=5$) and returned to baseline at 4 hr. In contrast, in SSc cells, ERK1/2 was significantly phosphorylated at 10 min and remained phosphorylated at 4 hr (2 fold increase vs. US, $p<0.05$). PDGF increased PTP1B protein expression significantly at 45 min and 2 hr in NL. In contrast, PTP1B expression in SSc fibroblasts remained the same, and at 45 min the level of PTP1B in NLs was significantly higher than that in SSc

($p<0.05$). PTP1B activities were 20.1 ± 2.7 and 11.9 ± 1.3 nmoles (phosphate released, $p<0.05$) in NL and SSc fibroblasts, respectively. In the presence of NAC, PTP1B activity was restored in SSc fibroblasts (from 11.9 ± 1.3 nmoles without NAC to 19.2 ± 2.1 nmoles with NAC, $p<0.05$). In contrast, the activity of PTP1B was unaffected with NAC treatment in NLs (20.1 ± 2.7 nmoles without NAC vs. 16.2 ± 0.4 nmoles with NAC, $p>0.05$). Superoxide was significantly higher in SSc than in NL dermal fibroblasts, and the level in SSc cells was reduced significantly after incubation with NAC ($p<0.05$).

Conclusions: The profile of ERK1/2 phosphorylation, which indicated PDGF-induced PDGFR activation, was different in NL and SSc dermal fibroblasts. The inability to dephosphorylate ERK1/2 in SSc fibroblasts suggests that the phosphatases that are responsible for ERK1/2 dephosphorylation are deficient in SSc. The ability to produce PTP1B after PDGF stimulation, and hence terminate PDGFR signaling, was hampered in SSc dermal fibroblasts. PTP1B activity was significantly inactivated in SSc fibroblasts, which may have resulted from higher levels of superoxide than in NL. NAC treatment both restored the low PTP1B activity and decreased superoxide levels in SSc dermal fibroblasts. Thus, we introduce a new class of proteins dysregulated in SSc. Our study also provides a novel molecular mechanism by which NAC therapy may act on these proteins to benefit SSc patients.

Disclosure: P.-S. Tsou: None; **N. N. Talia:** None; **S. Piera:** None; **S. A. Jimenez:** None; **J. R. Seibold:** None; **K. Phillips:** None; **A. E. Koch:** None.

2008

The Wnt Signalling Inhibitor Gene, WIF1, Expression Is Downregulated in Fibroblasts Derived from Systemic Sclerosis Patients by a Persistent Oxidative Stress. Silvia Svegliati[2], Giusi Marrone[3], Antonella Grieco[2], Tatiana Spadoni[2], Lucia De Gennaro[2], Gianluca Moroncini[2], Enrico Avvedimento[1] and Armando Gabrielli[2]. [1]Dipartimento di Biologia e Patologia Cellulare e Molecolare, Università Federico II, Napoli, Italy, [2]Dipartimento di Scienze Mediche e Chirurgiche, Università Politecnica delle Marche, Ancona, Italy, [3]Oncogenomic Center, NOGEC, CEINGE, Italy

Background: Systemic sclerosis is an autoimmune disease characterized by extensive fibrosis and vascular lesions. Primary fibroblasts derived from systemic sclerosis (SSc) patients contain high level of cytoplasmatic and peri-nuclear free radicals (ROS) and breaks in the genomic DNA.

Stimulatory IgG auto-antibodies to the PDGF receptor were identified in sera from systemic sclerosis patients. These autoantibodies were capable of converting normal fibroblasts into SSc-like cells inducing excessive oxygen species (ROS) production by activating membrane NADPH oxidase complex. Wnt family constitutes a large group of highly conserved glycoproteins that are implicated in developmental processes and recently in carcinogenesis, aging and fibrosis. Wnt signaling is tightly controlled by several groups of negative regulators that interfere either with receptor-ligand binding or with intracellular signaling.

Wnt inhibitor factor 1, WIF1, is frequently silenced in human cancer by DNA methylation. Recently, its inhibition has been associated to ageing of mesenchymal stem cells and fibrosis, induced by unrestrained Wnt signaling. In order to identify specific markers of the disease, we have decided to analyze WIF1expression in cells derived from patients affected by systemic sclerosis and explore the mechanism of WNT signaling regulation.

Materials and Methods: Human skin fibroblasts were obtained from punch biopsies taken from normal volunteers and from the involved skin of scleroderma patients. We have investigated WIF-1 expression by reverse transcription and quantitative real-time PCR. Total RNA isolation was performed with total RNA mini kit (BioRad) and reverse transcription PCR was performed using iScript cDNA synthesis kit from BioRad. Quantitative PCR was performed in triplicate with SYBR Green (Biorad).

Results: WIF gene expression was significantly down-regulated in cells derived from systemic sclerosis patients. Moreover, the gene was not methylated, as in breast cancer cells, and its expression was reactivated by inhibiting histone de-acetylase enzymes, trichostain (TSA). PDGF in 24 hours robustly stimulated WIF-1 expression and this effect was prevented by inhibiting NADPH oxidase. Prolonged oxidative stress induced by IgG SSc silenced WIF1 by triggering DNA damage. Inhibition of ATM kinase by the specific inhibitor KU-55933 rescued WIF expression in fibroblasts exposed to long term oxidative stress.

Conclusions: These data indicate that in SSc fibroblasts a persistent oxidative stress, triggered by PDGF or anti PDGF receptor autoantibodies, induce WIF-1 downregulation and possibly altered WNT signaling. Our data indicate that the ultimate cause of silencing WIF-1 is DNA damage.

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ACR Poster Session C
Vasculitis II
Wednesday, November 10, 2010, 9:00 AM–6:00 PM

2009

Alveolar Hemorrhage (AH) in ANCA-Associated Vasculitis: Characteristics and Prognostic Factors in 65 Patients. Alex M. Kostianovsky[2], Thomas Hauser[2], Christian Pagnoux[2], Pascal Cohen[2], Eric Daugas[3], Luc Mouthon[2], Jean-Francois Cordier[4] and Loic P. Guillevin[1]. [1]Hopital Cochin-Paris Univ, Paris, France, [2]Internal Medicine, Hopital Cochin, APHP, Universite Paris Descartes, Paris, France, [3]Nephrology, Assistance Publique de Paris, Paris, France, [4]Pulmonology, Hopsice Civils de Lyon, Lyon, France

AH can be a mild or a life-threatening sign of ANCA-associated vasculitis, but its prognostic impact and specific characteristics have not been determined. To do so, we retrospectively analyzed AH episodes that occurred, between 1991 and 2010, in patients with ANCA-associated vasculitis entered in the FVSG database.

Patients and Methods: We selected confirmed AH cases, as assessed by the presence of hemoptysis and ground-glass images on X-rays or CT scans and/or bloody bronchoalveolar lavage fluid. Renal insufficiency was defined as creatininemia >150 mmol/l. Severity criteria were: hypoxia, Hb decline >1 g/dl over 48 h after AH occurred and requiring mechanical ventilation.

Results: For the 65 cases (35 men and 30 women) analyzed, their mean age at the 1st AH episode was 53 years. ANCA-associated vasculitis diagnoses were: 55% Wegener's granulomatosis (WG), 34% microscopic polyangiitis (MPA) and 9% Churg–Strauss syndrome (CSS). Pre-AH hemoptysis occurred in 41 (63%) patients: 39% the week preceding, 29.3% 2–4 weeks before and 19.5% >1 month prior to AH diagnosis, which led to ANCA-associated vasculitis diagnosis for 45 (69.2%) patients. Among 10 (15.4%) patients (4 WG, 4 MPA, 2 CSS) requiring mechanical ventilation, 4 had hemoptysis previously. Twenty-three (35%) patients were hypoxic and 23 (35%) had major Hb decreases; 36 (55%) had concomitant renal insufficiency (pulmo-renal syndrome): 18 WG (51% of all WG) and 18 MPA (81% of all MPA). Paucimmune glomerulonephritis was seen in 31/33 kidney biopsies. Intriguingly, no CSS patient had renal impairment when AH occurred.

Treatments included a combination of corticosteroids and intravenous cyclophosphamide (CYC) for 55 (85%) patients; oral CYC was used in 5, methotrexate in 4 and plasma exchange in 7. Rituximab and remicade were prescribed to 1 patient each. Mean time between AH and treatment onset was 5.87 (range 0–60) days. Mean follow-up was 8.3 years (range 1 month–19 years). Follow-up information was not available for 8 patients. A total of 38 (58%) patients relapsed: 7 with AH and other organ involvement, 21 with non-AH manifestation(s) and 10 with AH alone. Three patients underwent kidney transplantation.

The 13 (20%) deaths (6 WG and 7 MPA) were attributed to: septic shock for 4, lung cancer for 2, and 1 each of the following: bladder cancer, AH, sudden death, hemorrhagic stroke, ARDS due to misplaced nasogastric tube and probably drug-related (methotrexate). Although 9/13 patients with pulmo-renal syndrome died, no death resulted directly from the initial AH.

Conclusion: These findings highlight the importance of recognizing premonitory hemoptysis as an early sign of AH in ANCA-associated vasculitides, since 63% of the cohort patients had bloody sputum before AH was diagnosed. Also, patients with AH and renal insufficiency have poorer survival prognoses. As demonstrated by the five-factor score, AH alone is not predictive poor prognosis; conversely, kidney involvement dictates a poor outcome.

Disclosure: A. M. Kostianovsky: None; **T. Hauser:** None; **C. Pagnoux:** None; **P. Cohen:** None; **E. Daugas:** None; **L. Mouthon:** None; **J.-F. Cordier:** None; **L. P. Guillevin:** None.

2010

Baseline Characteristics of Patients with Non-Infectious Mixed Cryoglobulinemia Vasculitis: Results from the French Nationwide CryoVas Survey. Benjamin Terrier[8], Isabelle Marie[9], Adeline Lacraz[2], David Launay[5], Emmanuelle Plaisier[11], Jean-Emmanuel Kahn[10], Luc de Saint-Martin[3], Fabrice Bonnet[2], Guillaume Le Guenno[4], Elisabeth Diot[12], Patricia Rullier[6], Raphaël Seror[1], Estabaliz Lazaro[2], Olivier Hermine[7], Jean-Marc Léger[8], Patricia Senet[11], Xavier Mariette[1] and Patrice Cacoub[8]. [1]Bicêtre, [2]Bordeaux, [3]Brest, [4]Clermont-Ferrand, [5]Lille, [6]Montpellier, [7]Necker, [8]Pitié-Salpéterière, [9]Rouen, [10]Suresnes, [11]Tenon, [12]Tours

Background: Hepatitis C virus infection is the main cause of mixed cryoglobulinemia vasculitis (CryoVas). Data are lacking regarding demographical, clinical and biological features of patients with non-infectious mixed CryoVas.

Objectives: To analyze the baseline features of patients with non-infectious mixed CryoVas included in the French CryoVas survey. The objective of this survey is to describe the presentation and evaluate efficacy and tolerance of treatments in patients with non-hepatitis C virus CryoVas, in the absence of large series and therapeutic guidelines.

Methods: Fifty-four French centres of Internal Medicine, Nephrology, Rheumatology, Hematology, Dermatology and Neurology from Universitary and general hospitals have included 211 patients with non-infectious mixed CryoVas diagnosed between January, 1995 and June, 2010. Demographical, clinical and biological data, as well as first line therapy, were assessed.

Results: Hundred and forty-five women and 60 men (sex ratio F/M 2.4), mean age 63.2 ± 14.6 years were included. Main causes of CryoVas included autoimmune disorders in 66 patients (31%) [mainly primary Sjögren syndrome in 56 and systemic lupus erythematosus in 4], and B-cell lymphoma in 44 (21%). Mixed CryoVas was essential in 101 patients (49%). At inclusion, clinical manifestations included purpura (74%), peripheral neuropathy (52%), glomerulonephritis (36%), Raynaud's phenomenon (27%), arthralgia/arthritis (41%), skin ulcers (17%), skin necrosis (14%), gastrointestinal (6%), central nervous system (2%) and pulmonary involvement (2%). Immunochemical characterization and quantification of cryoglobulinemia were available in 200 (95%) and 140 (66%), respectively. Cryoglobulinemia was type II in 175 patients (88%) and type III in 25 (12%). Median cryoglobulin level was 0.36 g/L (0.05–10.0), and median C3 and C4 complement levels were 0.82 (0.14–1.94) and 0.04 g/L (0.01–0.44). Histological confirmation of vasculitis was available in 74%.

Most patients (n=194) were treated and received as first-line therapy corticosteroids in 85% [median dose of 57.5 mg/day (5–180)], cyclophosphamide in 24%, rituximab in 19%, plasma exchange in 14% [median number of 9 (2–46)], and colchicine in 4%. Seventeen patients (8%) were not treated because of mild symptoms attributable to CryoVas (n=8), spontaneous remission without relapse (n=5), or because patients were lost to follow-up before starting therapy (n=3) or refused treatment (n=1).

Conclusion: Our study is the largest clinical and epidemiological survey describing the features of mixed cryoglobulinemia vasculitis to date. This provides interesting findings for further comparisons. The analysis of response to therapy will be helpful to determine the best therapeutic strategies.

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2011

Baseline Characteristics of Patients with Type I Monoclonal Cryoglobulinemia Vasculitis: Results from the French Nationwide CryoVas Survey. Benjamin Terrier[8], Isabelle Marie[9], Jean-Emmanuel Kahn[10], Guillaume Le Guenno[4], Alexandre Karras[5], Adeline Lacraz[2], Olivier Hermine[7], Luc de Saint-Martin[3], Elisabeth Diot[12], Philippe Modiano[6], Véronique Leblond[8], Patricia Senet[11], Jean-Marc Léger[8], Emmanuelle Plaisier[11], Xavier Mariette[1], David Saadoun[8] and Patrice Cacoub[8]. [1]Bicêtre, [2]Bordeaux, [3]Brest, [4]Clermont-Ferrand, [5]HEGP, [6]Lille, [7]Necker, [8]Pitié-Salpéterière, [9]Rouen, [10]Suresnes, [11]Tenon, [12]Tours

Objectives: To analyze the baseline clinical and biological features of patients with type I monoclonal cryoglobulinemia vasculitis (CryoVas) included in the French CryoVas survey. The objective of this survey is to describe the presentation and to evaluate efficacy and tolerance of treatments in patients with non-hepatitis C virus CryoVas.

Methods: Twenty-three French centers of Internal Medicine, Nephrology, Rheumatology, Hematology, Dermatology and Neurology from Universitary and general hospitals have included 51 patients with type I monoclonal CryoVas diagnosed between January, 1995 and June, 2010. Demographical, clinical and biological data, as well as first line therapy, were assessed.

Results: Twenty-seven women and 24 men (mean age: 66 ± 12 years) were included. B-cell lymphoproliferative disorders were present in all patients, including monoclonal gammopathy of unknown significance (n=25), Waldenström macroglobulinemia (n=9), multiple myeloma (n=6) and other low grade B-cell non Hodgkin lymphoma (n=11).

At inclusion, clinical manifestations of type I CryoVas included purpura (72%), peripheral neuropathy (45%), Raynaud's phenomenon (35%), skin necrosis (29%), arthralgia/arthritis (29%), glomerulonephritis (25%), skin ulcers (25%), livedo (8%), urticaria (6%), angioedema (2%) and nasal septal perforation (2%). Most patients had a severe clinical presentation as only 13 patients (25%) had mild to moderate manifestations (i.e. Raynaud's phenomenon, skin purpura without ulcers/necrosis, or sensory peripheral neuropathy). Median cryoglobulin level was 1.55 g/L (0.1–10.43), and median C3 and C4 complement levels were 0.87 (0.3–1.93) and 0.06 g/L (0.01–0.34). Histological confirmation of vasculitis was available in 71%.

Seventeen patients received specific chemotherapy of B-cell lymphoma. The remaining treated patients (n=28) received as first-line therapy corticosteroids in 89% [median dose of 60 mg/day (20–120)], rituximab in 20%, cyclophosphamide in 16% and plasma exchange in 12%. Only 6 patients were not treated because of mild symptoms attributable to CryoVas and absence of underlying malignant lymphoproliferative disorder.

Conclusion: Our study is the largest clinical and epidemiological survey describing the features of type I monoclonal cryoglobulinemia vasculitis to date. Type I CryoVas was always associated with B-cell lymphoproliferative disorders, including malignant B-cell lymphoma in almost 50% of cases. Cutaneous manifestations were the most frequent manifestations, and CryoVas presentation was considered as severe in 75% of cases.

Disclosure: B. Terrier: None; **I. Marie:** None; **J.-E. Kahn:** None; **G. Le Guenno:** None; **A. Karras:** None; **A. Lacraz:** None; **O. Hermine:** None; **L. de Saint-Martin:** None; **E. Diot:** None; **P. Modiano:** None; **V. Leblond:** None; **P. Senet:** None; **J.-M. Léger:** None; **E. Plaisier:** None; **X. Mariette:** None; **D. Saadoun:** None; **P. Cacoub:** Roche, 5.

2012

Circulating Markers of Vascular Injury in ANCA-Associated Vasculitis. Paul A. Monach[1], Ronald D. Snyder, Ulrich Specks, John H. Stone[8], David Cuthbertson, Linna Ding, Fernando C. Fervenza, Barri J. Fessler[10], Gary S. Hoffman[4], David Ikle, Cees G. M. Kallenberg[11], Carol A. Langford[3], Mark Mueller, Philip Seo[7], E. William St Clair[5], Robert Spiera[6], Nadia Tchao, Steven R. Ytterberg[9] and Peter A. Merkel[2]. [1]Boston University, Boston, MA, [2]Boston University School of Medicine, West Newton, MA, [3]Cleveland Clinic Foundation, Cleveland, OH, [4]Cleveland Clinic Foundation, Pepper Pike, OH, [5]Duke University Medical Center, Durham, NC, [6]Hospital for Special Surgery, New York, NY, [7]Johns Hopkins Bayview Medical Center, Baltimore, MD, [8]Massachusetts General Hospital, Sudbury, MA, [9]Mayo Clinic, Rochester, MN, [10]UAB Rheumatology, Birmingham, AL, [11]Univer Med Center Groningen, Groningen, The Netherlands

Background: There is a need for biomarkers associated with ANCA-associated vasculitis that are associated with disease activity, are useful in guiding clinical care, and reflect underlying pathophysiology. We investigated multiple markers of vascular injury and angiogenesis before and after induction of remission in a large clinical trial.

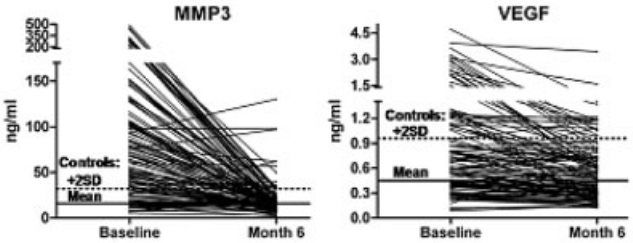
Methods: Subjects (n=127) enrolled in the Rituximab in ANCA-Associated Vasculitis (RAVE) trial were selected if they were in remission (BVAS/WG = 0) at 6 months after starting treatment with glucocorticoids and either rituximab or cyclophosphamide. Serum levels of E-selectin, ICAM-3, MMP1, MMP3, MMP9, P-selectin, thrombomodulin, and VEGF were measured by immunoassays (Meso Scale Diagnostics). ESR and CRP levels were used for comparison. Change in marker level from baseline to 6 months was analyzed by paired T-test. Marker levels in subjects with AAV were compared to marker levels in a group of 20 healthy controls (T-test). Correlations were calculated using Pearson coefficients.

Results: All subjects had highly active vasculitis (mean BVAS/WG score 8.6 +/− 3.2 SD) at baseline; 49% (n = 62) had active renal disease, and 27% (n = 34) had pulmonary hemorrhage. All subjects were clinically in remission (BVAS/WG = 0) at month 6; only 7 subjects were still receiving prednisone for minor flares that occurred before month 6. All markers levels except E-selectin and MMP9 were significantly elevated at baseline compared to controls, and all except E-selectin declined significantly by 6 months

(Table). MMP3 and VEGF, as well as ESR, were the only markers whose mean values at remission were no longer significantly elevated relative to controls (Table). MMP3 was both elevated at baseline and normal at 6 months in 70% of subjects; 18% showed such a trend for VEGF levels (Figure). There were modest correlations among VEGF, P-selectin, MMP1, MMP9, and ESR (maximum r = 0.48). MMP3 correlated with thrombomodulin (r = 0.40) but poorly with all other markers including ESR and CRP.

Marker	Active (Baseline) Mean ± SD	Remission (Month 6) Mean ± SD	Healthy Controls Mean ± SD
CRP	3.29 +/− 5.19*	1.25 +/− 2.20*†	Ref < 0.5
ESR	**44 +/− 31***	**18 +/− 16†**	**Ref < 20**
E-selectin	14.0 +/− 5.9	13.7 +/− 5.6	14.7 +/− 7.7
ICAM3	2.29 +/− 0.96*	1.88 +/− 0.76*†	0.55 +/− 0.30
MMP1	40.4 +/− 38.8*	22.8 +/− 17.2*†	10.6 +/− 6.9
MMP3	**99 +/− 95***	**22 +/− 32†**	**16 +/− 8.3**
MMP9	409 +/− 267	154 +/− 102*†	465 +/− 227
P-selectin	124 +/− 43*	107 +/− 34*†	87 +/− 24
Thrombomodulin	5.76 +/− 2.58*	5.18 +/− 2.10*†	2.60 +/− 0.69
VEGF	**0.93 +/− 0.85***	**0.56 +/− 0.41†**	**0.45 +/− 0.26**

*P<0.01 compared to healthy controls.
†P<0.001 compared to Baseline.
Markers that were elevated vs. controls at Baseline, reduced vs. Baseline at 6 months, and not significantly elevated vs. controls at 6 months are in bold.



Conclusions: Many markers of vascular injury and angiogenesis are elevated in highly-active ANCA-associated vasculitis and decline with treatment. Further study of MMP3 and VEGF is warranted to determine their clinical utility in combination with conventional markers of inflammation.

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2013

Clinical and Autoimmune Manifestations of Levamisole-Adulterated Cocaine Abuse. Korey R. Ullrich[3], Sterling G. West[4], Whitney High[5], Robert J. Koval[3], Erin Koval[5], Srinivas Bapoje[2] and Joel M. Hirsh[1]. [1]Denver Health Hospital Authority, Louisville, CO, [2]Denver Health Hospital Authority, [3]University of Colorado-Denver Medical School, Denver, CO, [4]University of Colorado-Denver Medical School, Aurora, CO, [5]University of Colorado-Denver Medical School

Background: Levamisole (LVS) has been detected as an adulterant in cocaine with increasing frequency, and has been implicated as a cause of neutropenia in cocaine users. Here we describe a novel syndrome of a cocaine-associated vasculopathy likely secondary to LVS, and suggest possible mechanisms to explain this association.

Materials and Methods: Patients presented consecutively between August 2009 and April 2010. We prospectively followed all patients on inpatient consultation and in the rheumatology clinic at our public health hospital. It was possible to perform human neutrophil elastase (HNE) testing on 2 patients.

Results: Patient characteristics are detailed in Table 1.

5 patients with a history of crack cocaine use presented with arthralgias and purpuric skin lesions affecting the ears and extremities. There was no definable systemic autoimmune process or evidence of infection. Rapid skin improvement occurred in all with cessation of cocaine. Patient 5 was treated with cyclophosphamide (CYC) and prednisone for suspected systemic vasculitis, but therapy was discontinued once the association with LVS was identified. Patient 2 initially received no immunosuppression, but was subsequently treated with CYC and steroids after developing ILD with features of desquamative interstitial pneumonia and hypersensitivity pneumonitis on biopsy.

Table 1: Patient characteristics

Patients	Skin Histology	ANCA	aPL	Levamisole	Outcome
1	Erythema nodosum-like nodules Patient refused biopsy of purpura	pANCA 1:5120 MPO 59 PR3 21 HNE positive	DRVVT IgM ACL	Positive	Purpura improved, but continues to have nodules. aPL improved, but ANCA remain elevated after 3 months.
2	Vascular thrombosis with rare perivascular neutrophil and karyorrhectic debris	cANCA 1:1280 MPO neg PR3 3.9 HNE positive	Hex	Negative (checked 8th hospital day)	ANCA and aPL improved. CYC and steroids for ILD.
3	Leukocytoclastic vasculitis with evidence of thrombosis	pANCA 1:640 MPO 56 PR3 34 HNE not done	Hex IgM ACL IgM B2-GP1	Not checked	Subsequently developed arthritis responsive to a short steroid course. Symptoms recurred with crack relapse. No follow-up labs.
4	Not performed	pANCA 1:1280 MPO 23 PR3 180 HNE not done	DRVVT Hex IgM ACL	Negative	Persistent arthralgias. aPL improving, but ANCA remain elevated after 2 months.
5	Leukocytoclastic vasculitis with prominent intravascular thrombosis	pANCA 1:10240 MPO 235 PR3 31.5 HNE not done	PTT prolonged IgM ACL	Positive	Lost to follow-up.

ACL: anticardiolipin antibodies; ANCA: antineutrophil cytoplasmic antibodies (N: < 1:20); aPL: antiphospholipid antibody assays; B2-GP1: beta-2 glycoprotein 1 antibody; cANCA: cytoplasmic ANCA; DRVVT: dilute Russell viper venom time; Hex: hexagonal phase phospholipid neutralization; HNE: human neutrophil elastase; MPO: myeloperoxidase antibodies (N: < 20); pANCA: perinuclear ANCA; PR3: proteinase 3 antibodies (N: < 3.5); PTT: partial thromboplastin time

Discussion: We have described a novel syndrome of a cocaine-associated cutaneous vasculopathy likely secondary to LVS. Cardinal features include antiphospholipid (aPL) positivity, polyspecific ANCA, the tendency for purpura to involve the ears, and a lack of evidence of systemic vasculitis. Interestingly, HNE reactivity was detected in both of the patients tested.

Several lines of evidence support the role of LVS in the pathogenesis of this syndrome, but the most noteworthy is the similarity to previous descriptions of levamisole-associated purpura of the ears in children with nephrotic syndrome. We suspect the pathogenesis of this syndrome is multifactorial, related to the vascular and immunogenic effects of cocaine, the presence of pro-thrombotic aPLs, the immunoenhancing properties of LVS, and the effects of LVS on peripheral sympathetic activity.

It is important for clinicians to recognize LVS exposure through adulterated cocaine as a cause of a cutaneous vasculopathy that can be mistaken for a systemic ANCA-associated vasculitis. Owing to its short half-life of approximately 5 hours LVS may be undetectable in the urine in as little as 48 hours after ingestion, so negative test results do not exclude the diagnosis. As demonstrated by our patients' diverse courses, the natural history of this disorder and the relationship to lung disease are unclear at this time. The role of immunosuppression also remains uncertain, but may be warranted in severe cases. Cessation of cocaine is necessary, and relapses of the syndrome do occur with ongoing use.

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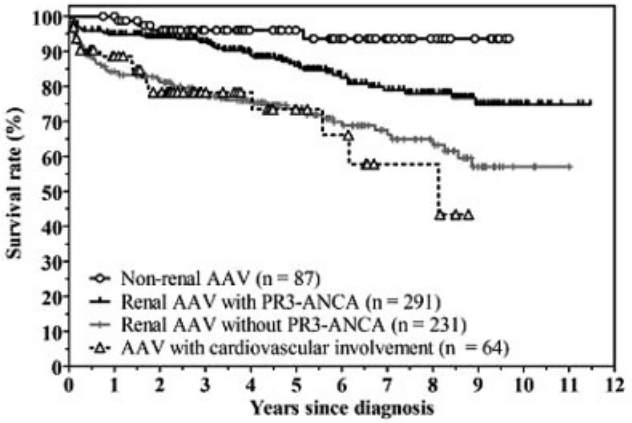
2014

Cluster Analysis and Clinical Phenotypes of ANCA-Associated Vasculitis. Alfred Mahr[3], Sandrine Katsahian[1], Loïc Guillevin[4], E. Christiaan Hagen[5], Peter Höglund[2], Peter A. Merkel[9], Christian Pagnoux[4], Niels Rasmussen[8], Kerstin Westman[6] and David Jayne[7]. [1]Clinical Epidemiology and Biostatistics, Hospital Saint-Louis, Paris, France, [2]Clinical Pharmacology, Department of Laboratory Medicine, Lund University, Lund, Sweden, [3]Internal Medicine, Hospital Cochin, Paris, Paris, France, [4]Internal Medicine, Hospital Cochin, Paris, France, [5]Internal Medicine, Meander Medical Center, Amersfoort, Netherlands, [6]Nephrology and Transplantation, Skane University Hospital Malmö, Lund University, Sweden, [7]Nephrology, Addenbrooke's Hospital, Cambridge, United Kingdom, [8]Otolaryngology, Rigshospitalet, Copenhagen, Denmark, [9]Rheumatology and Clinical Epidemiology Unit, Boston University School of Medicine, Boston, MA

Background: Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA) have widely overlapping clinical, serological, and histological features and are increasingly considered phenotypic variants of a single entity termed "ANCA-associated vasculitis (AAV)". Applying current definitions to distinguish between WG and MPA is sometimes problematic, and physicians' and researchers' disease classifications are heterogeneous. In addition, clinical practice and observational study findings suggest that WG and MPA clinical forms may not reflect the full range of AAV expressions. This study applied cluster analysis of a large combined cohort to explore the clinical phenotyping spectrum of AAV.

Methods: A large dataset of patients with newly diagnosed WG and MPA originally enrolled in 5 clinical trials on AAV was analyzed. Eleven baseline variables, including 9 clinical variables (age at diagnosis, sex, ear/nose/throat, ocular, lung, renal, neurological, skin and cardiovascular manifestations), PR3-ANCA, and MPO-ANCA, served as primary variables for the cluster analysis. The clinical relevance of the generated clusters was analyzed by describing their summary characteristics and their patient outcomes.

Results: The dataset comprised 673 subjects, diagnosed as follows: 396 (59%) WG and 281 (41%) MPA. Over a mean follow-up of 4.4 years, 136 (20%) patients died. The analyses yielded 4 distinct phenotypic classes: 87 (13%) non-renal AAV, 291 (43%) renal AAV with PR3-ANCA, 231 (34%) renal AAV without PR3-ANCA, and 64 (10%) AAV with cardiovascular involvement. The distribution of WG-diagnosed patients into those 4 respective classes was 95%, 79%, 18% and 64%. Those 4 classes represented highly distinct mortality rates ($P < 0.0001$, log-rank test) (Figure) and frequencies of patients relapsing ≥ 1 times (range: 20–53%; $P < 0.0001$, χ^2 test). Using 3 of the 9 variables (presence or absence of renal involvement, cardiovascular involvement, and PR3-ANCA), 651 of the 673 subjects (97%) were accurately allocated to 1 of the 4 classes.



Conclusion: Our cluster analysis results suggest that AAV encompasses 4 phenotypic classes: non-renal AAV, renal AAV with PR3-ANCA, renal AAV without PR3-ANCA and AAV with cardiovascular involvement, associated with different outcomes. Compared to the traditional WG–MPA separation, this new classification might better reflect the phenotypic groupings within the AAV spectrum and more accurately stratify patients into homogeneous disease groups for clinical, epidemiological and basic research.

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2015

CpG Stimulation of Neutrophils; a Possible Role for Bacterial DNA in Neutrophil-Mediated Pathogenesis of ANCA-Associated Vasculitis?
Henko Tadema[2], Cees G. M. Kallenberg[2], Sandra E. Thamerl[2], Nikola Lepse[2], Coen A. Stegeman[1] and Peter Heeringa[3]. [1]University Medical Center Groningen, Dept of Nephrology, Groningen, The Netherlands, [2]University Medical Center Groningen, Dept of Rheumatology and Clinical Immunology, Groningen, The Netherlands, [3]University Medical Center Groningen, Dept Pathology and Medical Biology, Groningen, The Netherlands

Background: Bacterial infections are often associated with autoimmunity, and CpG-motifs from bacterial DNA are suggested to play a role in the pathogenesis of anti-neutrophil cytoplasmic autoantibodies (ANCA) associated vasculitides. Binding of ANCA to autoantigens on pre-activated (primed) neutrophils results in full activation, causing the release of lytic enzymes and reactive oxygen species, thereby contributing to vascular inflammation. Here we investigated effects of CpG-motifs on ANCA-mediated neutrophil responses.

Methods: To study if CpG could prime neutrophils, we stimulated neutrophils from healthy controls and AAV patients *in vitro* with TNF-α, CpG, or both. Membrane expression of PR3 (mPR3), before and after stimulation, was analyzed by flowcytometry, and interleukin-8 release was measured by ELISA. Full activation of neutrophils in response to anti-PR3 and anti-MPO monoclonal antibodies after priming with CpG, TNF-α, or the combination, was studied by measuring superoxide production and degranulation.

Results: Both CpG and TNF-α induced increased mPR3 expression by neutrophils. Most donors have a $mPR3^-$ and a $mPR3^+$ subset within the neutrophils. TNF-α generally increased mPR3 expression on the $mPR3^+$ subset, whereas CpG increased mPR3 expression on both the $mPR3^-$ and $mPR3^+$ subsets. TNF-α primed neutrophils for full activation with anti-PR3 or anti-MPO antibodies, resulting in superoxide production, whereas CpG alone did not. Priming with the combination of TNF-α and CpG resulted in increased superoxide production and IL-8 release, compared to TNF-α priming. Furthermore, forward-sideward scatter plots of TNF+CpG primed and activated neutrophils indicated rapid degranulation, which was confirmed by preliminary data showing increased MPO release.

Conclusions: Although CpG-stimulation increased mPR3 levels on neutrophils, it did not prime neutrophils for full activation with anti-PR3 or anti-MPO antibodies. Preliminary data indicate that combined priming with TNF-α and CpG induced strong neutrophil responses including enhanced oxidative burst and degranulation. These data indicate that unmethylated CpG-motifs of bacterial origin may be of importance in ANCA-associated vasculitis, as it influences mPR3 expression and neutrophil responses. Bacterial DNA may prime neutrophils for rapid activation by ANCA in the presence of additional pro-inflammatory stimuli such as TNF-α, and may therefore contribute to the pathogenesis of ANCA-associated vasculitis.

Disclosure: H. Tadema: None; **C. G. M. Kallenberg:** None; **S. E. Thamerl:** None; **N. Lepse:** None; **C. A. Stegeman:** None; **P. Heeringa:** None.

2016

CXCL16 Antagonist Ameliorates the Progression of Vasculitis in McH5/lpr Mice.
Hitoshi Hasegawa[1], Jin Lei[2], Takuya Matsumoto[2], Masaki Yasukawa[2], Tatsuhiko Miyazaki[2] and Masato Nose[2]. [1]Ehime University Graduate School of Medicine, Toon, Ehime, Japan, [2]Ehime University Graduate School of Medicine

Background: Several chemokines associate with the initiation and progression of vasculitis. A recombinant congenic strain, McH5/lpr, was established by rearrangement of the genetic background of MRL/lpr mice by hybridization with C3H/lpr mice. McH5/lpr mice developed severe granulomatous polyarteritis but not glomerulonephritis, referred as a mouse model of periarteritis nodosa. CXCL16 is expressed at low levels by macrophages and vascular endothelial cells, but it undergoes marked up-regulation after stimulation of TNF-alpha and IFN-gamma. We investigated the expression of CXCL16 during the process of granulomatous polyarteritis in McH5/lpr mice and the therapeutic effect of CXCL16 antagonist (CXCL16-AT) on vasculitis.

Methods: The NH_2-terminally truncated CXCL16 analogs were converted to secreting forms by addition of signal sequence of IFN-beta, inserted into the pCXN2 expression vector and transfected into a non-metastatic fibroblastoid cell line, MRL/N-1. These transfectants were injected subcutaneously into McH5/lpr mice.

Summary of the Results: CXCL16 analogs (secreting form) truncated by 4 or more amino acid residues from N-terminus failed to induce chemotaxis by CXCR6-expression cells. Significantly increased expression of CXCL16 was induced mainly endothelial cells, epithelial cells, and infiltrating macrophages in the perivascular region at 8–10 weeks of age. CXCL16-AT-transfected MRL/N-1 cells were injected subcutaneously into McH5/lpr mice aged 8 wk (at the early stage of polyarteritis). CXCL16 antagonist was present in the serum of mice 2 wk after injection. After 8 weeks, inoculation of CXCL16-AT into McH5/lpr mice significantly reduced infiltrating mononuclear cells and destruction of the vessel wall associated with the formation of granulomatous lesions

compared with control mice. This seemed to be due to a marked reduction in macrophage and activated T-cell accumulation.However, there were no significant differences in serum anti-DNA antibodies and circulating immune complex at low levels among control, and CXCL16-AT-bearing McH5/lpr mice.

Conclusion: CXCL16 antagonist may provide a new therapeutic approach to vasculitis.

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2017

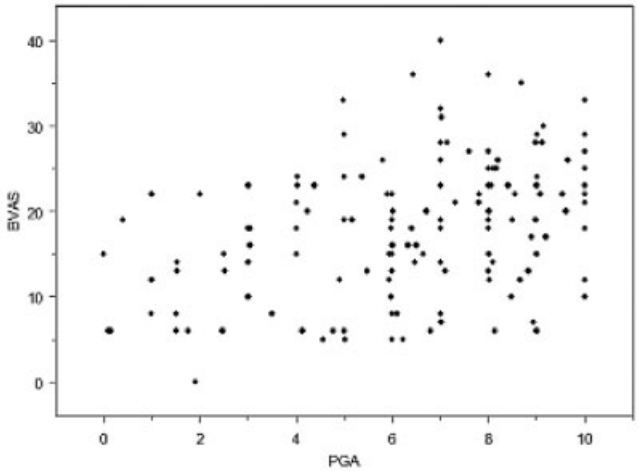
Describing the Performance of the Birmingham Vasculitis Activity Score (BVAS) at Diagnosis for Children with ANCA-Associated Vasculitis (AAV) in A Registry for Children with Vasculitis (ARChiVe). Kimberly A. Morishita[2], America Uribe[2], Jaime Guzman[2], Leslie S. Abramson[37], Matthew D. Adams[8], Susanne M. Benseler[31], Elizabeth B. Brooks[4], Sarah S. C. Campillo[22], Peter Chira[30], B. Anne Eberhard[28], Kaleo C. Ede[26], Aimee O. Hersh[33], Gloria C. Higgins[23], Adam Huber[18], Lisa F. Imundo[13], Rita S. Jerath[14], Susan Kim[11], Daniel J. Kingsbury[19], Marisa S. Klein-Gitelman[15], Suzanne C. Li[7], Daniel J. Lovell[12], Thomas G. Mason[21], Deborah K. McCurdy[20], Renee F. Modica[34], Lakshmi N. Moorthy[27], Eyal Muscal[1], Lorien A. Nassi[32], Kathleen M. O'Neil[24], Egla C. Rabinovich[17], Andreas O. Reiff[10], Margalit E. Rosenkranz[9], Kenneth N. Schikler[35], Anne M. Stevens[25], Mary B. Toth[6], Linda Wagner-Weiner[16], Dawn M. Wahezi[5], Andrew J. White[29], Amy L. Woodward[38], Andrew S. Zeft[36], David A. Cabral[3] and ARChiVe Investigators of CARRA. [1]Baylor College of Medicine, Houston, TX, [2]BC Children's Hospital, [3]BC Children's Hospital, Vancouver, BC, Canada, [4]Case Western, Beachwood, OH, [5]Children's Hospital at Montefiore, Bronx, NY, [6]Children's Hospital Med Ctr, Akron, OH, [7]Children's Hospital of Boston, Short Hills, NJ, [8]Children's Hospital of Michigan, Huntington Woods, MI, [9]Children's Hospital of Pittsburg, Pittsburgh, PA, [10]Childrens Hosp LA MS60, Los Angeles, CA, [11]Childrens Hospital Boston, Boston, MA, [12]Childrens Hospital Medical Center, Cincinnati, OH, [13]Childrens Hospital of NY, New York, NY, [14]Childrens Med Ctr Med Schl GA, Augusta, GA, [15]Childrens Mem Hosp/NW Univ, Chicago, IL, [16]Corner Children's Hospital, Chicago, IL, [17]Duke University Medical Center, Durham, NC, [18]IWK Health Centre, Halifax, NS, Canada, [19]Legacy Emanuel Children's Hosp, Portland, OR, [20]Mattel Children's UCLA, Los Angeles, CA, [21]Mayo Clinic Rochester, Rochester, MN, [22]Montreal Children's Hospital, Montreal, QC, Canada, [23]Nationwide Childrens Hosp, Columbus, OH, [24]OU Health Science Center, Oklahoma City, OK, [25]Pediatrics, U. of Washington, Seattle, WA, [26]Phoenix Children's Hospital, Phoenix, AZ, [27]Robert Wood Johnson Medical School, Metuchen, NJ, [28]Schneider Children's Hospital, New Hyde Park, NY, [29]St Louis Childrens Hosp, St Louis, MO, [30]Stanford Univ Schl of Med, Stanford, CA, [31]The Hospital for Sick Children, Toronto, ON, Canada, [32]TX Scottish Rite Hosp, Dallas, TX, [33]UCSF, San Francisco, CA, [34]University of Florida, Orlando, FL, [35]University of Louisville SOM, Louisville, KY, [36]University of Utah, Salt Lake City, UT, [37]University of Vermont, Morrisville, VT, [38]Vanderbilt Univ. School of Medicine, Nashville, TN

Background: There are no validated paediatric assessment tools for measuring disease activity in chronic vasculitis. The BVAS, a valid and reliable assessment tool for measuring disease activity in adults with vasculitis, may not necessarily capture the clinical features or components of disease activity assessment that might be unique to, or more characteristic of, the growing and developing child. In adult vasculitis, BVAS correlates highly (rho = 0.91) with physician's global assessment of disease activity (PGA).

Objectives: To describe the performance of BVAS applied at the time of diagnosis in children with AAV in relationship to PGA.

Methods: Eligible patients were those diagnosed since 2004 with an AAV, according to expert site rheumatologist (MD-diagnosis) at 37 ARChiVe centers. Data collection items in the registry included all elements of BVAS and a PGA for patients at the time of diagnosis. After BVAS items were extracted and individual patient scores calculated, the association between BVAS (version 3) and PGA scores was assessed using the Spearman rank correlation coefficient. The statistical analysis was performed using SPSS statistical software.

Results: 155 patients with an AAV were recruited into the ARChiVe cohort between January 2004 and March 2010. Five patients were excluded from analysis because data was insufficient to score BVAS. The MD-diagnosis of the remaining 150 patients were Wegener's granulomatosis (n = 98), microscopic polyangiitis (n = 25), Churg-Strauss syndrome (n = 3), ANCA-positive pauci-immune glomerulonephritis (n = 5), and unclassified vasculitis (n = 19). The correlation between BVAS and PGA scores was weak in children (rho = 0.379, 95% CI 0.233 to 0.509, p < 0.0001) (Figure).



Conclusion: The poor correlation of BVAS with PGA suggests either that BVAS requires significant paediatric specific modification, or, that there is no uniformity or standards of disease activity assessment among paediatric rheumatologists. The tool may also perform better measuring change of activity between visits rather than quantifying disease activity at diagnosis. Development of a standardized tool to enable clinical trials in children to improve outcomes is essential.

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2018

Differences between PR3 and MPO-ANCA Associated Vasculitis—Population Based Study from Southern Sweden. Aladdin Mohammad[1] and Mårten Segelmark[2]. [1]Helsingborg Hospital, Helsingborg, Sweden, [2]Skåne University Hospital

Background: Antineutrophil cytoplasmic antibodies (ANCA) are useful serologic markers for diagnosis of small vessel vasculitis. Two main specificities are recognized by ELISA; proteinase 3 (PR3-ANCA) and myeloperoxidase (MPO-ANCA). Even though PR3-ANCA is usually found in patients with Wegener's granulomatosis (WG) and MPO-ANCA in microscopic polyangitis (MPA), there are many exceptions to this rule. The lack of diagnostic criteria for WG and MPA make distinction between these disease phenotypes difficult, especially early during the disease course. A separation based on serology is, however, simple and reproducible.

Objectives: To study differences at disease presentation and outcome based on ANCA type among patients diagnosed with ANCA associated systemic vasculitis (AASV) from a defined population in southern Sweden.

Method: Demographic, clinical and laboratory data at presentation in patients with AASV diagnosed during 13 years period (1997–2009) retrieved from a defined population in southern Sweden were compared by ANCA type (PR3- vs. MPO-ANCA). Organ involvement was recorded using the definitions of the Birmingham Vasculitis Activity Score. Differences in renal and patients survival were studied by Kaplan-Meier analysis.

Results: A total of 163 patients for whom positive test for either PR3- (n=92) or MPO-ANCA (n=71) was available were included in the study. The demographics, clinical and laboratory characteristics are listed in Table 1. Among patients with PR3-ANCA 56 (61%) were men compared with 31 (43%) for MPO-ANCA, p=0,029. Patients with PR3-ANCA have had significantly higher inflammatory activity and larger number of organ involvement at diagnosis. Ear-Nose-Throat involvement was more common in patients with PR3-ANCA while renal disease was more prevalent in

MPO-ANCA disease (Table 1). Among patients with MPO- ANCA and renal involvement at diagnosis, nineteen (32%) went in End Stage Renal Disease compared to 10 (16%) of PR3-ANCA (p=0.032). There were no differences in the mortality rates between the 2 groups.

Conclusions: In this population based cohort of patients with AASV, statistically significant differences in clinical and laboratory characteristics at presentation were clearly evident. In term of outcome, renal survival was worse for patients with MPO-ANCA. These findings should be taken in consideration when stratifying patients with AASV in different therapeutic strategies.

Table 1.

	PR3-ANCA N. 92	MPO-ANCA N. 71	p-value
Sex, Male (87), N. (%)	56 (61%)	31 (43%)	0,029
Age at diagnosis, median (range), years	65 (20–88)	70.5 (32–92)	0,203
Diagnosis delay, median (range), months	2 (0–12)	2 (0–62)	0,037
Laboratory results, median (range)			
C-Reactive Protein g/l	119 (13–294)	50 (1–328)	<0,001
Erythrocyte sedimentation rate mm/hr	80 (4–126)	55 (8–150)	0,029
Hemoglobin g/l	111 (75–155)	107 (72–142)	0,012
Thrombocytes	410 (150–838)	324 (90–652)	<0,001
White Blood Cells	12 (7–26)	9.5 (2–20)	0,002
Creatinine μmol/l	134 (41–1214)	205 (43–1369)	0,024
N. of patients with >=3 organ systems involved	70 (76%)	40 (56%)	0,008
N. (%) of patients went in ESRD[1]	10 (16%)	19 (32%)	0,032
N. of patients died during follow-up[2]	26 (28%)	25 (35%)	0,423
Organ systems involved at diagnosis N. (%)			
General	86 (93%)	60 (84%)	0,063
ENT	56 (61%)	12 (17%)	<0,001
Chest	48 (52%)	27 (38%)	0,072
Nervous	12 (13%)	7 (10%)	0,530
Cutaneous	4 (4%)	4 (6%)	0,706
Mucocutaneous and eyes	10 (11%)	2 (3%)	0,051
Cardiovascular	4 (4%)	4 (6%)	0,706
Abdominal	5 (5%)	7 (10%)	0,284
Renal	62 (67%)	59 (83%)	0,023

[1]patient with renal involvement at diagnosis (PR3: 61; MPO: 59), [2]between January 1997 and June 2010

Disclosure: A. Mohammad: None; **M. Segelmark:** None.

2019

Early Predictors of Neurological Long-Term Deficits in Children with Primary CNS Vasculitis. Gordon S. Soon, Ivanna Yau, Gabrielle Deveber, Derek Armstrong, Pascal Tyrrell, Jeffrey Templeton, Suzanne Laughlin and Susanne M. Benseler. The Hospital for Sick Children

Purpose: Childhood non-progressive primary CNS vasculitis (NPcP-ACNS) accounts for the majority of strokes in children. The aims of the study were 1) to report the neurological long-term outcome of NPcP-ACNS and 2) to determine early risk factors of long-term deficits in childhood vasculitis and stroke.

Methods: A single-centre cohort study of consecutive children diagnosed with cPACNS based on Calabrese criteria between January 1990 and December 2009 was performed. Patients were included if they 1) had non-progressive cPACNS (unilateral proximal stenoses and no evidence of progression >3 months) and 2) had serial clinical assessments and neuroimaging. The study excluded progressive cPACNS and angiography negative cPACNS. Data collection: 1) Demographics, preceding chickenpox; 2) Clinical characteristics, diffuse and focal neurological deficits recorded by two independent investigators, recurrence of ischemic events, 3) laboratory tests including inflammatory and prothrombotic markers and CSF analysis; 3) neuroimaging: serial Magnetic Resonance Imaging (MRI), MR angiography (MRA) and conventional angiography were blindly reviewed by two independent neuroradiologists following a previous developed protocol; 5) treatment with initial anticoagulation, antiplatelet and adjunctive immunosuppressive therapy. Outcome: Neurological deficit impacting on function as determined by Pediatric Stroke Outcome Measure (PSOM) at last follow-up. Analysis: putative early predictors of long-term deficits were tested in univariate and multivariable regression analyses.

Results: A total of 44 children with NP-cPACNS were included; were 32 were boys and 12 were girls; median age at diagnosis was 5.5 years (range 0.5–16.4 years) and median follow-up was 6.4 years; 25 (57%) had preceding chickenpox <12 months. All children presented with arterial ischemic stroke, 28 (64%) had right-sided symptoms. Headache was seen in 17 (39%), 16 (36%) had diffuse deficits and only 6 (14%) seizures. Recurrent ischemic events were observed in 13 (30%). Inflammatory markers were elevated 23 (52%). All patient had unilateral ischemic MRI lesions, including 21 (48%) with isolated basal ganglia lesions. The majority (58%) had vessel stenoses of >50%. Initial therapy: Anticoagulation in 61%, antiplatelet in 31%, both in 6% and adjunctive corticosteroids in 13 (30%). Outcome: Neurological long-term deficits were seen in 20 (45%). Children presenting with seizures (p=0.006), evidence of MRI beyond the basal ganglia (p=0.001) and/or high degree of vascular stenosis (p=0.04) were at highest risk for long-term deficits.

Conclusions: The long-term outcome of childhood vascular stroke is devastating: Neurological deficits impacting on function can be found in 45% of children with non-progressive primary CNS vasculitis, the most common cause of childhood stroke. Early predictors including seizures at diagnosis, evidence of extensive MRI lesions and high degree of vascular stenosis can identify children at highest risk for long-term deficits. Innovative, tailored treatment strategies have to target high risk patients to prevent long-term neurological damage.

Disclosure: G. S. Soon: None; **I. Yau:** None; **G. Deveber:** None; **D. Armstrong:** None; **P. Tyrrell:** None; **J. Templeton:** None; **S. Laughlin:** None; **S. M. Benseler:** None.

2020

Effects of Imatinib Mesylate on Pulmonary Vascular Remodeling of Allergic Vasculitis in Murine Mode. Nobuhito Sasaki[2], Kohei Yamauchi[2] and Takashi Sawai[1]. [1]Department of Pathology, Iwate Medical University School of Medicine, Morioka, Iwate, Japan, [2]Division of Pulmonary Medicine, Allergy and Rheumatology, Department of Internal Medicine, Iwate Medical University School of Medicine, Morioka, Iwate, Japan

Objectives: We investigated the effects of imatinib mesylate (IM) on vascular remodeling using the murine model of allergic vasculitis with eosinophil infiltration (Exp. Lung Res. 2009. in press).

Methods: C57BL/6 mice (6–8 weeks) were sensitized with ovalbumin (OVA) and alum. The positive controls (n=12) were exposed to aerosolized OVA daily for 7 days. The other group of mice (IM treated mice) were administered with IM (4.5mg/kg, p.o.) in parallel with daily exposure to aerosolized OVA for 7 days (n=12). On 7th day, bronchoalveolar lavage (BAL) was performed and the lungs were excised for pathological analysis. Cell differentials were determined and concentrations of IL-2, IL-4, IL-5, IFN gamma and TNF-alpha in BAL fluid were measured.

Results: While there was no significant difference of total cell number in BAL fluids in between the control and the IM treated group, the ratio of eosinophils reduced significantly in the IM treated group. (control *vs* IM treated; 64.8±2.1 vs 37.6±4.3 %, p=0.004). There was no significant difference of concentrations of IL-2, IL-4, IL-5, IFN gamma or TNF-alpha in BAL fluids or serum in between the control and the IM treated group. The pathological scores reduced significantly in the IM treated group compared to the control group (control *vs* IM treated; 3.67±0.2 *vs* 2.20±0.2, p=0.0043). Intra luminal infiltration and proliferation of myofibroblasts in pulmonary arteries were reduced dramatically in the IM treated group compared to the control group. Intra luminal infiltration and proliferation of MIB1 positive myofibroblasts in pulmonary arteries were reduced dramatically in the IM treated group compared to the control group.

Conclusion: IM suppressed pulmonary vascular remodeling in the murine model of allergic vasculitis with eosinophil infiltration.

Immunostaining for MIB-1

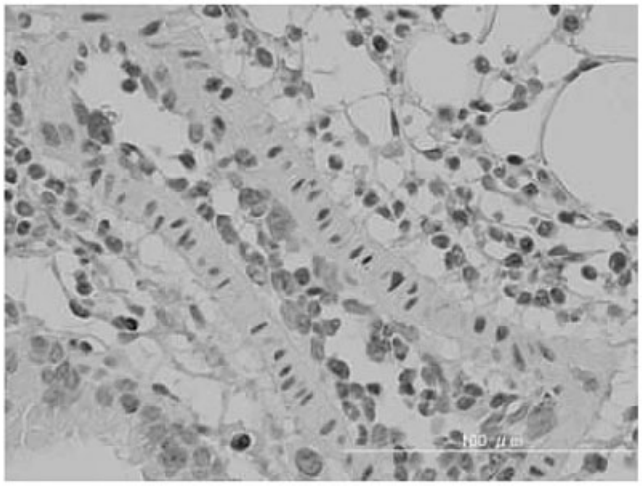

Figure 1. IM treated

MIB-1 positive inflammatory cells were seen in vascular lumen

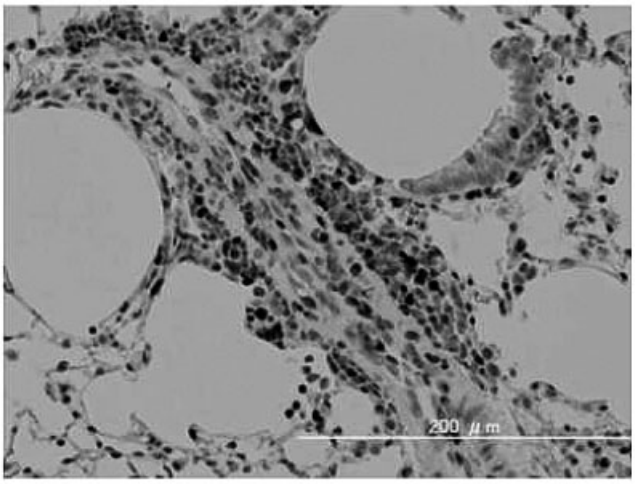

Figure 2. Control

Intra-luminal space was occluded by MIB-1-positive myofibroblasts.

Disclosure: N. Sasaki: None; **K. Yamauchi:** None; **T. Sawai:** None.

2021

Endothelial Lineage Impairment and Increased PR3 Expression on Peripheral Cells of Endothelial Phenotype in Wegener's Granulomatosis. Susann Patschan, Daniel Patschan, Elvira Henze, Johannes Wessels, Sabine Blaschke and Gerhard Anton Müller. Department of Nephrology and Rheumatology, University Hospital Göttingen

Wegener's Granulomatosis (WG) is characterized by microvascular endothelial damage and by alterations of the endothelial progenitor cell (EPC) system. Interactions between anti-Proteinase 3 antibodies and their respective antigens (PR3) on neutrophils are pathogenetically relevant in WG. Aim of this study was (I) to analyze total circulating EPCs and regenerative activity of blood-dereived EPCs, and (II) to evaluate PR3 expression patterns on circulating myelomonocytic and endothelial cells in WG.

Blood samples from WG patients were analyzed for total and for Flk-1+ myolomonocytic cells (cytometric analysis). Healthy donors served as controls. For evaluating the proliferative activity of EPCs, a colony forming unit assay (CFU) was performed. PR3 expression by the cells was quantified by cytometric analysis. Serum Angiopoietin 1 and serum TNF-α were measured by ELISA technique.

A total of 21 healthy donors (12 female, 9 male [40.3 ±9.2 years]) and 31 WG patients (13 female, 18 male [59.2 ±15.3 years]) were included into the study. The total percentages of EPCs were not different between the two groups. WG patients displayed lower proliferate activity of EPCs (22.3 ±4.1 vs. 45.9 ±6.8, CFU-ECs, p=0.0027). In addition PR3 expression was significantly higher in the total as well as in the Flk-1+ (sub)population of myelomonocytic cells in WG (10.4 ±14.4% vs. 0.3 ±0.4%, p=0.02 bzw. 0.3 ±0.3% vs. 0.1 ±0.1%, p=0.04). Finally, WG patients showed lower mean serum levels of Angiopoietin 1 and higher mean serum levels of TNF-α as compared to controls (689 ±224 pg/ml vs. 1542 ±315 pg/ml, p=0.034 and 13 ±1 vs. 8.9 ±0.5 pg/ml, p=0.04), the serum levels of both cytokines did not linearily correlate with either clinical activity or the total number of circulating EPCs or the numbers of colonies formed (EPC regeneration).

In addition to reduced EPC regeneration and decreased serum levels of Angiopoietin 1, both indicating impairement of the endothelial system, patients with WG show significantly increased expression of PR3 in the total and in the Flk-1+ myelomonocytic cell population. These data imply, that PR3 could be involved in the pathogenesis of microvascular endothelial damage in patients with WG.

Disclosure: S. Patschan: None; **D. Patschan:** None; **E. Henze:** None; **J. Wessels:** None; **S. Blaschke:** None; **G. A. Müller:** None.

2022

Epidemiology of Lupus Nephritis (LN) and ANCA Associated Nephritis (AAN)—Comparison Study from a Defined Population. Aladdin Mohammad[1], Christina Ståhl-Hallengren[3], Ola Nived[3], Gunnar K. Sturfelt[3], Anders Bengtsson[3] and Mårten Segelmark[2]. [1]Helsingborg Hospital, Helsingborg, Sweden, [2]Skåne University Hospital, Lund, Sweden, [3]Skåne University Hospital, Lund, Lund, Sweden

Purpose: The aims of this study were to compare incidence rates, renal and patients' survival between Lupus Nephritis (LN) and ANCA Associated Nephritis (AAN) during a 12 year-period in a well defined population in southern Sweden.

Method: The study was carried out over a 12 year period (1997–2008) in a health care district in southern Sweden with a total population (> 95% Caucasian) of 238 069. Patients were retrieved from two existing cohorts of patients with systemic lupus erythematosus (SLE) and ANCA Associated Vasculitis (AAV). To be included in the study, patients had to (i) reside within the study area at the time of diagnosis, (ii) have a clinical diagnosis of either SLE or AAV and (iii) experience a first flare of biopsy proven nephritis during the study period. The indications for kidney biopsy were the same in both cohorts; and includes rising s-creatinine, excessive proteinuria and /or urinary sediment consistent with active nephritis. The clinical diagnosis of all patients was verified by review of case records. All patients with SLE fulfilled the American College of Rheumatology (ACR) classification criteria 1987. For AAV patients, classification was made according to an algorithm based on the ACR criteria 1990 and the Chapel Hill Consensus Conference definitions 1994.

Results: We identified a total of 43 patients with AAN (33 microscopic polyangitis, 10 Wegener's granulomatosis) and 13 patients with LN, with new onset of biopsy proven nephritis (Table 1). The annual incidence per million of the population (95 % Confidence Interval) was estimated to be 15.1(10.6–19.6) for AAN and 4.6 (2.1–7.0) for LN. 42 patients with AAN tested positive for ANCA (20 with pos. c-/PR3-ANCA and 22 with p-/MPO-ANCA). One patient with MPA was ANCA-negative. Eight patients (62%) with LN tested positive for anti-ds-DNA and 11 had complement consumption. Patients were followed until June, 1st, 2010 (median 48 months; range 1–144). During follow up 19 patients died [AAN 18; LN 1 (p=0.049)], and 13 patients went into ESRD (all with AAN). Among patients who were alive and not on renal replacement therapy at the end of follow up, 41 % of the AAN patients had an estimated GFR <50 mL/min/1.73 m^2 compared to 8.3% for the LN patients (p=0.046). The 1-, 5-, and 10-year survival for patients with AAN was 84%, 59% and 53% respectively.

Table 1.

Disease	n. of patients	Sex F/M	Age at diagnosis, median yrs (range)	s-creatinine at diagnosis µmol/l, median (range)	Incidence/10^6 (95% CI)	Mortality (n.)	ESRD (n.)
AAN	43	17/26	70 (20–88)	267 (66–1369)	15.1 (10.6–19.6)	18	13
MPA	33	16/17	71 (29–88)	339 (79–1369)	11.6 (7.6–15.5)	16	12
WG	10	1/9	58.5 (20–88)	203 (66–419)	3.5 (1.3–5.7)	2	1
LN	13	10/3	43 (25–72)	78 (51–173)	4.6 (2.1–7.0)	1	0

AAN: ANCA associated nephritis; LN: lupus nephritis; MPA: microscopic polyangiitis; WG: Wegener's granulomatosis; CI: confidence interval; ESRD: end stage renal disease.

Conclusions: In our area, AAN was three times as common as LN, and outcome was considerably worse. SLE is often diagnosed before the onset of nephritis; active and centralized follow-up at our hospital may contribute to a low incidence and benign course for LN in our area, while AAN is still often diagnosed at a later stage.

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2023

Expression of Toll-Like Receptors 2, 4 and 9 by Peripheral Blood Leukocytes in Patients with ANCA-Associated Vasculitis. Henko Tadema[3], Wayel H. Abdulahad[3], Coen A. Stegeman[1], Cees G. M. Kallenberg[3] and Peter Heeringa[2]. [1]University Medical Center Groningen, Dept of Nephrology, Groningen, The Netherlands, [2]University Medical Center Groningen, Dept of Pathology and Medical Biology, Groningen, The Netherlands, [3]University Medical Center Groningen, Dept of Rheumatology and Clinical Immunology, Groningen, The Netherlands

Background: Bacterial infections have been linked to the pathogenesis of ANCA-associated vasculitis (AAV), and nasal carriage of *Staphylococcus aureus* is associated with an increased risk for relapses. Toll-like receptors (TLRs) are important sensors of pathogen associated molecular patterns, and these receptors may be important during the development of relapses in AAV. Here, we characterized the expression of TLRs 2, 4, and 9 by peripheral blood leukocytes from AAV patients in remission. We compared TLR expression in patients who were nasal carriers of *S. aureus* and non-carriers. Furthermore, we studied the effect of *in vitro* ANCA-priming on TLR expression by monocytes.

Methods: Expression of TLRs was determined using 9-color flowcytometry. Whole blood from 29 AAV patients (17 PR3-ANCA and 12 MPO-ANCA) and 19 matched healthy controls was stained for membrane markers CD3, CD14, CD16, CD19, CD27, and CD56 to distinguish between cell populations, and expression of membrane toll-like receptors (mTLR) 2, 4, and 9, and intracellular levels of TLR9 were determined. We compared TLR expression in AAV patients who were nasal carriers of *S. aureus* (n=9), and non-carriers (n=20). Peripheral blood mononuclear cells were stimulated *in vitro* with monoclonal anti-PR3 or PR3-ANCA IgG, and mTLR2 and mTLR4 expression by monocytes was determined.

Results: Membrane expression of TLRs 2, 4, and 9 by B lymphocytes and T lymphocytes was comparable in AAV patients and controls. In AAV patients, we observed increased percentages of $mTLR2^+$ (median=0.46% in AAV *vs* 0.18% in HC, $p=0.01$), and $mTLR4^+$ (median 0.37% in AAV *vs* 0.22% in HC, $p=0.02$) NK cells. Monocytes from AAV patients expressed increased levels of mTLR2, compared to HC (median ΔMFI=31.7 in AAV *vs* Δ19.8 in HC, $p=0.01$). mTLR-expression by granulocytes was comparable in patients and controls. Intracellular levels of TLR9 (iTLR9) were decreased in B lymphocytes, T lymphocytes and NK cells from AAV patients, whereas monocytes and granulocytes expressed comparable iTLR9 levels. Within AAV patients, we observed increased mTLR4 expression by monocytes from nasal carriers of *S. aureus*, compared to non-carriers (mean ΔMFI=12.6 in $Aureus^+$ *vs* mean ΔMFI=5.8 in $Aureus^-$, $p=0.02$). Priming with PR3-ANCA *in vitro* did not influence mTLR2 and mTLR4 expression by monocytes.

Conclusions: We observed increased TLR expression by a proportion of NK cells and monocytes in AAV patients in remission, compared to healthy controls. It has been suggested that ANCA trigger monocytes to increase TLR expression, but we did not observe increased TLR expression after priming with PR3-ANCA *in vitro*. Interestingly, monocytes from nasal carriers of *S. aureus* expressed increased mTLR4 levels compared to non-carriers, indicating proinflammatory conditions. Increased TLR levels on NK cells and monocytes may reflect increased activation of these cells in AAV patients, but whether relapses can be triggered via TLRs will need further investigation.

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2024

Hepatitis C Virus-Associated Polyarteritis Nodosa. David Saadoun, Benjamin Terrier, Damien Sene, Thierry Maisonobe, Lucile Musset, Zahir Amoura, Mathieu Resche Rigon and Patrice Cacoub. Pitie Salpetriere Hospital

Objective: To analyse the main characteristics and outcome of polyarteritis nodosa (PAN)-type vasculitis associated with hepatitis C virus (HCV).

Methods: We reported characteristics and outcome of 31 patients chronically infected with HCV who satisfied American College of Rheumatology and Chapel Hill criteria of PAN, seen between 1990 and 2009, in a university center.

Results: Among a cohort of 161 patients with HCV-related vasculitis, 31 (19.2%) were diagnosed as having PAN. The median (Q1,Q3) age was 64.5 (49.5, 70.5) years with 54.8% of female. Compared with HCV-mixed cryoglobulinemia (MC) vasculitis, HCV-PAN displayed a more severe and acute clinical presentation with more frequent fever and weight loss ($p<0.0001$), severe hypertension ($p=0.0006$), gastrointestinal tract involvement ($p<0.0001$), severe acute sensory-motor multifocal mononeuropathy ($p<0.0001$), kidney and liver microaneurisms ($p=0.0002$) and increased C-reactive protein ($p<0.0001$). Complete clinical remission of vasculitis was achieved in 79.3% of HCV-PAN compared to 57.5% HCV-MC ($p=0.050$). In multivariate analysis, skin involvement (OR, 2.81; 95% CI 1.27 to 6.33), and PAN type vasculitis (OR, 3.01; 95% CI 1.16 to 8.96) were independently associated with a complete clinical response of HCV-vasculitis. A glomerular filtration rate lower than 70 ml/min (OR 0.54; 95% CI 0.24 to 1.21) was negatively associated with a complete clinical response of HCV-vasculitis. Clinical relapse rate was higher in HCV-PAN compared to HCV-MC (75% versus 12%, $p=0.002$, respectively under rituximab). Five-years survival rate was 86% in the whole cohort, regardless of the vasculitis type.

Conclusion: HCV-PAN account for 19.2% of our cohort of HCV vasculitis. HCV-PAN dysplay a more severe and acute clinical presentation and higher rate of clinical remission.

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2025

IL-25: A Cytokine Linking Eosinophils and Adaptative Immunity in Churg-Strauss Syndrome. Benjamin Terrier[1], Ivan Bieche[2], Thierry Maisonobe[1], Ingrid Laurendeau[2], Michele Rosenzwajg[1], Marie-Claude Diemert[1], Lucile Musset[1], Michel Vidaud[2], Damien Sène[1], Nathalie Costedoat-Chalumeau[1], Du Le Thi Huong[1], Zahir Amoura[1], David Klatzmann[1], Patrice Cacoub[1] and David Saadoun[1]. [1]Pitié-Salpétrière, [2]UMR745 INSERM

Background: Churg-Strauss Syndrome (CSS) is characterized by systemic vasculitis, and blood and tissue eosinophilia. Blood eosinophils correlate with disease activity. Activated T cells from CSS patients are predominantly Th2. IL-25 has been shown to license innate and adaptive immunity by enhancing Th2 cytokines production.

Objective: To analyze whether eosinophils could elicit a Th2 mediated immune response in CSS, we sought to determine the implication of IL-25 and its receptor IL-17RB in the pathogenesis of CSS.

Methods: We performed quantitative measurement of serum human IL-25 by ELISA, analysis of cell surface markers and cytokine production by flow cytometry and Luminex. Immunohistochemical analysis and gene quantification with mRNA on peripheral nerve biopsy samples of active CSS patients, patients with microscopic polyangiitis (MPA; disease controls) and controls with non-inflammatory axonopathy.

Results: We found increased level of IL-25 in the serum of active patient with CSS (952±697 vs. 75±49 pg/ml in inactive patients and 47±6 pg/ml in healthy donors). IL-25 correlated with disease activity and eosinophils blood level. Eosinophils were the main source of IL-25, whereas activated CD4 memory T cells were the main IL-17RB (IL-25 receptor) expressing cells in CSS. IL-25 enhanced the production of IL-4, IL-5 and IL-13 by activated peripheral blood monocytes. IL-25 and IL-17RB were observed within the vasculitic lesions of patients with CSS, and IL-17RB co-localized with T cells. Increased expression of IL-17RB, TRAF6 and JunB in vasculitic lesions of CSS underscored the IL-25-mediated activation, whereas up-regulation of GATA3 and IL-10 supported Th2 differentiation.

Conclusion: Our study is the first to demonstrate the implication of IL-25 in the pathogenesis of CSS and its correlation with disease activity. Eosinophils, through the production of IL-25, may exert a critical role in promoting Th2 responses in peripheral blood and target tissues in CSS, and represent a potential target for novel therapy.

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2026

Incidence and Predictors of Urotoxic Adverse Events in Cyclophosphamide-Treated Patients with Systemic Necrotizing Vasculitides. Guillaume Le Guenno[3], Alfred Mahr[2], Christian Pagnoux[3], Robin Dhote[1] and Loïc Guillevin[3]. [1]Internal Medicine, Hospital Avicenne, Bobigny, France, [2]Internal Medicine, Hospital Cochin, Paris, France, [3]Internal Medicine, Hospital Cochin, Paris, France

Background: Cyclophosphamide (CYC) is widely used to treat systemic necrotizing vasculitides (SNV) but its urotoxic side effects, i.e., hemorrhagic cystitis (HC) and urinary tract cancer (UTC), have raised important concerns. However, reported UTC incidence rates in CYC-treated SNV patients varied according to the study. In addition, while the cumulative CYC dose was identified as a major determinant of urotoxicity, it is not clear whether a cutoff exists below which cumulative CYC has no urotoxic effect and whether oral or intravenous CYC administration affects the urotoxic risk. Moreover, no information is available on CYC-related urotoxicity for SNV other than Wegener's granulomatosis (WG). To address these questions, we undertook a study that aimed at assessing the frequencies and predictors of HC and/or UTC in CYC-treated SNV patients.

Patients and Methods: The French Vasculitis Study Group database, which contains longitudinal data on SNV patients, was searched for UTC and/or HC occurrences in SNV patients diagnosed with WG, microscopic polyangiitis, Churg–Strauss syndrome or polyarteritis nodosa. The observed UTC incidence was compared to that expected in the French general population by calculating age- and sex-standardized incidence ratios (SIR). UTC and/or HC relationships with 10 variables, including CYC dose and administration route, were investigated by uni- and multivariate Cox proportional hazard models for a nested subgroup of patients with detailed information on CYC exposure; the variables "prior HC episode" and "cumulative CYC dose" were analyzed as time-varying covariates.

Results: Among the 805 patients analyzed (mean follow-up: 5.3 years), 22 HC and 7 UTC (6 bladder cancers, 1 ureter cancer) were identified in 27 patients. SIR for UTC was 5.00 ($P = 0.001$) and 5.96 for WG-diagnosed patients ($P = 0.03$). Based on 467 patients with detailed CYC information (mean cumulative CYC dose: 25.1 ± 38.0 g), cumulative CYC dose (hazard ratio [HR] for 10-g increments: 1.08; $P = 0.03$), ever-oral CYC administration (HR: 5.69; $P = 0.001$) and WG (HR: 2.98; $P = 0.01$) independently predicted UTC and/or HC development. Results of analyses using the effect of cumulative CYC doses as a categorical variable suggested that UTC and/or HC risk increased steadily with increasing cumulative CYC doses. Ever-tobacco smoking (HR: 7.64; $P = 0.02$) and a prior HC episode (HR: 10.91; $P = 0.006$) significantly predicted UTC.

Conclusion: CYC treatment of SNV is associated with a 5-fold higher risk of developing UTC. The urotoxicity risk for SNV patients is determined by the cumulative CYC dose and its oral intake, and might be higher for WG patients. This study's findings also support that HC should be recognized as a precursor of UTC and plead for sustained heightened awareness when prescribing this drug to tobacco smokers.

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2027

Inflammatory Aortitis: Diagnostic Performance of Aorta Wall Thickness CT-scan Measuring. Maia Forgues[8], Jacques Giron[12], Anne Hitzel[11], Anne Julian[11], Pierre Payoux[11], Daniel Adoue[10], Frédéric Degraeve[2], Serge Madaule[1], Laurent Prudhomme[3], Yann Leveneur[4], Francis Gaches[6], Xavier Delbrel[5], Leonardo Astudillo[9], Bruno Marchou[7], Philippe Arlet[10] and Laurent Sailler[8]. [1]CHG, Albi, France, [2]CHG, Auch, France, [3]CHG, Castres, France, [4]CHG, Lannemezan, France, [5]CHG, Pau, France, [6]Hôpital J Ducuing, Toulouse, France, [7]Hôpital Purpan, Infectious Diseases Department, Université de Toulouse, [8]Hôpital Purpan, Internal Medicine Department, Université de Toulouse, Toulouse, France, [9]Hôpital Purpan, Internal Medicine Department, Université de Toulouse, Toulouse, [10]Hôpital Purpan, Internal Medicine Department, Université de Toulouse, [11]Hôpital Purpan, Nuclear Medicine Department, Université de Toulouse, [12]Hôpital Purpan, Radiology Department, Université de Toulouse

Background: The measure of the aorta wall thickness (AWT) by computed tomography (CT-scan) is often used as diagnostic criteria for inflammatory aortitis. However, its diagnostic performance has not been studied.

Objective: to describe the diagnostic performance of AWT for inflammatory aortitis.

Method: This was a retrospective study from January 2005 to March 2010 including only patients who 1) had received a diagnosis of aortitis (expert diagnosis); 2) had performed a CT-scan and a PET-scan. For each case, one control was selected among patients who had performed a CT-scan and a PET-scan for the diagnosis of lymphoma in our institution. Cases and controls were matched for gender and age. Maximal AWT was measured by the same physician (JG) using a standardized procedure at the ascending aorta, descending thoracic aorta and abdominal aorta. AWT increase was validated only when it was circumferential and extended in the absence of obvious calcified atheroma plaque. The diagnostic performances of three different aortitis definitions were tested. Definition 1: at least one AWT value above the 99° percentile observed in the control group at one of the following site: ascending aorta, thoracic descending aorta and abdominal aorta; definition 2: increase of AWT above the 99° percentile of the maximal value observed in the control group whatever the aorta portion; definition 3: increase of AWT at one site or more above the more discriminating threshold determined using ROC curves.

Results: Thirty-one aortitis patients (24 women and 7 men) were recorded. Mean age was 58.1 years (range: 20 – 82). They suffered from giant cell arteritis (GCA; n=16), Takayasu arteritis (TA; n=8), ANCA-vasculitis (n=2), spondylarthritis (n=1) or unclassified aortitis (n=4). Among controls, the 99° percentile of AWT was 3 mm at the ascending aorta, 2.6 mm at the descending aorta and 2.7 mm at the abdominal aorta; the 99° percentile of maximal AWT was 3.2 mm. The best discriminating threshold determined by the ROC curves analysis was 2.6 mm, 2.2 mm and 2.4 mm respectively for the ascending, the descending and the abdominal aorta.The diagnostic performances of each definition are reported below.

Table 1. Diagnostic performance of three inflammatory aortitis definitions based on the measure of the aorta wall thickness using computed-tomography.

	Se	Sp	PPV	NPV
Definition 1	71	100	100	77.5
Definition 2	61	100	100	72
Definition 3	91,7	71	75,7	91.7

Se: sensibility; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value

The diagnosis of aortitis had not been mentioned on the routine CT-scan report in 11 patients despite an increased AWT, an arterial wall contrast enhancement and/or peri-aortic edema. All these patients had a clearly abnormal PET-scan vessels imaging. All patients with a maximal AWT below 2 mm had a normal vessel's PET-scan.

Conclusion: The diagnosis of aortitis is frequently missed on routine CT-scan despite clear abnormalities. PET-scan seemed especially useful when the AWT was thicker than 2 mm and thinner than 3 mm at the ascending aorta, 2.6 mm at the descending aorta and 2.7 mm at the abdominal aorta.

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2028

Interleukin-32 and Its Autoantibody Are Elevated in Patients with Wegener's Granulomatosis and Correlated with Treatment Response. Suyoung Bae[3], Yong-Gil Kim[2], Siyoung Lee[4], MinWook So[2], Chang-Keun Lee[2], Bin Yoo[1], Yong-Beom Park[5] and Soohyun Kim[3]. [1]ASAN Medical Ctr, Seoul, Korea, Republic of, [2]ASAN Medical Ctr, [3]Konkuk University, Seoul, Korea, Republic of, [4]Konkuk University, [5]Yonsei University

Background: Wegener's granulomatosis (WG) is a primary small systemic vessel vasculitis, involved prominently the respiratory tract and the kidneys. However, the etiology and pathogenesis are currently not characterized precisely. Human proteinase 3 (PR3), the major autoantigen, and anti-neutrophil cytoplasmic antibody to PR3 (PR3-ANCA) are associated with the pathogenesis of vascular damages in WG and cytokines including IFNγ and TNFα have been thought to be pivotal signal transmitters in granulomatous lesions due to recruiting lymphoid cells and activating macrophages in WG. PR3 has the ability to bind and activate IL-32, which has been recently described as a novel cytokine that induces proinflammatory cytokines (IL-1β, IL-6 and TNFα) and chemokines (IL-8 and MIP-2).

Objective: To evaluate the role of IL-32 in WG patients and the relationship between IL-32 and disease activity.

Methods and Results: The blood samples were collected from nine WG patients and the disease activity was assessed using Birmingham Vasculitis Activity Score (BVAS). We investigated the plasma levels of PR3, IL-32, TNFα, and IL-6 in WG patients using ELISA. Among them, we observed that IL-32 and PR-3 level of WG patients were increased significantly compared with healthy volunteers and each was tightly associated ($p < 0.01$). Northern blot analysis revealed that the mRNA level of IL-32 was significantly elevated in leukocytes of WG patients. The intracellular colocalization of IL-32 and PR3 in leukocyte from WG patients versus healthy volunteers was verified by immunofluorescence staining. Furthermore, the specificity in plasma concentration of IL-32 and IL-32 autoantibodies between healthy controls and WG patients was more noticeable than that in plasma levels of PR3 and PR3-ANCA. Although the significant relationship between IL-32 level and BVAS was not found, the change of IL-32 levels between pre- and post-treatment sample of three WG patients was well correlated with the change of BVAS.

Conclusion: In WG patients, the plasma level of IL-32 was increased and the decrease of this might imply the good response of treatment. Our results suggest that IL-32 could be a helpful index in WG patients and may have an important role in the disease pathogenesis.

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2029

Investigation of the Effect of Histone Deacetylase 2 Function on Wegener's Granulomatosis. Dai Takagi[1], Yuji Nakamaru[2], Shigeru Akazawa[2] and Satoshi Fukuda[2]. [1]Department of Otolaryngology and Head & Neck Surgery Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan, [2]Department of Otolaryngology and Head & Neck Surgery Hokkaido University Graduate School of Medicine

Background: Wegener's Granulomatosis (WG) is a systemic vasculitic disease characterized by necrotizing granulomas and vasculitis of arterioles and venules. It has been reported that anti-neutrophil cytoplasmic antibodies (ANCA) activate neutrophils result in induction of glomerulonephritis in WG by released hydrogen peroxide.

Histone deacetylase (HDAC) deacetylates histone and deacetylation of histone associates with gene repression or gene silencing. Even more importantly, HDAC2 is also key molecule of steroid action, and this reduction causes steroid insensitive inflammation, which is seen in COPD, severe asthma, rheumatoid arthritis.

In this study, we investigated whether HDAC2 function decreased in WG patients, and effect of oxidative stress on function of HDAC2.

Patients and Methods: A549 cells (lung epithelial cells) were stimulated by H_2O_2 (200 μM) to induce oxidative stress and expression of HDAC 2 were measured. We also measured HDAC 2 activity.

Six patients of WG (mean $\pm$ S.D. age $62 \cdot 5 \pm 17 \cdot 5$) diagnosed according to American College of Rheumatology criteria were examined.

Fresh PBMCs were isolated from heparinized blood by Ficoll-Conray separation and then whole cell protein was prepared. Target proteins were detected by Western blot analysis. We also measured HDAC 2 activity of PBMCs on patients.

Results: Treatment of A549 cells with H_2O_2 did not suppress expression of HDAC2. However, treatment of H_2O_2 significantly decreased total HDAC2 activity ($p < 0.05$).

We found that HDAC 2 activity was significantly decreased in WG patients compared to those from healthy subjects (HS), 75.5 ± 7.4 Arbitral Units at HS, 35.2 ± 12.3 Arbitral Units at WG ($p < 0.05$). Furthermore, we found negative correlation between HDAC 2 activity and titer of c-reactive protein and titer of PR3-ANCA. However, expression of HDAC2 did not decreased in WG patients.

Discussion: These results suggest that function of HDAC 2 is reduced in WG and that this reduction affects inflammation and vasculitis of WG. We have also confirmed that oxidative stress suppressed HDAC activity in lung epithelial cell line. Oxidative stress may worsen the disease via reduction of HDAC2 function without reduction of HDAC2 expression.

Thus, HDAC2 may serve therapeutic targets by modulating the function, which eventually regulates the development of WG.

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2030

Low 25-OH Vitamin D Serum Levels Correlate with Extra-Hepatic Manifestations in Chronic Hepatitis C Virus Infection. Benjamin Terrier[2], Jean-Claude Souberbielle[1], David Saadoun[3], Guillaume Geri[3], Yoland Schoindre[3], Damien Sène[3], Lucile Musset[3] and Patrice Cacoub[4]. [1]Necker, [2]Pitié-Salpéterière, Paris, France, [3]Pitié-Salpéterière, [4]Pitié-Salpétrière

Background: Recent studies have suggested the critical role of vitamin D in the regulation of the immune system, in promoting the development of regulatory T cells and decreasing pro-inflammatory cytokines and B cell differentiation. Correlation between low levels of 25-OH vitamin D and disease activity have been reported in various autoimmune disorders. The beneficial role of vitamin D administration was also suggested in chronic HCV infection.

Objective: To evaluate the association between serum 25-OH vitamin D levels and the presence of extra-hepatic manifestations and immunological abnormalities during chronic HCV infection.

Patients and Methods: Ninety-four HCV+ RNA+ untreated patients [36 without mixed cryoglobulinemia (MC), 10 with asymptomatic MC and 48 with MC-vasculitis) were included. Clinical and biological characteristics were recorded and compared according to vitamin D status. Vitamin D status was classified as: deficiency if serum 25-OH vitamin D level < 12, insufficiency between 12 and 30, and sufficiency > 30 ng/ml. Kruskal-Wallis test was used to compare groups. Correlations between serum 25-OH vitamin D levels and biological and immunological features were analyzed using nonparametric Spearman correlation.

Results: Overall, 84 (89%) patients had hypovitaminosis D (< 30 ng/ml). Patients were distinguished according to vitamin D status: sufficiency (n=10), insufficiency (n=52), and deficiency (n=32). Demographical and HCV infection characteristics were similar between groups. Patients with vitamin D deficiency vs. insufficiency vs. sufficiency had more frequently: vasculitis (75 vs. 42 vs. 20%; P=0.002), arthralgia (50 vs. 31 vs. 20%; P=0.11), neuropathy (59 vs. 38 vs. 20%; P=0.048), purpura (63 vs. 35 vs. 10%, P=0.004), and renal involvement (28 vs. 12 vs. 10%, P=0.11). Biologically, patients with vitamin D deficiency vs. insufficiency vs. sufficiency had more frequently type II MC (77 vs. 46 vs. 10%; P=0.002) and low C4 serum levels (86 vs. 47 vs. 0%; P<0.0001). A negative correlation was found between 25-OH vitamin D and C4 serum levels (r^2=0.20; P=0.001) and the level of marginal zone B cells (r^2=0.24; P=0.001), and a positive correlation with regulatory T cells (r^2=0.23; P=0.005).

Conclusion: In chronic HCV infection, low 25-OH vitamin D serum levels correlate with clinical and biological immune extra-hepatic manifestations. These findings suggest the potential benefit of vitamin D supplementation in HCV infected patients with extra-hepatic manifestations.

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2031

Patulous Eustachian Tube: A Novel Form of Damage in Wegener's Granulomatosis. Philip Seo[1] and Howard W. Francis[2]. [1]Johns Hopkins Bayview Medical Center, Baltimore, MD, [2]Johns Hopkins University

Background: The patulous eustachian tube (PET) is an uncommon syndrome caused by intermittent inappropriate patency of the eustachian tube that results in autophony. We explored whether this disorder might be more common among patients with Wegener's granulomatosis.

Methods: Symptoms associated with the patulous eustachian tube were elicited from patients with a known diagnosis of systemic vasculitis using a standardized survey form. Demographics, vasculitis type, and treatment history were also recorded. Descriptive statistical analyses were performed based on patients who reported symptoms commonly associated with this disorder. Pearson chi-square analysis was used for group comparisons.

Results: One hundred fifty-two surveys were sent to patients evaluated at the Johns Hopkins Vasculitis Center; 123 subjects (80.9%) completed the survey and returned for tabulation. The respondents were comprised of 43 men and 80 women (1:2 ratio), who had a median age of 50 years (range: 17–85). One hundred twenty (97.6%) of subjects had autoimmune disease. One hundred thirteen subjects (91.2%) had a diagnosis of vasculitis that had been confirmed by a rheumatologist; these patients carried a diagnosis of vasculitis for a median of 7 years. 64.2% of subjects had ANCA-associated vasculitis (i.e., Wegener's granulomatosis, microscopic polyangitis, or the Churg-Strauss syndrome).

Of the patients who had been diagnosed with vasculitis, 2/113 had been diagnosed previously with patulous eustachian tube; neither subject had received treatment for this diagnosis. Fifty-four subjects (47.8%) reported at least one symptom associated with PET, most commonly ear fullness (44.2%). Forty subjects (35.4%) complained of an increased awareness of his or her own voice. Based on their reported symptoms, 16 subjects were considered "highly probable" for having PET. These patients had symptoms for a median of 5 years, and 11/16 (68.6%) are still symptomatic. On a Likert scale of 0–5, where 5 represents "intolerable" symptoms, these subjects rated their current symptoms with a median score of 2. Nine patients report having developed symptoms prior to or at the time they were diagnosed with vasculitis; 3 patients report developing symptoms only after they had been in remission.

Of the 60 patients surveyed who had Wegener's granulomatosis, 36 (60%) had at least one symptom attributable to PET. Eleven patients with Wegener's granulomatosis (18.3%) were "highly probable" for having PET.

Conclusions: Symptoms attributable to PET are common among patients with Wegener's granulomatosis, possibly due to direct involvement of the eustachian tube. The majority of these patients are both symptomatic and undiagnosed. In many cases, these symptoms predate the diagnosis of vasculitis, implying that this may be a presenting symptom of Wegener's granulomatosis in some patients.

Disclosure: P. Seo: None; **H. W. Francis:** None.

2032

Phase 1 Clinical Safety, Pharmacokinetic and Pharmacodynamic Evaluation of the Novel C5aR Antagonist CCX168, a Potential Therapeutic for ANCA-Vasculitis. Daniel J. Dairaghi, Juan C. Jaen, Kara Deshayes, Daniel A. Johnson, Manmohan R. Leleti, Shichang Miao, Jay P. Powers, Lisa C. Seitz, Yu Wang, Thomas J. Schall and Pirow J. Bekker. ChemoCentryx

Purpose: A single and multiple-ascending dose Phase 1 study has been conducted in healthy volunteers (HVs) to establish the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) profile of the orally administered C5aR antagonist CCX168. This compound has been shown to completely block anti-MPO induced glomerulonephritis (GN) in mice. This work has paved the way for clinical evaluation of CCX168 in patients with ANCA-associated vasculitis/glomerulonephritis.

Methods: In the Phase 1 program, 40 male or female HVs received either placebo or 1–100 mg CCX168 orally, in a single-dose or a multiple-dose (7 days) regimen. Blood was collected at pre-specified time points for PK and PD analyses. Ex vivo analysis of C5aR receptor coverage on blood neutrophils was performed based on C5a-induced chemotaxis and CD11b expression. A similar PD assay was performed on blood samples from mice dosed orally with CCX168. PK/PD requirements were defined for complete inhibition of C5aRmediated neutrophil activation and anti-MPO induced GN by CCX168 in transgenic C5aR knock-out mice expressing human C5aR.

Results: CCX168 potently blocks C5a-mediated chemotaxis of human neutrophils in human blood (IC_{50} 2 nM) and CD11b upregulation (IC_{50} 4 nM). CCX168 was well tolerated, with excellent oral bioavailability and dose-proportional increases in exposure in both periods of the Phase-1 clinical study. No serious adverse events or withdrawals due to adverse events were observed. Plasma levels of CCX168 of 197 ng/mL (~400 nM) were reached after a 100-mg dose. These levels of CCX168 far exceed those required in the anti-MPO mouse model for near-maximal GN prevention. Twelve hours following a 100-mg single dose of CCX168 in HVs, there was a 94% reduction in C5a-induced CD11b upregulation on blood neutrophils (*ex vivo* PD assay). At this dose, plasma distribution half-life was 7.8 hours and terminal half-life was about 29 hours.

Conclusions: CCX168 showed an excellent safety and tolerability profile in HVs. PK and PD data indicate that 30–50 mg CCX168 bid in humans should result in greater than 90% C5aR coverage in blood at all times, considered optimal for CCX168 evaluation in Phase 2 trials in vasculitis.

Disclosure: D. J. Dairaghi: Chemocentryx, 3; **J. C. Jaen:** Chemocentryx, 3; **K. Deshayes:** Chemocentryx, 3; **D. A. Johnson:** Chemocentryx, 3; **M. R. Leleti:** Chemocentryx, 3; **S. Miao:** Chemocentryx, 3; **J. P. Powers:** Chemocentryx, 3; **L. C. Seitz:** Chemocentryx, 3; **Y. Wang:** Chemocentryx, 3; **T. J. Schall:** Chemocentryx, 3; **P. J. Bekker:** Chemocentryx, 3.

2033

Predictors of Outcome in Juvenile Polyarteritis Nodosa: A Multicenter Study. Fernanda Falcini[1], Francesco La Torre[7], Giorgia Martini[7], Fabio Vittadello[7], Antonella Boncompagni[10], Fabrizia Corona[6], Maria Alessio[3], Elisabetta Cortis[2], Silvia Magni-Manzoni[8], Giuseppina Calcagno[5], Luciana Breda[4], Matilde Beltramelli[6], Manuela Pardeo[9], Serena Capannini[1], Marco Matucci Cerinic[1] and Francesco Zulian[7]. [1]Dpt of BioMedicine, Division of Rheumatology, Transition Unit, University of Florence, [2]Dpt of Medicine, Division of Rheumatology, Ospedale Pediatrico, [3]Dpt of Pediatrics, Rheumatology Unit, Ospedale Federico II, [4]Dpt of Pediatrics, University of Chieti, Chieti, [5]Dpt of Pediatrics, University of Messina, [6]Dpt of Pediatrics, University of Milan, [7]Dpt of Pediatrics, University of Padua, [8]San Matteo Hospital, Pavia, [9]Scientific Institute Bambino Gesu, Rome, [10]Scientific Institute G. Gaslini, Genoa

Background: Polyarteritis nodosa (PAN) is a necrotizing vasculitis, seldom reported in childhood and adolescence. The disease is more frequent in Asian populations but it has been reported in all ethnical groups.

Aims: 1.To describe the clinical features, at onset and during the disease course; 2.To look for possible predictive factors related with outcome or persistent damage in a cohort of Italian pts with paediatric onset PAN.

Method: A retrospective data collection of demographic, clinical and therapeutic characteristics from 50 Caucasian pts (21M, 29F) fulfilling EULAR/PRES criteria for the diagnosis of PAN, from 8 Paediatric Rheumatology Units and 1 Transition Unit, were collected. Mean age at onset was 7.9 yrs (range 2–16 yrs) and the mean follow up 6.2 yrs (range 0.3–16.4 yrs).Correlation among symptoms and internal organs involvement at onset, during the disease course and final outcome or persistent damage was made.

Results: At onset, skin involvement and systemic symptoms were the most common findings in 36/50 pts (72%); nodules the main cutaneous manifestation (40%), fever the most frequent systemic symptom (66%). Other early clinical manifestations were musculo-skeletal symptoms (54%), renal (12%), CNS involvement (10%), peripheral nervous system (6%), cardiac involvement (6%), and gastrointestinal manifestations (4%). All pts received corticosteroids either oral or IV, 16 pts (32%) azathioprine, 20 pts cyclophosphamide (20%, 15 oral and 5 iv), 9 (18%) thalidomide, 7 (14%) IVIG, 5 (10%) methotrexate, 4 (8%) mycophenolate mofetil, and 2 (4%) biological agents (etanercept and infliximab). At the last follow up visit, 25 pts (50%) were in remission off therapy, 17 (34%) were under control on immunosuppressive drugs and 6 (12%) had persistent relapsing course. Two pts deceased because of ischemic cerebral infarction. At onset, the presence of renal involvement and fatigue significantly correlated with a bad outcome. CNS involvement, as seizures and paralysis, and nephrogenic hypertension, during the disease course, significantly correlated with the development of persistent damage.

Conclusion: The present study shows that in Caucasian children, PAN is quite severe despite the use of immunosuppressive drugs. Renal and CNS involvement seem to be the main factors affecting the final outcome.

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2034

Pregnancies in Systemic Necrotizing Vasculitides: Report on 12 Women and Their 20 Pregnancies. Christian Pagnoux[3], Véronique Le Guern, François Goffinet[1], Elisabeth Diot, Nicolas Limal, Emmanuelle Pannier, Ursula Warzocha, Vassilis Tsatsaris, Robin Dhote, Alexandre Karras, Pascal Cohen, Richard Damade, Luc Mouthon and Loic P. Guillevin[2]. [1]Gynecology and Obstetrics, [2]Hopital Cochin-Paris Univ, Paris, France, [3]Hopital Cochin-Paris Universite Descartes, APHP, Paris, France

Objective: To describe pregnancies of women with systemic necrotizing vasculitides (SNV), i.e., polyarteritis nodosa (PAN), Wegener's granulomatosis (WG), Churg–Strauss syndrome (CSS) or microscopic polyangiitis (MPA), followed over the past 15 years at 4 French centers.

Methods: Retrospective analysis of women whose SNV appeared during pregnancy or who became pregnant after SNV diagnosis.

Results: Among the 12 women identified, 1 had rupture of pancreatic artery microaneurysms at 27 weeks of gestation revealing PAN, leading to surgical hemostasis and cesarean delivery. Other 11 had 19 pregnancies after SNV diagnosis (8 in 4 WG, 6 in 3 CSS, 1 each in 3 PAN, and 2 in 1 MPA); 14 conceived during vasculitis remission. Two ended in first-trimester

abortions, 4 miscarried; the remaining 13 yielded 14 live newborns (1 twin pregnancy), with 7 preterm births. Life-threatening complications occurred during 3 of these latter 13 pregnancies and required cesarean deliveries. The twin pregnancy (in a CSS patient with initial vasculitis-related cardiac involvement, but in remission at conception) was complicated by transient maternal cardiac failure at 32 weeks. One WG patient with vasculitis-related renal damage developed thrombotic microangiopathy-associated renal impairment at 32 weeks, and another WG patient had severe pneumonia at 37 weeks. Other pregnancies were uneventful or with minor vasculitis manifestations.

Conclusion: Pregnant SNV patients should be closely monitored, since miscarriages and preterm births are not uncommon. Pregnancy does not seem to have a major impact on vasculitis activity. However, life-threatening manifestations can occur, especially in patients with vasculitis-related cardiac or renal damage.

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2035

Pregnancy Related Morbidity and Mortality in Patients with Systemic Vasculitis—A Single Centre Controlled Study. Shirish R. Sangle[1], Periklis Vounotrypidis[2], Ahlem Chaib[2], Veronica Salas-Manzanedo[2], Annette I. Briley[1], Simon Angel[1], Andrew Shennan[1], Munther A. Khamashta[1] and David P. D'Cruz[1]. [1]St Thomas' Hospital, London, United Kingdom, [2]St Thomas' Hospital

Objective: To study the outcome of pregnancy and effect of pregnancy on disease activity in patients with systemic vasculitis (SV) compared to age and ethnicity matched controls

Patients and Methods: We retrospectively studied 20 SV patients and 25 pregnancies attending the clinic since 1998. There were 4 with Wegener's WG), 3 Churg-Strauss syndrome (CSS), 3Takayasu arteritis (TA), and 2 ANCA positive vasculitis with renal involvement and 1 Henoch Schonlein purpura (HSP). All fulfilled the Chapel Hill Consensus Criteria and/ or ACR Criteria for SV. Two others had Behcet's disease, 3 urticarial vasculitis (UV), 1 adult onset Still's disease (AOSD) and 1 primary cerebral vasculitis (PCV). Two patients with WG had 2 pregnancies each and each patient with CSS, TA and UV had 2 pregnancies. Details regarding the duration of SV, antibody and hepatitis profile, disease activity—Birmingham vasculitis disease activity score (BVAS) and vasculitis damage index (VDI) were retrospectively evaluated from the notes during the pregnancy. Pregnancy outcome along with maternal and foetal complications were documented. Data regarding 19 healthy women who were matched for age, ethnicity and year of delivery formed the control group which was collected from the Obstetrics database of St Thomas' Hospital.

Results: The median age of the patients at the conception was 36 (24–46) and in the control group 36 (25–43) years. There were 16 Caucasian, 3 Asian and 1 Afro Caribbean in the SV group and 16 Caucasian, 2 Asian and 1 Afro Caribbean in the control subjects. The mean duration of SV was 3 (0–14) years. Six patients were receiving prednisolone, 10 azathioprine, 3 hydroxychloroquine and 2 no treatment during the pregnancy.

In the SV group, there were 19 successful pregnancies. There were 16 miscarriages in 7 patients. Median age of the gestation in SV was 38 (34–42) and in the controls 40 (37–42) weeks. Median birth weights in the SV group was 3.0 (2.0–5.2) and in the control subjects was 3.5 (2.28–4.32) kgs (p = NS). Six patients had pregnancy morbidity: 2 had pre-eclamptic toxemia (PET), 2 each had still births and premature deliveries and 1 patient had a post partum haemorrhage (she received heparin during pregnancy). In the control group 2 had miscarriages and 1 had PET. One patient with WG and HSP flared during the pregnancy and one other with WG required surgery in the 3rd trimester for subglottic stenosis. Eight patients with SV (2 WG, 1 each of HSP, CSS, TA, UV, AOSD and ANCA positive) flared after delivery. Four women were positive for antiphospholipid antibodies (aPL) and 2 had previous miscarriages. Three patients in the SV and 4 in the control groups were smokers. The median BVAS during pregnancy was 2 (range 1–5) and VDI was 2 (range 1–3).

Pregnancies	Miscarriages	PET*	Still birth	Premature	Postpartum bleed	Smoking	Med Gest age*	Medn Birth wt**	Median age
Vasculitis N=25	16 in 7 patients	2	2	2	1	3	38	3.0	36
Control N=21	2	1	0	0	0	4	40	3.5	36

*+PET: Pre-eclamptic toxaemia
+*Median gestational age
**Median birth weight

Conclusions: Patients with systemic vasculitis are likely to flare during pregnancy and the post-partum period and may have significant pregnancy morbidity.

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2036

Preliminary Classification Criteria for the Cryoglobulinemic Syndrome. Salvatore De Vita[18], Franca Soldano[3], Miriam Isola[3], Giuseppe Monti[12], Armando Gabrielli[14], Athanasios Tzioufas[7], Clodoveo Ferri[20], Gianfranco Ferraccioli[19], Luca Quartuccio[17], Laura Corazza[17], Ginevra De Marchi[17], Manuel Ramos-Casals[16], Michael Voulgarelis[5], Marco Lenzi[4], Francesco Saccardo[12], Paolo Fraticelli[14], Maria Teresa Mascia[20], Domenico Sansonno[23], Patrice Cacoub[2], Matja Tomsic[8], Antonio Tavoni[21], Maurizio Pietrogrande[11], Anna Linda Zignego[1], Salvatore Scarpato[22], Cesare Mazzaro[6], Paolo Pioltelli[13], Serge Steinfeld[9], Peter Lamprecht[10], Stefano Bombardieri[21] and Massimo Galli[15]. [1]Center for Systemic Manifestations of Hepatitis Viruses (MaSVE), Department of Internal Medicine, University of Florence, Florence, Italy, [2]Centre de Références Maladies Auto-Immunes, Service de Médecine Interne II, Hôpital Pitié-Salpêtrière, Paris, France, [3]Chair of Statistics, University of Udine, [4]Department of Clinical Medicine, University of Bologna, S. Orsola-Malpighi Hospital, Bologna, Italy, [5]Department of Hematology, Medical School, University of Athens, Greece, [6]Department of Internal Medicine, Pordenone General Hospital, Pordenone, Italy, [7]Department of Pathophysiology, Medical School of Athens, Athens, Greece, [8]Department of Rheumatology, University Medical Centre, Ljubljana, Slovenia, [9]Erasme University Hospital, Department of Rheumatology, Brussels, Belgium, [10]Institute of Immunology, University of Kiel, Kiel, Germany, [11]Internal Medicine Unit, Policlinico San Marco, Bergamo, Italy, [12]Internal Medicine Unit, Saronno Hospital, Azienda Ospedaliera di Busto Arsizio, Saronno, VA, Italy, [13]Internal Medicine, Donizetti Hospital, Monza, Italy, [14]Internal Medicine, Università Politecnica delle Marche, Ancona, Italy, [15]Istituto di Malattie Infettive e Tropicali, Università di Milano c/o Ospedale L. Sacco, Milan, Italy, [16]Laboratorio de Enfermedades Autoinmunes Josep Font, IDIBAPS, Hospital Clínic, Barcelona, Spain, [17]Rheumatology Clinic, AOU SMM, University of Udine, [18]Rheumatology Clinic, AOU SMM, University of Udine, Udine, Italy, [19]Rheumatology Division, Catholic University of the Sacred Heart, School of Medicine, Rome, Italy, [20]Rheumatology Unit, Department of Internal Medicine, University of Modena, Italy, [21]Rheumatology Unit, Department of Internal Medicine, University of Pisa, Pisa, Italy, [22]Rheumatology Unit, M. Scarlato Hospital, Scafati, Salerno, Italy, [23]Section of Internal Medicine and Clinical Oncology, Department of Biomedical Sciences and Human Oncology, University of Bari, Medical School, Bari, Italy

Objectives: To develop international classification criteria for the CS.

Methods: The study was proposed by the GISC (Italian Study Group on Cryoglobulinemia), discussed between European EULAR experts, and divided in Part I, developing a questionnaire to be included in the formal, second part of the study (Part II). Positivity of serum cryoglobulins was defined as a "condition sine qua non" for CS classification. In Part I experts agreed on 17 questions putatively more sensitive and specific for CS. The questionnaire was administered to CS patients and controls (with diseases to be differentiated from CS). Study Part II involved 16 Centres from Italy and Europe. A dedicated chart included 1) a questionnaire for CS (with the discriminant questions identified by study Part I); 2) the pattern of organ involvement; 3) laboratory tests; 4) instrumental tests, as agreed. New patients with the CS (Group A) and controls, i.e., subjects with serum cryoglobulins but lacking a CS based on the golden standard judgment (Group B) and subjects without serum cryoglobulins but with clinico-laboratory features which can be observed in the course of CS (Group C)), were studied. Monovariate and multivariate analyses, additive or multiplicative combinations of items in terms of sensitivity and specificity, and the best combination

among the set of questions, clinical features and laboratory tests, were analyzed.

Results: In Part I, among 472 questionnaires (188 cases, 284 controls), a positive response to at least 2 of 3 selected resulted the best combination, showing a sensitivity of 81.9% and a specificity of 83.5% for CS. Study Part II included 272 patients in Group A, 228 controls in Group B, and 425 controls in Group C (173 C1 and 252 C2). The questionnaire developed in study Part I was validated, showing 83.8% $CI_{95\%}$ [79.4–88.2] sensitivity and 93.8% $CI_{95\%}$ [90.7–97.0] specificity for CS. The final Classification Criteria for CS, by pooling Group A and Group B data, are shown: at least 2 out of the following three anamnestic, clinical and laboratory items (questionnaire+ clinical; questionnaire + laboratory; or clinical + laboratory) provided a sensitivity of 88.5% $CI_{95\%}$ [84.3–92.8] and a specificity of 93.6% $CI_{95\%}$ [89.5–97.7] for CS. The same criteria proved also useful for the comparison of group A vs. C, to suspect a CS in patients cryoglobulin-negative by initial testing, since sensitivity for CS was 88.5% $CI_{95\%}$ [84.3–92.8]) and specificity 97.0% $CI_{95\%}$ [94.6–99.4] (a sensitivity of 88.5% [84.3–92.8] and a specificity of 95.4% [90.9–99.8] respectively, when comparing A only with the C1/ systemic vasculitis subgroup).

Preliminary Classification Criteria for the CS

satisfied if at least 2 of the 3 items (questionnaire, clinical , laboratory) are positive

i. Questionnaire item: at least 2 out of the following

- Do you remember one or more episodes of small red spots on your skin, particularly involving the lower limbs?
- Had you ever had red spots in your lower extremities which leave a brownish color after their disappearance?
- Did a doctor ever tell you that you have viral hepatitis?

ii. Clinical item : at least 3 out of the following 4 (present or past)

• Constitutional symptoms	Fatigue
	Low grade fever (37-37.9°C, >10 days, no cause)
	Fever (>38°C, no cause)
	Fibromyalgia
• Articular involvement	Arthralgias
	Non erosive arthritis
	Erosive arthritis
• Vascular involvement	Raynaud's phenomenon
	Purpura
	Necrotizing vasculitis
	Skin ulcers
	Hyperviscosity syndrome
• Neurologic involvement	Peripheral neuropathy
	Cranial nerve involvement
	CNS involvement
	Autonomic dysfunction

iii. Laboratory item : at least 2 out of the following 3 (present)

- Reduced serum C_4
- Positive serum rheumatoid factor
- Positive serum M component

Conclusion: International classification criteria for the CS were developed, including items easily accessible, and showing a very high specificity and a good sensitivity. A validated questionnaire is available for epidemiologic studies.

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2037

Primary Central Nervous System Vasculitis Presenting with Intracranial Hemorrhage. Carlo Salvarani[1], Robert D. Brown, Jr[3], Kenneth T. Calamia[2], Teresa J. H. Christianson[3], John Huston III[3], James F. Meschia[2], Caterina Giannini[3] and Gene G. Hunder[3]. [1]Hospital of Reggio Emilia, Italy, [2]Mayo Clinic, Jacksonville, FL, [3]Mayo Clinic, Rochester, MN

Objective: Primary Central Nervous System Vasculitis (PCNSV) is an uncommon and heterogeneous condition that affects the brain and spinal cord. This study was undertaken to evaluate the clinical features and outcomes of patients who presented with intracranial hemorrhage (IH) in the context of the largest cohort of consecutive patients with PCNSV studied to date.

Methods: We identified 131 consecutive patients with PCNSV seen over the 25 year period of 1983 to 2007. PCNSV diagnoses were based on findings from a central nervous system (CNS) biopsy or conventional angiography (or both). We compared patients presenting with IH (within 3 months of the date of PCNSV diagnosis) to those without. We evaluated data on demographics, clinical findings, laboratory studies, imaging, biopsy of brain or spinal cord (or both), treatment and neurologic outcome.

Results: 16 (12.2%) cases had IH at presentation.12 patients had intracerebral hemorrhage (ICH), and 4 subarachnoid hemorrhage. Cerebral angiography was performed in 13 patients and showed multiple-vessel vasculitic changes in all. CNS biopsy findings were positive in 4 patients. Three patients had an acute necrotizing pattern, one had a granulomatous inflammatory pattern. Amyloid angiopathy was observed in 2 biopsy-positive specimens.

Compared with the 115 patients without, the 16 patients presenting with IH were more frequently females (100% versus 50.4%, $p < 0.001$), persistent neurological deficit or stroke (12.5% versus 42.6%, $p = 0.027$) and altered cognition (25% versus 56.5%, $p = 0.030$) occurred less frequently, and the frequency of patients who had discontinued therapy by the last follow-up visit was higher (37.5% versus 14.2%, $p = 0.031$). MRI and angiographic findings (excepted the presence of ICH), type of therapy (corticosteroids only or associated to immunosuppressive agents), therapy duration, frequencies of relapses, cerebrospinal fluid abnormalities, and Rankin disability score at last follow-up were similar. The survival curves of patients with and without IH were not different.

Conclusion: IH is not a rare presenting finding of PCNSV. These patients are predominantly females. The higher frequency of patients not requiring therapy at last follow-up suggests a more favorable response to therapy. An association with amyloid angiopathy may be present

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2038

Primary Central Nervous System Vasculitis: Analysis of 131 Patients. Carlo Salvarani[1], Robert D. Brown, Jr[3], Kenneth T. Calamia[2], Teresa J. H. Christianson[3], John Huston III[3], James F. Meschia[2], Caterina Giannini[3] and Gene G. Hunder[3]. [1]Hospital of Reggio Emilia, Reggio Emilia, Italy, [2]Mayo Clinic, Jacksonville, FL, [3]Mayo Clinic, Rochester, MN

Purpose: To analyze the clinical findings, response to therapy, outcome, and clinical subsets of primary central nervous system vasculitis (PCNSV) in a large cohort from a single center.

Methods: In the present study we use our updated cohort of 131 consecutive patients with PCNSV seen over the 25 year period of 1983 to 2007 at Mayo Clinic, Rochester, MN. The diagnosis of PCNSV was based on brain/spinal cord biopsy or cerebral angiography. The modified Rankin scale was used to evaluate the functional status. CNS tissue specimens from 63 cases were examined histologically. Clinical findings and outcomes were compared among patients categorized by method of diagnosis, response to therapy, survival, and degree of disability.

Results: Ninety patients were diagnosed by angiography and 41 by CNS biopsy. A granulomatous inflammatory histologic pattern was found in 23 patients (accompanied by vascular deposits of amyloid beta peptide in 11), a granulomatous and necrotizing pattern in 1, an acute necrotizing pattern in 9, and a lymphocytic pattern in 6. Headache (61.8%), altered cognition (52.7%), hemiparesis (40.5%), and persistent neurologic deficit or stroke (38.9%) were the most common initial symptoms. Intracranial hemorrhage occurred 16 cases (12.2%) within 3 months of the date of PCNSV diagnosis. Erythrocyte sedimentation rates at diagnosis were normal in most of the patients (median: 8 mm/hr, range: 0–110 mm/hr). Cerebrospinal fluid specimens showed 1 or more abnormal findings for 81/101 (80.2%) patients. Of the 97 patients with angiograms showing vasculitic changes, multiple-vessel abnormalities were bilateral in 94.8%. Magnetic resonance imaging (MRI) was performed initially in 118 patients and showed abnormal findings in 113 (95.8%). Infarctions were seen in 65 (55.1%). Bilateral multiple infarctions were found in 48 of the 65 (73.8%) patients. Gadolinium-enhanced intracranial lesions were observed in 39% of the patients. Glucocorticoid therapy was prescribed for 128 of the 131 patients. In 55 patients, glucocorticoids were the only therapeutic agents used, while 73 patients received medication in addition to glucocorticoids (cyclophosphamide in 60 patients). A favourable response to glucocorticoid alone was observed in 78% and to glucocorticoid plus cyclophosphamide in 76%. 26% had relapses that led to a change in therapy. Survival of patients with PCNSV was significantly reduced. The reduced survival rate was due to 10 patients who died for stroke-related fatalities within 6 months after the diagnosis. These patients more frequently had paraparesis/quadriparesis at presentation, angiographic presence of bilateral, larger-vessel vasculitis, and MRI evidence of multiple and bilateral cerebral infarctions.

Conclusions: PCNSV is a rare disease that may result in serious neurological outcomes or death. Angiography and brain biopsy may complement each other when determining the diagnosis. Early recognition and treatment may reduce poor outcomes.

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2039

Prognostic Factors in Hepatitis C Virus Patients with Systemic Vasculitis. Benjamin Terrier[1], Oren Semoun[2], David Saadoun[1], Damien Sène[1], Matthieu Resche-Rigon[2] and Patrice Cacoub[1]. [1]Pitié-Salpéterière, [2]Saint-Louis

Objective: Hepatitis C virus (HCV)-related systemic vasculitis can cause significant morbidity and mortality. Most of the prognostic studies reported in the literature are derived from old heterogeneous studies performed before the antiviral therapy era.

Methods: 151 consecutive HCV RNA+ patients with systemic vasculitis prospectively followed-up between 1993 and 2009 were analyzed for clinical, biological and therapeutic factors associated with survival.

Results: After a median follow-up of 54 months, 32 patients (21%) died, mainly of infection (n=10) and end-stage liver disease (n=10). One-year, 3-year, 5-year and 10-year survival rates were 96, 86, 75 and 63%, respectively. Baseline factors associated with a poor prognosis were the presence of severe liver fibrosis (Metavir score $\geq$ 3) [hazard ratio (HR) 5.31], central nervous system (HR 2.74), kidney (HR 1.91), and heart involvement (HR 4.2). The Five Factor Score (FFS), a vasculitis scoring system, was significantly associated with outcome in HCV-related systemic vasculitis patients. In multivariate analysis, the Metavir liver fibrosis score (HR 10.8) and the FFS (HR 2.49) were significantly associated with a poor prognosis. During the follow-up, the use of the Peg-interferon plus ribavirin combination was associated with a good prognosis (HR 0.34). on the contrary, the use of immunosuppressant agents was associated with a poor outcome after adjustment for vasculitis severity (HR 4.05). In patients without severe liver fibrosis, the FFS was a good predictor of outcome, while in those with severe fibrosis, the vasculitis severity no longer had prognostic value.

Conclusion: In HCV-related systemic vasculitis patients, at the time of vasculitis diagnosis, severe liver fibrosis and vasculitis severity are the main prognostic factors. Use of antivirals is associated with a good prognosis, whereas immunosuppressants have a negative impact.

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2040

Risk Factors for Aortitis among Patients with Pathological Examination after Resection of the Thoracic Aorta in Denmark 1997–2009: A 12-Year Nationwide Population-Based Cross-Sectional Study. Jean Schmidt[1], Kaare Sunesen[2], Jette Kornum[2], Pierre Duhaut[1] and Reimar Thomsen[2]. [1]Amiens University Hospital and RECIF, Amiens, France, [2]Department of Clinical Epidemiology, Aarhus University Hospital, Aalborg, Denmark

Background: Population-based data on prevalence and risk factors for aortitis are scarce. The aim of our study was to assess them in a nationwide population-based cross-sectional study in Denmark.

Patients and Methods: We identified all adults hospitalized for first surgery of the thoracic ascending aorta between January 1, 1997 and March 1, 2009. Aortic inflammation was ascertained by linkage with nationwide pathology databases. We used logistic regression to examine whether sex, age at surgery, cardiovascular risk factors, cancer, and infectious diseases were associated with aortitis.

Results: During the study period, 1,210 adults underwent a resection of the ascending part of the aorta, and 610 (50.4%) had a pathological examination. Aortitis was found in 37 (6.1%). Ten of the 37 patients were diagnosed with conditions associated with aortitis or aortic aneurysm: five with temporal arteritis, one with Crohn's disease, one with rheumatoid arthritis, one with systemic lupus erythematosus, one with infectious aortitis, and one with Marfan's disease. Twenty-seven patients had idiopathic aortitis. Predictors of aortitis included a history of connective tissue disease (adjusted OR 4.7, 95 % CI 1.6 to 13.6), diabetes (OR 5.2, 96% CI 0.9–29.7), age > 67 years (OR 2.5, 95% CI 0.8–7.6), and aortic valve pathology (OR 2.3, 95% CI 1.1–4.9).

Conclusions: Aortitis was present in 6.1 % of adults with ascending aorta resection. This highlights the relevance of systematic pathological examinations of aorta. Predictors of inflammation included connective tissue disease, with a tendency for diabetes and advanced age.

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2041

Rituximab Maintenance Therapy for Relapsed Wegener's Granulomatosis and Microscopic Polyangiitis. Claire Roubaud-Baudron[3], Christian Pagnoux[3], Julien Le Guen[3], Mathilde de Menthon[3], Sandra Camps[1], Jessie Aouizerate[3], Véronique Le Guern[3], Pascal Cohen[3], Luc Mouthon[3] and Loic P. Guillevin[2]. [1]Department of Pharmacy, Hopital COchin, APHP, Universite Paris Descartes, [2]Hopital Cochin-Paris Univ, Paris, France, [3]Internal Medicine, Hopital Cochin, APHP, Universite Paris Descartes, France

Background: After induction therapy, 50% of Wegener's granulomatosis (WG) and 33% of microscopic polyangiitis (MPA) patients relapse. Rituximab (RTX) effectively induced remission of 1st relapses and refractory disease, but its place in remission maintenance is unknown. In this study, we retrospectively analyzed RTX efficacy as maintenance therapy.

Methods: Patients entered in our department database who had received $\geq$2 RTX maintenance infusions, regardless of induction regimen, between 2003 and 2010, were selected. Their main characteristics (diagnosis, clinical and biological data (ANCA, CD19 and Ig levels) and treatment histories), RTX maintenance details (number, dose and periodicity), tolerance and outcomes were analyzed.

Results: Four MPA and 24 WG patients (median age 55.5 (range 18–78) yr; 18 (58%) men) were included. The cumulative median cyclophosphamide (CYC) dose was 48 (range 10–250) g. At last relapse, patients had several organ involvements: 19 ENT, 17 lung, 11 arthralgias, 11 fever, 9 nephropathy, 3 neuropathy and/or 4 eyes.

Induction treatment had been RTX for 21, conventional corticosteroid (CS)+CYC for 5, and IVIg for 2 (1 also with methotrexate). RTX maintenance (375 mg/m^2 biannually for 15 patients, 1 g biannually for 4, 1 g yearly for 3 and different regimens for 6) was chosen because RTX had obtained remission for 21, cytotoxic agent side effects for 2, persistent manifestations after >4 yr of azathioprine (AZA) or mycophenolate mofetil (MMF) for 1 each, previous relapse(s) under cytotoxic maintenance therapy for 2, or renal failure for 1. Patients had received 4 (range 2–10) RTX infusions at 38 (range: 21–97) months of follow-up since their last relapses. Cotreatments included CS for 23 (82%) patients and other cytotoxic agents (AZA for 5, MMF for 5, leflunomide for 1 and/or MTX for 4) for 14 (50%). At the last assessment, 5 (17%) patients were still taking cytotoxic agent(s); median CS dose was 5 (range: 2–20) mg/day. RTX infusions were well-tolerated; 3 patients developed infections (1 cutaneous abscess, 1 otitis and 1 H1N1-flu death).

Two major pulmonary relapses (at follow-up months 48 & 6) and 2 minor ENT relapses (at follow-up months 108 & 34) occurred. Fifteen patients had hypogammaglobulinemia (predominantly IgM). Notably, the 3 patients not CD19-depleted did not relapse. Nine (including 3/4 who relapsed) patients' CD19 levels rose before their biannual RTX infusion. Five patients ANCA-negative at vasculitis onset, remained so. ANCA levels increased before reinfusion in 7 (including 3/4 who relapsed) patients. Overall, at their last assessment, mean ANCA titers for all 28 patients had declined significantly since the last relapse and the last RTX infusion (ANOVA, $p<0.0001$).

Conclusions: RTX effectively maintained remission and was well-tolerated. It can be indicated, especially for noncompliant patients or when cytotoxic drugs are contraindicated. Only 2 major relapsed occurred. It is too early to conclude as to the place of CD19 and ANCA levels as indicators to determine infusion periodicity. The ongoing randomized controlled "MAINRITSAN" trial was designed to compare RTX to AZA maintenance therapy for ANCA-associated vasculitides.

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2042

Safety and Efficacy of Rituximab in Non-Viral Cryoglobulinemia Vasculitis: Prospective Data from the French AIR Registry. Benjamin Terrier[15], David Launay[6], Gilles Kaplanski[10], Arnaud Hot[9], Claire Larroche[1], Pascal Cathebras[12], Bernard Combe[11], Jean-Pierre Jaureguiberry[14], Olivier Meyer[3], Thierry Schaeverbeke[8], Alexandre Somogyi[5], Leila Tricot[13], Thierry Zenone[4], Philippe Ravaud[3], Jacques-Eric Gottenberg[7], Xavier Mariette[2] and Patrice Cacoub[15]. [1]Avicenne, [2]Bicêtre, [3]Bichat, [4]CH Valence, [5]CHI Saint-Germain, [6]CHRU Lille, [7]CHRU Strasbourg, [8]CHU Bordeaux, [9]CHU Lyon, [10]CHU Marseille, [11]CHU Montpellier, [12]CHU St Etienne, [13]CMC Foch, [14]HIA Toulon, [15]Pitié-Salpétrière

Background: Therapeutic management of non-hepatitis C virus cryoglobulinemia vasculitis (CryoVas) has still to be defined, although it is traditionally based on a combination of corticosteroids and immunosuppressants or plasmapheresis. Rituximab (RTX) has emerged as a novel and promising therapeutic alternative, but data are scarce since only few case reports have been reported in the literature.

Objectives: To evaluate safety and efficacy of RTX in non-viral CryoVas in off-trial real life patients.

Methods: Prospective data from the French AutoImmunity and Rituximab (AIR) registry, which includes patients with autoimmune disorders treated with RTX, were analyzed. The epidemiologic, clinical, and biologic data from every patient were collected at baseline, 3 and 6 month follow-up and then every 6 months. Toxicity and side effects were recorded on the standardized e-CRF.

Results: Twenty-three patients received treatment with RTX for non-viral CryoVas. Tolerance was marked by the occurrence of side effects in almost half of patients, including severe infections in 6/23 (26%), with a rate of 14.1/100 patient-years. These infections occurred in a particular subset of patients with age $>$ 70 years, essential type II mixed cryoglobulinemia, renal failure with GFR $<$ 60 mL/min and using high dose corticosteroids. Three of these patients died. In contrast, clinical and immunological efficacy was noted in all evaluable patients. Clinical relapses occurred in half of patients after a median time of 13.5 months following RTX administration and were more frequent in patients refractory to previous immunosuppressive therapy than in previously untreated patients.

Conclusion: Data from the AIR registry show a dramatic efficacy and a steroid-sparing effect of RTX, but the occurrence of severe infections in aged patients with renal failure and high dose steroids. The role of RTX in non-viral CryoVas remains to be defined in well designed randomized controlled trials.

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2043

Seasonal- (SFV) and H1N1-Flu Virus (HFV) Vaccination for Patients with Autoimmune Diseases (AID): The Prospective MAIVAX Trial on 174 Patients. Alex Kostianovsky[2], Michele Goulet[2], Jean Francois Alves[2], Veronique Le Guern[2], Christian Pagnoux[2], Pascal Cohen[2], Alice Berezne[2], Anne Krivine[2], Luc Mouthon[2], Odile Launay[2] and Loic P. Guillevin[1]. [1]Hopital Cochin-Paris Univ, Paris, France, [2]Internal Medicine, Hopital Cochin, APHP, Universite Paris Descartes, Paris, France

Objective: The theoretical risk for AID and immunosuppressed patients exposed to the new H1N1 flu pandemic in June 2009, along with the historical debate on the role of vaccination in the context of AID relapses, led us to evaluate the efficacy and safety of SFV and HFV vaccinations in AID patients treated or not with immunosuppressants (IS).

Patients and Methods: A monocenter vaccine phase III prospective open study on 174 patients was conducted from September 2009 to June 2010. Subjects received SVF (1 dose, Mutagrip®) and/or non-adjuvant HFV (Panenza®, 2 doses at a 3-wk interval) vaccines. Due to their dates of commercial availability, SFV was administered 3 wk before HFV. The primary judgment criterion was the seroprotection rate: the % patients with positive anti-hemagglutinin–Ab titers (PAT) $\geq$1/40: 3 or 9 wk after SFV and 3 wk after the 2nd HFV shots. Secondary outcome measures were seroconversion rates, vaccine tolerance (no fever $>$37.8°C and/or local signs during the 3 days postinoculation), and numbers of flu syndromes (fever + cough and/or throat pain) and AID flares throughout the pandemic.

Results: AID included were: 62 systemic vasculitides (polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome (CSS), Behçet's disease and cryoglobulinemia), 32 progressive systemic sclerosis (PSS), 29 systemic lupus erythematosus (SLE), 23 Sjögren syndrome (SS, with detectable autoAb) and 28 others. After SFV inoculation, 79.13% of the patients were seroprotected (110/139, 106 tested 3 wk and 4 tested 9 wk postvaccination, had PAT), 64 (46%) seroconverted (prevaccination PAT rose 4-fold for 14), 37 (26.6%) had prevaccination PAT; 2 (1.4%) became febrile and 27 (19.4%) developed local signs post-vaccination. After HFV immunization, 65% of the patients (113/174 with PAT) were seroprotected, 94 (54%) seroconverted (prevaccination PAT rose 4-fold for 7), 19 (10.9%) had prevaccination PAT; 6 had become HFV-positive after SFV immunization; 8 (4.6%) developed a fever (6 after the 1st dose and 2 after the 2nd dose) and 39 (22.4%) had local signs.

Concerning adverse events occurring during the study, among 12 patients developing 15 flu syndromes, 2 were temporally related to both vaccines (same patient); 1 patient died of septic shock and 2 AID flares were temporally related to inoculation: polyneuritis in a CSS patient (3 days after the 1st HFV dose), and severe myalgias and arthralgias in a PSS patient (10 days post SFV injection); 4 temporally unrelated AID flares occurred (2 PSS, 1 SLE and 1 SS).

Conclusion: Given the low rates of temporally associated events, tolerance of both vaccines was acceptable. The seroprotection rate was higher after SFV than HFV immunization, for similar seroconversion rates. Potential relationships between these data and ongoing IS are being analyzed. Notably, SFV induced PAT against the H1N1 virus in a minority of patients. Our findings demonstrated the safety and efficacy of SFV and HFV vaccination in AID patients.

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2044

Small-Vessel Vasculitis Surrounding an Uninflamed Temporal Artery: A Population-Based Italian Study. Giovanna Restuccia, Luigi Boiardi, Alberto Cavazza, Luca Magnani, Maria Grazia Catanoso, Gianluigi Bajocchi, Fulvia Rossi, Pierluigi Macchioni, Ilaria Chiarolanza, Andrea Caruso, Nicolò Pipitone and Carlo Salvarani. Arcispedale S Maria Nuova, Reggio Emilia, Italy

Purpose: Small-vessel vasculitis (SVV) surrounding an uninflamed temporal artery (TA) is an often neglected pathological form of giant cell arteritis (GCA). A recent study showed a strong association between SVV and polymyalgia rheumatica (PMR). The aim of this study was to evaluate the prevalence and clinical significance of SVV surrounding an uninflamed temporal artery (TA) in an Italian population-based cohort of patients who received TA biopsy for a suspected diagnosis of GCA.

Methods: All TA biopsies performed in our Hospital between January 1986 and December 2005 were reviewed by a pathologist (AC) who was blinded to the clinical diagnosis. SVV was defined as aggregates of mononuclear inflammatory cells surrounding a capillary, distant from an uninflamed temporal artery. 180 patients residing in Reggio Emilia area with biopsy-proven GCA and 44 with SVV were identified. The identified patients with SVV were randomly matched to an equal number of biopsy-proven GCA patients. All inpatient and outpatient medical records were reviewed. Demographic, clinical, and laboratory data of patients in SVV group (n = 44) were compared with data of control group with biopsy proven GCA (n = 47).

Results: The table shows the comparisons between the patients with SVV and those with biopsy proven GCA.

Table. Characteristic of the patients with SVV compared to those of the patients with biopsy proven-GCA

	Patients with SVV (N=44)	Patients with biopsy proven GCA (N=47)	P
Male/female	18 (40.9%)/27 (59.1%)	13 (27.7%)/34 (72.3%)	0.194
Age at disease onset, Years mean ±	72 ± 11	75 ± 7	0.285
Headache	17/43 (39.5%)	33/47 (70.2%)	0.006
Scalp tenderness	1/42 (2.4%)	14/45 (31.1%)	0.000
Abnormalities of temporal arteritis	10/21 (47.6%)	29/33 (87.9%)	0.002
Visual loss	6/43 (14.0%)	7/47 (14.9%)	1.000
Jaw claudication	2/43 (4.7%)	14/47 (29.8%)	0.002
Systemic signs/symptoms	25/43 (58.1%)	37/47 (58.1%)	0.042
Polymyalgia rheumatica	24/43 (55.8%)	22/47 (46.8)	0.408
ESR at diagnosis, mm/hour; mean ± SD	84 ± 32	102 ± 21	0.008
CRP at diagnosis, mg/dl; mean ± SD	6.4 ± 6.4	9.9 ± 5.7	0.001
Initial prednisone dose, mg/day; mean ± SD	31.4 ± 17.5	65.1 ± 84.8	0.0001
Duration of prednisone therapy, months; mean ± SD	30.84 ± 35.60	35.14 ± 48.02	0.639
Cumulative prednisone dose, mg; mean ± SD	5,997 ± 7,610	9,459 ± 7,627	0.006
Duration of follow-up, months; mean ± SD	68.51 ± 52.56	48.30 ± 39.54	0.068
Relapse/recurrences	7/24 (29.2%)	14/40 (35.0%)	1.000

Conclusion: SVV appears to be a less severe form of GCA characterized by a reduced frequency of cranial manifestations, lower values of ESR at diagnosis, and lower cumulative prednisone dose. Differently from previous findings, SVV was not associated with PMR.

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2045

Systemic Necrotizing Vasculitides in the Elderly: Baseline Data on the 101 Patients ≥65 Years Old Enrolled in the CORTAGE Multicenter Trial. Christian Pagnoux[8], Florence Rollot[9], Thomas Quemeneur[7], Jacques Ninet[4], Elisabeth Diot[3], Xavier Kyndt[7], Benoît de Wazières[12], Jean-Luc Reny[2], Xavier J. Puechal[1], Pierre-Yves Leberruyer[13], Olivier Lidove[11], Pascal Godmer[10], Aimé Albath-Sadiki[14], Severine Poignant[14], Pascal Cohen[8], Luc Mouthon[8], Loic P. Guillevin[6] and The FVSG[5]. [1]Centre Hospitalier Du Mans, Le Mans, France, [2]CH Béziers - Narbonne, [3]CHRU TOurs, Medecine Interne, [4]CHU de Lyon - Hôpitale Edouard Herriot, Médecine Interne-Pathologie Vasculaire, [5]France, [6]Hopital Cochin-Paris Univ, Paris, France, [7]Internal Medicine, CH Valenciennes, [8]Internal Medicine, Hopital Cochin, APHP, Universite Paris Descartes, [9]Internal Medicine, Hopital Cochin, APHP, Universite Paris Descartes, [10]Medecine Interne, Centre Hospitalier Bretagne-Atlantique, BP 70555 56017 VANNES, [11]Medecine Interne, CHU Bichat, Paris Diderot, [12]Medecine Interne, CHU de Nimes, [13]Service de Medecine Interne. CHU Robert Debré. Avenue du Général Koenig. 51092 REIMS, [14]URC Cochin Tarnier, Paris Descartes

Objective: To analyze baseline characteristics of patients with systemic necrotizing vasculitides (SNV; polyarteritis nodosa (PAN), Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), Churg–Strauss syndrome (CSS)) enrolled in the corticosteroid-based treatment for SNV patients aged ≥65 yr (CORTAGE) trial.

Methods: We analyzed their baseline clinical and biological manifestations, i.e., at diagnosis. At that time, patients were classified according to their prognostic five-factor score (FFS) and randomized to receive conventional treatment (corticosteroids alone for ~28 months for CSS or PAN patients with FFS=0; or combined with 500-mg/m2 cyclophosphamide pulses every 2 wk for the first 3 pulses then every 3 wk until remission, for WG or MPA patients, and CSS or PAN patients with FFS≥1, then switched to azathioprine or methotrexate for maintenance) or the experimental regimen (for all patients, corticosteroids for ~9 months, combined with cyclophosphamide pulses at a fixed 500-mg dose every 2 wk for the first 3 pulses then every 3 wk until remission, and switched after a maximum of 6 pulses to azathioprine or methotrexate for maintenance). The CORTAGE primary endpoint is morbidity at 3 years.

Results: Between July 2005 and February 2008, 108 patients were randomized; 7 were excluded (early consent withdrawn, protocol violation, wrong diagnosis). Mean age at diagnosis of the 101 analyzed patients (54 males, 47 females; 8 PAN, 12 CSS, 34 WG, 47 MPA) was 75.3 ± 6.3 yr, with a maximum of 92 years for 1 MPA patient. Sixteen PAN or CSS patients had FFS=0 (7/8 PAN, 9/12 CSS). Complete data on clinical features at diagnosis were comparably distributed between arms: 50 (50%) with fever, 36 (36%) arthralgias, 58 (57%) lung (15 nodules, 16 alveolar hemorrhages, 4 ARDS), 37 (37%) ENT, 20 (20%) GI, 18 (18%) heart (4 severe cardiac insufficiencies), 16 (16%) skin purpura, 13 (13%) ophthalmological (5 episcleritises), 24 (24%) PNS and 3 (3%) CNS manifestations. Mean creatinine was 236±210 μmol/l (61 microscopic hematuria, 8 initially required dialysis). Mean hemoglobin level was 10.2±2.0 g/dl, neutrophils 8538±4098/mm3, lymphocytes 1452±674/mm3, C-reactive protein 103±89 mg/l, albumin 28.0±6.3 g/l.

Seven (6.9%; 4 conventional-arm, 3 experimental-arm) patients died during induction. All had received cyclophosphamide: 4 (3 MPA, 1 WG) died of SNV progression, 2 (WG) of sepsis and 1 (MPA) of previously unknown cholangiocarcinoma.

Conclusion: Despite having severe disease, as reflected by their high mean creatinine level at diagnosis, mortality of SNV patients ≥65 years old included in the CORTAGE trial was relatively low during induction. Treatment-related morbidity and relapse rate remain to be determined (end of trial follow-up: April 2011).

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2046

Systemic Vasculitis in Patients with Hepatitis C Virus Infection with and without Detectable Mixed Cryoglobulinemia: Towards a Unique Entity. Benjamin Terrier[1], Damien Sène[1], Agnès Dechartres[2], David Saadoun[1], Lucile Musset[1], Matthieu Resche-Rigon[2], Thierry Maisonobe[1] and Patrice Cacoub[1]. [1]Pitié-Salpéterière, [2]Saint-Louis

Background: More than 80% of mixed cryoglobulinemia (MC) are associated with hepatitis C virus (HCV) infection. Some patients develop symptomatic MC, a systemic vasculitis that mainly affects the small and, less frequently, medium-sized vessels. MC vasculitis leads to clinical manifestations ranging from the so-called MC syndrome (purpura, arthralgia, and asthenia) to more serious lesions with neurologic and renal involvement. It has been described few patients with peripheral neuropathy occurring with HCV infection without detectable MC.

Objectives: To describe HCV-related systemic vasculitis without detectable MC and to compare them to typical HCV-MC vasculitis.

Methods: The study population consisted of 60 patients with HCV infection (HCV RNA+) and chronic active liver disease. The 12 cases (men/women 5/7, mean age 60±17 years) were defined as patients with histologically proven systemic vasculitis who had not shown evidence of MC on numerous occasions during a follow-up of 55±38 months. Each case was matched for age and sex with 4 controls. The 48 controls (men/women 20/28, mean age 60±14 years) were randomly selected from our data base of patients with typical HCV-MC, i.e. patients who had serum MC levels > 0.05 g/L on at least on two occasions associated with the triad of purpura/arthralgia/asthenia and sometimes renal or neurological involvement.

Results: The main epidemiological and virologic features were similar between cases and controls. No clinical difference was found, except for lower rates of arthralgia (33% vs. 71%, p=0.02) and purpura (50% vs. 83%, p=0.03) in cases. Cases compared to controls showed higher mean serum C3 (1.17 ± 0.21 vs. 0.93 ± 0.23 g/L, p=0.01) and median C4 levels (0.25 vs. 0.04 g/L, p<0.001), lower median serum IgM levels (0.6 vs. 1.9 g/L, p<0.001), and lower rates of rheumatoid factor positivity (8% vs. 82%, p<0.001). Main pathologic features were similar between cases and controls. After treatment, overall clinical response of vasculitis (75% vs. 83%) and sustained virological response (40% vs. 64%, p=0.3) were similar between cases and controls, except for higher complete clinical response (42% vs. 73%, p=0.05) in controls.

Conclusions: Practitioners should be aware of the occurrence of systemic vasculitis during HCV infection in the absence of detectable serum MC. Systemic vasculitis without MC showed quite similar epidemiological, clinical, biological, virologic and pathological features as MC vasculitis. Therapeutic management and response to therapy were also comparable between patients with and without MC. Such similarities suggest that vasculitis induced by chronic HCV infection, whatever the presence or the absence of MC, should be considered as a unique entity.

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2047

The Correlation between Circulating Microparticles and Platelet Aggregation and Disease Activity in Wegener Granulomatosis. Rula Hajj-Ali[3], Roy Silverstein[1], Gary Hoffman[1], Li Zhang[1], Peter Imrey[1] and Carol A. Langford[2]. [1]Cleveland Clinic, [2]Cleveland Clinic Foundation, Cleveland, OH, [3]Clevelnad Clinic, Cleveland, OH

Background: The objective of this study is to determine whether there are correlations between platelet aggregation and/ or circulating microparticles (MP) and disease activity in Wegener's granulomatosis (WG)

Methods: Eligible consenting adult patients who met the ACR 1990 classification criteria for WG were enrolled from the Cleveland Clinic Center for Vasculitis Care and Research. Controls were subjects who did not have WG or other chronic inflammatory diseases. Exclusion criteria for patients and controls included acute or chronic infection within the past 3 months, NSAID or aspirin use within a week of platelet and MP studies, or diagnosis of a chronic inflammatory diseases, an autoimmune disease, or thrombophilia. Data on WG disease activity was captured by BVAS-WG.

Platelet aggregation was assessed turbidometrically with a dual channel aggregometer using graded doses of ADP (1, 2, 5, and 10 μM). The change in light transmission after addition of ADP was recorded and expressed as a percentage of maximum deflection. MP counts were assessed by flow cytometry from platelet poor plasma. MP were stained by Annexin V and further characterized for cellular origin using specific antibodies to endothelial cells (CD105, CD144), platelets (CD41), leukocytes (CD18), neutrophils (CD16b) and monocytes (CD14). Each marker was assessed separately.

Results: 46 patients were included; 38 in remission and 8 during acute disease relapse. The two groups did not differ in age or gender. Subjects in relapse had

1- a significant increase in leukocyte derived MP compared to those in remission, and

2- platelets with increased sensitivity to activation by ADP (Table 1).

Table 1. Comparison of MP counts and platelet aggregation between flare and remission groups

Factor	Flare (N=8)	Remission (N=38)	P value
Age (years)	61 ± 13	54 ± 13	0.20
Female	5 (63)	17 (45)	0.45
CD14 - MP counts	477 (386, 797)	249 (67, 409)	0.030*
CD16 - MP counts	182 (127, 219)	56 (26, 100)	0.006*
CD18 - MP counts	257 (210, 314)	63 (36, 106)	0.002*
Platelet aggregation (1μM ADP)	28 (18, 38)	5 (2, 10)	0.005*
Platelet aggregation (2 μM ADP)	49 (43, 71)	19 (7, 26)	0.005*
Platelet aggregation (5 μM ADP)	82 (78, 98)	36 (26, 57)	0.009*
Platelet aggregation (10 μM ADP)	87 (78, 92)	51 (38, 70)	0.008*

Normally distributed data were expressed as mean ± SD and analyzed with the P from the T-test; Non-normally distributed data were expressed as median (25th, 75th) percentiles and analyzed with the P from the Wilcoxon rank sum test. N and percentage for categorical variables with Fisher exact test.

We also assessed the association of MP levels to platelet aggregation in WG vs. healthy controls (N=21). There were moderately positive linear relationships between levels of CD14, CD16 and CD18 expressing MP and platelet aggregation responses in WG patients. There were no statistically significant associations in the control group (Table 2).

Table 2. Correlation of Platelet aggregation and MP counts in WG and healthy controls

	Platelet aggregation	MP	N	rho	95%CI	P value
WG Patients	ADP 1μM	CD14	41	0.43	(0.14, 0.65)	0.006
		CD16	41	0.47	(0.19, 0.68)	0.002
		CD18	41	0.64	(0.41, 0.79)	<0.001
	ADP 2 μM	CD14	44	0.38	(0.09, 0.61)	0.011
		CD16	44	0.40	(0.12, 0.63)	0.007
		CD18	44	0.54	(0.28, 0.72)	<0.001
	ADP 5 μM	CD14	44	0.35	(0.06, 0.58)	0.021
		CD16	44	0.31	(0.01, 0.55)	0.042
		CD18	44	0.45	(0.18, 0.66)	0.002
	ADP 10 μM	CD14	41	0.32	(0.02, 0.57)	0.039
		CD16	41	0.30	(−0.01, 056)	0.058
		CD18	41	0.43	(0.14, 0.65)	0.005
Controls	ADP 1 μM	CD14	19	0.31	(−0.11, 0.84)	0.13
		CD16	19	0.25	(−0.18, 0.79)	0.13
		CD18	19	0.28	(−0.21, 0.77)	0.25
	ADP 2 μM	CD14	21	0.25	(−0.21, 0.72)	0.27
		CD16	21	0.18	(−0.29, 0.65)	0.43
		CD18	21	0.28	(−0.18, 0.74)	0.22
	ADP 5 μM	CD14	21	0.41	(−0.03, 0.85)	0.067
		CD16	21	0.37	(−0.08, 0.81)	0.1
		CD18	21	0.44	(0.01, 0.87)	0.046
	ADP 10 μM	CD14	20	0.08	(−0.41, 0.58)	0.73
		CD16	20	0.07	(−0.43, 0.56)	0.78
		CD18	20	0.15	(−0.33, 0.64)	0.52

Conclusions: Levels of leukocyte derived MP and sensitivity of platelets to ADP-induced aggregation correlate with disease flares in WG. The correlation between MP counts and platelet reactivity seen in WG but not controls suggest that elevated levels of leukocyte-derived MP generated during chronic inflammation may sensitize platelets to activation and contribute to athero-thrombotic complications. Whether these events also contribute to injury in WG is worthy further studies.

Disclosure: R. Hajj-Ali: American Heart Association, 2; **R. Silverstein:** NIH, 2; **G. Hoffman:** None; **L. Zhang:** American Heart Association, 2; **P. Imrey:** None; **C. A. Langford:** None.

2048

The Human C5a Receptor (hC5aR) Antagonist CCX168 Effectively Ameliorates a Model of ANCA Glomerulonephritis (GN) in hC5aR Knock-in Mice. Hong Xiao[2], J. C. Jennette[3], D. J. Dairaghi[1], L. Ertl[1], T. Baumgart[1], S. Miao[1], J. P. Powers[1], L. C. Seitz[1], Y. Wang[1], P. Hu[3], R. J. Falk[3], T. J. Schall[1] and J. C. Jaen[1]. [1]ChemoCentryx, [2]University of North Carolina, Chapel Hill, NC, [3]University of North Carolina

Purpose: Intravenous injection of mouse anti-myeloperoxidase (anti-MPO) IgG causes GN and vasculitis in mice that mimics antineutrophil cytoplasmic autoantibody (ANCA) disease in patients. We have shown that alternative pathway complement activation and resultant C5a are involved in pathogenesis. Here we study the effects on this model of CCX168, an orally active antagonist of human C5a receptor (hC5aR) that has completed Phase 1 trials. We also evaluated CCX168 pharmacokinetic, pharmacodynamic and therapeutic endpoints in mice using the same assays of hC5aR blockade used in the human Phase 1 trial.

Methods: Humanized mice with knock-in of human C5aR and knock-out of mouse C5aR (hC5aR KI mice) were injected with anti-MPO IgG; and received CCX168 doses ranging from 0.1–30 mg/kg qd, or vehicle alone. The potency of CCX168 for C5aR in hC5aR KI mice was assessed by 125I-C5a binding and chemotaxis assays. C5a-induced neutrophil CD11b expression was used to assess CCX168 C5aR blockade in mice and compared to results using the same assay in humans.

Results: CCX168 had similar C5aR antagonist potency on human and hC5aR KI mouse neutrophils (inhibition of C5a-mediated chemotaxis in blood, IC50 2 nM; inhibition of C5a-induced CD11b upregulation in blood, IC50 4 nM). 30 mg/kg CCX168 markedly reduced the severity of anti-MPO induced GN. Glomerular crescent formation was reduced from 29.3% with vehicle alone to 3.3% with CCX168 ($p<0.0001$) and glomerular necrosis from 8.2% to 1.1% ($p<0.0001$). Urine protein, leukocytes and RBCs, and serum BUN and creatinine also were reduced in mice receiving CCX168. 0.1 mg/kg/d CCX168 caused 30% reduction in crescents. The lowest dose that produced a near-maximal therapeutic benefit was 4 mg/kg CCX168 bid (with plasma levels from 35 to 200 ng/mL throughout the day, and C5aR blockade ranging from 95 to 99%). As reported in

a separate meting abstract, plasma CCX168 levels of 197 ng/mL (~400 nM) were reached with a 100-mg dose in a human Phase 1 trial.

Conclusions: Orally active human C5aR antagonist CCX168 markedly suppresses the induction of GN by anti-MPO IgG in mice with knocked-in human C5aR. CCX168 doses that induce a near-maximal therapeutic benefit in mice produce CCX168 plasma levels and C5aR blockade that were attainable and well tolerated in Phase I human trials. These results support an important role for C5aR engagement by C5a in the pathogenesis of anti-MPO induced GN, which is a model for human ANCA GN, and thus support the possible therapeutic benefit of C5aR blockade in human ANCA disease.

Disclosure: H. Xiao: Chemocentryx, 9; **J. C. Jennette:** Chemocentryx, 9; **D. J. Dairaghi:** Chemocentryx, 3; **L. Ertl:** Chemocentryx, 3; **T. Baumgart:** Chemocentryx, 3; **S. Miao:** Chemocentryx, 3; **J. P. Powers:** Chemocentryx, 3; **L. C. Seitz:** Chemocentryx, 3; **Y. Wang:** Chemocentryx, 3; **P. Hu:** Chemocentryx, 9; **R. J. Falk:** Chemocentryx, 9; **T. J. Schall:** Chemocentryx, 3; **J. C. Jaen:** Chemocentryx, 3.

2049

The Relationship between Disease Status in Wegener's Granulomatosis with the Development of Subclinical Atherosclerosis. Rula Hajj-Ali[5], Roy Silverstein[2], Douglas Joseph[1], Peter Imrey[2], Gary S. Hoffman[4], Li Zhang[2] and Carol A. Langford[3]. [1]Cleevland Clinic, [2]Cleveland Clinic, [3]Cleveland Clinic Foundation, Cleveland, OH, [4]Cleveland Clinic Foundation, Pepper Pike, OH, [5]Cleveland Clinic, Cleveland, OH

Background: A role for inflammation in the development of accelerated atherosclerosis in patients with chronic inflammatory disease has been proposed. However, the pathophysiology of this process is not fully understood. The objective of this study was to asses the relationship between inflammatory disease in Wegener's granulomatosis (WG) with the development of subclinical atherosclerosis.

Methods: Eligible consenting adult patients who met the 1990 ACR classification criteria for WG were enrolled from the Cleveland Clinic Center for Vasculitis Care and Research. Exclusion criteria included history of coronary heart disease, heart failure, stroke, peripheral vascular diseases, acute or chronic infection within the past 3 months, NSAID or aspirin use within a week of MP and platelet studies, or diagnosis of chronic inflammatory disease, an autoimmune disease, or thrombophilia. Disease status was measured by BVAS-WG, VDI, disease duration and numbers of relapses (from onset of disease diagnosis until enrollment in the current study). Classic atherosclerotic risk factors and other co-morbidities were recorded in addition to platelet aggregation responses and circulating microparticle (MP) levels. All patients underwent ultrasound of the carotid arteries to assess intima media thickness (IMT) as an outcome for subclinical atherosclerosis.

Results: 45 WG patients were included. In univariate analyses, systolic and diastolic blood pressure, creatinine, and age at onset of disease were significantly associated with a higher IMT with rho values of 0.37, 0.38, 0.35 and 0.54 respectively ($p < 0.02$ for all), determined by Spearman rank correlation (Table 1).

Table 1. Spearman rank correlation between IMT and patient characteristics

Outcome	Variable	N	rho	95%CI	P value
IMT	BMI	44	0.19	(−0.12, 0.49)	0.23
IMT	Systolic blood pressure	45	0.37	(0.09, 0.66)	0.012
IMT	Diastolic blood pressure	45	0.38	(0.09, 0.66)	0.011
IMT	Creatinine	45	0.35	(0.06, 0.64)	0.019
IMT	HDL	45	−0.21	(−0.51, 0.10)	0.18
IMT	LDL	45	−0.19	(−0.50, 0.11)	0.2
IMT	FBG	45	0.12	(−0.18, 0.43)	0.42
IMT	Age at onset of disease	45	0.54	(0.28, 0.80)	<0.001
IMT	Disease Duration	45	0.23	(−0.07, 0.53)	0.13
IMT	Azathioprine Duration	45	−0.24	(−0.53, 0.06)	0.12
IMT	Methotrexate Duration	45	0.11	(−0.20, 0.41)	0.48
IMT	Cyclophosphamide Duration	45	−0.13	(−0.43, 0.18)	0.41
IMT	Cumulative Dose of cyclophosphamide	45	−0.15	(−0.45, 0.16)	0.34
IMT	Total MP counts	45	−0.18	(−0.48, 0.12)	0.23
IMT	Annexin counts	45	−0.2	(−0.50, 0.10)	0.18
IMT	CD_14 MP counts	45	−0.04	(−0.34, 0.27)	0.81
IMT	CD_16 MP counts	45	−0.12	(−0.42, 0.19)	0.45
IMT	CD_18 MP counts	45	0	(−0.31, 0.31)	0.99
IMT	CD_41 MP counts	45	−0.16	(−0.47, 0.14)	0.29
IMT	CD_105 MP counts	45	−0.21	(−0.51, 0.09)	0.16
IMT	CD_144 MP counts	45	0	(−0.31, 0.31)	0.99
IMT	CD_235 MP counts	43	−0.05	(−0.37, 0.26)	0.73
IMT	Platelet aggregation	40	0.24	(−0.08, 0.56)	0.14

When all variables were considered in a multiple regression model that included the total number of disease relapses, and after adjusting for the other significant factors, higher relapse number, older age at onset of disease, and higher diastolic blood pressure were found to be associated with higher IMT as shown in Table 2.

Table 2. Multiple regression model for assessing the association between IMT and sum of Flares

Outcome	Parameter	Estimate (%95 CI)	P value
IMT	Flare sum	0.0119 (0.0001, 0.0236)	0.003
	Age at onset of disease	0.005 (0.003, 0.008)	<0.001
	Diastolic blood pressure	0.0033 (0.0003, 0.0064)	0.031

Conclusion: This is the first study that addresses disease status as it relates to atherosclerosis in WG. Our data suggests that total number of disease relapses, but not disease duration, is a more important risk factor for atherosclerosis and implies that the cumulative inflammatory events contributes to the development of atherosclerosis.

Disclosure: R. Hajj-Ali: American Heart Association, 2; **R. Silverstein:** NIH, 2; **D. Joseph:** None; **P. Imrey:** None; **G. S. Hoffman:** None; **L. Zhang:** American Heart Association, 2; **C. A. Langford:** None.

ACR Poster Session C

ACR/ARHP Poster Session C: ARHP: Physical Exercise

Wednesday, November 10, 2010, 9:00 AM–6:00 PM

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'Specialized Generalists': How Do Rehabilitation Therapists Practice in Rural Areas? Robin K. Roots, Linda C. Li, Lesley Bainbridge and Helen Brown. University of British Columbia, Vancouver, BC, Canada

Background: The health disparity between rural and urban residents, including higher rates of arthritis and other chronic diseases, necessitates innovative practice models for rehabilitation professionals, who are already in short supply in rural areas. The **purpose** of this research is to better understand the barriers and facilitators to rehabilitation practice from the perspectives of occupational therapists (OTs) and physical therapists (PTs) working in rural regions.

Methods: OTs and PTs living and working in rural communities within a provincial health authority were recruited through a mail out to workplaces. Using purposive sampling, therapists were selected according to their range of experience in rural practice and the health care setting, source of funding and service delivery model in which they worked. Following a semi-structured interview guide, therapists were asked to describe how the rural context shapes their practice using an example of service provision for a patient with arthritis. Face-to-face interviews were recorded and transcribed. Guided by the methodological approach of interpretive description, data was analysed inductively to identify concepts of rural practice and extrapolate practice insights and exemplary strategies used by therapists. An analytic framework was used to map relationships between themes, concepts and cases. Rural rehabilitation practice paradigms will be interpreted to consider implications for practice change.

Results: Of the 43 eligible clinicians, 11 PTs, 6 OTs and 2 combined trained OT/PTs agreed to participate. Consistent with the literature, rural therapists described themselves as 'specialized generalists' referring to the broad scope of practice deemed essential to providing service to the diversity of their caseloads. While maintaining competency in a large number of practice areas presents significant challenges, therapists articulated strategies based on the unique context and features of rural practice. Skills and knowledge listed by therapists as essential to rural practice included: 1.) waitlist priority setting; 2.) drawing upon a large network of professional and community resources; 3.) recognizing boundaries to competency through reflective practice; and 4.) the importance of collaborating with other practitioners. Collaborative practice was seen as optimal in providing client centred care but not always achievable given limited resources, isolation and professional barriers. When asked what supports would be beneficial for practitioners new to rural practice, participants highlighted the importance of practice education placements in rural communities during training, formal mentoring programs, and a greater emphasis on interprofessional education.

Conclusion: Despite the growing interest in professional specialization, rural therapists appear to maintain general practice and interprofessional collaborative service delivery models in order to equitably meet the demands of the rural population and transcend the limited local health resources and services.

Disclosure: R. K. Roots: None; **L. C. Li:** None; **L. Bainbridge:** None; **H. Brown:** None.

2051

An Update of the Dutch Physical Therapy Guideline on Hip and Knee Osteoarthritis (HKOA). Wilfred F. H. Peter[5], Mariette J. Jansen[1], Emalie J. Hurkmans[6], Hans Bloo[12], Leatitia M. M. C. J. Dekker-Bakker[11], Roelien G. Dilling[10], Wim K. H. A. Hilberdink[10], Clarinda Kersten-Smit[3], Mariette de Rooij[8], Cindy Veenhof[9], Eric M. Vermeulen[2], Ineke de Vos[7], Jan W. Schoones[13] and Thea P. M. Vliet Vlieland[4]. [1]Centre for Evidence Based Physiotherapy (CEBP), University of Maastricht, Maastricht, The Netherlands, [2]Department of Physical Therapy, LUMC, Leiden, The Netherlands, [3]Department of Physical Therapy, St. Maartenskliniek, Nijmegen, The Netherlands, [4]Department of Rheumatology, Leiden University Medical Center (LUMC), Leiden, The Netherlands, Dept of Orthopaedics, Leiden, University Medical Center, [5]Department of Rheumatology, Leiden University Medical Center (LUMC); Jan van Breemen Instituut, Centre for Rheumatology and Rehabilitation, Amsterdam, Leiden, The Netherlands, [6]Dept of Rheumatology, Leiden, University Medical Center, [7]Exercise Therapy Private Practice, Leiden, The Netherlands, [8]Jan van Breemen Instituut, Centre for Rheumatology and Rehabilitation, Amsterdam, The Netherlands, [9]Netherlands Institute for Health Services Research, Utrecht, The Netherlands, [10]Paramedical Center for Rheumatology and Rehabilitation, Groningen, The Netherlands, [11]Physical Therapy Private Practice, Amstelveen, The Netherlands, [12]Veenendaal en Roessingh Research & Development, Enschede, The Netherlands, [13]Walaeus Library, Leiden University Medical Center, Leiden, The Netherlands

Background: In 2001 the *Royal Dutch Society for Physical Therapy (KNGF) Guideline for hip and knee osteoarthritis (HKOA)* was developed. Since then, many scientific papers on physical therapy interventions as well as national and international guidelines were published.

Objectives: To update the physical therapy guideline based on current evidence and best practice.

Methods: Topics concerning the three guideline chapters: initial assessment, treatment and evaluation were selected by a guideline development committee consisting of 10 expert physical therapists. With respect to treatment a systematic literature search (up to June 2009) within various databases was performed aiming to identify reviews and randomized controlled trials (RCTs) on the effectiveness of physical therapy interventions and the evidence was graded (1–4). For initial assessment and evaluation mainly review papers and textbooks were used. Based on evidence and expert opinion, recommendations were formulated (5 consensus meetings and 8 feedback rounds) and graded (A-D). A first draft of the guideline was reviewed by 17 experts from different professional backgrounds (2 feedback rounds). A second draft was field-tested by 45 physical therapists.

Results: For the initial assessment, a description of relevant health related topics in HKOA was made according to *the International Classification of Functioning, disability and health (ICF) core set for osteoarthritis (OA)*. Concerning treatment, 22 systematic reviews and 74 RCTs were reviewed. Recommended were: exercise therapy, education and self management interventions, a combination of exercise and manual therapy, and postoperative exercise therapy in HKOA, and taping of the patella in knee OA. Neither recommended nor advised against were: balneotherapy, hydrotherapy, and preoperative physical therapy in HKOA; thermotherapy, TENS, and Continuous Passive Motion in knee OA. Not recommended were: massage, ultrasound, electrotherapy, electromagnetic field and Low Level Laser Therapy. For the evaluation of treatment goals the use of one or more of the following measurement instruments was recommended: daily activities and participation: Lequesne index, Western Ontario and McMaster Universities osteoarthritis index questionnaire, Hip and Knee disability and Osteoarthritis Outcome Scores, 6 Minute Walk test, Timed Stand Up and Go test and Patient Specific Complaint list; body functions and structures: Visual Analogue Scale for pain, Intermittent and Constant OsteoArthritis Pain questionnaire, goniometry, Medical Research Council for strength, Handheld Dynamometer.

Conclusions: This update of the Dutch physical therapy guideline on HKOA included recommendations on the initial assessment, treatment and evaluation. The revised guideline will be launched in February 2010 and published on www.kngf.nl (including an English translation).

Members of the HKOA Guideline Development Committee: H Bloo, L Dekker-Bakker, R Dilling, W Hilberdink, C Kersten-Smit, M de Rooij, C Veenhof, H Vermeulen, I de Vos.

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2052

Clinical Measures Associated with Self-Reported Knee Instability in Knee Osteoarthritis (KOA). G. Kelley Fitzgerald, Sara R. Piva and Stephen R. Wisniewski. University of Pittsburgh

Background: Self-reported knee instability is a common symptom that can affect physical function in people with KOA. Very little has been reported concerning factors that may be associated with self-reported knee instability in KOA. Understanding factors associated with knee instability is the first step in understanding how to treat this symptom. The purpose of this study was to examine the association between clinical assessment variables and self-reported knee instability in subjects with KOA.

Method: 158 subjects (107 female) with KOA participated in the study. Person specific measures of independent clinical variables included age, gender, body mass index, fear of physical activity, anxiety, and depression. Knee specific variables were taken on the index knee (most symptomatic knee as reported by the subject) and included radiographic severity of the medial, lateral, and patellofemoral compartments, knee pain, quadriceps muscle strength, lower extremity muscle flexibility (hip flexors, quadriceps, hamstrings, gastrocnemius) knee range of motion, frontal plane and sagittal plane passive knee laxity, and knee alignment. The dependent measure was the Knee Outcome Survey Self-Reported Instability item (KOS-SRI)(5 = no instability, 4 = instability present but does not affect function, 3 = instability minimally affects function, 2 = instability moderately affects function, 1 = instability severely affects function) participated in the study. Subjects were dichotomized as stable if the KOS-SRI score was ≥ 4 and unstable if ≤ 3. A stepwise, forward (likelihood ratio), logistic multiple regression analysis was performed to identify which clinical variables were associated with the KOS-SRI score.

Results: Table 1 summarizes the results of the regression analysis. Medial compartment radiographic severity, knee pain, depression, and hamstring flexibility were associated with the KOS-SRI score.

Table 1. Results of Stepwise Linear Regression. Nagelkerke $R^2=0.45$

Variable	beta	Odds Ratio	95% CI	p
Medial Compartment Knee OA				.054
Severity (KL grade)				
KL=1	−2.62	0.07	0.01; 0.87	.04
KL=2	2.76	15.77	0.95; 290.99	.054
KL=3	−0.29	0.75	0.22; 2.49	.63
KL=4	−0.20	0.82	0.27; 2.51	.73
Knee Pain (VAS)	−0.39	0.68	0.56; 0.82	< .001
Depression (CES-D)	−0.09	0.91	0.86; 0.97	.01
Hamstring Tightness	0.07	1.07	1.03; 1.11	<.001

Conclusion: The results indicate that a medial compartment Kellgren and Lawrence (KL) grade < 2, lower numeric knee pain rating, less depression, and tighter hamstring muscles are protective against self-reported knee instability in our sample of subjects with KOA. Longitudinal study is needed to determine if changes in these variables mediate the progression of self-reported knee instability over time.

Disclosure: G. K. Fitzgerald: None; **S. R. Piva:** None; **S. R. Wisniewski:** None.

2053

Describing the Pattern of Outpatient Physical Therapy Utilization Following Total Knee Replacement (TKR). Carol A. Oatis[1], Jessica M. DiRusso[1], Mindy J. Hoover[1], Katherine K. Johnston[1], Monika Kasinova[1] and Patricia D. Franklin[2]. [1]Arcadia University, Glenside, PA, [2]Univ of MA Med Schl, Worcester, MA

Purpose: Incidence of TKR is projected to rise 673% by 2030 to 3.48 million from 450,000 procedures in 2005. According to the 2003 NIH Consensus Statement, post-operative rehabilitation is the most understudied aspect of the management of TKR. The purpose of this study was to examine outpatient physical therapy (PT) utilization by patients who have undergone primary TKR surgery.

Methods: PT records from TKR patients participating in a NIAMS-funded clinical trial at the University of Massachusetts Medical Center were included in the study. Patients who attended outpatient PT, completed their course of care and the study's 6-month assessment were eligible for review. Records from 65 patients who underwent primary TKR were eligible for review. Forty-four outpatient PT records were reviewed from 18 facilities. Twenty-one records were not reviewed because the facilities did not respond to requests for the records. Of these 21 records, 14 were from facilities that had sent at least 1 other record. Frequency and duration of physical therapy and total number of visits were recorded. "Usual care" was operationally defined as more than 50% agreement in PT delivery. "Consensus" was operationally defined as more than 85% agreement in delivery. Univariate regression analysis assessed the associations between PT utilization and patient baseline characteristics that could be associated with greater PT need (e.g., poorer pre-op function or self-care).

Results: No agreement or consensus existed regarding timing of initiation of outpatient PT (2–8 weeks postoperatively). There was no agreement on the total number of outpatient visits (7–34) or on when to discontinue outpatient PT (7–30 weeks postoperatively). The average number of visits was 15 (SD 6.3). Although there was a trend toward correlation between time to start of post-operative outpatient PT and age ($p = .08$; $r^2 = .07$), no other relationship existed between PT utilization and baseline characteristics, including function (PCS scale of the SF36, WOMAC), emotional health (MCS scale of SF36), arthritis self-efficacy, depression (CESD) or BMI.

Conclusions: Considerable variability exists in outpatient PT utilization despite the prevalence of the procedure. Utilization appears unrelated to preoperative patient characteristics that could be associated with greater PT need. People who undergo a primary TKR still have varied functional gains one year after the surgical intervention. Research is needed to determine if the variability in post-operative outpatient PT utilization contributes to sub-optimal patient outcomes. Better understanding of outpatient PT utilization may lead to rehabilitation practices that yield optimal outcomes and are cost efficient.

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2054

Describing the Pattern of Physical Therapy Intervention Following Total Knee Replacement (TKR). Jessica M. DiRusso[1], Mindy J. Hoover[1], Katherine K. Johnston[1], Monika Kasinova[1], Patricia D. Franklin[2] and Carol A. Oatis[1]. [1]Arcadia University, Glenside, PA, [2]Univ of MA Med Schl, Worcester, MA

Purpose: The incidence of TKR is projected to rise 673% by 2030 to 3.48 million from 450,000 procedures in 2005. According to the 2003 NIH Consensus Statement, post-operative rehabilitation is the most understudied aspect of the management of TKR. Quadriceps strength remains diminished one year after surgery and aggressive quadriceps strengthening has been shown to improve functional outcomes. The purpose of this study was to describe the outpatient physical therapy (PT) provided to patients who have undergone primary TKR surgery.

Methods: PT records from patients participating in the Joint Action clinical trial at the University of Massachusetts Medical Center were included in the study. Only records from patients who had attended outpatient PT, completed their course of care and their 6-month study assessment were eligible for review. Records from 65 patients who underwent primary TKR were eligible for review. 44 records were reviewed from 18 facilities. 21 records were not reviewed because the facilities did not respond to requests for the records. Of these 21 records, 14 were from facilities that had sent at least 1 other record. Outpatient PT records were reviewed to identify all interventions provided. Physical therapy exercise interventions were classified into open chain, functional mobility, closed chain, and advanced closed chain. Progression was operationally defined as one or more exercises that increased resistance or difficulty. "Usual care" was operationally defined as interventions used with more than 50% of patients. "Consensus" was operationally defined as interventions used with more than 85% of patients.

Results: No agreement was reached regarding strength progression. 9% of records reported no exercise progression. 30% of patients progressed in only 1 exercise (5/13 progressed straight leg raising). Specific quadriceps strength progression reached usual care (60%). Step-up exercises were the only closed chain activity that reached consensus. Step-downs reached usual care. There was no agreement on bridging or wall slides. No agreement existed in the use of advanced closed chain activities (squats was the closest at 48%). Balance and coordination training reached usual care (59%). The only modalities that reached usual care were cold packs (68%) and patellar mobilizations (57%).

Conclusions: Little uniformity exists in the post-acute outpatient physical therapy treatment of patients following TKR. Patients who undergo a primary TKR have varied functional outcomes one year after the surgical intervention. Research is needed to determine if the variability in post-operative physical therapy interventions contributes to patient outcomes.

Disclosure: J. M. DiRusso: None; **M. J. Hoover:** None; **K. K. Johnston:** None; **M. Kasinova:** None; **P. D. Franklin:** NIA, 2, NIAMS-NIH, 2, Robert Wood Johnson Foundation, 2; **C. A. Oatis:** NIAMS-NIH, 2.

2055

Factors Associated with the Use of Physical Therapy by People with Hip and Knee Osteoarthritis. Renata T. B. Jorge[1], Eric C. Sayre[4], Jacek Kopec[2], Jolanda Cibere[2], John M. Esdaile[2], Sherry Bar[3] and Linda C. Li[2]. [1]Arthritis Research Centre of Canada, Vancouver, BC, Canada, [2]Arthritis Research Centre of Canada, [3]BC Ministry of Health Services, [4]University of British Columbia

Background: Current guidelines recommend exercise as a first-line management for hip and knee osteoarthritis (OA). Physical therapists (PTs) are trained to prescribe exercise for managing arthritis; however, little is known about the factors associated with the use of physical therapy services by people with OA. This study aimed to assess factors associated with the use of physical therapy by people with hip and/or knee OA.

Methods: Eligible participants were those identified from a provincial administrative database between 1992 and 2006 as meeting the case definitions for OA, and had two or more medical visits or one hospitalization for OA within a 365-day period. We collected information on the WOMAC, use of healthcare service such as physical therapy in the past 12 months, and sociodemographics. Logistic regression was used to assess the factors associated with PT visits. Guided by the Andersen Model of Health Services Use, the dependent variables were grouped into *predisposing characteristics* (age, sex, body mass index), *enabling factors* (education, employment status, health authority region), and *need factors* (duration of diagnosis, number of comorbid conditions, estimated baseline WOMAC score). Because WOMAC was collected after the PT visits, we penalized the WOMAC scores of those who visited a PT by 15% (i.e., assuming that those who saw a PT improved by 15% after treatment). Sensitivity analyses were done by varying this assumption from 10 to 20%. Contribution of the enabling factors to PT visits was estimated by the difference of 100 minus the ratio of R^2 of the reduced model (with predisposing and need factors only) versus the R^2 of the full model.

Results: 1,349 participants completed the survey and reported having knee/hip OA (knee OA only=700; hip OA only=261; knee and hip OA=388). The mean age was 67.1 (SD=11.1), 816 (60.5%) were females, and 921 (68.3%) were diagnosed with OA 6 years ago or longer. They had an average of 1.8 (SD=1.5) comorbid conditions. 325 participants (24.1%) visited a PT in the past 12 months. Mean estimated baseline WOMAC score was 34.3 (SD=20.4). Higher education (OR=3.17, 95% CI=2.02, 4.97), living in the Fraser Health Authority (OR=0.62, 95% CI=0.40, 0.96) or Northern Health Authority (OR=0.46, 95% CI=0.29, 0.74), and having an estimated baseline WOMAC score $\geq$50 vs. $\leq$10 (OR=3.57, 95% CI=2.07, 6.16) were significant predictors for seeing a PT. Assuming physical therapy improved the WOMAC score by 15%, enabling factors accounted for 68.3% of the variance for seeing a PT that the full model accounted for. Sensitivity analyses indicated that this percentage ranged from 61.4% to 77.1%.

Conclusion: Enabling factors, rather than patients' needs, appeared to be the largest driver of the use of physical therapy by people with hip/knee OA. The findings indicated potential inequity in the use of physical therapy for the management of hip/knee OA.

Disclosure: R. T. B. Jorge: None; **E. C. Sayre:** None; **J. Kopec:** None; **J. Cibere:** None; **J. M. Esdaile:** None; **S. Bar:** None; **L. C. Li:** None.

2056

Impaired Knee Frontal Plane Neuro-Muscular Stabilization in Persons with Knee Osteoarthritis (KOA): A Biomechanical Study. Alison H. Chang[1], Song Joo Lee[1], Yupeng Ren[4], Heng Zhao[3] and Li-Qun Zhang[2]. [1]Northwestern University, [2]Northwestern University; Rehabilitation Institute of Chicago, [3]Rehabilitation Institute of Chicago, [4]Rehabilitation Institute of Chiicago

Purpose: Persons with KOA often report instability during activities. Lower passive capsulo-ligamentous stiffness or poor muscular stabilization in the frontal plane may compromise knee stability and lead to excessive varus-valgus (V-V) motions during walking. Understanding these frontal plane neuro-mechanical properties in KOA will help elucidate the factors contributing to knee instability and aid in the development of targeted intervention strategies. The objectives of this study were to quantify knee frontal plane passive and active stiffness and muscle strength in persons with medial KOA.

Method: 28 subjects: 14 with symptomatic radiographic medial KOA and 14 age- and gender-matched healthy controls (8 women/6 men in each group) were evaluated. A joint driving device (JDD) with a customized motor and a 6-axis force sensor measured knee frontal plane neuro-mechanical parameters. With the participant sitting on a custom built chair at knee extension, the JDD moved the knee into varus and valgus with controlled external torques, and recorded joint angle and torque outputs. For passive tissue V-V stiffness, the motor moved the knee into varus and valgus at 1 degree/sec with a maximum torque limit of 12 Nm in each direction and recorded the hysteresis curves of passive knee tissues for 12 cycles. Varus stiffness was analyzed by the ratio of the applied external torques to the resulting varus angular motion at the range of 0 to 1 degree (deg) varus. Valgus stiffness was computed similarly. For active muscle contribution to V-V stiffness, similar protocol described above was used; expect the participant was asked to contract his/her muscles to stiffen the knee and stabilize the knee against V-V motion imposed by the motor. Contribution of active muscle activity on V-V stiffness was computed by the difference in stiffness with vs. without voluntary muscle contraction. For V-V muscle strength, the participant performed knee adductor (varus) and abductor (valgus) maximal voluntary contractions, 3 trials in each direction. Visual feedback of torque output was displayed to facilitate muscle torque generation. Body weight normalized maximal V-V torque was used for analysis. We used ANCOVA with BMI as a covariate to test for differences between OA and control groups with $p < 0.05$ as significant.

Results: The mean age was 60 ± 8 (OA) and 58 ± 9 years (control); BMI 30 ± 8 (OA) and 24 ± 3 kg/m2 (control). There were no between-group differences in passive tissue V-V stiffness (varus: 3.57 ± 1.47 vs. 3.96 ± 1.25 Nm/deg, $p > 0.05$; valgus: 4.11 ± 1.83 vs. 4.07 ± 1.07 Nm/deg, $p > 0.05$). OA group had a significantly smaller change of V-V stiffness with voluntary muscle contraction (OA: 4.67 ± 2.86 vs. control: 8.26 ± 5.95 Nm/deg, $p < 0.05$), decreased varus muscle strength (0.013 ± 0.008 vs. 0.018 ± 0.008, $p < 0.05$), and a trend toward decreased valgus muscle strength (0.013 ± 0.007 vs. 0.019 ± 0.010, $p = 0.054$).

Conclusion: Persons with medial KOA had impaired active neuromuscular control in the frontal plane, including diminished ability to actively stabilize the knee in the frontal plane and to generate varus and valgus muscle torques; but did not show comprised stiffness in the passive capsuloligamentous tissues.

Disclosure: A. H. Chang: None; **S. J. Lee:** None; **Y. Ren:** None; **H. Zhao:** None; **L.-Q. Zhang:** None.

2057

Physical Activity Level and Poor Disability Profile: A Population-Based Study of US Adults with Arthritis. Jennifer M. Hootman[2] and David Brown[1]. [1]CDC, [2]Centers for Disease Control, Kennesaw, GA

Background: Physical activity (PA) has been shown to improve pain and function among adults with arthritis but the relationship between PA and an overall disability profile based on the International Classification of Function (ICF) is unknown.

Methods: Data were from the 2009 Behavioral Risk Factor Surveillance System, an annual telephone health survey conducted in all 50 states and the District of Columbia (n = 424,592 adults). Arthritis (ARTH; n= 151,120) was defined as a 'yes' response to "Have you ever been told by a doctor or other health care professional that you have arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?". Three outcome measures, based on ICF domains, were created: 1) impairment = severe pain (PAIN), 2) limitation = activity limitation (AL) and 3) restriction = social participation restriction (SPR). PAIN was defined as 7 or higher on a 0–10 point scale. AL was defined as a limitation in usual activities due to arthritis. SPR was defined with a question asking about the extent that arthritis interfered with social activities such as shopping, going to movies or social gatherings. Respondents reporting "A lot" (versus "A little/Not at all") were defined as having SPR. Persons who reported PAIN, AL, and SPR were classified as having a POOR disability profile. Respondents were asked how often (frequency) and for how long (duration) they did moderate and vigorous intensity PA outside of their occupation for at least 10 minutes at a time (minimum value 10 minutes/week). Minutes per week of moderate and vigorous intensity self-reported PA were summed (1 vigorous minute = 2 moderate minutes) and categorized as: Inactive (0 min/wk = referent group), Insufficient (10–149 min/wk), and Recommended (150+ min/wk). Logistic regression was used to estimate the relationship (odds ratio = OR, 95% confidence interval = CI) between PA level and each ICF domain separately and overall POOR disability profile adjusting for age, sex, race/ethnicity, education, body mass index, and self-rated health status. All analyses used statistical weights to account for the complex sample design.

Results: Among adults with arthritis, 26.3% reported PAIN, 45.6% AL, 16.8% SPR, and 11.9% were classified as having a POOR disability profile. The prevalence of having a POOR disability profile by PA level was 26.2% (CI 25.2–27.2) inactive, 12.7% (CI 12.0–13.4) insufficient, and 6.7% (CI 6.4–7.1) recommended. Higher levels of PA were associated with significantly lower odds of PAIN, AL, and SPR and a 41–63% reduced likelihood of having a POOR disability profile even after adjusting for age, sex, race/ethnicity, education, body mass index and self-rated health status (table).

	ICF Domain Adjusted OR (95% CI)			POOR Disability Profile
	PAIN	AL	SPR	
PA level				
Insufficient vs. Inactive	0.66 (0.62–0.71)	0.84 (0.79–0.90)	0.55 (0.51–0.59)	0.59 (0.54–0.64)
Recommended vs. Inactive	0.58 (0.54–0.61)	0.64 (0.61–0.68)	0.37 (0.34–0.40)	0.37 (0.34–0.41)

Conclusions: At least 1 in 10 adults with arthritis have a poor disability profile. Increasing PA in this population may improve one's disability profile, although this needs to be tested in prospective randomized controlled trials.

Disclosure: J. M. Hootman: None; **D. Brown:** None.

2058

The Association of Arm and Back Pain with Incidence of Slow Walking in Persons with Knee Osteoarthritis: The MOST Study. Daniel White[1], Yuqing Zhang[2], Jingbo Niu[2], Michael Nevitt[3], C. Elizabeth Lewis[4], James Torner[5] and Tuhina Neogi[2]. [1]Boston University, Boston, MA, [2]Boston University, [3]University California San Francisco, [4]University of Alabama, [5]University of Iowa

Slow walking is a marker for adverse outcomes such as persistent limitation and mortality. Due to factors such as knee pain, persons with knee osteoarthritis (OA) are already at increased risk for slow walking. However, it is not known if upper body pain, such as shoulder pain affecting arm swing during gait, or back pain that may limit activity, is associated with the development of slow walking speed. Thus, we examined the independent effects of pain in the arm and back with the incidence of slow walking speed among persons with or at risk for knee osteoarthritis (OA).

The Multicenter Osteoarthritis Study (MOST) is a NIH funded longitudinal study of persons who have or are at high risk for knee OA. Pain assessments were taken at baseline, and walking speed at baseline and 30 months. We defined incidence of slow walking as < 1.0 meter per second (m/s) at 30 months, a speed shown to be a risk factor for persistent functional limitation and death in older adults, among participants whose walking speed was ≥1m/s at baseline. We quantified pain as the number of areas subjects marked on a homunculus, counted as 0, 1, or > 2. For the arm, this included both hands, wrists, elbows and shoulders, and for the back, the lumbar, thoracic, and cervical areas. We examined the association of the number of

painful areas within arm and back areas with the incidence of slow walking using risk ratios adjusted for age, sex, BMI, race, radiographic knee OA (ROA), knee pain, and pain in the hip, ankle, or foot. We additionally adjusted for the presence of widespread pain in separate analyses.

Of the 2204 persons walking at least 1.0 m/s at baseline (mean age 62 ± 8 yrs, BMI 30 ± 6 kg/m2, female 57%) 8% had incidence of slow walking at 30 months. Arm pain was present in 0, 1, and >2 areas in 39%, 15%, and 46% of persons, and back pain in 32%, 48%, and 20%, respectively. Adjusting for potential confounders, persons with arm pain in 1 and 2 or more areas were 1.6 and 1.5 times more likely to have incidence of slow walking, respectively, compared with persons without any arm pain. No association between back pain and incident slow walking was found. (see table) We found similar results in analyses adjusted for the presence of widespread pain.

The presence of arm but not back pain was associated with the incidence of slow walking. Providers should consider that pain not only in the lower body, but also in the arms is important for future walking function.

		% (Number with incident slow walking/total number of subjects)	Adjusted Risk Ratio*	95% CI
Number of arm areas with pain	0	4 (39/882)	1.0	Ref
	1	10 (31/324)	1.6	[1.1, 2.5]
	≥2	10 (102/983)	1.5	[1.0, 2.2]
Number of back areas with pain	0	7 (50/741)	1.0	Ref
	1	7 (77/1031)	0.8	[0.6, 1.1]
	≥2	11 (45/422)	0.9	[0.6, 1.4]

*Mutually adjusted for age, sex, BMI, depressive symptoms, ROA, knee pain, and pain in the lower body apart from the knee (the hip, ankle, or foot)

Disclosure: D. White: None; **Y. Zhang:** None; **J. Niu:** None; **M. Nevitt:** None; **C. E. Lewis:** None; **J. Torner:** None; **T. Neogi:** None.

2059

The Effect of an Exercise Program in Gait Asymmetry in Patients after Total Knee Arthroplasty. Francisco J. Maia Neto[3], Gustavo J. M. Almeida[2], G. Kelley Fitzgerald[1] and Sara R. Piva[3]. [1]Univ of Pittsburgh, Pittsburgh, PA, [2]University of Pittsburgh, [3]University of Pittsburgh, Pittsburgh, PA

Purpose: Total knee arthroplasty (TKA) relieves pain and improves quality of life in end-stage knee osteoarthritis (OA). Unfortunately, significant functional deficits, such as gait asymmetry, often persist for years after TKA. Gait asymmetry may expose subjects to greater risk of developing OA in other weight-bearing joints. To prevent possible consequences of gait asymmetry, exercise interventions should target such impairment. We have developed and implemented an intense exercise program after TKA. The program includes balance exercises and movement control activities. The aim of this study was to determine if an intense exercise program that included balance and movement control activities decreases gait asymmetry in subjects after TKA.

Methods: Pre-test/post-test design. Subjects underwent unilateral TKA 2–6 months prior to the study. Patients completed 12 sessions of supervised exercise over 6 weeks, followed by 4 months of home exercise program (2x/week). Data were collected prior to intervention (pre) and at the end of the home exercise program (6 mo). Gait parameters were measured using the GAITRite walkway (CIR Systems Inc). Patients walked at a self-selected pace over the GAITRite. Step length was the spatial gait parameter; while the temporal parameters were loading, single support, and unloading times of the stance phase. To account for the effect of gait speed, the temporal parameters were analyzed as a percentage of the gait cycle. Spatial and temporal gait parameters between the surgical and non-surgical legs (at pre and 6mo) were analyzed using paired t-test.

Results: Twenty-five subjects participated. Mean age and BMI were 68.8±7.7 years and 29.9±4.5 respectively. Nineteen patients were females (76%), and 13 patients (52%) had surgery on the right side. At baseline, loading time was significantly longer in the surgical than the non-surgical side (15.3 ± 1.6 vs 14.7 ± 1.6 % of gait cycle, p=.02). Single support time was shorter in the surgical (34.8 ± 1.6 vs 35.4 ± 1.6 % of gait cycle, p=.02). Differences were not statistically significant for unloading time and step length. At 6 months, there were no significant differences between surgical and non-surgical sides. The Figure demonstrates that, at 6 months, the subjects decreased the time spent during loading, and increased the time spent during single support in the surgical side. Although not significant, step length became slightly larger in the surgery side compared to the non-surgical.

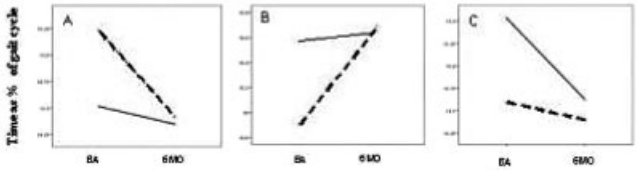

Figure. Loading (A), single support (B), and unloading (C) phases of gait from pre-intervention to the 6 months follow-up. Dashed lines represent the surgical lower extremity, whereas the solid lines represent the non-surgical side.

Conclusion: Spatial and temporal gait asymmetries after TKA were mainly during the loading and single support phases of stance. The exercise program seemed beneficial to decrease temporal gait asymmetries. If our results are confirmed in larger studies, intense exercises programs that include balance and movement control activities should be considered for subjects after TKA with asymmetrical gait.

Disclosure: F. J. Maia Neto: Student work was supported by the Clinical and Translational Science Institute Predoctoral Fellowship program, awarded through the Clinical and Translational Science Institute and the Institute for Clinical Research Education; **G. J. M. Almeida:** None; **G. K. Fitzgerald:** None; **S. R. Piva:** Study funded by: Claude D. Pepper Older American Independence Center (P30-AG024827), the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), NIH Roadmap for Medical Research (KL2R.

2060

The Effectiveness of Thoracic Spine Manipulation on Pain and Disability in Patients with Neck Pain: A Pilot Randomized Clinical Trial. Samannaaz Shamsuddin Khoja, Daniel Daliman and Piva Regina Sara. University of Pittsburgh, Pittsburgh, PA

Background: Mechanical neck pain is generally treated with a multimodal neck program (MNP) that includes electro/thermal modalities, active exercises and some form of manual therapy (commonly non thrust) directed at the cervical spine. Recent studies reported beneficial effects of using Thoracic Thrust Manipulation (TTM) to treat mechanical neck pain. The aim of this pilot study was to compare the effects of a MNP and the same MNP supplemented by TTM on neck pain and disability, and to gather preliminary data to calculate sample size for future larger studies.

Methods: Subjects were randomized to receive MNP only or MNP +TTM for a maximum of 12 sessions 2x/week. Primary outcomes were 11-point numeric pain rating scale (NPS), Neck Disability Index (NDI), and a 15-point Global Rating of Change (GRC) to measure perceived change in health status. Neck active range of motion (AROM) was secondary outcome. Outcomes were collected at baseline, 2, 4, and 6 weeks (GRC was not collected at baseline). As the goal of the study was parameter estimate, hypotheses testing were not done. We determined clinically important changes by comparing the point estimates of within-patient changes for NPS and NDI to their established minimal clinical important differences (MCIDs). MCIDs for the NPS and NDI are 2 points and 10% change respectively. We calculated the percentage of subjects in each group who reported a moderate or higher improvement in the GRC at each follow-up. For neck AROM, changes greater than the published values of minimal detectable change (MDC) were considered a noticeable change. The between-groups differences at 6 weeks in primary outcomes were used to estimate sample size.

Results: Twenty two subjects were randomized (68% female, mean age 38.2±10.7 yrs). Characteristics of both groups were similar at baseline. Both groups showed clinically important changes at 6 weeks on all primary outcome measures. Clinically important changes on the NDI were observed for the MNP+TTM group at 4 weeks as well. The only improvement in neck AROM was observed for right side rotation in the MNP+TTM group at 6 weeks. Compliance with intervention was similar in both groups. The difference between the two groups was very small for all outcomes (Figure). Results of sample size indicated that to have 80% power, α of.05, we would require over 150 subjects per group for pain and NDI, and over one thousand subjects per group for the GRC, which do not seem feasible.

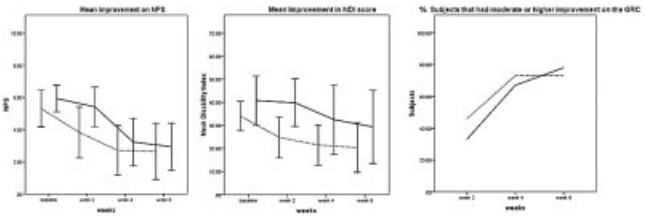

Figure. Pain, disability, and perceived change in health status across time for primary outcomes. Dashed lines represent NMP+TTM, and solid lines represent MNP group. Error bars show 95% CI around the means.

Conclusion: Adding TTM to MNP seemed to accelerate improvement on the NDI, but no additional benefits were observed on pain, perceived change in health status, or AROM at 6 weeks. It may not be beneficial to supplement MNP with TTM while treating mechanical neck pain. Results suggest it may not be worth to allocate additional resources to pursue the same research question in a larger randomized trial. Communication of these preliminary data may prevent unworthy research expenses.

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2061

Validity of Portable Devices To Assess Physical Activity in Patients with Total Knee Arthroplasty. Gustavo J. M. Almeida[1], Kelly S. Brower[2], Derya Celik[2], Hua-Chen Chang[2] and Sara R. Piva[1]. [1]University of Pittsburgh, Pittsburgh, PA, [2]University of Pittsburgh

Total knee arthroplasty (TKA) is one of the most successful surgeries to reduce pain, improve function, and health-related quality of life in end-stage knee osteoarthritis. Thus, patient expectations on having a more active lifestyle after surgery are increasing, and accurate/valid measures of physical activity (PA) are needed to monitor these changes. To date, there is limited information about the validity of portable PA monitors in patients after TKA. The aim of this study was to compare measures of energy expenditure (EE) given by the SenseWear armband (SWA) (Bodymedia, Pittsburgh, PA) and the Actigraph (ACT; Pensacola, FL), against measures of EE estimated by indirect calorimetry. In addition, we aimed at characterizing PA of patients with TKA measured by the SWA and ACT in a free-living condition.

EE (kcal/min) was estimated by indirect calorimetry (MedGraphics VO2000), and by the SWA and ACT simultaneously. Patients performed several standardized activities in a laboratory setting while concurrently wearing the SWA on the arm, the ACT on the waist, and the facemask of the indirect calorimeter. Each activity was performed during 7 minutes (see table). To characterize PA in a free-living condition, patients wore the SWA and ACT over 8 consecutive days. Pearson correlation or Spearman coefficients were calculated according to data distribution.

Table. Correlation coefficients between energy expenditure measured by indirect calorimetry and the Sensewear Armband (SWA) and the Actigraph (ACT)

	Indirect Calorimetry (kcal/min)								
	Lying down	Seating Reading	Seating Typing	Standing Talking	Standing Moving Arms	Mopping	Usual walk	Slow walk	Fast walk
SWA (kcal/min)	0.80**	0.68**	0.71**	0.82§**	0.4§*	0.75**	0.31	0.40	0.52*
ACT (kcal/min)	0.63**	0.60**	0.46*	0.61**	0.33	0.17	0.76**	0.67**	0.68**

§Spearman's rho; *p ≤ .05; **p ≤ .01

21 patients, 14 females (67%), with unilateral TKA underwent one testing session. Mean age and BMI were 68±7 and 29±4 respectively; time after surgery was 3.3±0.3 years; and physical function measured by the Western Ontario and McMaster Universities Osteoarthritis Index 14.6±9.6, indicating only moderate functional limitations. During the standardized activities (Table) the correlations between EE measured by indirect calorimetry and SWA ranged from moderate to high (r=.31 to.82), and between indirect calorimetry and ACT they ranged from weak to high (r=.17 to.76). In a free-living condition, patients wore the SWA and ACT for 97% of the time each day (23:20hr/24hr). Daily values of physical activity EE (PAEE) measured by the SWA (145 [73–260]kcal/day) was lower than the one measured by the ACT (268 [222–281]kcal/day). The correlation between these two measures was weak (rho=.22, p=.37).

Results of correlations between measures from the portable PA monitors and indirect calorimetry support the validity of the SWA and the ACT to measure EE in patients with TKA in a laboratory setting. The SWA was more accurate in measuring EE during non-walking activities, whereas the ACT was more accurate in measuring EE during walking activities. Measures of PA EE given by the SWA and ACT in a free-living condition did not agree. When assessing EE in patients with TKA, it is essential to consider type of PA monitor to use according to type of activity performed. Studies comparing SWA and ACT to a reference standard measure of PA in free-living condition are warranted.

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ACR Poster Session C

ACR/ARHP Poster Session C - ARHP: Research Methods

Wednesday, November 10, 2010, 9:00 AM–6:00 PM

2062

A Meta-Analytic Assessment of the Effects of Stanford's Small Group English Version of the Arthritis Self Management Program. Teresa J. Brady[1], Benita J. O'Colmain[3], Brandy S. Mobley[4], Michael C. Greenberg[4] and Louise Murphy[2]. [1]Center for Disease Control, Atlanta, GA, [2]Centers for Disease Control and Prevention, [3]ICF Macro, Calverton, MD, [4]ICF Macro

Background: Meta-analyses of arthritis self management education (SME) generally concludes it has modest, time limited effects. However, past analyses combined a variety of SME and examined only pain and disability. The purpose of this study was to examine the effects of Stanford's Arthritis Self Management Program (ASMP) using meta-analysis.

Methods: 7 Electronic databases (i.e. Medline, EMBASE) were searched using arthritis education-related keywords; reviews, reference lists, and expert recommendations guided hand searches to locate missed or gray literature.

All ASMP studies were included, regardless of language or delivery mode, if conducted in an English speaking country, containing data on at least 1 primary outcome, and reported in English. Primary outcomes: Fatigue (FAT), Self Rated Health (SRH), Pain, Self Efficacy (SE), Health Distress (HD), Physician Visits (MD-V). Secondary outcomes: Disability (DIS), Social/Role Limitations (LMTS), Anxiety (ANX), Depression (DEP), Aerobic Exercise (A.EX), Stretching/Strengthening Exercise (ST.EX), Cognitive Symptom Management (CSM), and Communication with MD (COMM).

Full random-effects meta-analysis was conducted for all available outcomes at 4–6 and 9–12 months. Heterogenity (HTG) was assessed using the Q Value (statistically significant at $a = 0.05$). Sensitivity analyses explored differences by study design (RCT vs. longitudinal [LONG]).

Results: 297 studies were identified; this report focuses on the 20 eligible studies (6 RCT, 14 LONG) of the Small Group English ASMP.

In analysis of 4–6 mo. data, there was significant HTG in 5 of 6 primary outcomes (all but SE) and 2 of 8 secondary outcomes (LMTS, CSM), indicating significant inter-study variation in effect sizes (ES) for most primary but few secondary outcomes. Only Pain and MD-V showed significant between group (RCT-LONG) HTG, indicating variation was not due to study design, and analysis of Overall effects (RCT and LONG combined) was valid.

RCT only analysis showed significant benefits in FAT (ES = −0.214), SE (0.34), ANX (−0.204), DEP (−0.201), and COMM (0.277) at 4–6 mo. At 9–12 mo. improvements in SE, ANX and DEP remained significant but slightly reduced (ES 0.21, −0.193, −0.132 respectively); no 12 mo. data were available on FAT or COMM.

In 4–6 mo. Overall analysis, all variables significant in RCT analysis were significant. HD (ES = −0.359), DIS (−0.049), A.EX (0.209), ST.EX (0.179), and CSM (0.533) were also significant with small to moderate ESs. At 9–12 mo., all variables except DIS, A-EX, and ST.EX remained significant with similar ESs. Pain and MD-V were significant in LONG 4–6 mo. analysis (ES −0.225, −0.120 respectively) but not in RCT only or Overall analyses.

Conclusions: Based on RCT analysis, the small group English ASMP has robust psychological benefits (ANX, DEP, SE) that persist at 12 mo., along with short term benefits in FAT and COMM. In Overall analysis, benefits were also seen in health behaviors and HD; most persisted at 12 mo. Consistent with previous meta-analyses, the impact of ASMP on DIS at 4–6 mo. is significant but small, and not maintained at 12 mo. The impact of ASMP on Pain and MD-V is only found in LONG studies, and should be interpreted cautiously.

Disclosure: T. J. Brady: None; **B. J. O'Colmain:** None; **B. S. Mobley:** None; **M. C. Greenberg:** None; **L. Murphy:** None.

2063

Development of the UK-Evaluation of Daily Activity Questionnaire (UK-EDAQ): Phase 2. Alison Hammond[3], Rachel E. Gill[3], Sarah Tyson[3], Ulla Nordenskiold[1] and Alan Tennant[2]. [1]Sahlgrenska Academy, Goteborg, Sweden, [2]University of Leeds, Leeds, Yorkshire, United Kingdom, [3]University of Salford, Salford, Greater Manchester, United Kingdom

Aims: The Swedish Evaluation of Daily Activity Questionnaire (S-EDAQ) is a comprehensive tool for reporting activity/activity limitations in Rheumatoid Arthritis (RA) [1]. It includes: 11 sub-scales of personal and instrumental activities of daily living (with 4–13 items in each; 102 in total). It is used in Occupational Therapy (OT) for clinical, audit and research purposes. We have already undertaken linguistic validation and generated potential new activity items for the UK from analysis of patient activity diaries and OT assessments (Phase 1). In Phase 2 we evaluated acceptability of wording and relevance of items for the UK.

Methods: Three stages were undertaken: (i) cognitive debriefing interviews with people with RA (n=20) who completed the prototype UK-EDAQ and then rated importance of items for inclusion on a 1=not to 5=very important scale; (ii) postal questionnaires with Rheumatology OTs (n=11) similarly rating items and (iii) 4 focus groups with RA participants (n=18) and 1 with OTs (n=7) to obtain consensus on item retention and wording. Items were considered for exclusion if RA participants and/or OTs rated these ≤3. The Project Steering Group (PSC) reviewed results from all stages to finalise the UK-EDAQ.

Results: RA participants (16 women: 4 men) were aged 61.55 (range 26–85); RA duration (16.42y SD 14.14); HAQ score 0.87 (range 0.12–1.88); 4 employed; 4 with children at home. Participants took between 25–120 minutes to complete the EDAQ. Whilst OTs rated 73/152 items with a median score ≤3, RA participants only rated 18/152 items ≤ 3; with only 15 items agreed for exclusion between groups.

Focus groups thus discussed items for modification or exclusion. From the S-EDAQ the consensus was for: 4 items to be deleted (get to toilet; get to bathroom; move round kitchen; open balcony door – as included in "move round house"); 20 S-EDAQ items merged to 10 items (eg slicing bread & slicing cheese to "slicing"). 53 new UK items were included: 26 to S-EDAQ sub-scales (eg "use a computer and mouse" "use a kettle") and 25 to 3 new scales (Hobbies; Caring; Household Maintenance). The PSC recommended 7 S-EDAQ items were slightly reworded (eg "go for a long walk" specified as 1 mile).

Many RA and OT participants expressed initial concerns on assessment length. However, once its purpose and completion at home were understood, most considered it appropriately detailed. RA participants were confident it would help an OT get a clearer picture of their abilities and difficulties in order to better help them. Comments from OTs were: "it is more patient oriented. . . It takes out the time of having to actually go through it all with them." "A lot of our patients say the time they spent with OT was very fleeting. . .filling this out would be very thorough." "You identify the talking points straight away, which helps focus it [assessment] a lot more." Both groups considered the length meant not all patients could complete it.

Conclusion: UK-EDAQ content was finalised reflecting what people with RA consider the most important daily activities to assess in the UK. We will next psychometrically test for reliability and validity.

References:

[1] Nordenskiold et al 1996 Clin Rheumatol 17:6–16.

Disclosure: A. Hammond: None; **R. E. Gill:** None; **S. Tyson:** None; **U. Nordenskiold:** None; **A. Tennant:** None.

2064

Factors Associated with Attrition in a Longitudinal Rheumatoid Arthritis (RA) Registry. Christine K. Iannaccone[2], Anne Fossel[2], Hsun Tsao[2], Jing Cui[2], Michael E. Weinblatt[1] and Nancy A. Shadick[1]. [1]Brigham & Womens Hospital, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA

Background: Loss of participants in longitudinal data collection can affect the validity of RA registries if the characteristics of patients who drop out are systematically different from those who remain. Several studies have previously assessed factors associated with attrition with different conclusions. Some reports suggest that psychosocial and socioeconomic factors play an important role while others indicate attrition is more likely associated with population demographics. This study looks at multiple factors of attrition in a hospital-based registry over five years to identify contributors to attrition in the BRASS cohort.

Methods: The attrition patterns of RA patients enrolled in a prospective observational registry were examined. Follow-up of patients occurred every six months. Attrition rates were calculated as the proportion of patients who dropped out of the study over five years of follow-up. Demographics, clinical factors, and psychological factors were evaluated in univariate analyses to determine differences between participants who dropped out of the study and participants who completed five years of follow-up. Univariate factors with a $p<0.05$ were used in a survival analysis to determine significant factors associated with attrition.

Results: Overall, 1095 RA patients were enrolled in the registry with 461 patients completing five years of follow-up, 327 still actively enrolled and 307 having dropped out. At baseline, the mean age was 56.2(±14.1), the mean disease duration was 13.8 (±12.4) years, 93% of patients were Caucasian and 82% were female. The attrition rate for each 6 month follow-up cycle was 3.23%. Level of education, disease duration, DAS28-CRP3 score (disease severity), MDHAQ depression score, total MHAQ score (functional status) and Self-Efficacy score were associated with attrition in univariate analyses. However, in survival analyses, shorter disease duration, higher MHAQ and higher DAS28-CRP3 scores were the only factors associated with attrition this population.

Table 1. Multivariate survival analysis of factors associated with attrition

Characteristic	Hazard Ratio	95% Confidence Intervals
Disease Duration, years	0.97	0.95–0.98*
DAS28-CRP3	1.29	1.19–1.40*
MHAQ Score	1.50	1.24–1.82*

*P < 0.001

Conclusions: The attrition rate for this registry is similar to rates reported by other registries. In contrast to previous studies, worse functional status and higher disease activity were associated with attrition in this population. This suggests that in some populations, disease specific measures are major contributors to attrition. Specific population differences in each registry may play a greater role in attrition than general demographic factors indicating that each longitudinal registry may need to conduct its own analyses.

Disclosure: C. K. Iannaccone: Biogen Idec, 2, Crescendo Bioscience, INC, 2; **A. Fossel:** Biogen Idec, 2, Crescendo Bioscience, INC, 2; **H. Tsao:** Biogen Idec, 2, Crescendo Bioscience, INC, 2; **J. Cui:** Biogen Idec, 2, Crescendo Bioscience, INC, 2; **M. E. Weinblatt:** Biogen Idec, 5, Crescendo Bioscience, 5; **N. A. Shadick:** Amgen Inc., 2, Biogen Idec, 2, Crescendo Bioscience, 2.

2065

Measuring Fatigue in Patients with Inflammatory Arthritis in Clinical Practice: Single Dimension and Multidimensional Scale Comparison. Patricia Minnock[1], Barry Bresnihan[2], McKee Gabrielle[3], Oliver FitzGerald[2] and Douglas Veale[2]. [1]Rheumatology Rehabilitation, Our Lady's Hospice and Care Services, Dublin, Ireland, [2]St Vincent's University Hospital, Dublin, Ireland, [3]Trinity College Dublin, Dublin, Ireland

Background: The ease of use of a measurement instrument frequently determines instrument choice and is an important consideration for outcome assessment in routine clinical practice. The aim of this study was to compare the measurement properties of one-dimensional and multidimensional fatigue scales in patients with inflammatory arthritis.

Methods: Patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA) commencing anti-TNF therapy were clinically evaluated using the 6-core outcome measures, and fatigue at baseline, 3-months and 6-months. Fatigue was measured using 2 fatigue scales validated for use in RA 1) a one

dimensional 5 point ordinal scale (OS), and 2) a multidimensional assessment of fatigue scales (MAF). Fatigue levels were quantified and the properties of a one-dimensional scale versus a multidimensional fatigue scale were evaluated.

Results: One-hundred thirty patients were evaluated (RA, 90; PsA, 40). Mean age (SD) years, and disease duration at inclusion were 52 (13), 12 (11), respectively. Mean (SD) MAF levels (range 1–50) were 27.5 (11.1) at baseline, 18.07 (12.1) at 3-months, and 19.04 (11.8) at 6-months and demonstrated statistical difference (ANOVA $p \leq 0.001$). Change in fatigue captured by the OS were statistically significant at both 3–months and 6-months χ^2 (2) = 31.5; p= 0.000 (Friedman test). MAF and OS scores demonstrated strong and significant correlations at the 3 time points, r=0.587; r=0.689, and r=0.686 ($p \leq 0.000$), respectively, (Kendall's tau_b). Fatigue scores corresponded as follows

Fatigue Scores	None	Mild	Moderate	Severe	Very Severe
Baseline					
5-point ordinal scale (%)	10 (8)	19 (15)	47 (38)	41 (33)	7 (6)
MAF Mean (SD) (Range 1–50)	8.7 (8.4)	18. (8.2)	27 (8.1)	35 (7.1)	40 (5.1)
3-months					
5-point ordinal scale (%)	17 (16)	40 (37)	41 (38)	11 (10)	
MAF Mean (SD) (Range 1–50)	6 (11.9)	10 (10.2)	19 (10)	24 (11)	21 (11)
6-months					
5-point ordinal scale (%)	12 (14)	33 (39)	29 (34)	9 (11)	1 (1.2)
MAF Mean (SD) (Range 1–50)	6.7 (6.1)	11 (11)	19 (10)	26 (11)	24 (7)

MAF scores moderately correlated with Pain 0.423 (0.578), (0.482); GH 0.425 (0.578), (0.500) and HAQ 0.470 (0.345), (0.344) ($p \leq 0.001$) at baseline, at 3-months, and at 6-months, respectively. Similarly, OS scores correlated with Pain 0.489 (0.495), (0.456); GH 0.532 (0.536), (0.515) and HAQ 0.407; (0.346), (0.347) (p= 0.001) at baseline, at 3-months, and at 6-months, respectively. The correlations between fatigue and the core outcome measures were equivalent at all time points regardless of the scale employed. Using the standardised response mean (SRM), sensitivity to change of MAF was moderate (0.78) at 3-months and large (0.66) at 6-months. Fatigue ranked third at 3-months, next to TJC and SJC, and sixth at 6-months relative to the other measures. Noteworthy was the observation that fatigue was ranked higher than CRP at 6-months.

Conclusion: These finding support the use of a single-item ordinal fatigue scale, in the quantification of this multi-dimensional patient reported symptom, in busy routine clinical practice.

Disclosure: P. Minnock: None; **B. Bresnihan:** None; **M. Gabrielle:** None; **O. FitzGerald:** None; **D. Veale:** None.

2066

One Monthly Patient Reported Disability, Disease Activity and Fatigue Shows More Fluctuation Then Expected Based on the 3-Monthly Clinical Evaluation by DAS-28. Margot Walter, Siti Haslinda Binti Mohd Din, Mieke Hazes and Jolanda Luime. Erasmus MC

Background: In clinical practice disease activity is monitored using a physician based instrument such as DAS or SDAI. In between these clinical measurement disease activity could fluctuate which is currently missed by the clinicians. Patient Reported Outcomes (PRO) may pick these fluctuations enabling early identification of disease activity increase requiring treatment change.

Objective: i To describe the monthly change of functional status (HAQ),self-reported disease activity (RADAI) and VAS fatigue among patient diagnosed with RA ii To identify patients with DAS28 >3.2 by proposed cut off points for RADAI and HAQ.

Methods: RA patients and patients with poly arthritis using DMARD's for at least 3 months from one outpatient clinic in Rotterdam were invited to participate in this study. They were asked to complete online the HAQ, RADAI, VAS fatigue monthly during 1 year and were clinically assessed by the DAS28 3-monthly. Descriptive statistics were used to analyze the data. HAQ>1 and RADAI>2.2 for moderate to high disease activity were used to identify DAS28>3.2

Results: 159 out of 174 invited patients (53 yrs (sd 13); 76% female, median 4.5 yrs disease, median DAS28 2.66; 37% erosions) consented to the study in September-December 2008. Stratified summary of the PRO's by DAS28 categories showed the increased values when the DAS increased (table 1) which stayed stable over time (data not shown).

Table 1.

DAS28	HAQ (median; IQR)	RADAI (median; IQR)	VAS Fatigue (median; IQR)
<2.6 (n=72)	0.19 (0–0.50)	1.09 (0.6–1.82)	43 (20–66)
2.6 <=3.2 (n=29)	0.5 (0.25–1.12)	1.47 (0.92–2.20)	53 (21–79)
>3.2&<5.1 (n=39)	0.75 (0.38–1.38)	2.73 (1.46–3.61)	59 (40–70)
>5.1 (n=9)	1.25 (1.00–2.13)	4.53 (4.05–4.81)	80 (75–82)
Overall (n=159)	0.50 (0.13–1.00)	1.63 (0.84–2.99)	56 (29–70)

Between 8% and 18% of the patients had an increase of DAS28>3.2 at any of the time points. On individual level the DAS28 and the PRO's fluctuated over time (figure 1).

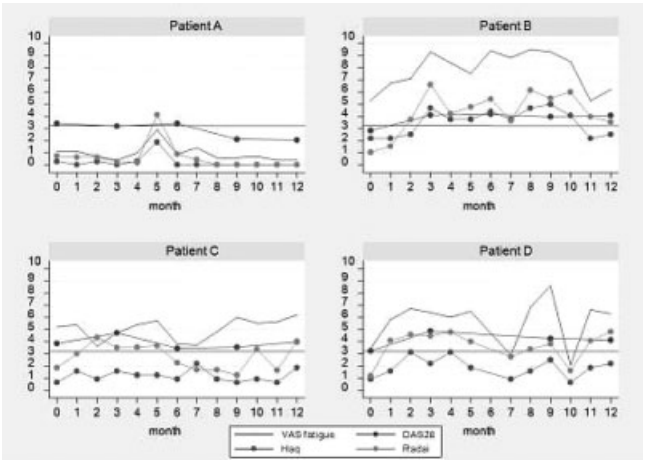


Figure 1.

Using the baseline data, the sensitivity of HAQ>1.0 to identify patients with DAS28>3.2 was 0.51 with a specificity of 0.75. For the RADAI>2.2 the sensitivity was 0.61 with a specificity of 0.83.

Conclusion: Individual patients showed fluctuating patterns of disease activity, while on group level the DAS28 and the PRO were stable over time. To identify individual patients with DAS28>3.2 the proposed cut off points for the HAQ and RADAI showed moderate sensitivity and high specificity.

Disclosure: M. Walter: None; **S. H. Binti Mohd Din:** None; **M. Hazes:** None; **J. Luime:** None.

2067

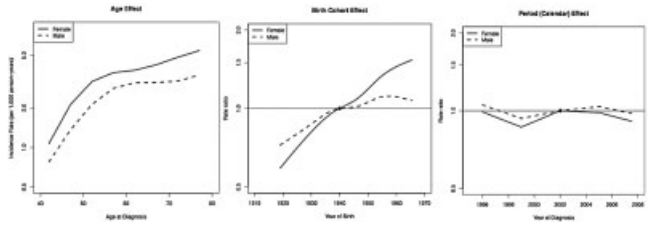
Secular Trend of Adhesive Capsulitis over 13 Years: A United Kingdom General Population Cohort. Daniel K. White[1], Hyon K. Choi[4], Christine Peloquin[3], Yanyan Zhu[2] and Yuqing Zhang[2]. [1]Boston Univ School of Med, Boston, MA, [2]Boston Univ School of Medicine, Boston, MA, [3]Boston Univ School of Medicine, [4]Univ of British Columbia, Vancouver, BC, Canada

Purpose: Adhesive capsulitis (AC) is a shoulder disorder characterized by a loss in range of motion and pain, resulting in restrictions with activities of daily living. Though common, few population-based studies have investigated the epidemiology of AC. Given the recent epidemic of diabetes, a known risk factor for AC, one would expect that the incidence of AC may be rising. The purpose of this study was to estimate effect of age, sex, birth cohort (birth year) and period (year of diagnosis) on the incidence of AC in a United Kingdom (UK) general population cohort.

Methods: Incident cases of AC were identified from The Health Improvement Network (THIN), an electronic medical record database of 6.3 million patients from general practices across the UK from 1995 to 2008. General practitioners recorded diagnosis of AC. We included subjects aged 40 to 79 years and defined an incident case of AC as the first diagnosis of AC following at least one year of enrollment in the database and had no prior AC diagnosis prior to their enrollment within the practice. Crude incidence rates were calculated as number of incident AC cases divided by total person-years. We plotted age- and gender-specific incidence rates of AC, and the relative incidence rates of AC for birth cohorts and periods using an age-period-cohort spline curve based on a Poisson-type likelihood. We estimated the effects of age, sex, birth cohort (born 1920–29, 1930–39, 1940–49, 1950–59, 1960–69), and period (1995–98, 1999–2002, 2003–06, 2007–08) using a proportional hazard model.

Results: Of 2,209,672 subjects included (mean age 51.7 yrs, 50.0% women, mean follow-up 7 years), the incidence rates of AC were 2.20 and 3.15 per 1000 person-years for men and women, respectively. Incidence rate of AC increased with age in both men and women. For every 5-year age increment, AC incidence increased by 9.1% (Relative Risk [RR]=1.09, 95%CI: 1.08, 1.10). The incidence rate was higher in women than in men (RR=1.43, 95%CI: 1.40, 1.45), and was higher for more recent birth cohorts compared with later (older) cohorts (RR for each 10-year increment=1.10, 95% CI: 1.08, 1.12). We did not observe a period effect for the incidence of AC. (See figure)

Conclusion: We found that more recent birth cohorts had a higher risk of incident AC independent of age, sex, and calendar year at diagnosis within the UK general population compared with later cohorts. An increased presence of risk factors, such as diabetes, in those born more recently may account for this increase, though future research should formally identify and examine these factors.



Disclosure: D. K. White: None; **H. K. Choi:** None; **C. Peloquin:** None; **Y. Zhu:** None; **Y. Zhang:** None.

2068

The American Myositis Activities Profile—A Valid Disease-Specific Activity/Participation Measure. Helene Alexanderson[1], Ann M. Reed[2] and Steven R. Ytterberg[2]. [1]Department of Medicine, Karolinska Institutet, Department of Physical Therapy, Karolinska University Hospital, Solna, Stockholm, Sweden, [2]Rheumatology Division, Mayo Clinic, Rochester, MN

Background: The Myositis Activities Profile is an activity limitation measure developed and validated for patients with polymyositis and dermatomyositis in Sweden. It was recently translated into American English.

Objectives: To evaluate validity and reliability of the American version of the disease-specific 31-item Myositis Activities Profile (MAP) in patients with polymyositis (PM) and dermatomyositis (DM) in the USA.

Methods: Patients diagnosed with PM or DM seen during March-May 2007 and May-July 2008 were included. To assess content validity 30 strategically chosen patients as to gender, age, ethnicity, disease activity, disease duration and employment status were selected. They rated difficulty and importance of each activity of the American MAP on a 10-grade scale and were invited to suggest additional items. Based on the initial findings a second draft of the American MAP was developed. For construct validity purpose unselected patients with PM and DM (n=64) were included. The six-item core set for myositis disease activity, the Manual Muscle test (MMT) and measures of muscle endurance using the Functional Index 2 (FI-2) were performed. Patients filled out the second draft of the American MAP, the Health Assessment Questionnaire (HAQ) and rated disease impact on general well-being. All patients with stable disease activity and medication for three months (n=48) were given another copy of the American MAP to fill out one week later.

Results: The median value for pooled difficulty and importance of each item was 5.00 (2.10–5.95) for the 31 activities in the first draft of the American MAP. Although two activities were rated < 5.0; "Standing for a longer period" and "Using public transportation" they were still taken to the second draft of the MAP as they were considered relevant to patients living in larger cities. Five patients suggested the activity "Opening jars" which was added to the Movement subscale, giving a 32-item second draft of the American MAP. Correlations between median of subscales of the American MAP and disease impact on general well-being and the HAQ were $r_s = 0.68$ and r_s 0.70 respectively. There were lower correlations between the American MAP and MMT 8 ($r_s = -0.36$), the FI-2 (ranging between $r_s = -0.29$ to -0.44) and physician's global assessment of disease activity (r_s 0.40). Thirty-three patients sent back questionnaires to assess test-retest reliability. Weighted Kappa (K_w) ranged between 0.65 and 0.81 for the 4 subscales and between 0.52 and 0.73 for the four single items of the American MAP without systematic variations, $p>0.05$. The single item 'avoid overexertion' were excluded due to poor test-retest reliability ($K_w=0.52$) giving a 31-item final draft of the American MAP.

Conclusion: The American MAP seems to be a valid and reliable outcome measure assessing activity / participation in patients with adult PM and DM in the USA and could potentially improve clinical assessment of treatment of these patients although further studies are needed to establish sensitivity to change of the American MAP.

Disclosure: H. Alexanderson: None; **A. M. Reed:** None; **S. R. Ytterberg:** None.

ACR Poster Session C
ACR/ARHP Poster Session C: ARHP: Quality of Life
Wednesday, November 10, 2010, 9:00 AM–6:00 PM

2069

Arthritis Hurts . . . Your Resume: State-Specific Arthritis-Attributable Work Limitation and Employment among Working-Age (18–64) Adults. Kristina Theis[3], Jennifer M. Hootman[2] and Charles G. Helmick[1]. [1]CDC, Atlanta, GA, [2]Centers for Disease Control, Kennesaw, GA, [3]Centers for Disease Control and Prevention

Background: State-specific estimates of arthritis-attributable work limitation (AAWL) help define and raise awareness of an important consequence of arthritis, and provide state programs and policy-makers with data for planning interventions. We estimate the state-specific prevalence of AAWL and employment status among people with and without arthritis.

Methods: The Behavioral Risk Factor Surveillance System (BRFSS) survey is a state-based, random-digit-dialed telephone health survey of noninstitutionalized US civilian adults ≥18 years conducted annually in all 50 states and the District of Columbia. Data were from the 2009 BRFSS survey (n = 424,592). Arthritis was defined as 'yes' to: "Have you ever been told by a doctor or other health care professional that you have arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?" AAWL was defined as 'yes' to: "In this next question, we are referring to work for pay. Do arthritis or joint symptoms now affect whether you work, the type of work you do, or the amount of work you do?" Employment rate, as defined by the Bureau of Labor Statistics, requires information on specific efforts to find employment, which is unavailable in BRFSS; so, we examined employment status by report of being: employed, out-of-work, or retired/unable to work. Students and homemakers were excluded from the analysis. Weighted point estimates and 95% confidence intervals (95% CI) were calculated for AAWL and employment, accounting for the complex survey design. Statistical significance was $p < 0.05$.

Results: Median state-specific prevalence of AAWL among all working-age adults was 6.4% (range 4.3% (NJ) to 13.2% (KY)). Among working-age adults with arthritis, median AAWL was 33.9% (range 26.2% (CT) to 44.9% (KY)) The median percent employed among people without arthritis was 81.9% (range 73.5% (NV) to 90.5% (SD)), was significantly lower in every state for those with arthritis (median 64.2%, range 50.0% (TN) to 77.3% (SD)), and lowest for adults with AAWL (median 44.5%, range 32.4% (TN) to 64.0% (IA)). There were few statistically significant differences in the prevalence of being out-of-work. With the exception of 6 states (same patterns but not significant), those with AAWL reported being retired/unable to work statistically significantly more often than those with arthritis but no AAWL (median 40.9% vs. 26.0%) In all states, those with arthritis (with or without reported AAWL) reported being retired/unable to work statistically significantly more often than those without arthritis (median 6.5%).

Conclusion: AAWL affects approximately 1-in-16 working-age adults. Working-age adults with arthritis (with and without AAWL) are more likely to report being retired/unable to work than out-of-work, suggesting that they may have given up on trying to be an active part of the labor force. These data identify higher risk states which can be targeted for expanding the reach of evidence-based programs addressing disability, as well as increasing the use of vocational rehabilitation and job retraining programs.

Disclosure: K. Theis: None; **J. M. Hootman:** None; **C. G. Helmick:** None.

2070

Assessement of Physical and Mental Health Related Quality of Life, Disease Activity and Damage, Mental Health Status, and Cognitive Impairment in Chilean Women with Systemic Lupus Erythematosus. Carla Henríquez[1], Patricia Flores[2], Babul Marcela[3], Jorge Calderón[3] and Loreto Massardo[3]. [1]Pontificia Universidad Católica de Chile, Santiago, Chile, [2]Pontificia Universidad Católica de Chile, Santiago, [3]Pontificia Universidad Católica de Chile

Background: Psychosocial factors play an important role in the course of SLE. The aim of this study is to characterize the health-related quality of life (HRQoL) in Chilean women with SLE and their relationship with disease activity, and mental health status including cognitive function.

Methods: In this cross sectional study, 52 non selected Chilean women with SLE attending out patient clinic in Santiago were recruited in an 18 months period, they pay their medications from their own pocket. Completed the following measurements (i) HRQoL using the SF-12 questionnaire (assessing general health status [GHS], physical component summary [PCS] and mental component summary [MCS], (ii) SLE disease activity (SLEDAI-2K), (iii) damage (SLICC-ACR), (iv) 26 common mental disorders (CMD), according to the DSM-IV, using the Mini-International Neuropsychiatric Interview (MINI-plus), and (v) cognitive impairment (CI) in five domains of the Cambridge neurospychological auttomated test battery (CANTAB): memory, attention, executive function, work memory, and desicion making. CI was considered one or more test with a -1SD perfomance compared to 26 Chilean healthy controls paired by sex, age, and educational level.

Results: Characteristics of participants: median age: 33 years (range= 17–64); median disease duration from diagnosis: 2 years (0.1–26); stable couple: 37%; active working/students: 65%; median years of formal education: 14 (9–19); median SLEDAI-2K: 7 (0–25); median SLICC: 0 (0–4). At least one CMD was present in 27 (53%), 14 (28%) major depressive episode (MDE), 15 (30%) at suicidal risk (29%): four were at high level, 5 at moderate and 6 at low risk.

Patients considered their GHS as poor (16%), regular (47%), good or very good (37%). PCS median was 39.1 (24.28–57.58) and MCS median was 35.8 (16.2–59.4). PCS and MCS inversely correlated with disease activity (Spearman Rho= −0.327; *P= 0.023;* R= −0.349; *P= 0.015*, respectively). Accrued disease damage inversely correlated with PCS (R= −0.347; *P=0.015*). Patients affected with MDE had lower PCS and MCS than those without MDE (*P=0.045; P=0.00*, respectively). Disease activity was similar in both groups. CI in two domains attention and executive function were found in 22 (42%) not associated with MDE (*P*=NS).

Conclusions: This survey found 53% of presence of CMD and 28% of MDE. These frequencies are considerably higher than those previously reported in the general population living in Santiago, Chile (18% and 8%, respectively), moreover the number of patients at suicidal risk is high (<0.1%). HRQoL components PCS and MCS were > 1 SD lower compared to Chilean general population (score 50 ± 10). Disease activity related to a worse HRQoL in both components while accrued damage associated only with lower PCS score. MDE affected both components of HRQoL. CI in attention and executive function is a relevant problem in this study. Overall 63% of patients considered their general health status as bad or regular implying a challenge for a the rheumatology staff to provide a better health care involving transdisciplinary teamwork.

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Disclosure: C. Henríquez: None; **P. Flores:** None; **B. Marcela:** None; **J. Calderón:** None; **L. Massardo:** GlaxoSmithKline, 8.

2071

Change in Physical Activity on Sleep Quality in Persons with Arthritis. Jennifer Lias[2], Leigh F. Callahan[1] and Jack H. Shreffler[2]. [1]Univ of North Carolina, Chapel Hill, NC, [2]University of North Carolina, Chapel Hill

Background: The role of exercise or physical activity on sleep quality in persons with arthritis has had minimal investigation, although sleep disorders are prevalent. This study examines the role of physical activity (PA) on sleep quality in older adults with arthritis who participated in an intervention trial evaluating the Active Living Everyday Program (ALED), a 20-week behavioral theory-based program designed to increase PA.

Methods: Subjects included 350 inactive persons, 18 years or older with doctor-diagnosed arthritis or joint pain/stiffness who were in either the intervention or delayed control group. Baseline and 20-week follow-up data included self report health status, physical functioning, PA and a self report assessment of sleep. Participants were asked: do you 1) Have trouble falling asleep? 2) Wake up several times per night? 3) Have trouble staying asleep, including waking up too early? 4) Wake up after your usual amount of sleep feeling tired and worn out? Responses are 0–5 with higher scores indicating more disturbances. A total sleep score summed the four responses (0–20). The Community Healthy Activities Model Program for Seniors (CHAMPS) frequency and Kcal/wk self-reports were used to measure PA level (e.g., 40 physical activities, scored by the number of times and hours per week engaged in the activity). Higher frequency and caloric expenditure indicate higher weekly PA levels. Sleep and CHAMPS baseline, post ALED and change scores were examined. Bivariate and multivariate regression analyses examined the relationship of CHAMPS change variables to sleep change variables. Age, gender, race, education, comorbidities and depression were controlled for during the analysis.

Results: Mean age of the study population was 69 years and consisted of 84% females, 79% white, and 58.1% with greater than a high school education. Baseline mean (s.d.) CHAMPS weekly energy expended and frequency for exercise were 2167 Kcal (2577) and 11.9 (10.14), respectively. The corresponding mean changes after 20 weeks were 992 (3175) Kcal and 7.39 (11.9). For the regression analyses, energy was divided by 1000 and frequency by 10 to avoid numerically small parameter estimates (β). Unadjusted analysis revealed a significant association between increased energy expenditure and improved sleep: waking up tired (β = -.095, p=.006) and sleep total score (β = −.279, p=.008). Increased frequency of activity was related to less waking up tired (β = −.211, p=.011) and improved total sleep score (β = −.549, p=.029). Adjusting for covariates, greater energy expenditure was associated with less waking up tired (β = −.102, p=.005), improved total sleep score (β = −.328, p=.003), and less waking up during the night (β = −.081, p=.019); increased frequency of activity was associated with less waking up tired (β = −.193, p=.024).

Conclusions: Sleep disturbances in people with arthritis can be significantly improved by increased weekly PA. An average increase in caloric expenditure of approximately 1000 Kcal/week produced results. These findings have important clinical implications in management of sleep disorders in older persons with arthritis, especially those that are inactive.

Disclosure: J. Lias: None; **L. F. Callahan:** None; **J. H. Shreffler:** None.

2072

Depression Rates Reported by Scleroderma (SSc) Patients Using Online Subject Recruitment and Questionnaire Completion. Feasibility of Data Collection Method and Comparison of Reported Depression Rates. Evelyn Rajan[1], Meagan Crofoot[3], Jibran Fateh[3] and Ann J. Impens[2]. [1]Briarcliff High School, [2]University of Michigan, Ann Arbor, MI, [3]University of Michigan

Objective: To evaluate the effectiveness and quality of online survey data in the assessment of depressive symptoms in SSc patients.

Methods: Data was obtained from SSc patients through a link posted on The Scleroderma Foundation website informing patient members about a study conducted by a high school student as part of the Intel Science Competition. Local IRB approval was obtained. Patients completed demographic information and the Center for Epidemiologic Studies Depression Scale (CES-D) which has been validated in SSc. CES-D is a 20-item instrument scored from 0 to 3 for a total possible score of 0 (best) to 60 (worst). Scores 16 and above indicate significant depressive symptoms.

Results: 186 completed surveys were received over a period of 2 weeks. 171 (91.9%) were female. Mean age was 49.9 ± 11yrs; 47.1 ± 10.6yrs for males and 50.2 ± 11yrs for females. Average disease duration was 8.2 ± 8.2 yrs; 7.1 ± 7.7 yrs for males and 8.3 ± 8.3yrs for females.

The mean CES-D was 18.9 ± 12.7 with 51.6% reporting a score of 16 and higher. Total CES-D score for males was 23.9 ± 14.1 and 18.6 ± 12.6 for females. This difference was not statistically significant. Mean scores on each item were compared and differences between males and females were small. Males scored significantly ($p < 0.05$) higher on 2 items: "I felt as good as other people" (1.71 vs 1.06) and "My sleep was restless" (2.29 vs 1.6). A significant, although low, negative correlation was found for females between CES-D scores and age (r = −.160), implying that with age there was less reported depression. The correlation between CES-D and years of illness was not significant (r = −.09).

Conclusion: A CES-D score of 16 or higher is commonly considered as a cut-off for significant depression. Rates of depression between 35 to 65% have been reported in studies of SSc patients. The rate of significant depression, 51.6%, found in this online sample falls within the range depression rates previously reported in clinic samples. This is also similar to depression rates reported in other chronic diseases. A recent study (Thombs, Fuss et al. 2008) compared SSc patients with online gender and age/race matched controls (no SSc). They noted that online respondents scored differently on certain items (higher on items related to appetite, sleep, effort, and bothered) suggesting qualitative differences in depressive symptom presentation between data collection methods. The item differences found in this study between males and females need to be further investigated and compared to gender item differences found in clinical and/or other community samples. The ease of administration and scoring makes the use of online questionnaires a very attractive method of data collection. The effectiveness of this method was proven by a high rate of completed surveys within a short period of time. More research is needed in comparing the composition of respondent characteristics (demographic as well as clinical) and the impact of data collection methods on results in SSc patients.

Thombs, B., S. Fuss, et al. (2008). High rates of depressive symptoms among patients with systemic sclerosis are not explained by differential reporting of somatic symptoms.Arthritis and rheumatism **59**(3): 431–7.

Disclosure: E. Rajan: None; **M. Crofoot:** None; **J. Fateh:** None; **A. J. Impens:** None.

2073

Effects of Tadalafil on Sexual Activity and Quality of Sexual Functioning in Female Scleroderma (SSc) Patients. Ann J. Impens[2], Elena Schiopu[2], Kristine Phillips[2] and James R. Seibold[1]. [1]University of Connecticut Health Center, Farmington, CT, [2]University of Michigan, Ann Arbor, MI

Objective: To evaluate the potential effects of Tadalafil on quality and frequency of female sexual function as assessed by Female Sexual Function Index (FSFI) and sexual activity log.

Methods: Prospective randomized, double-blinded, placebo controlled, cross-over study comparing oral Tadalafil at fixed 20 mg dose daily for 4 weeks compared to placebo in female SSC patients. FSFI assesses six domains of sexual functioning: desire, subjective arousal, lubrication, orgasm, satisfaction, and pain.

Results: 39 patients met inclusion criteria, agreed to attempt sexual activity at least once per week, and completed a series of 5 visits. Mean scores on the FSFI domains and frequency of sexual activity are as follows:

Baseline, Drug, Placebo Mean scores FSFI Domains

	Baseline (sd)	Drug (sd)	Placebo (sd)
Desire	2.77 (1.28)	3.23 (1.21)*	2.98 (1.37)
Arousal	3.38 (1.77)	3.92 (1.85)	3.64 (1.86)
Lubrication	3.60 (2.11)	3.89 (2.14)	3.77 (2.15)
Orgasm	3.54 (1.90)	4.02 (1.96)	3.73 (2.0)
Satisfaction	4.06 (1.56)	4.43 (1.50)	4.23 (1.55)
Pain	4.30 (2.43)	4.51 (2.26)	4.37 (2.37)

*p=.007, 2-tailed

Frequency sexual activity

Baseline (sd)	Drug (sd)	Placebo (sd)
5.75	7.24 (4.53)	6.12 (3.3)

*p=.021, 2-tailed

Conclusions: To our knowledge this is the first study to report on the use of PDE-5 inhibitor and its impact on sexual function in female SSc patients. Patients reported a significantly higher frequency of sexual activity on drug than placebo. Greater change from baseline was reported on all domains of FSFI on drug versus placebo but none of these were statistically significant. A statistically significant difference was found in change from baseline in the sexual desire domain for drug although this was not statistically different from the change in the placebo group.

While the majority of scleroderma patients are female most studies on sexual function have focused on male sexual dysfunction. Same holds true for the study of sexual function in the general population where many studies focus on the use of PDE-5 inhibitors in the treatment of erectile dysfunction. Few studies exist on the use of PDE-5 inhibitors in the treatment of female sexual arousal problems and their effectiveness is in question (Chivers and Rosen 2010). Chivers et al (Chivers and Rosen 2010) attribute this lack of efficacy of PDE-5 inhibitors in women to gender differences in the concordance between physiological and psychological components of sexual response. This study did not include physiological outcome measures which are likely to measure the pharmacological effects of PDE-5 inhibitors as direct vasodilators. Classification and measurement of FSD in women lacks meaningful endpoints due to the complexity of female sexual response. Research is needed for a better understanding of outcome measures (physiological and patient-reported) specifically for female sexual dysfunction.

Chivers, M. L. and R. C. Rosen (2010). Phosphodiesterase Type 5 Inhibitors and Female Sexual Response: Faulty Protocols or Paradigms? The journal of sexual medicine 7(2): 858–872.

Disclosure: A. J. Impens: None; **E. Schiopu:** None; **K. Phillips:** None; **J. R. Seibold:** None.

2074

Fibromyalgia Patients Often Visit Many Physicians before Receiving a Diagnosis. Robert S. Katz[2], Jessica L. Polyak[1] and Lauren Kwan. [1]Rheumatology Associates, [2]Rush University Medical Center, Chicago, IL

Introduction: Fibromyalgia patients see many types of medical professionals and often have difficulty obtaining a diagnosis. This study utilized on-line and written surveys to investigate the number and types of health professionals consulted before receiving a diagnosis of the fibromyalgia syndrome (FMS). To avoid confounding by gender, only female patients were included in the analyses.

Methods: 606 self-described female fibromyalgia patients responded to a survey through the community volunteer fibromyalgia organization, AFFTER (Advocates for Fibromyalgia Funding, Treatment, Education and Research). Respondents were asked about who had diagnosed their fibromyalgia and the number of physicians they had seen for fibromyalgia symptoms before reaching a diagnosis. Spearman correlations were obtained to assess linear relationships between non-categorical variables.

Results: Respondents were predominately middle-aged (58% aged 36–55) and Caucasian (91%). Fifty percent were diagnosed with fibromyalgia by rheumatologists, 13% by internists, 4% by neurologists, 26% by other physicians, and 2% by chiropractors. Only 30% of patients obtained a diagnosis after seeing 1 or 2 physicians, while 24% saw 7 or more physicians before being diagnosed, and 10% saw 11 or more physicians before being diagnosed. A statistically significant, negative correlation was found between the number of physicians seen before reaching a diagnosis and how well the respondent coped with fibromyalgia (rho = −0.14, $p = 0.001$). In addition, statistically significant, positive correlations were found between the number of physicians seen before reaching a diagnosis and the amount of pain (rho = 0.16, $p < 0.001$) and fatigue (rho = 0.16, $p < 0.001$) experienced during an average week and the total number of areas with pain or tenderness (rho = 0.17, $p < 0.001$).

Conclusions: Most fibromyalgia patients saw at least three physicians before receiving a diagnosis, and a quarter went to at least 7 doctors for fibromyalgia related symptoms before obtaining a diagnosis. Larger numbers of physicians seen before reaching the diagnosis of FMS was associated with worse symptoms and worse ability to cope with fibromyalgia. Those with more intense symptoms tended to 'doctor shop' looking for a diagnosis they could understand. Rheumatologists made the diagnosis much more often than other physicians. Better education of non-rheumatologists in the diagnosis of fibromyalgia and more acceptance of the diagnostic criteria in the general medical community would help patients with fibromyalgia receive an earlier diagnosis.

Disclosure: R. S. Katz: None; **J. L. Polyak:** None; **L. Kwan:** None.

2075

Impact of Fibromyalgia (FMS) on Work. Robert S. Katz[3], Sharon M. Ferbert[1], Susan Shott[4] and Katrin F. Katz[2]. [1]Advocates for Funding Fibromyalgia Treatment, Education and Research (AFFTER), Libertyville, IL, [2]Rheumatology Associates, [3]Rush University Medical Center, Chicago, IL, [4]Rush University Medical Center

Purpose: The pain, fatigue, and cognitive difficulties associated with FMS can make it difficult for patients to perform well in most work environments. In order to investigate the extent to which FMS affects the capacity to work, we asked fibromyalgia patients about their work experiences.

Method: 115 FMS patients and 63 control patients with other rheumatic diseases answered a 2010 rheumatology clinic questionnaire that included questions about the impact of FMS and other medical problems on their ability to work and the coping mechanisms they use to deal with work. The chi-square test of association and Fisher's exact test were used to compare percentages, and the Mann-Whitney test was done to compare FMS and control patients with respect to age. A 0.05 significance level was used and all tests were two-sided.

Results: 81.7% of the FMS patients and 61.9% of the control patients were women ($p = 0.004$). The mean age was 48.1 12.3 years for FMS patients and 50.7 13.6 for control patients ($p = 0.092$). Only 42.1% of FMS respondents reported that they were working full-time, compared to 57.1% of controls, although the difference was not statistically significant ($p = 0.064$). In response to the question, If you are working part-time, why are you not working full-time?34.8% of FMS patients reported that they were unable to work full-time because of FMS. Only 30.4% of FMS respondents who worked part-time said they choose to work part-time, compared to 55.6% of controls who worked part-time, although the difference was not statistically significant ($p = 0.24$). The majority of FMS respondents who were unable to work or unable to work full-time reported that pain (80.0%), fatigue (60.0%), or concentration difficulties (73.3%) hindered their ability to work. In addition, 13.3% of FMS respondents who were unable to work or unable to work full-time reported that employers aren't sensitive to the impairments of FMS, and 46.7% reported that they were frequently late or missed work. In response to the question, If you have FMS and work full-time or part-time, what helps you cope?the most common answer was that they were taking medications that allowed them to work (66.7%). Other responses included having to work because they needed the money (56.7%), flexible work hours (26.7%), alternative treatments such as yoga and acupuncture (18.3%), and work environment changes that made work easier (13.3%).

Conclusion: FMS has a major impact on patients' ability to work. Pain, fatigue, and concentration difficulties have a strong impact on job performance among FMS patients. Medications were the most frequently reported means of coping with work, followed by the need for money.

Disclosure: R. S. Katz: None; **S. M. Ferbert:** None; **S. Shott:** None; **K. F. Katz:** None.

2076

Improvement of Hand Function in African Americans with Scleroderma: Use of a Hand Continuous Passive Motion. Paula Fenter[2], Samina Hayat[1] and Carla Saulsbury[1]. [1]Shreveport, LA, [2]Louisiana State University Health Sciences Center, Shreveport, Shreveport, LA

Introduction: Movement in the hands is essential to daily functional activities however persons with Scleroderma are at high risk for loosing this function which can lead to loss of independence. It is therefore essential that rehabilitation healthcare professionals work to maintain hand function in these individuals so that independent living can continue while living with this disease and that a good quality of life can be preserved.

Subjects: Three African American individuals who were diagnosed with Scleroderma and had hand involvement were assessed for hand function and given standard exercise program.

Methods: Active range of motion (ROM) was performed on bilateral wrists and hands and the Arthritis Hand Function Test (AHFT) was performed. Each individual was instructed to participate in a daily active motion exercise program for both hands. A continuous passive motion (CPM) machine was placed on the right hand of each individual and the left hand received no CPM intervention. The Arthritis Hand Function Test was also administered. Each individual wore the CPM at night from 2–4 hours on the right hand only. Measurements were taken after at least four weeks of CPM for comparison. The medical records of these individuals were reviewed for this study.

Results: Two of the subjects gained greater than 60 degrees of total active movement of the digits on the hand that received the CPM as compared to the hand that had only active exercise. The other subject gained more active movement in the hand that did not have CPM treatment but did have daily active exercise. All of the subjects had improvement in the AHFT.

Significance: This pilot study shows that improvement in hand function can improve with intervention addressing motion of the hands. Whether active motion alone or active motion with the addition of continuous passive motion is optimal treatment intervention is not clear. This pilot should provide a basis for further research into which is the best treatment for individuals at risk of losing hand function and independence.

Disclosure: P. Fenter: None; **S. Hayat:** None; **C. Saulsbury:** None.

2077

The Mary Kirkland Center for Lupus Care (MKCLC): A Multi-Disciplinary Specialized Disease Center. Pretima Persad[2], Suzy Kim[2], Monica Richey[3], Jane E. Salmon[1], Doruk Erkan[2] and Kyriakos A. Kirou[2]. [1]Hospital for Special Surgery, New York, NY, [2]Hospital for Special Surgery, New York, NY, [3]Hospital for Special Surgery

Background: The complexity of disease in Systemic Lupus Erythematosus (SLE) and Antiphospholipid Syndrome (APS) creates management challenges that require a multi-disciplinary approach for optimal patient outcomes. Additionally, the increased interest of research in the field has generated the need for better organization in rheumatology practices and clinics in order to more efficiently recruit for research. We responded to these challenges by founding the MKCLC with the primary goal of integrating *patient care, patient/physician education, and research*.

Purpose: To report on the organization and growth of the MKCLC over the last year and show that the MKCLC is a candidate model for other multi-disciplinary specialized disease centers at our hospital.

Methods and Structure: Creation: The Center was launched by its current Co-Directors and Steering Committee with the generous support from Rheuminations, Inc.

Patient Care and Multidisciplinary Model: The Center was built around the Friday Lupus Clinic and its corresponding multi-disciplinary conference with participation of fellows, "lupus attendings" and social workers (SW). A Center Manager was given the key task to oversee the execution of the Center's goals and its growth. Additional important support roles have been the Center's Nurse Practitioner, who performs initial patient triage and the SW Manager who screens all new patients for their psychosocial needs.

Patient/Physician Education: Formal multi-disciplinary monthly conferences integrate SLE and related fields, embracing all aspects of care, with an emphasis on lupus nephritis. The Center has created a unique website within the hospital's main site, which highlights the Center's developments and provides resources for patients and staff.

Research: Patient access to research has been streamlined through the Center's Manager in order to maximize recruitment for industry or investigator-initiated research.

Results: Since April 2007, 186 SLE and/or APS clinic patients (87% female, mean age: 40, range: 18–78) have been included in the MKCLC database. Of 186 patients: a) 161 (87%) have been assessed by the SW Manager and referred to one of the five culturally relevant support and education programs offered by the Department of SW Programs; b) 99 (53%) have participated in our pre-existing Autoimmune Disease Registry and Repository; c) 88 (47%) have been referred to the Cardiovascular Disease Prevention Counseling Program and d) 42 (23%) have participated in cross sectional, observational or interventional research studies.

Conclusion: A multi-disciplinary specialized disease center dedicated to SLE and APS has been created to facilitate comprehensive care of patients, physician education, and research. Our Center provides the opportunity to examine whether: (1) specific patient-related education and support initiatives improve clinical outcomes; (2) our coordinated multi-disciplinary approach improves physician education and patient quality of care; and (3) a structured research database and patient screening improves research participation at our center.

Disclosure: P. Persad: None; **S. Kim:** None; **M. Richey:** None; **J. E. Salmon:** None; **D. Erkan:** None; **K. A. Kirou:** None.

2078

TNF Blockage in Spondyloarthritis: Induction of Alveolar Bone Growth in Teeth with Periodontal Disease? Gisele Maria Campos Fabri[1], Cynthia Savioli[2], Carla G. S. Saad[5], Ana Luisa Garcia Calich[5], Julio Cesar Bertacilli Moraes[5], Ana Cristina Medeiros Ribeiro[5], Jozélio Freire Carvalho[5], Percival Sampaio-Barros[5], Clovis Almeida Silva[4], Rosa Maria Pereira[5], José Tadeu Tesseroli Siqueira[3] and Eloísa Bonfá[5]. [1]Dentistry and Rheumatology Division (CEDMAC), Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]Dentistry and Rheumatology Division (CEDMAC), Faculdade de Medicina da Universidade de São Paulo, [3]Dentistry Division, Faculdade de Medicina da Universidade de São Paulo, [4]Paediatric Rheumatology Unit, Rheumatology Division (CEDMAC), Faculdade de Medicina da Universidade de São Paulo, [5]Rheumatology Division (CEDMAC), Faculdade de Medicina da Universidade de São Paulo

Purpose: Previous studies have shown that patients with spondyloarthritis (SpA) have a significant higher risk of periodontal disease (PD). SpA also can induce periosteal bone formation suggesting that the impact of inflammation on bone is specific to the site at which inflammation occurs. We therefore have evaluated the local effect of TNF-antagonist therapy in PD of SpA patients.

Methods: Nineteen SpA patients (ESSG criteria) were prospectively evaluated at baseline(BL) and after 6 months(6M) of anti-TNF therapy. A dentist performed systematic periodontal assessment that included: clinical measurements of periodontal disease severity [probing pocket depth(PPD), cementoenamel junction(CEJ), clinical attachment level(CAL)], gingival inflammation (gingival bleeding index), and oral hygiene (plaque index). All patients were examined by a rheumatologist, blinded to dentist assessment, in order to evaluate demographic data and outcome measures (BASDAI, BASMI, BASFI, ASQoI, CRP, ESR).

Results: Eleven patients (58%) were male, with median age 45(20–61) years and median disease duration 8(1–41) years. Infliximab was used by 12(63%) patients, adalimumab by 6, and etanercept by 1. CRP (16 vs. 4.2mg/L, p=0.003), BASDAI (5.25 vs. 2.65, p=0.001) and BASFI (5.25 vs. 1.95, p=0.017) improved significantly at 6M. No differences were observed in the median of clinical measurements of periodontal disease severity, gingival inflammation and oral hygiene 6M after TNF antagonist use in the whole group. Eight patients (42%) had PD; in these patients, the periodontal assessment of all teeth showed no differences in the median of plaque, gingival bleeding indices, PPD, CEJ, CAL at BL *versus* 6M period (p>0.05). However, the specific longitudinal analysis of teeth with periodontal disease revealed that only PPD had a significant improvement comparing BL *versus* 6M visit [3.67 (3.8–4.27) vs. 2.77mm (2.47–3.03), p=0.003] whereas CEJ [0.53 (−0.58–2.03) vs. 1.66mm (−0.74–2.04), p=1.0] and CAL [3.98 (2.83–5.93) vs. 3.54mm (2.09–4.7), p=0.130] remained stable; this isolated PPD improvement without change in other PD measurements suggests a local bone formation. Despite the PPD improvement, there was no significant resolution of the local inflammation after 6M of anti-TNF therapy, as demonstrated by the persistence of plaque [75.3 vs. 79.8%, p=0.749] and gingival bleeding index [52.4 vs. 39.6%, p=0.641].

Conclusions: This study suggests that blockade of TNF activity in SpA patients with periodontal disease may induce a local bone growth. The most likely mechanism underlying this process is a persistent periodontal inflammation disrupting local bone remodeling.

Disclosure: G. M. C. Fabri: None; **C. Savioli:** None; **C. G. S. Saad:** None; **A. L. G. Calich:** None; **J. C. B. Moraes:** None; **A. C. M. Ribeiro:** None; **J. F. Carvalho:** None; **P. Sampaio-Barros:** Abbott Immunology Pharmaceuticals, 8, Merck Pharmaceuticals, 8, Pfizer Inc, 8, Schering-Plough, 8, Wyeth Pharmaceuticals, 8; **C. A. Silva:** None; **R. M. Pereira:** None; **J. T. T. Siqueira:** None; **E. Bonfá:** None.

2079

What Do We Really Know about Arthritis Impact on Employment from Prospective Studies? A Systematic Review of the Literature. Kristina A. Theis, Ross Wilkie, Lucy Busija, Gerald Elsworth and Richard Osborne. Deakin University

Background: Work disability results from many rheumatic conditions and is known to have substantial personal and societal consequences. Much of what we know about arthritis impact on employment comes from condition-specific cross-sectional studies. A comprehensive search strategy was conducted to identify prospective studies demonstrating how arthritis impacts work.

Methods: Publications were identified by an online electronic search of 6 databases (MEDLINE, JSTOR, PsychINFO, CINAL, EMBASE, and Social Science Abstracts) conducted in early 2010 together with a hand search of references in all obtained literature. Searches were performed with the following terms: "arthritis (in title or abstract) AND work (in title or abstract)" in combination (independently) with: moderate, mediat*, interaction, buffer, buffering, "path analysis", longitudinal, causal, "risk factor", mitigate, associat*, predictor, and explanatory. Inclusion criteria for review: prospective study design assessing work impact at 2 or more time points in adults (≥ 18 years) with an arthritis/rheumatic condition, published in English. Biomedical, scale/instrument development, drug trial, and intervention studies were out of scope. Compliance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) consensus statement was examined as a marker for study quality.

Results: Electronic searches returned 2,877 potential publications; after duplicate removal and title/abstract review 90 remained and were retrieved for complete review. An additional 110 records were identified through hand searching and assessed for eligibility. In total, 15 publications met inclusion criteria for abstraction, 10 of which concerned rheumatoid arthritis, 1 each on fibromyalgia and osteoarthritis, 2 on systemic lupus erythematosus, and 1 included multiple conditions. No study included all relevant STROBE items, with the most commonly omitted including discussion of potential biases and clear reporting of participants at each stage. Definitions of work impact varied but were most often related to work cessation; 3 studies examined more subtle impacts (i.e., productivity, sick leave, work transitions). Methodological approaches were diverse including path and survival analyses and logistic and Cox regression. Characteristics examined could be categorized into 4 general groups (demographics, arthritis-specific, general health/disability, and work-specific). Preliminary results indicated that disability/functional limitation and age were the strongest and most consistently identified predictors of work impacts with less consistent results for work-specific, arthritis-specific, and social characteristics.

Conclusion: With the exceptions of age and disability, there is little consistent evidence for predictors of arthritis impact on employment from prospective studies. Robust conclusions are limited by differences in potential predictors examined, work impact definitions, and methods. However, findings from this systematic review indicate reasonable starting places for policy and public health efforts to mitigate arthritis impact on work.

Disclosure: K. A. Theis: None; **R. Wilkie:** None; **L. Busija:** None; **G. Elsworth:** None; **R. Osborne:** None.

ARHP Concurrent Abstract Sessions
Be Creative with Rheumatic Education: Where and How to Get It
Wednesday, November 10, 2010, 9:15 AM–10:15 AM

2080

Where Do Adults with Arthritis Get Information about Arthritis? Louise Murphy[3], Kristina A. Theis[3], Teresa J. Brady[2], Julie Bolen[3] and Patience White[1]. [1]Arthritis Foundation, [2]Center for Disease Control, Atlanta, GA, [3]Centers for Disease Control and Prevention

Background: Knowing what sources people with arthritis rely upon for information is important for identifying channels for disseminating arthritis information. Our study objective was to identify what existing sources adults with arthritis rely on for information about arthritis and to assess their interest in specific potential resources.

Method: We analyzed data from a national U.S. phone survey of white and black adults (n=1,002), ages 40–70 years old, who have doctor diagnosed arthritis ("Have you EVER been told by a doctor or other health professional that you have some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?), and "some" or "many" limitations due to arthritis. Participants rated how much (a lot, somewhat, a little, not at all) they relied on the following sources for information about arthritis: doctor, pharmacist, family/friends, magazine/newspaper, internet, TV/radio. They also reported how likely (very or somewhat likely or very or somewhat unlikely) they would be to use a 1–800 number, arthritis expo (with exhibits and booths), and periodic 1–4 page publication for general information on arthritis. For each information source, we studied the distribution of ratings overall and by socio-demographic (S-D) variables (age, sex, race, education, income, employment status).

Results: Two thirds (68%) reported relying "a lot" on doctors for information about arthritis, with considerably less reliance on other information sources: "a lot" ratings for other sources ranged from 20% for pharmacists to 8% for TV/radio. The high reliance on doctors and substantial gap in "a lot" of reliance on other sources persisted across S-D groups. There was variation in the S-D characteristics of those reporting "a lot" of reliance on the other information sources (e.g., 28% of blacks reported "a lot" of reliance on pharmacists compared with 18% of whites). Whereas almost half of respondents reported "not at all" for reliance on TV/radio (47%) and the internet (46%), only 6% indicated no reliance on doctors for arthritis information. When asked about potential resources, 20% were "very likely" to use a 1–800 number and 24% for both an arthritis expo and the periodical. For each proposed resource, approximately a quarter indicated they would be "very unlikely" to access. Likelihood of using resources varied across S-D characteristics (e.g., 38% of blacks reported being "very likely" to use a toll-free number compared with 16% of whites).

Conclusion: Doctors were the most relied upon information source, eclipsing all other existing information sources studied; this was consistent across all S-D groups. There was some variation in the S-D characteristics of those who reported "a lot" of reliance on information sources other than doctors. This indicates that the choice of these channels should vary according to the target group. The high percent indicating no reliance on the internet or TV/radio suggests that these are less desirable channels for disseminating arthritis information to the general population of adults with arthritis.

Disclosure: L. Murphy: None; **K. A. Theis:** None; **T. J. Brady:** None; **J. Bolen:** None; **P. White:** None.

2081

Rheuma on the Road—The Rheuma Truck Mass Communication, Educational Advertising and Creative Community Care. Matthias K. Schneider[2] and Martina Blumenroth[1]. [1]Cooperative Rheumatology Association Rhine-Ruhr MNR-Klinik, Duesseldorf, Germany, [2]MNR-Klinik, Duesseldorf, Germany

Aim: In Germany, the public is uninformed about symptoms and treatment of RA.

People are entertaining an outmoded image, e.g. that RA is an old-age disease. This has undesired consequences for early diagnosis in young RA-patients.

As the disease needs public relation in Germany, an educational advertising campaign with "The Rheuma Truck" as a mass communication medium was initiated. The truck was sent to public places to generate awareness, especially with younger people. Early diagnosis of the disease was promoted by informing the public about early symptoms of RA and to check people for RA.

Methods: The German Coop. Rheumatology Assn. Rhine-Ruhr (RZ-RR) hired a 35-ton truck, furnished with a spectacular design, slide-out extended floors on both sides, and equipped with facilities suitable for educating and screening several thousand people for rheumatic diseases. The Rheuma Truck was scientifically guided and evaluated as a screening tool for early diagnosis and mass communication.

The truck visited 22 cities during 26 days in the Rhine-Ruhr area. Participation was at no charge, there were no restrictions for participation except established diagnoses of inflammatory rheumatic disease.

Twelve medical students from the whole range of medical education accomplished the tests. Rheumatologists from RZ-RR gave advice to visitors who were assigned a consultation depending on test results.

We used the German version of the CSQ, called RheumaCheck, and also a questionnaire for ankylosing spondylitis (AS), a computer network, a rapid diagnostic bloodtest for RF and MCV-antibodies yielding qualitative results in 15 minutes, venous blood collection for quantitative results of RF and MCV-antibodies and HLA-B27, a capillary microscope and an ultrasonic device for arthrosonography.

The German patients' organization "Deutsche Rheuma-Liga" supported the crew with information leaflets and talks about early symptoms.

Results: 193 press releases with 42,728,291 contacts and 6,250 google hits were counted for the event. 3,196 visitors were tested, 2/3 female, with an average age of 54.9 years. The RheumaCheck questionnaire yielded 347 times a positive result, 65 visitors were positive for MCV-antibodies and 230 for RF, 34 were positive for RF+MCV. The AS-check was positive 711 times with 11% of those being positive for HLA-B27, too.

The costs were $ 97,000.00 ($30 for each tested person, $ 15 for each google hit and $ 0.002 for each contact).

Conclusion: The Rheuma Truck with its eye-catching design highly attracted attention. It achieved great awareness with 42,728,291 contacts for a low price of $ 0.002 each. Visitors became aware about their risk and know the symptoms of RA, in order not to lose time when they occur, and thus achieve specialized treatment within six months. It was therefore suitable for informing the public and identifying people at early stages of RA and those at risk even before symptoms occur.

Disclosure: M. K. Schneider: None; **M. Blumenroth:** None.

2082

A Study of Pictorial Representation (Mind Map) To Convey Health Education on Osteomalacia to People with Low Language Literacy Skills. Adewale O. Adebajo[5], David Walker[3], Sandra Robinson[4], Yogenjagat Singh[3], Philip Helliwell[2] and Anisur Rahman[1]. [1]University College London, London, United Kingdome, [2]University of Leeds, Leeds, United Kingdom, [3]University of Newcastle, Newcastle, United Kingdom, [4]University of Newcastler, Newcastle, United Kingdom, [5]University of Sheffield Medical School Sheffield United Kingdom, Sheffield, United Kingdom

Background: It is well recognised that health education needs to be provided in different ways to match different learning styles and literacy skills in order to ensure effective patient education for everyone. In order to acheive this, we have through an iterative process and in partnership with Arthritis Research UK developed a Mind Map based on pictorial representation which provides health education on the topic of osteomalacia. We were particualrly keen to ascertain whether this novel health education tool was acceptable to ethnic minorities who originate from the South Asian Sub Continent and particualrly those wih low language literacy skills. Against this background we have performed this ethnicity study using this Mind Map.

Methods: In depth studies were carried out amongst ten English speakers, six Bangali speakers, ten Gujerati speakers, ten Hindi speakers, ten Punjabi speakers and ten Urdu speakers (N=56). Participants were given sample images from the Mind Map and asked to comment on meaning to ascertain suitability, effectiveness and potential to cause inadvertant offence.

Results: Overwhelmingly, the respondents felt that the Mind Map was an effective and appropriate way of communicating health education on osteomalacia, particularly for those people with low language literacy skills. The Mind Maps were also felt to be of particular benefit to those ethnic minorities, for whom English is not their first language.

Cultural specific comments were made in relation to the depiction of food with 4/20 Gujerati and Hindu speakers saying that the picture should represent what they eat, for example depicting a vegetarian diet. Appropriateness responses divided into those which are generic and would apply to anyone, and those that were culturally specific. The general comments were that the bone metabolism depiction could be confusing (31/56), the muscle weakness could be confused with knee pain (16/56), the mending and cracking bone was confusing (22/56) and the picture of a man with bone pain could be confused with toochache (21/56). Inadvertent offence was felt to be highly unlikely and only related to the picture of an old lady in a bed (1/56) and venepuncture (2/56).

Conclusions: Our study indicates that the use of pictorial representation (Mind Maps) are an effective way of achieving patient education. Specifically our study has shown this novel health education tool to be considered appropriate and effective by participants from several ethnic minority groups arising from the South Asian Sub Continent. We recommend Mind Maps as part of the range of tools available for Health Care Professionals to provide health education about musculoskeltal conditions, espeically for people who have low language or literacy skills.

Disclosure: A. O. Adebajo: None; **D. Walker:** None; **S. Robinson:** None; **Y. Singh:** None; **P. Helliwell:** None; **A. Rahman:** None.

2083

Using Social Media To Recruit for a Translational Lupus Research Study for the Millennial Generation—The SisSLE Experience. Marlene H. Kern[2], Sally Kaplan[2], Bonnie Gonzales[2], Betty Diamond[1] and Peter K. Gregersen[2]. [1]Feinstein Institute for Medical Research, Manhasset, NY, [2]The Feinstein Institute for Medical Research, Manhasset, NY

We report on our experience with a pilot registry with the goal to enroll 400 sisters, one diagnosed with lupus, along with one or more sisters without lupus to determine early risk factors of lupus. The enrollment age group is 10–35 years of age. Initially, recruitment by traditional means (i.e. newspaper articles, posters, flyers, health fair recruitment) was not effective and we moved to the use of the Internet and social media. Incorporating the use of the internet enhanced the

response rate. Most people in this age group are "connected" to the internet and we recognized we needed to utilize new methods.

We developed an interactive website that would appeal to this age group: www.SisSLE.org. The nature of the photos, graphics and presentation were intended to attract young users to the site. Study forms are available for *read only* to prepare the potential study subject for their interview. A *contact us* page allows users to email us directly from the website.

We developed standard press releases; template email letters and responses for pre-approval by the IRB. We established liaisons with lupus support organizations throughout the United States asking them to add our website link to *their* website, Facebook page, Twitter feeds, and any other social networking accounts.

As we enrolled young women into our study, we asked them to add a link to our website on their Facebook pages, Twitter feeds and any other internet interaction with lupus groups. Some study subjects took it upon themselves to *blog* about their participation in the study or add a step-by-step accounting of the process of joining the study. While HIPAA is still respected and research confidentiality has been maintained, these women have taken it upon themselves to share their lives with the world creating a ripple effect and reaching other potential study subjects. The bloggers share their written experiences with others thus becoming ambassadors for the study. Our newest recruitment addition is the use of Craigslist. Every 48 hours our posting can appear in a new city. Inquiries are directed to our email address. We have begun to receive responses at this time.

Social networking in research recruitment is new and rapidly evolving. These are new enrollment methods for many healthcare professionals and IRB's and present challenges to maintaining order and confidentiality while keeping current with trends.

Disclosure: M. H. Kern: None; **S. Kaplan:** None; **B. Gonzales:** None; **B. Diamond:** None; **P. K. Gregersen:** None.

ACR Plenary Sessions
ACR Plenary Session III: Discovery 2010
Wednesday, November 10, 2010, 11:00 AM–12:30 PM

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Rates of Malignancy Associated with Juvenile Idiopathic Arthritis and Its Treatment: An Observational Study of National U.S. Medicaid Administrative Claims Data. Timothy Beukelman[4], Kevin Haynes[2], Jeffrey R. Curtis[3], Fenglong Xie[1], Lang Chen[1], Elizabeth Delzell[1], Hopiy Kim[2], Kenneth G. Saag[5] and James D. Lewis[2]. [1]Univ of Alabama at Birmingham, [2]Univ of Pennsylvania, [3]University of Alabama-Birmingham, Birmingham, AL, [4]University of Alabama-Birmingham, Birmingham, AL, [5]University of Alabama-Birmingham, Birmingham, AL

Background: A possible increased risk of malignancy in children with juvenile idiopathic arthritis (JIA), particularly in those receiving treatment with tumor necrosis factor alpha inhibitors (anti-TNF) has been reported. We analyzed national Medicaid administrative claims data to determine standardized rates of malignancy among children with JIA.

Methods: Using Medicaid data from all 50 U.S. states from 2000 through 2005, we identified a cohort of children with JIA based on physician diagnosis codes and dispensed medication prescriptions. We identified non-JIA control cohorts of children diagnosed with asthma and attention deficit hyperactivity disorder (ADHD). Subjects were excluded if they had any physician diagnosis code for malignancy prior to study entry. All subjects had a minimum 9 month baseline assessment period prior to study entry in which to identify prevalent malignancies. For all subjects this baseline assessment period included at least 3 months subsequent to satisfying the disease cohort definitions in order to identify potential incident cancers that were initially misdiagnosed as JIA. Exposure to methotrexate (MTX) and anti-TNF was determined based on dispensed medication prescriptions. Exposed subjects were considered forever exposed and all follow-up time was categorized into 3 groups: (1) no MTX and no anti-TNF; (2) any MTX and no anti-TNF; (3) any anti-TNF. Subjects could contribute follow-up time to more than 1 exposure category sequentially. Malignancy outcomes were defined using physician diagnosis codes, medication codes, and procedure codes using an extension of a previously validated algorithm. Follow-up was censored at loss to follow-up, malignancy outcome, and study end. We calculated crude incidence rates for all malignancies and lymphoma/leukemia for all study groups. Crude rates were standardized to the age, sex, and race distribution of the overall JIA cohort.

Results: The JIA cohort included 7,321 subjects with a median follow-up study time of 1.1 years. Among the JIA subjects, 3,194 were exposed to MTX and 1,413 were exposed to anti-TNF. The asthma (N = 623,663) and ADHD (N = 308,454) cohorts had median follow-up study times of 0.7 and 0.9 years, respectively. Malignancies were identified in 183, 63, and less than 11 patients with asthma, ADHD, and JIA respectively. Crude and standardized rates for all malignancies and for lymphoma/leukemia are shown in the Table. The standardized malignancy rates for JIA were 2 to 3-fold higher than those for ADHD and asthma. No cases of malignancy were identified in JIA subjects who had been exposed to anti-TNF.

	All Malignancy		Lymphoma & Leukemia	
Disease and Exposure Group	Crude Rate per 100K pt-years	Standardized Rate	Crude Rate per 100K pt-years	Standardized Rate
All JIA	58.6 (27.9–122.9)	58.6	25.1 (8.1–77.9)	25.1
JIA no MTX, no TNF	89.8 (37.4–215.8)	93.5	18.0 (2.5–127.5)	21.7
JIA any MTX, no TNF	54.8 (13.7–219.3)	49.3	54.8 (13.7–219.3)	49.3
JIA any TNF	(none)	(none)	(none)	(none)
Asthma	28.0 (24.3–32.4)	26.8	9.8 (7.7–12.5)	9.3
ADHD	16.8 (13.2–21.6)	22.8	7.0 (4.7–10.2)	9.4

Conclusions: Children diagnosed with JIA, irrespective of MTX use, appeared to have an increased risk of malignancy compared to children with asthma and ADHD. There were no cases of malignancy identified in more than 2,700 person-years of anti-TNF exposure in more than 1,400 subjects with JIA.

Disclosure: T. Beukelman: None; **K. Haynes:** None; **J. R. Curtis:** Amgen Inc., 2, Centocor, Inc., 2, 5, Corrona, 2, 5, Roche, 2, 5, 8, UCB, Inc., 5, 8; **F. Xie:** None; **L. Chen:** None; **E. Delzell:** Amgen Inc., 2; **H. Kim:** None; **K. G. Saag:** Amgen Inc., 2, 5, 8, AstraZeneca, 5, Eli Lilly and Company, 2, 5, Genentech and Biogen IDEC Inc, 5, GlaxoSmithKline, 2, 5, Merck Pharmaceuticals, 2, 5, NicOx, 5, Nitec, 5, Novartis Pharmaceuticals Corporation, 2, 5, 8, Pfizer Inc; **J. D. Lewis:** Amgen Inc., 5, AstraZeneca, 5, Centocor, Inc., 2, GlaxoSmithKline, 5, Millenium Pharmaceuticals, 5, Roche, 5, Shire, 2, Takeda Pharmaceuticals North America, 2.

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Aspreva Lupus Management Study (ALMS): Maintenance Results. Ellen M. Ginzler[4], Gerald B. Appel[1], Mary Anne Dooley[7], David A. Isenberg[5], David Jayne[3], David Wofsy[6], Neil Solomons[8], Laura Lisk[9] and David R. Close[2]. [1]Columbia University, New York, [2]MedImmune Ltd, [3]Renal Unit, Addenbrooke's Hospital, Cambridge, United Kingdom, [4]SUNY-Downstate Medical Center, Brooklyn, NY, [5]University College London, London, United Kingdom, [6]University of California, San Francisco, San Francisco, CA, [7]University of North Carolina at Chapel Hill, Chapel Hill, NC, [8]Vifor Pharma (formerly Aspreva Pharmaceuticals), BC, Canada, [9]Vifor Pharma, UK, Bagshot, Surrey, United Kingdom

Background: The 36-month, maintenance phase of the ALMS study (NCT00377637) compared the efficacy and safety of mycophenolate mofetil (MMF) with azathioprine (AZA) in patients with active lupus nephritis (LN) achieving partial or complete response during the 6-month induction phase.

Methods: Patients were re-randomized 1:1 to a double-blind comparison of either oral MMF (2 g/day) plus placebo or oral AZA (2 mg/kg/d) plus placebo. Patients were permitted to receive corticosteroids (CS; maximum dose: 10 mg/d prednisone or equivalent). The primary efficacy outcome measure was time to treatment failure (death, end-stage renal disease [ESRD], sustained doubling of serum creatinine, renal flare [proteinuric or nephritic], and/or requirement for rescue CS). Key secondary parameters included time to event for each individual component of treatment failure: complete renal remission; combined renal and extra-renal remission; major extra-renal flare (British Isles Lupus Assessment Group score category A in 1 extra-renal system or 3 systems with concurrent category B scores); and adverse events (AEs).

Results: Of 227 patients randomized (intent-to-treat population), 127 completed (MMF, 73/116 [62.9%]; AZA, 54/111 [48.6%]). Demographic and disease characteristics were similar across groups at baseline. MMF was superior (log-rank test) to AZA in time to treatment failure (primary endpoint, P=0.003). MMF was superior to AZA (log-rank test) with respect to the following components of treatment failure: time to renal flare (P=0.027) and time to rescue therapy for LN (P=0.017). All other elements of the primary efficacy parameter showed numerical benefit in favor of MMF: time to ESRD (P=0.069) and time to sustained doubling of serum creatinine (P=0.073). MMF was superior to AZA with respect to the key secondary endpoint: time to first confirmed or suspected renal flare (P=0.012). Times to combined renal and extra-renal remission, and major extra-renal flare did not differ between the 2 groups (P=0.416 and P=0.936, respectively). The superiority of MMF over AZA was consistent regardless of induction treatment (MMF or

cyclophosphamide [IVC]), race, or geographic region. The incidence of AEs was similar between MMF and AZA groups; the most common AEs in both groups were infections/infestations and gastrointestinal disorders. Numerically fewer patients treated with MMF than AZA reported at least 1 serious AE (27/115 [23.5%] vs 37/111 [33.3%]. One death (AZA group, unrelated to treatment) occurred during the study.

Conclusions: MMF was superior to AZA in maintaining renal response and preventing relapse in patients with active LN who responded to induction therapy with CS and either MMF or IVC.

Disclosure: E. M. Ginzler: Aspreva, 2, Bristol-Myers Squibb, 5, EMD Serono, 5, Genentech and Biogen IDEC Inc, 2, Human Genome Sciences, Inc., 2, MedImmune, 5; **G. B. Appel:** Centocor, Inc., 5, Genentech and Biogen IDEC Inc, 5, Roche, 5, Teva Pharmaceuticals, 5, Vifor Pharma (formerly Aspreva Pharmaceuticals), 2, 5, 9, Vifor Pharma, 2, 5, 9; **M. A. Dooley:** Amgen Inc., 2, Bristol-Myers Squibb, 2, Roche, 2, Teva Pharmaceuticals, 5, UCB, Inc., 9, Vifor Pharma, 2, 5, 9; **D. A. Isenberg:** Bristol-Myers Squibb, 9, Human Genome Sciences, Inc., 9, Merck Serono, 9, Teva Pharmaceuticals, 9; **D. Jayne:** Hoffmann-La Roche, Inc., 9, Vifor Pharma, 9; **D. Wofsy:** Bristol-Myers Squibb, 5, Genentech and Biogen IDEC Inc, 5, Merck Serono, 5, Teva Pharmaceuticals, 5; **N. Solomons:** Vifor Pharma, 3; **L. Lisk:** Vifor Pharma, 3; **D. R. Close:** None.

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Efficacy of Tadalafil in Raynaud's Phenomenon Secondary to Systemic Sclerosis: A Double Blind Randomized Placebo Controlled Parallel Group Multicentric Study. Vikas Agarwal[8], Parasar Ghosh[6], Aman Sharma[7], Darshan Singh Bhakuni[5], Sudeep Kumar[1], Upendra Narayan Singh[1], Rajesh Vijayvergiya[3], Mukesh Kumar Yadav[4], Geetabali Devi Laishram[2], Alakendu Ghosh[2], Bhuban Majhi[2], Dipankar Mukherjee, S. S. Islam and Aditya Kapoor. [1]Lucknow, India, [2]Kolkata, India, [3]Chandigarh, India, [4]Chandigarh, India, [5]Army Hospital Research & Refferal, New Delhi, India, [6]IPGMER, Kolkata, [7]PGIMER, Chandigarh, India, [8]SGPGIMS, Lucknow, UP, India

Objective: To evaluate the efficacy of Tadalafil in Raynaud's phenomenon (RP) secondary to systemic sclerosis (SSc).

Methods: Patients with scleroderma (as per ACR criteria) having ≥4 Raynaud's attacks/week were randomized to receive either placebo or Tadalafil (20 mg) on alternate days as add-on-therapy to their current vasodilators for eight weeks. Primary end points were improvement in RP parameters (daily frequency, duration and Raynaud's condition score [RCS]) and healing of existing digital ulcers (DU). Secondary outcome measures were appearance of new DU and improvement in scleroderma specific health assessment questionnaire (SHAQ) and quality of life (QoL) indices.

Results: We conducted a multicenter, randomized, placebo-controlled study with a 1-week run-in period to determine baseline severity, followed by a 8-week double-blind treatment phase. Fifty three patients (26 limited, 27 diffuse SSc, 50 females) with mean age 36.8 years and mean disease duration 62.8 months were recruited in the study. All the patients were receiving vasodilators (Calcium channel blockers n=38, angiotensin receptor blockers n=16, angiotensin converting enzyme inhibitors n=8 and a combination of two vasodilators n=13. Twenty six patients were randomized to placebo and 27 to Tadalafil arm. Baseline frequency, duration and severity of RP were not different between the two groups. Improvement in mean daily frequency, mean daily duration of RP and mean daily RCS was significant in the Tadalafil group ($p<0.001$, <0.001, <0.05, respectively), placebo ($p=0.77$, 0.821, 0.209, respectively) as compared to the baseline RP parameters. The mean change in daily frequency ($p=0.01$), duration ($p=0.063$) and severity ($p=0.039$) of RP was significantly better in the Tadalafil group as compared to placebo group. Eighteen patients in the Tadalafil group had DU as compared to 13 patients in the placebo group at baseline. Following treatment, DU healed completely in 14/18 patients in the Tadalafil group as compared to 5/13 patients in the placebo group ($p=0.026$). New DU appeared in one patient in the Tadalafil group as compared to 9 patients in the placebo group ($p=0.004$). Questions related to dyspnea (Q2), Raynaud's phenomenon (Q4) and digital ulcers (Q5) of SHAQ improved significantly in the Tadalafil group. Adverse events (AE) were similar between the two groups. No serious AE was observed.

Conclusion: Tadalafil as add-on therapy improves symptoms of RP, heals the existing DU and prevent new DU in patients with scleroderma.

Clinicaltrials.gov identifier: NCT01117298

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Efficacy of Canakinumab (ACZ885), a Fully Human Anti-Interleukin (IL)-1beta Monoclonal Antibody, in the Prevention of Flares in Gout Patients Initiating Allopurinol Therapy. Naomi Schlesinger[8], Hsiao-Yi Lin[7], Marc De Meulemeester[6], Evgeny L. Nasonov[2], Jozef Rovensky[4], Eduardo F. Mysler[5], Udayasankar Arulmani[3], Gerhard Krammer[3], Alison Balfour[3], Dominik Richard[3], Peter Sallstig[3] and Alexander K. So[1]. [1]CHUV Vaudois, Lausanne, Switzerland, [2]Institue of Rheumatology RAMS, Moscow, Russian Federation, [3]Novartis Pharma AG, Basel, Switzerland, [4]NURCH, Piestany, Slovakia, [5]OMI Organizacion Medica de Investigacion, Buenos Aires, Argentina, [6]Private Practice, Gozée, Belgium, [7]Taipei Veterans General Hospital, Taipei, [8]UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ

Background: Gout patients initiating urate lowering therapy have an increased risk of flares. Inflammation in gouty arthritis is induced by IL-1β. Canakinumab targets and inhibits IL-1β effectively in clinical studies. This study compared different doses of canakinumab vs colchicine in preventing flares in gout patients initiating allopurinol therapy.

Methods: In this 24 week double blind study, gout patients (20–79 years) initiating allopurinol were randomized (1:1:1:1:1:1:2) to canakinumab s.c. single doses of 25, 50, 100, 200, 300 mg, or 150 mg divided in doses every 4 weeks (50+50+25+25 mg [q4wk]) or colchicine 0.5 mg p.o. daily for 16 weeks. Primary outcome was to determine the canakinumab dose giving comparable efficacy to colchicine with respect to the number of gout flares occurring during first 16 weeks. Secondary outcomes included number of patients with gout flares and C-reactive protein (CRP) levels during the first 16 weeks.

Results: 432 patients were randomized and 391 (91%) completed the study. All canakinumab doses were better than colchicine in preventing flares and therefore, a canakinumab dose comparable to colchicine could not be determined. Based on a negative binomial model, all canakinumab groups, except 25 mg, reduced the flare rate ratio per patient significantly compared to colchicine group (rate ratio estimates 25 mg 0.60, 50 mg 0.34, 100 mg 0.28, 200 mg 0.37, 300 mg 0.29, q4wk 0.38; $p\leq0.05$). The percentage of patients with flares was lower for all canakinumab groups (25 mg 27.3%, 50 mg 16.7%, 100 mg 14.8%, 200 mg 18.5%, 300 mg 15.1%, q4wk 16.7%) compared to colchicine group (44.4%). All patients taking canakinumab were significantly less likely to experience at least one gout flare than patients taking colchicine (odds ratio range [0.22 – 0.47]; $p\leq0.05$ for all). The median baseline CRP levels were 2.86 mg/L for 25 mg, 3.42 mg/L for 50 mg, 1.76 mg/L for 100 mg, 3.66 mg/L for 200 mg, 3.21 mg/L for 300 mg, 3.23 mg/L for q4wk canakinumab groups and 2.69 mg/L for colchicine group. In all canakinumab groups with median CRP levels above the normal range at baseline, median levels declined within 15 days of treatment and were maintained at normal levels (ULN=3 mg/L) throughout the 16 week period. Adverse events (AEs) occurred in 52.7% (25 mg), 55.6% (50 mg), 51.9% (100 mg), 51.9% (200 mg), 54.7% (300 mg), and 58.5% (q4wk) of patients on canakinumab vs 53.7% of patients on colchicine. Serious AEs (SAE) were reported in 2 (3.6%; 25 mg), 2 (3.7%, 50 mg), 3 (5.6%, 100 mg), 3 (5.6%, 200 mg), 3 (5.7%, 300 mg) and 1 (1.9%, q4wk) patients on canakinumab and in 5 (4.6%) patients on colchicine. One fatal SAE (myocardial infarction, not related to study drug) occurred in colchicine group.

Conclusion: In this large randomized, double-blind active controlled study of flare prevention in gout patients initiating allopurinol therapy, treatment with canakinumab led to a statistically significant reduction in flares compared with colchicine (standard of care), and was well tolerated.

Disclosure: N. Schlesinger: Novartis Pharmaceuticals Corporation, 2; **H.-Y. Lin:** None; **M. De Meulemeester:** None; **E. L. Nasonov:** Roche, 5; **J. Rovensky:** None; **E. F. Mysler:** Novartis Pharmaceuticals Corporation, 9; **U. Arulmani:** Novartis Pharma AG, 1, 3; **G. Krammer:** Novartis Pharma AG, 1, 3; **A. Balfour:** Novartis Pharma AG, 1, 3; **D. Richard:** Novartis Pharma AG, 1, 3; **P. Sallstig:** Novartis Pharma AG, 1, 3; **A. K. So:** Abbott Laboratories, 5, Bristol-Myers Squibb, 5, Essex, 5, MSD, 5, Novartis Pharma AG, 5, Pfizer Inc, 5, Roche, 5, UBC, 5, Wyeth Pharmaceuticals, 5.

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Effects of Urate Lowering Therapy on Cardiovascular Mortality: A Taiwanese Cohort Study. Jiunn-Horng Chen[1] and Wen-Harn Pan[2]. [1]China Medical University, Taichung City, Taichung, Taiwan, [2]Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan, Province of China

Objective: Gout and elevated serum uric acid (sUA) level have been associated with cardiovascular disease (CVD); however, whether urate lowering therapy (ULT) is beneficial is still inconclusive. This study aimed

to clarify whether controlling sUA with ULT can improve outcomes of CVD.

Method: This prospective cohort study linked baseline clinical data of examinees from the MJ Health Clinical Center in Taiwan with drug dispensed database from the National Health Insurance, and outcome information from the National Mortality Registry for CVD death (ICD-9 code 390–459). Multivariate Cox proportional hazard model was applied to adjust for confounders including age, sex, hyperuricemia (>7.7 mg/dl for men or >6.6 mg/dl for women), overweight (BMI >24 kg/m^2), hyperglycemia (>100 mg/dl), hypertension (SBP ≥130 mmHg, or DBP ≥80 mmHg), hypercholesterolemia (>200 mg/dl), hyper-triglyceridemia (>150 mg/dl), renal insufficiency (GFR <90 ml/min per 1.73 m^2), and heart disease, kidney disease, arthritis, prior use of antihypertensive, anti-diabetic, steroid or analgesics, cigarette smoking, alcohol consumption, exercise, education, occupation, and working load.

Results: Among 45,215 participants (20,677 men and 24,538 women), 519 subjects died of CVD (308 men and 211 women) after a mean follow-up of 11.3 years. A preventive effect of ULT on CVD and stroke mortality was defined with respective hazard ratio (HR) of 0.56 (95% confidence interval, 0.46–0.70) and 0.42 (0.29–0.59) after multivariate adjustment. These effects were prominent for mortalities of hemorrhagic stroke and hypertension with corresponding HR of 0.12 (0.05–0.28) and 0.29 (0.13–0.63). Comparing with participants who did not use ULT, the users who continued treatment until outcome event or censor had better outcome (HR, 0.32; 0.21–0.49) than subjects who discontinue ULT for more than one year (HR, 0.68; 0.53–0.84). In the renal failure status (glomerular filtration rate <30 ml/min per 1.73 m^2), allopurinol usage was more beneficial (HR, 0.04; 0.01–0.25) than benzbromarone (HR, 0.60; 0.11–3.18) for CVD outcomes.

Conclusion: This study demonstrates a preventive effect of ULT for CVD mortality. Further replication studies are needed in the future.

	Model I (Crude)				Model II (Age, gender)				Model III (Multivariate)			
Total=45,215	HR	95% CI		p	HR	95% CI		p	HR	95% CI		p
CVD (n=519)	2.34	1.93	2.83	<0.01	0.89	0.73	1.06	0.24	0.56	0.46	0.70	<0.01
Stroke (n=223)	1.76	1.29	2.42	<0.01	0.65	0.47	0.89	<0.01	0.42	0.29	0.59	<0.01
Hemorrhagie Stroke (n=66)	0.60	0.26	1.39	0.24	0.24	0.10	0.55	<0.01	0.12	0.05	0.28	<0.01
Ischemic Stroke (n=145)	2.48	1.73	3.56	<0.01	0.87	0.60	1.25	0.44	0.63	0.42	0.94	0.02
Hypertension (n=47)	1.48	0.72	3.06	0.29	0.56	0.27	1.17	0.12	0.29	0.13	0.63	<0.01

Disclosure: J.-H. Chen: None; **W.-H. Pan:** None.

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Increased Fracture Rates among Female Osteoporosis Patients Taking Oral Bisphosphonates and Proton Pump Inhibitors Concurrently. Neetu Agashivala[1] and Wing Chan[2]. [1]Novartis Pharmaceuctical Corp, East Hanover, NJ, [2]Novartis Pharmaceuctical Corp

Background: Oral bisphosphonates can cause upset stomach and inflammation, and erosions of the esophagus. Oesophageal and stomach symptoms have been reported in patients taking oral bisphosphonates which may require proton pump inhibitor (PPI) therapy. However, PPIs may interfere with calcium absorption through induction of hypochlorhydria resulting in increased bone resorption. Recent epidemiologic studies have also found that people receiving high doses of PPIs or using them for one year or more are at an increased risk of fractures of the hip, wrist, and spine. The objective of this study was to determine the fracture rates among female osteoporosis patients taking oral bisphosphonates and PPI therapy.

Methods: A retrospective database analysis was conducted using the commercial and Medicare data from the MarketScan claims database for year 2005–06. All osteoporosis females age 50 years or above currently on oral bisphosphonates (alendronate or risedronate) for at least 90 days were included in this study. These patients were stratified into two groups based on PPI intake. The PPI group included lansoprazole, esomeprazole, omeprazaole, pantoprazole, and rabeprazole. PPI usage was defined as concurrent use of bisphosphonates and PPIs for 90 days or more. Combined fracture rates for hip, vertebral, and non-vertebral fractures were assessed among the two groups. Chi square analysis was performed by age categories using *SAS* software, version [8.2] of the *SAS* system for Windows.

Results: Of the 153,899 female osteoporosis patients age 50 and above taking oral bisphosphonates that were identified in the database, 28,304 were taking PPI concurrently. There were a total of 13,388 patients who had experienced a fracture, 3,780 in the PPI group and 9,608 in the non-PPI group. The chi square analysis showed that there was an increased fracture risk in the PPI group compared to the non-PPI group by all age groups (cmh=1.7044; p<.0001). The odds ratio were 1.8216, 1.9074, 1.6091, and 1.5166 in the >=50 and <65, >=65 and <75, >=75 and <85 and >=85 respectively (p<.0001).

Conclusion: PPIs appear to be associated with an increased fracture risk among female osteoporosis patients taking oral bisphosphonates. Further research in the area is required using case-control cohorts.

Disclosure: N. Agashivala: Novartis Pharmaceuticals Corporation, 3; **W. Chan:** Novartis Pharmaceuticals Corporation, 3.

ACR Concurrent Abstract Sessions
Epidemiology and Health Services Research: Osteoarthritis
Wednesday, November 10, 2010, 2:30 PM–4:00 PM

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Quality-Adjusted Life Expectancy Losses Due to Disparities in Total Knee Replacement (TKR) Offer and Acceptance Rates in African American (AA) Men and Women. Elena Losina[4], Lisa G. Suter[6], Alexander M. Weinstein[2], Ilya Golovaty[2], William M. Reichmann[3], Sara A. Burbine[2], Edward H. Yelin[5] and Jeffrey N. Katz[1]. [1]Brigham & Womens Hosp, Boston, MA, [2]Brigham and Women's Hospital, [3]Brigham and Women's Hospital, Boston University, Boston, MA, [4]Brigham and Women's Hospital, Boston University, Harvard Medical School, [5]University of California, San Francisco, CA, [6]Yale University, New Haven, CT

Background: The pathway to TKR in persons with end-stage knee OA requires both a health care provider's offer of surgery and patient's acceptance of that offer. A growing body of evidence has documented lower offer and acceptance rates of TKR in racial minorities. However, quality-adjusted life year (QALY) losses due to underutilization of TKR in racial minorities have not been described.

Methods: We defined the need for TKR as reaching Kellgren-Lawrence (K-L) grade 4 radiographic OA in persons with consistent pain. Based on published data we estimated that only about 50% of racial minorities deemed suitable for TKR are offered surgery, with immediate acceptance rates varying from 21% for African-American (AA) men to 10% for AA women for the first year followed by 7% during subsequent years. We defined index of participation (IoP) as a product of offer and acceptance rates. The base case IoP ranged from 11% for AA men to 5% for AA women. We used the Osteoarthritis Policy (OAPOL) model, a validated computer simulation model of knee OA natural history and treatment, combined with published population-based estimates of TKR outcomes and sex-race specific mortality, to determine the QALY losses due to lower IoP in AA men and women compared to White men (IoP=0.5; offer = 100%, accept = 50%). Future QALYs were discounted at 3% per year. We estimated QALYs across offer rates from 40 to 100% coupled with acceptance rates from 20% to 60% resulting in IoP varying from 8% to 60%.

Results: Estimated discounted QALYs in African American persons eligible for TKR at average age 73 years (SD 9) who did not receive TKR ranged from 6.0 QALYs for AA men to 7.1 QALYs for AA women. QALYs stratified by IoP for AA men and women are presented in the Figure. Base case IoP (11% and 5% for AA men and women respectively) resulted in estimated 6.2 QALYs for AA men and 7.2 QALYs for AA women. Compared to the IoP in White men the QALY losses were 0.62 and 0.92 QALYs for AA men and women respectively (Figure). For the same values of IoP, higher QALYs were evident in scenarios with greater acceptance (vs. offer) rates.

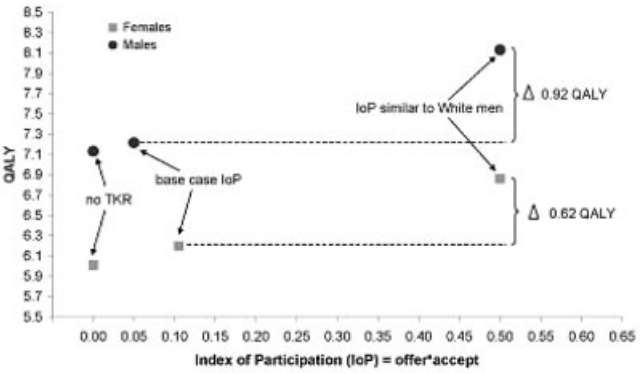

Figure. Quality-adjusted years of life losses due to lower rates of TKR offer and acceptance among African American men and women.

Conclusions: Documented underutilization of TKR in racial minorities leads to substantial losses in quality adjusted life expectancy. The same values of IoP for different offer and acceptance rates do not confer the same quality of life benefits. Interventions focused on better acceptance of TKR among those who have been offered TKR will lead to greater improvement in quality adjusted life expectancy in persons with end-stage knee OA.

Disclosure: E. Losina: None; **L. G. Suter:** None; **A. M. Weinstein:** None; **I. Golovaty:** None; **W. M. Reichmann:** None; **S. A. Burbine:** None; **E. H. Yelin:** None; **J. N. Katz:** None.

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Age of Symptomatic Knee OA Onset: Impact on Costs and Quality of Life. Elena Losina[5], William M. Reichmann[3], Ilya Golovaty[2], Edward H. Yelin[6], Hanna Gerlovin[2], Elizabeth A. Wright[2], David J. Hunter[7], Daniel H. Solomon[4] and Jeffrey N. Katz[1]. [1]Brigham & Womens Hosp, Boston, MA, [2]Brigham and Women's Hospital, [3]Brigham and Women's Hospital, Boston University, Boston, MA, [4]Brigham and Women's Hospital, Harvard Medical School, [5]Brigham and Womens Hospital, Boston, MA, [6]University of California, San Francisco, CA, [7]University of Sydney

Background: Symptomatic knee OA is debilitating and affects >4.5 million US adults. While traditionally viewed as a disease of the elderly, knee OA also affects younger adults, primarily due to history of sport-related injury or occupational exposure. Studies describing the age of patients with knee OA have focused on age at presentation to care or study initiation. Age of onset of symptomatic knee OA and its impact on quality of life and costs have not been described.

Methods: We used a validated computer simulation model of the natural history and management of knee OA, combined with published population-based estimates of incidence, progression, and impact on quality of life, to determine the age of onset, and the lifetime risk and costs associated with symptomatic knee OA and total knee replacement (TKR). We followed a simulated cohort representative of the US general population from age 45 to death. Knee OA treatment costs were derived from the Medicare reimbursement schedule and the Red Book, ranging from $609/yr for PT, NSAIDs, assistive devices and capsaicin to $20,456/yr for TKR. Costs related to comorbidities ranged from $557/yr for 0–1 to $3,603/yr for > 3 comorbidities. We defined TKR eligibility by Kellgren-Lawrence (K-L) grade 4 radiographic OA in persons with consistent pain. Costs (in 2008 US$) were reported as total direct medical costs and costs attributable to knee OA. Both costs and quality-adjusted life expectancy (QALE) were discounted at 3%/yr.

Results: The estimated lifetime risk of symptomatic knee OA was 15.3% with a mean age at onset of 68.7 (SD 13.6) years. Nineteen percent of those with symptomatic knee OA (2.9% of the overall population) developed it before the age of 55, 35.6% of those with symptomatic knee OA (5.4% of overall population) developed knee OA before age 65, and 62% (9.5% of overall population) developed symptomatic knee OA by 75 years of age. The discounted QALE in persons with early onset (before age 55) was 16.7 quality-adjusted life years (QALYs) compared to 17.8 for those with late onset (ages 75+). Early onset led to mean discounted lifetime costs attributable to knee OA of $14,156 per-person, compared to $1,658 for those with late onset. (Table) Among those who developed knee OA early, lifetime risk of TKR was 57.6% compared to 9.7% for those who developed knee OA late. Lifetime risk for revision TKR ranged from 12.1% for those with early onset to 0.4% for those with late onset of disease.

Age of symptomatic knee OA onset	QALE, discounted	Costs, discounted	Costs attributable to knee OA, discounted	Lifetime risk of TKR	Lifetime risk of revision TKR
45–54	16.7	$62,816	$14,156	57.6%	12.1%
55–64	17.0	$58,007	$ 9,191	46.2%	6.4%
65–74	17.5	$52,431	$ 3,714	24.6%	2.0%
75+	17.8	$50,375	$ 1,658	9.7%	0.4%

Conclusions: Early onset of symptomatic knee OA is prevalent in the general US population. It leads to substantial decrements in QALE and increases OA-associated costs. Early onset of symptomatic knee OA leads to 6- and 25-fold increases in the lifetime risk for primary and revision TKR. Injury prevention and weight management, implemented early in life, may delay the onset of symptomatic knee OA, improve quality of life and decrease the economic burden associated with knee OA.

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2092

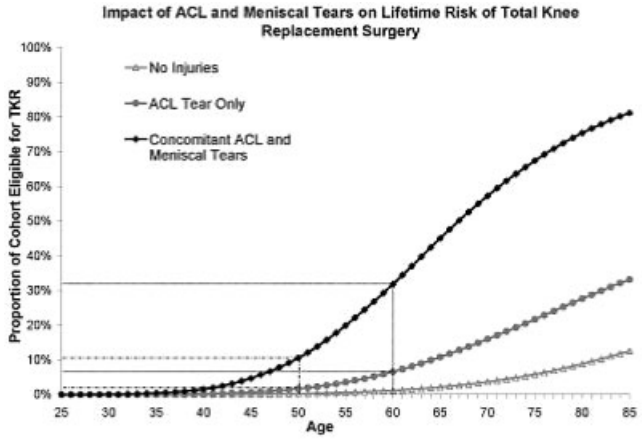
Projecting Lifetime Risk of Symptomatic Knee OA and Total Knee Replacement (TKR) in Persons Sustaining a Complete Anterior Cruciate Ligament (ACL) Tear in Early Adulthood. Elena Losina[4], Hanna Gerlovin[2], Lisa G. Suter[7], David J. Hunter[6], Sara A. Burbine[2], William M. Reichmann[5], Laurel Donnell-Fink[2], Daniel Hal Solomon[3] and Jeffrey N. Katz[1]. [1]Brigham & Womens Hosp, Boston, MA, [2]Brigham and Women's Hospital, [3]Brigham and Womens Hospital, Boston, MA, [4]Brigham and Womens Hospital, Boston, MA, [5]Brigham and Womens Hospital, Boston University, Boston, MA, [6]University of Sydney, [7]Yale University, New Haven, CT

Background: Over 175,000 persons sustain anterior cruciate ligament (ACL) tears annually in the US. ACL tears are especially common in active, younger persons. ACL tears are often accompanied by meniscal tears. We sought to forecast the lifetime risk of radiographic and symptomatic knee OA, and total knee replacement (TKR) in persons who sustain a complete ACL tear in early adulthood.

Methods: We used the Osteoarthritis Policy (OAPol) Model, a state-transition computer simulation model for the natural progression and management of knee OA, to estimate the lifetime risk of radiographic symptomatic knee OA, and TKR in persons with and without a history of a complete ACL tear by early adulthood (before age 25). Rates of OA progression in the absence of an ACL tear were estimated from the Johnston County Osteoarthritis Project. Rates of knee OA incidence in the absence of an ACL tear were derived from published literature and coupled with published estimates on the increased risk of incidence and progression of knee OA following an ACL tear, with or without a concomitant meniscal tear. Persons with symptomatic end-stage OA, defined as Kellgren-Lawrence grade 4 radiographic OA with knee pain, were considered eligible for TKA.

Results: By age 50, 43% of those who sustained a complete ACL tear in early adulthood (by age 25) developed radiographic knee OA and 19% had symptomatic knee OA, as compared with 8% and 3% respectively for those without an ACL tear. For those with a history of an ACL tear accompanied by a meniscal tear, 53% developed radiographic knee OA and 21% developed symptomatic knee OA by age 50. Among persons without an ACL tear, 0.3% were eligible for TKR by age 50, while among those sustaining an ACL tear by age 25, 2% were eligible for TKR, and for those with ACL and meniscal tears by age 25, 11% reached eligibility for TKR (Figure). By age 60, 32% of those with ACL and meniscal tears were eligible for TKR, as compared to 7% of those with an ACL tear alone and 1% of patients with neither ACL nor meniscal tears.

Conclusions: Based upon established evidence, our model-based analysis showed that sustaining an ACL tear at a young age accelerates lifetime risk of symptomatic knee OA and TKR. Subjects with an ACL tear history are likely to develop knee OA earlier than those without an ACL tear. Concomitant meniscal tears lead to even faster progression of knee OA. These findings provide a compelling rationale for developing and implementing sustainable injury prevention strategies for young adults.



Disclosure: E. Losina: None; **H. Gerlovin:** None; **L. G. Suter:** None; **D. J. Hunter:** None; **S. A. Burbine:** None; **W. M. Reichmann:** None; **L. Donnell-Fink:** None; **D. H. Solomon:** Pfizer Inc, 6; **J. N. Katz:** None.

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Validation of an Internet-Based Questionnaire for Ascertaining Cases of Hip and Knee Osteoarthritis. Charles R. Ratzlaff[2], Jacek Kopec[2] and Mieke Koehoorn[1]. [1]University of British Columbia, [2]University of British Columbia/Arthritis Research Centre of Canada

Statement of Purpose: To evaluate the validity of an internet-based questionnaire to ascertain cases of osteoarthritis (OA) of the hip and knee, in a sub-sample of a population-based study, in comparison to the American College of Rheumatology (ACR) criteria.

Methods: The validation study was nested in the Physical Activity and Joint Health (PAJH) cohort study, a population-based, 3-cycle Internet study of Canadians, which included 4,269 subjects. A sub-cohort of 100 subjects from British Columbia were recruited for interviews and clinical examination. Interviews followed a standardized questionnaire format and reporting form. Clinical exams were conducted with the examiner blinded to subject history, interview and self-report status. ACR criteria for classification of hip and knee OA were used as the reference.

Questionnaire items on hip and knee joint health included current and historic pain, aching and stiffness, previous injury, surgery and joint replacement. Separate items inquired about knee and hip-related physical function. The questions regarding a diagnosis were as follows:

'Have you ever been diagnosed by a health professional with OSTEOARTHRITIS of the knee/hip? (Please note that osteoarthritis, rheumatoid arthritis, and osteoporosis are different conditions).'

This question was asked separately for each joint, and confirmation of response required.

Results:

Table 1. Characteristics of Participants in the PAJH baseline cohort and validity study sub-cohort

Characteristics	All PAJH Subjects *(N=4,244)*	Sub-Cohort* *(N=100)*
Age, *yr*	61.5 (7.6)	63.3 (7.2)
Height, *in*	67.4 (5.0)	66.8 (3.6)
Sex, *(%)*		
Male	37%	46%
Body weight, *lbs*	177.3 (39.5)	174.8 (40.4)
BMI	27.3 (5.9)	27.4 (4.91)
Prevalence SR knee OA	19.9%	15%
Prevalence SR hip OA	9.5%	14%
Prevalence KOA-ACR criteria	—	17.5%
Prevalence HOA-ACR criteria	—	10.5%
Marital Status, %		
Married/Common-law	58.0%	64%
Widowed/Separated/Divorced	33.0%	26%
Single	4.7%	10%
Ethnic Origin, *%*		
White	93.6%	91.0%
Other	6.3%	9.0%
Level of Education, *%*		
College/Univ/Post Grad	47.7%	54.1%
Elementary/High school	33.8%	30.1%
Technical or Trade school	17.4%	15.3%

*Sub-cohort subjects are part of Physical Activity and Joint Health (PAJH) cohort and participated in interviews and clinical exams

Table 2. Sensitivity, Specificity, Predictive values and Kappa for self-report of knee or hip OA, in comparison to ACR clinical criteria

	Value	95% CI
Knee OA		
Sensitivity	0.74	(0.60, 0.89)
Specificity	0.98	(0.96, 1.00)
PPV	0.87	(0.81, 0.93)
NPV	0.95	(0.93, 0.97)
Kappa	0.76	(0.64, 0.89)
Hip OA		
Sensitivity	0.81	(0.64, 0.97)
Specificity	0.94	(0.91, 0.97)
PPV	0.61	(0.52, 0.70)
NPV	0.98	(0.97, 0.99)
Kappa	0.65	(0.49, 0.81)

Validity subjects were older, had a more equal gender distribution, less self-reported knee OA and more hip OA, but did not differ significantly across physical characteristics and demographic variables including marital status, ethnic origin and highest level of education.

Self-reported health professional diagnosis had moderate sensitivity and very good specificity, and had better measurement properties than items on pain and symptoms. Cohen's kappa was 0.76 and 0.65 for knee and hip respectively indicating substantial agreement. Consistent with previous postal questionnaires and telephone surveys, this internet-based study reports that the greatest accuracy is achieved by asking about self-report of a health-professional diagnosis.

Conclusion: An Internet-based questionnaire using self-report of a health professional diagnosis of hip or knee OA appears to be a valid measure in large epidemiological studies for assessment of OA, though some misclassification results. Self-reported diagnosis is substantially more specific than asking about pain and symptoms. Estimation of error can be used to interpret and possibly correct results derived from this case definition in analytic studies.

Disclosure: C. R. Ratzlaff: None; **J. Kopec:** None; **M. Koehoorn:** None.

2094

Prevalence of Symptomatic Knee and Hip OA: A Population-Based Survey in France. Francis Guillemin[4], Anne-Christine Rat[5], Bernard Mazières[10], Jacques Pouchot[6], Liana Euller Ziegler[8], Bruno Fautrel[11], Patrice Fardellone[3], Johanne Morvan[9], Christian H. Roux[8], Evelyne Verrouil[2], Alain Saraux[1], Joel Coste[7] and (the KHOALA Group). [1]Brest University, Brest, France, [2]C.H.U Toulouse, Toulouse, France, [3]INSERM ERI 12, C.H.U Amiens, Amiens, France, [4]INSERM, CIC-EC CIE6, Nancy-Université, Paul Verlaine Metz, Paris Descartes, EA 4360 Apemac, Vandoeuvre les Nancy, France, [5]INSERM, CIC-EC CIE6, Nancy-Université, Paul Verlaine Metz, Paris Descartes, EA 4360 Apemac, Nancy, France, [6]Nancy-Université, Paul Verlaine Metz, Paris Descartes, EA 4360 Apemac, Toulouse, France, [7]Nancy-Université, Paul Verlaine Metz, Paris Descartes, EA 4360 Apemac, Paris, France, [8]Nice-University, Nice, France, [9]Quimper Hospital, Quimper, France, [10]Toulouse-University, Toulouse, France, [11]UPMC, C.H.U Pitie Salpetriere, Paris, France

Purpose: Although osteo-arthritis (OA) is a major public health problem, there is a lack of epidemiological data in Europe. The aim of our study was to estimate the prevalence of symptomatic knee and hip OA in a multiregional representative sample in France.

Methods: A two-phase survey was designed. Using a random digit dialing phone survey, subjects 40 to 75 years old were screened with a validated questionnaire. In case of a positive screening question (presence of at least one of the listed characteristic symptoms), subjects were invited to participate to the confirmation phase including physical examination and hip or/and knee X-rays. Cases were all the subjects with symptoms suggestive of symptomatic knee or hip OA according to the clinical examination and X-Rays (Kellgren-Lawrence≥ 2). Prevalence was determined using multiple imputation to account for refusals at different phases in order to obtain more accurate estimates and to limit non-response bias. Estimates were also corrected to account for the sensitivity error of the screening questionnaire. Standardised prevalence estimates were calculated using European age and sex distribution 2006 (Eurostat).

Results: The prevalence survey, conducted in 6 regions started in April 2007. In two years, 63 232 homes answered a phone call and 27 632 had at least one subject aged between 40 and 75 years old. Among them, screening detected 9621 positive subjects, of which 3707 (39%) participated fully to the

confirmation phase. Reasons for non participation in the latter phase included 514 subjects not reached for setting visit in the clinic, 3389 refusals and 933 subjects who did not show up at the visit. Among subjects having completed the whole ascertainment procedure, 1010 had a symptomatic OA: 317 hips, 756 knees.

Participation was different according to region, age, sex, socio-professional category and the different items of the screening questionnaire. Missing data were mostly not at random. Multiple imputation of all eligible subjects accounted for these characteristics: corrected estimates of the prevalence are given by joint, sex and age.

Table. Estimates of the prevalence according to joint, age and sex.

	Men		Women	
	Knee % [IC 95%]	Hip % [IC 95%]	Knee % [IC 95%]	Hip % [IC 95%]
40–49 years	2.1 [0.9; 3.9]	1.0 [0.3; 1.9]	1.6 [0.7; 2.6]	0.8 [0.2; 1.5]
50–59 years	4.7 [3.0; 7.0]	1.6 [0.6; 2.8]	5.9 [4.3; 7.5]	2.2 [1.2; 3.2]
60–69 years	6.8 [4.5; 9.9]	3.2 [1.6; 4.9]	10.5 [8.2; 12.9]	4.2 [2.6; 5.8]
70–75 years	10.1 [6.3; 15.3]	3.9 [1.4; 6.9]	15.0 [11.4; 18.5]	5.1 [2.9; 7.5]

Prevalence increases with age and after 50 years old is more frequent among women. Standardized prevalence was 1.9% in men and 2.5% in women, and 4.7% in men and 6.6% in women for hip and knee symptomatic OA, respectively.

Conclusion: This survey is the first estimation of the prevalence of symptomatic hip and knee OA in France, increasing knowledge about population-based estimates of this condition in Europe. The use of a screening questionnaire validated during pilot studies, the application of multiple imputation to account for missing data, and the correction method to account for the sensitivity error of the screening questionnaire warrant the accuracy of the results.

This study also confirms the feasibility of using a screening questionnaire in two-phase population based surveys in this disease.

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Modifiable Predictors of Racial Differences in Gait Velocity in an Elderly Urban Cohort. Irene Blanco[2], Joe Verghese[2], Richard B. Lipton[2], Chaim Putterman[1] and Carol A. Derby[2]. [1]Albert Einstein College of Med, Bronx, NY, [2]Albert Einstein College of Medicine, Bronx, NY

Background: Gait velocity (GV) is predictive of health status, hospitalizations and mortality and is used to assess functional status the elderly. In the US, elderly Blacks have higher rates of physical disability compared to Whites. Few studies have investigated modifiable risk factors predictive of GV and differences by race. Consequently, we performed a cross-sectional study within a longitudinal, elderly cohort to investigate racial differences in GV and what factors are associated with this measure.

Methods: The Einstein Aging Study (EAS) is a longitudinal study of community residing elderly. Participants are recruited using Medicare beneficiary lists and voter registration records. Demographics and medical history are collected as well as the Geriatric Depression Scale, Blessed Information Memory Concentration Test, the SF-36, and the Total Pain Index (TPI) which measures pain severity, location, duration and frequency over 3 months prior to the visit. GV is measured using the GAITrite gait mat embedded with pressure sensors (CIRsystems, Havertown, PA). Nested linear regression models, adjusted for possible confounders, were used to investigate racial differences in GV. To predict decreased GV, we fit linear regression models within each race strata.

Results: 157 Whites and 56 Blacks, recruited from 2004–2009, were included. Whites were older (median 79.9y v 75.5y, p=<0.01), more educated (median 14y v 12y, p<0.01), and had lower BMIs (mean 26.9±4.3 v 28.9±6.4, p=0.03). Blacks had higher proportions of female participants (80.4% v 59.9%, p<0.01), memory loss (7.1% v 1.0%, p=0.02) and diabetes (28.6% v 13.4%, p=0.01). There were no differences between races with regards to depression, osteoarthritis, history of heart attack, COPD, stroke, hip replacement/pinning, hip/femur/pelvis fracture, lower extremity pain or back pain. (All p-values >0.20) Blacks had higher pain levels on the TPI but the difference was not significant (median 3.2 v 2.0, p=0.09). Neither group had higher pain levels on the SF-36.

Blacks had a significantly slower GV (mean 90.19±17.87 v 99.06± 20.08cm/sec, p<0.01). This difference persists despite adjusting for: age, gender, BMI, education, the above listed comorbidities, TPI and pain as measured by SF-36.(β for racial differences: −7.80 cm/sec, p=0.01) In our predictive models, the modifiable risk factors that predicted decreased GV for Whites were: BMI(p<0.001), stroke (p=0.013), hip replacement (0.05), hip/pelvis/femur fractures (p=0.049) and lower extremity pain (p=0.011). For Blacks, lower GV was associated with back pain (p=0.007) and diabetes though not statistically significant (p=0.06)

Conclusion: Differences in GV persist between Blacks and Whites despite adjusting for many confounders like pain, depression, and comorbidities such as diabetes. When analyzed by race, both groups have modifiable risk factors for decreased GV and by extension decreased functional status. Gait velocity of less than 100cm/sec in the elderly has been associated with increased hospitalizations and mortality. Therefore using GV to screen and develop interventions may limit and reduce health disparities in functional decline in the elderly.

Disclosure: I. Blanco: None; **J. Verghese:** None; **R. B. Lipton:** None; **C. Putterman:** None; **C. A. Derby:** None.

ACR Concurrent Abstract Sessions
Osteoarthritis - Clinical Aspects: Pain and Biomechanics
Wednesday, November 10, 2010, 2:30 PM–4:00 PM

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Physical Activity Assessed by Accelerometry in Persons with Knee OA Compared to National Guidelines: The Osteoarthritis Initiative (OAI). Dorothy D. Dunlop[6], Jing Song[5], Pamela Semanik[8], Leena Sharma[5], Rowland W. Chang[4], Joan M. Bathon[3], Charles Eaton[1], Marc C. Hochberg[11], W. Jerry Mysiw[7], Rebecca Jackson[7], C. Kent Kwoh[10], Michael C. Nevitt[9] and Jennifer M. Hootman[2]. [1]Brown University, [2]Centers for Disease Control, Kennesaw, GA, [3]Johns Hopkins Univ Ste, Baltimore, MD, [4]Northwestern Univ, Chicago, IL, [5]Northwestern University, Chicago, IL, [6]Northwestern University Medical School, Chicago, IL, [7]Ohio State University, [8]Rehabilitation Institute of Chicago, Chicago, IL, [9]UCSF, San Francisco, CA, [10]Univ of Pittsburgh, Pittsburgh, PA, [11]University of Maryland, Baltimore, MD

Purpose: Knee osteoarthritis (OA) is the most prevalent form of arthritis in the US. OA clinical practice guidelines identify a substantial therapeutic role for physical activity. However, we lack objective evidence on the physical activity experience of this population. Reports of physical activity in OA populations are largely based on self-report, which can overestimate activity time and intensity. This study uses accelerometers to objectively assess physical activity intensity and duration from a national knee OA cohort.

Methods: Physical activity was measured via accelerometers at the year 4 clinic visit on 1056 participants in the OAI with baseline radiographic knee OA (KL grade ≥2), Of these, 1021 (97%) had 4–7 valid days of accelerometer monitoring. Activity intensity was determined from accelerometer count cutpoints: light (≤2019), moderate (2020– 5998), vigorous (≥5999). Time spent in bouts lasting≥10 minutes of moderate-to-vigorous physical activity (MVPA) was determined. Gender differences in median intensity times were compared using quantile regression. Attainment of Centers for Disease Control and Prevention (CDC) guidelines for arthritis populations (≥150 bouted MVPA minutes/week) was assessed.

Results: Persons with knee OA primarily engaged in light intensity activity and no measurable activity during a large portion of the day (Table). Overall, a median of only 9.9 minutes/day was spent in moderate-to-vigorous (MVPA) activity; less than 20% (1.4 minutes) of this time was done in bouts lasting more than 10 minutes. Men with knee OA had more minutes of no activity than women. However, men also had more MVPA minutes than women. These differences persisted after controlling for age and BMI. Recommended CDC physical activity guidelines were attained by only 18% of men and 10% of women.

Table. Median daily minutes of physical activity intensity among n=1021 persons with radiographic knee OA

Unadjusted Results	n	Minutes No activity (0 counts) Median	Minutes Light PA (1-2019 counts) Median	Minutes MVPA (>=2020 counts) Median	Minutes Any activity (>0 counts) Median
Men	469	429.6	433.9	15.9	458.0
Women	552	395.0	478.0	7.3	490.3
Men vs Women	Difference (95% CI)	34.6 (22.0, 47.2)	−44.1 (−58.2, −30.1)	8.6 (6.1, 11.1)	−32.3 (−46.5, −18.1)
Adjusted for Age, BMI, Race					
Men	469	432.1	438.9	14.7	457.0
Women	552	402.4	490.7	6.9	499.4
Men vs. Women	Difference (95% CI)	32.9 (17.3, 48.5)	−42.7 (−55.3, −30.1)	5.4 (3.3, 7.5)	−36.9 (−51.6, −22.1)

Conclusion: Despite substantial health benefits from physical activity, persons with knee OA were particularly inactive. Physical activity guideline attainment among persons with knee OA based on accelerometry was under half the proportion previously reported based on self-reported activity, underscoring the importance of objective measures for accurate assessments. Although men were more likely than women to meet recommended physical activity guidelines they were also more likely to be inactive. These findings point to the importance of public health efforts to increase physical activity among persons with knee OA.

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Brain Activity in Patients with Chronic Knee Pain Due to Osteoarthritis: Dissociating Evoked from Spontaneous Pain. Elle L. Parks[2], Marwan N. Baliki[2], Paul Y. Geha[3], Thomas J. Schnitzer[1] and Apkar V. Apkarian[2]. [1]Northwestern University, Chicago, IL, [2]Northwestern University, [3]Yale University

Background: Although chronic pain is a primary manifestation of osteoarthritis (OA), its properties and representation in the brain have not been fully explored. Prior work from our group indicated that brain activity for spontaneous pain and evoked pain in people suffering chronic pain activate brain areas distinct from that observed for acute pain in healthy subjects[1,2] but this has not been studied in people with OA.

Objectives: To define: 1) Psychophysical differences in knee joint pressure-induced pain between OA and healthy subjects, and between OA patients' reported better and worse knees; 2) brain activity differences for knee joint pressure-induced pain in these groups; 3) brain activity differences for evoked and spontaneous pain in OA; 4) the representation of clinical OA pain characteristics in the brain and their relationship with spontaneous and evoked pain-related activity;

Methods: Fourteen OA patients (10 males; age 56.1 ± 2.09 years) and nine healthy controls (6 males; age 46.55 ± 2.6 years) were recruited for this study. Subjects rated pain using a finger-span device in response to pressure applied by means of a custom-made apparatus to the most sensitive part of each knee for patients, and at the center of the knee joint in healthy controls. During each scan run subjects were presented with up to nine stimuli distributed in time in a pseudo-random design of variable intensities and durations. The pressure signal and finger-spanning device were synchronized and time locked with the fMRI acquisition sequence.

Results: Psychophysical properties and brain activation patterns of evoked pain were similar between OA patients and healthy controls, and between worse and better OA knees. In OA patients, stimulus-related brain activity could be distinguished from brain activity associated with ongoing pain. The former activated brain regions (bilateral insula, SII, ACc, SMA, inferior and posterior parietal cortices) commonly observed for acute painful stimuli in healthy subjects, while the spontaneous pain of OA engaged prefrontal-limbic regions closely corresponding to areas observed for spontaneous pain in other chronic pain conditions, such as chronic back pain and post-herpetic neuralgia. We also identified, for the first time, arthritis and chronic pain-related clinical characteristics in the brain, which mapped to distinctive but overlapping prefrontal-limbic regions similar to those involved in spontaneous OA pain.

Conclusion: This study demonstrates the existence of two distinct pain states in knee OA patients. Knee pressure-evoked pain activates brain regions commonly observed for acute pain in healthy subjects for the same stimulus while ongoing spontaneous OA pain activates mainly medial prefrontal-limbic cortical areas, corresponding closely to brain areas activated for spontaneous pain in chronic back pain patients[1,2].

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2098

Central Sensitization and Knee Pain in Osteoarthritis: Preliminary Results from the MOST Study. Tuhina Neogi[3], Jingbo Niu[4], Lars Arendt-Nielsen[1], Joachim Scholz[2], Laura Frey-Law[9], Clifford Woolf[2], Yuqing Zhang[4], Larry Bradley[8], Irina Tolstykh[7], Michael C. Nevitt[6] and David T. Felson[5]. [1]Aalborg University, Denmark, [2]Boston Childrens Hospital, [3]Boston Univ Schl of Med, Boston, MA, [4]Boston Univ School of Medicine, Boston, MA, [5]Boston University School of Medicine, Boston, MA, [6]UCSF, San Francisco, CA, [7]UCSF, [8]University of Alabama at Birmingham, [9]University of Iowa

Purpose: Mechanisms contributing to knee pain in osteoarthritis (OA) are not well understood. Sustained mechanical and inflammatory stimuli in the joint may lead both to changes in the peripheral threshold of nociceptors (peripheral sensitization) and a central amplification of signals in the CNS (central sensitization), resulting in heightened pain sensitivity. We hypothesized findings of central sensitization may be associated with symptomatic knee OA (SxOA).

Methods: The Multicenter Osteoarthritis (MOST) Study is cohort study of persons with or at high risk of knee OA. At the 60-month clinic visit, participants underwent knee radiography, answered pain questionnaires, and had an assessment of temporal summation (TS). TS is an augmented pain response to repetitive mechanical stimuli associated with central sensitization. A 60g monofilament was applied repeatedly over the skin of each patella at a frequency of 1 Hz for 30 seconds. TS was defined as being present when the subject reported an increase in pain following the mechanical stimulation at the site being tested. Knees were categorized according to presence of SxOA based on KL≥2 and presence of consistent frequent knee pain (answering yes to a question about frequent knee pain at a telephone screen and a subsequent clinic visit within 30 days). Pain severity was dichotomized as moderate or greater pain on any of the 5 knee-specific WOMAC pain questions versus none/mild. We used a within-person knee-matched approach to explore the relationships of interest while eliminating between-person confounding using matched conditional logistic regression. In the first matched analyses, we examined the relation of TS with presence of SxOA among persons with knees discordant for SxOA. In the second matched analyses, we examined the relation of TS with pain severity among persons with knees discordant for pain severity, adjusting for radiographic severity.

Results: To date, data on 920 participants' 60-month clinic visit are available (mean age 68.0, mean BMI 30.8, 67.3% female). Among persons with no SxOA, unilateral SxOA, and bilateral SxOA, the age- and sex-adjusted prevalences of TS at the patella were: 59%, 60%, and 61%, respectively. In the within-person knee-matched analyses for SxOA (N=135 that met criteria), radiographic knee OA without regards to knee pain symptoms was associated with 2.3 times higher odds of TS than no OA (95% CI 1.1–4.8, p=0.03), but SxOA itself was not significantly associated with TS once radiographic severity was accounted for (crude OR 1.7, 95% CI 0.7–3.8, adjusted OR 1.1, 95% CI 0.3–3.4). For the knee-matched analyses regarding pain severity (N=152 that met criteria), TS was associated with WOMAC pain severity (OR 3.3, 95% CI 1.3–8.3), but this was attenuated when adjusting for radiographic severity (OR 2.6, 95% CI 0.7–9.5).

Conclusions: In these preliminary results from a large cohort, TS was associated with the presence of radiographic knee OA and knee pain severity in the same knee, but not significantly with SxOA. Such findings suggest that the pathology of OA may be the source of prolonged sensory input required for central sensitization, and in turn, central sensitization may be related to pain severity.

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Gait Adaptation after 6 Months of Specialized Shoes in Knee Osteoarthritis. Najia Shakoor[3], Roy H. Lidtke[4], Markus A. Wimmer[2], Kharma C. Foucher[2], Rachel A. Mikolaitis[2], Louis F. Fogg[2], Alan J. Shoelson[2] and Joel A. Block[1]. [1]Rush University Medical Center, Chicago, IL, [2]Rush University Medical Center, [3]Rush-University Medical Center, Chicago, IL, [4]University of Iowa

Purpose: Biomechanical interventions for knee osteoarthritis (OA) aim to improve pain and retard disease progression by decreasing knee loading. These interventions require chronic use to achieve maximum efficacy and may have a delayed response. Chronic load alterations may also result in neuromuscular gait adaptations that persist even after the intervention is removed. Here, we evaluate the effects of 6 months' use of a "mobility shoe", intended to replicate the advantages of barefoot gait, on knee loading in symptomatic knee OA.

Methods: Subjects with radiographic (KL grades ≥ 2) and symptomatic (at least 30mm pain of 100mm scale while walking) medial compartment knee OA were recruited. Baseline gait analyses were performed using an optoelectronic camera system and multi-component force plate in subjects' "own shoes", "mobility shoes", and barefoot. Subjects were instructed to wear the mobility shoes at least 6 hours/day for 6 days/week. Gait analysis was then repeated at 6, 12, and 24 weeks. The peak knee adduction moment (PAddM), a validated marker of medial compartment loading, represented the primary endpoint. An intent to treat analysis (ITT) was performed using repeated measures analyses of variance and simple main effects were used to further evaluate differences between shoes at various time points.

Results: Complete data are available for 16 subjects. Three terminated early: two due to lack of efficacy (6 and 12 weeks), and one was unable to return for study visits after 8 weeks. All data were carried forward for the ITT analysis. Mean PAddMs during all footwear conditions are represented over time in Figure 1. Overall, in comparison to conventional shoes, the "mobility" shoes were associated with significantly decreased loads during gait ($p=0.001$)(Figure 1). Whereas at baseline the reduction in load with the mobility shoe compared to conventional shoes was only 3.7% ($p=0.081$), this increased to 9.4% ($p<0.001$) after 6 weeks of use, and reached an overall reduction of 18% at 6 months compared to conventional shoes at baseline ($p<0.001$). Interestingly, by 24 weeks, a gait adaptation was evident yielding an 11% ($p<0.001$) reduction in PAddM from baseline even when tested in conventional shoes (Figure 1).

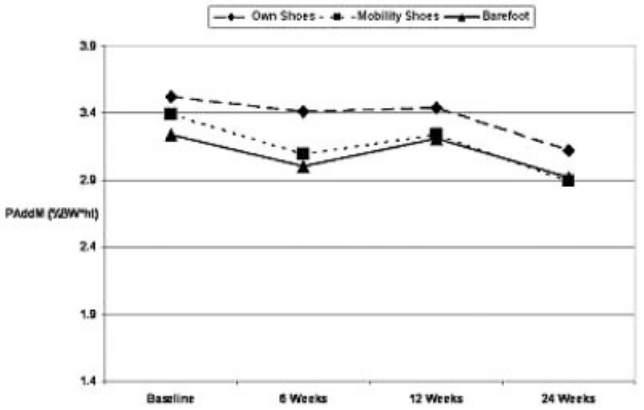

Figure 1.

Discussion: This study suggests that 6 months' use of mobility shoes results in significant reductions in knee loading in subjects with knee OA. This effect is delayed, taking 6 weeks to achieve significant reductions, and it is associated with a gait adaptation by 24 weeks that maintains load reduction even when the mobility shoes are removed. This gait adaptation, likely resulting from beneficial neuromuscular and behavioral changes, may be especially important in OA, which progresses slowly and for which subtle alterations may have profound long-term consequences. The durability of these adaptations will need to be evaluated in longer term studies.

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The Role of Varus and Valgus Alignment in the Initial Development of Cartilage Damage at the Knee: The MOST Study. Leena Sharma[3], Orit Almagor[4], Joan S. Chmiel[4], David T. Felson[1], Ali Guermazi[2], Frank Roemer[2], James Torner[9], Cora E. Lewis[6], Neil Segal[9], John A. Lynch[8], Derek Cooke[5], Jean Hietpas[8] and Michael C. Nevitt[7]. [1]Boston University, Boston, MA, [2]Boston University, [3]Northwestern University, Chicago, IL, [4]Northwestern University, [5]Queens University, [6]UAB, [7]UCSF, San Francisco, CA, [8]UCSF, [9]University of Iowa

Purpose: Varus and valgus alignment are each associated with subsequent progression of knee OA but their role in incident disease is less certain. Radiographic measures of incident OA cannot capture cartilage tissue change directly or reveal the compartment of initial disease. We identified knees with normal cartilage morphology by MRI in all tibial and femoral subregions at baseline to test the hypothesis: varus alignment is associated with incident medial cartilage damage and valgus alignment is associated with incident lateral cartilage damage.

Methods: MOST includes persons at risk for or with knee OA. In all participants, full-limb x-rays were acquired at baseline, and MRI (1.0T extremity system) at baseline and 30 months later. Varus malalignment was defined as ≤ 178° (hip-knee-ankle angle) and valgus as ≥ 182°. Cartilage and menisci were assessed using WORMS. In knees with normal baseline cartilage morphology (WORMS score 0 in all subregions), we used logistic regression with GEE to examine the association between baseline alignment and incident cartilage damage (WORMS score ≥ 2 at 30 months in ≥ 1 subregion) adjusting for age, gender, BMI, laxity, and meniscal tear and extrusion.

Results: Of 1881 knees, 293 knees (110 varus, 55 valgus, 128 neutral) from 256 persons (mean age 60 years, BMI 28.6, 67% women) had normal cartilage morphology in all subregions at baseline. At 30 months, 34 had incident medial and 15 had incident lateral cartilage damage. As shown in Table 1, varus alignment was associated with a significantly increased risk of new medial cartilage damage vs. either reference group (non-varus or neutral) and when analyzed as a continuous variable. This relationship held even when knees with medial meniscal tear or extrusion were excluded (adjusted OR 1.37/1° varus, 95% CI 1.11, 1.68). Significant relationships were not detected for valgus and incident lateral disease (Table 2), possibly due in part to the low frequency of this outcome. In addition, varus was protective against incident lateral damage [adjusted OR 0.75/1°, 95% CI 0.59, 0.95] and valgus against incident medial damage [adjusted OR 0.72/1°, 95% CI 0.63, 0.83].

Table. Median daily minutes of physical activity intensity among n=1021 persons with radiographic knee OA

Unadjusted Results	n	Minutes No activity (0 counts)	Minutes Light PA (1–2019 counts)	Minutes MVPA (≥2020 counts)	Minutes Any activity (>0 counts)
		Median	Median	Median	Median
Men	469	429.6	433.9	15.9	458.0
Women	552	395.0	478.0	7.3	490.3
Men vs Women	Difference (95% CI)	34.6 22.0, 47.2)	−44.1 −58.2, −30.1)	8.6 (6.1, 11.1)	−32.3 −46.5, −18.1)
Adjusted for Age, BMI, Race					
Men	469	432.1	438.9	14.7	457.0
Women	552	402.4	490.7	6.9	499.4
Men vs. Women	Difference (95% CI)	32.9 17.3, 48.5)	−42.7 −55.3, −30.1)	5.4 3.3, 7.5)	−36.9 −51.6, −22.1)

Table 2. Valgus Alignment (Baseline) and Incident Lateral Cartilage Defect (Outcome Variable) between Baseline and 30 Month Follow-up (n=293 knees with normal cartilage morphology at baseline)

Alignment	OR (95% CI) adjusted for age, gender, BMI, medial laxity	OR (95% CI) adjusted for age, gender, BMI, medial laxity, lateral meniscal tear, lateral meniscal extrusion
Non-valgus (reference)	reference	reference
Valgus	1.49 (0.40, 5.50)	0.97 (0.26, 3.70)
Neutral (reference)	reference	reference
Valgus	0.97 (0.25, 3.83)	0.62 (0.14, 2.77)
Valgus (continuous), OR per 1*	1.31 (1.04, 1.66)	1.18 (0.94, 1.48)

Conclusion: In knees with normal cartilage morphology, varus alignment was associated with the initial development of cartilage damage in the more loaded compartment, and both varus and valgus were associated with a reduced risk of incident damage in the less loaded compartment. These results

suggest that varus alignment is a risk factor for incident cartilage damage in knees without OA and provide further evidence that varus alignment increases the risk of incident knee OA.

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Varus Thrust Is Associated with Worse Physical Function. William F. Harvey[3], Grace H. Lo[1], Erica McAdams[4], Melanie A. Ripley[4], Melynn Nuite[3] and Timothy E. McAlindon[2]. [1]Tufts Medical Center, Houston, TX, [2]Tufts Medical Center Box 406, Boston, MA, [3]Tufts Medical Ctr, Boston, MA, [4]Tufts Medical Ctr

Purpose: Varus Thrust (VT) is rapid lateral bowing of the knee during ambulation and represents a combination of malalignment and instability. VT has been associated with knee cartilage loss, medial joint space narrowing and knee pain. It is unknown how presence of VT affects function in knee osteoarthritis (KOA). We hypothesize that presence of VT would be associated with worse functional outcomes in persons with KOA.

Method: This is a cross-sectional study of a convenience sample selected from participants of a randomized controlled trial of vitamin D for symptomatic radiographic KOA. All those in the RCT were eligible to participate in this study except participants who used ambulatory devices. Participants were video recorded in the frontal plane using a standard digital video camera (60 Hz) walking at a self-selected speed. These videos were viewed at separate reading sessions by two rheumatologists trained to evaluate VT. Participants were classified as VT present vs. absent. Disagreements were adjudicated by consensus of both (achieved in all cases). The functional outcomes were WOMAC function subscale and SF-36 function subscale. We also examined the standard functional performance measures chair stand (total time for 5 sequential sit-to-stand movements) and timed 20 meter walk. We used linear regression to model the association of these functional outcomes and presence of VT. As a 'control' we examined a variable we hypothesized should not be associated with VT, the SF-36 Mental Health Subscale.

Results: Participants (N=82) had a mean age 63.0 (±8.5), BMI 30.2 (±5.4), 60% female, 49% with varus alignment, 23% with valgus alignment, and 31% with definite VT. Those with VT and without VT were not different in mean age or height, but were more likely to be male (68% vs. 29% male, $p<0.01$). Although not reaching statistical significance, those with VT were somewhat heavier (Mean weight 87 ± 16 kg vs. 81 ± 15 kg $p=0.35$). Results did not change when adjusting for age, BMI or sex. Table 1 shows the results of the linear regression of functional outcomes. For WOMAC function, chair stand and walk time (for all higher number = more functional impairment), the presence of VT was associated with worse function. VT was also associated with worse functional status by SF-36 (lower number = more functional impairment).

Table 1. Linear Regression of Functional outcomes.

Functional Outcome	VT Absent (n = 57)	VT Present (n = 25)	p-value
WOMAC function (Mean (SD))*	12.4 (9.4)	21.4 (13.5)	<0.01
SF-36 Physical Function Subscale (Mean (SD))**	44.6 (8.7)	38.2 (12.3)	<0.01
SF 36 Mental Health Subscale (Mean (SD))**	51.5 (8.7)	49.9 (8.5)	0.43
Walk Time (Mean (SD)) seconds*	15.3 (2.7)	17.4 (3.9)	<0.01
Chair Stand Time (Mean (SD)) seconds*	14.8 (2.0)	17.0 (3.4)	<0.01

*Lower = better function
**Lower = worse function

Conclusion: VT is associated with worse physical function, as measured by WOMAC function and SF-36 and worse performance in the functional performance measures of chair stand and timed walk. The mental health component score was not associated with VT. The interpretation of the results is limited by the cross-sectional nature of the analysis and should be confirmed prospectively. The results also raise the question of whether a modification of VT (i.e. through bracing, shoe modification, gait modification, etc) may lead to improved physical function.

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2102

Pediatric Rheumatic Disease in the Intensive Care Unit: Lessons Learned from 15 Years Experience in a Tertiary Care Pediatric Hospital. Suhas M. Radhakrishna[2], Bracha Shaham[2], Katherine A. B. Marzan[2], Diane E. Brown[3] and Andreas O. Reiff[1]. [1]Childrens Hosp LA MS60, Los Angeles, CA, [2]Childrens Hospital of Los Angeles, Los Angeles, CA, [3]Childrens Hospital of Los Angeles

Purpose: Pediatric rheumatic diseases and their treatment can cause significant morbidity requiring admission and treatment in the pediatric intensive care unit (PICU). No studies describe the reasons for PICU admission and outcomes of pediatric rheumatology patients. This study describes a large urban single center experience for critically ill patients with rheumatic disease requiring PICU admission. Understanding these data may aid in decreasing morbidity and improving survival.

Methods: The PICU internal database at this tertiary care pediatric hospital was searched for patients with rheumatic disease admitted between January 1, 1995 and July 30, 2009. Medical records were reviewed for demographics, diagnosis, comorbidities, and prior treatments, reason for admission, types of organ dysfunction, supportive care needs, infections, and outcomes. PRISM III (Pediatric Risk of Mortality III) was calculated from the PICU database. Area under receiver operative characteristic curve (AUR) for PRISMIII was calculated. Standard mortality ratio (SMR) was calculated based on PRISMIII estimated mortality with mid-P exact 95% CI. Fisher's exact test was used to determine risk factors for patient mortality.

Results: 90 patients with 122 total admissions were identified. Female: male ratio was 7:3. Mean age at first PICU admission was 14.2 ± 4.3 years. 63% were Hispanic, 20% African American, 12% Caucasian, and 5% Asian. Rheumatic diagnoses included SLE (n=57), systemic vasculitides (n =13), JIA (n=12, 8 with systemic JIA), and dermatomyositis (n=8). Cause of admission was related to rheumatic disease in 61 (50%), infection in 26 (21%), both infection and rheumatic disease in 18 (15%), iatrogenic causes in 5 (4%), and other causes in 12 (10%). Multi-organ dysfunction was present in 39 (32%) and single organ dysfunction occurred as follows: pulmonary in 23 (19%), CNS in 13(10%), GI and renal each in 11 (9%), cardiac in 8(7%), and other in 17 (14%). In 30 admissions (24.6%) a new rheumatologic diagnosis was made. Median length of PICU stay was 3.1 (0–55) days. In 105 (86%) admissions, the patient was discharged from PICU. There were 18 deaths (20%): 9 from combined infection and active rheumatic disease, 4 from infection only, 2 from rheumatic disease only, and 3 from other causes. There were a higher proportion of SLE patients (83% vs 58%, $p=0.06$) and patients on hemodialysis (33% vs 13%, $p=0.07$) in the non-survivor group compared to survivors. AUR for PRISMIII was 0.84 (SE 0.06). SMR based on PRISMIII was 0.72 (95% CI 0.38 – 1.25) for pediatric rheumatology patients and 0.87 (95% CI 0.79–0.96) for all PICU patients.

Conclusions: Rheumatic disease related illness accounted for the majority of PICU admissions, most often with multi-organ dysfunction. Deaths occurred most often from severe infections in patients receiving multiple immunosuppressive medications for active rheumatic disease. Non-statistically significant risk factors for mortality included a diagnosis of SLE and concurrent hemodialysis. Observed mortality in pediatric rheumatology patients correlated well with PRISMIII and SMR was similar to the general PICU population at this institution.

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Rates of Hospitalized Bacterial Infection in Juvenile Idiopathic Arthritis and Its Treatment: An Observational Study of National U.S. Medicaid Administrative Claims Data. Timothy Beukelman[2], Fenglong Xie[2], Lang Chen[2], John W. Baddley[2], Elizabeth Delzell[2], Carlos G. Grijalva[3], Nivedita M. Patkar[2], Kenneth G. Saag[2], Kevin L. Winthrop[1] and Jeffrey R. Curtis[2]. [1]Oregon Health and Science University, [2]Univ of Alabama at Birmingham, Birmingham, AL, [3]Vanderbilt University

Purpose: We analyzed national Medicaid administrative claims data to examine incidence rates of hospitalized bacterial infection among children with juvenile idiopathic arthritis (JIA) in clinical practice.

Methods: Using Medicaid administrative claims data from all 50 U.S. states from 2000 through 2005, we identified a cohort of children with JIA based on physician diagnosis codes and dispensed medication prescriptions. We defined a control cohort of children diagnosed with attention deficit hyperactivity disorder (ADHD). All subjects had a 6 month baseline period for assessment of covariates prior to study entry. Exposures to MTX and anti-TNF were based on dispensed prescriptions and were classified as current use (within 30 days of a missed prescription refill) or recent use (current use within past 6 months). New and prevalent medication exposures were included. All anti-TNF agents were grouped together. Hospitalized bacterial infection outcomes were defined using inpatient discharge diagnosis codes in any position. Follow-up was censored at loss to follow-up, first hospitalized infection outcome, and study end. We calculated crude infection rates for children with JIA with various drug exposures and for children with ADHD. Using Cox proportional hazard models, we calculated hazard ratios (HR) for infection while adjusting for age, sex, race, baseline oral glucocortiocid (GC) use, time-varying current oral GC use, and hospitalized bacterial infection during the baseline period. A secondary analysis of JIA subjects restricted to new-users of MTX and anti-TNF was performed.

Results: The JIA cohort included 8,348 subjects with mean follow-up of 1.6 years. 3,482 JIA subjects were MTX users and 1,477 were anti-TNF users (89% etanercept). The ADHD cohort included 358,534 subjects with mean follow-up of 1.3 years. Crude rates of hospitalized bacterial infection are shown in Table. The crude rate for current oral GC users was 2 to 3-fold higher in all JIA drug exposure groups. The adjusted HR for JIA subjects without any MTX or anti-TNF use was 1.25 (1.07–1.47) compared to ADHD subjects. The adjusted HR for current and recent anti-TNF use was 1.2 (0.9–1.6) compared to JIA subjects without any MTX or anti-TNF use and was 1.3 (1.0–1.8) compared to current and recent MTX users without any anti-TNF use. The analysis of new-users produced an adjusted HR of 1.6 (0.8–3.1) for new anti-TNF compared to new MTX without any anti-TNF.

	No Oral Glucocorticoids		Current Oral Glucocorticoids	
Disease and Exposure Group	Person-years of observation	Infection Rate per 100 person-years (95% CI)	Person-years of observation	Infection Rate per 100 person-years (95% CI)
JIA MTX none, anti-TNF none	6148.4	2.4 (2.1–2.9)	326.0	9.8 (6.9–13.9)
JIA current or recent MTX, anti-TNF none	2824.7	2.3 (1.8–2.9)	640.0	7.2 (5.3–9.9)
JIA current or recent anti-TNF	1776.9	3.1 (2.4–4.0)	478.2	6.1 (4.2–8.7)
ADHD	446, 345	1.01 (0.98–1.04)	5100	5.3 (4.7–6.0)

Conclusion: Children with JIA appeared to have an increased risk of hospitalized bacterial infection compared to control children with ADHD. Current oral CG use was associated with a substantially increased rate of infection in all groups and overshadowed the rate differences associated with MTX and anti-TNF. The additional risk of hospitalized infection associated with anti-TNF use appeared relatively small, with a number needed to harm of 125 compared to non-users of anti-TNF.

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Outcomes of End-Stage Renal Disease Due to Lupus Nephritis among Children in the U.S., 1995–2006. Linda T. Hiraki[6], Bing Lu[3], M. Alan Brookhart[8], Tamara Shaykevich[4], Graciela S. Alarcon[1], Daniel Hal Solomon[5], Wolfgang Winkelmayer[7] and Karen H. Costenbader[2]. [1]Oakland, CA, [2]Brigham & Women, Boston, MA, [3]Brigham and Women's Hospital, Foxboro, MA, [4]Brigham and Women's Hospital, [5]Brigham and Womens Hospital, Boston, MA, [6]Harvard School of Public Health, Boston, MA, [7]Stanford University School of Medicine, [8]University of North Carolina, Chapel Hill

Purpose: Little information is available on kidney transplantation and overall survival among children with end-stage renal disease (ESRD) due to lupus nephritis in the U.S. We examined rates and predictors of kidney transplantation and overall survival among children with ESRD due to lupus nephritis from 1995–2006.

Methods: We identified children ages 5–19 years with new onset ESRD due to lupus nephritis from 1995–2006, as defined by Medicare eligibility and entry into the U.S. Renal Data System, which includes data on approximately 94% of all U.S. ESRD patients. Lupus was identified as the cause of ESRD on medical evidence forms. We investigated baseline demographic and clinical characteristics of patients at ESRD onset, rates of kidney transplantation and overall survival, and causes of death. Predictors of these outcomes in the first five years of ESRD were identified using Cox proportional hazards models, adjusting for sociodemographic and clinical factors.

Results: We identified 583 children in the U.S. who had incident ESRD due to lupus nephritis. Mean age at ESRD onset was 16.2 (SD 2.4) years. Sex, race, ethnicity, region of residence and medical insurance type at ESRD are shown in Table 1. Within 5 years after onset of ESRD, 193 (33% overall) received a kidney transplantation and 131 (22%) died. Mean age at kidney transplantation was 18.2 (SD 3.4) years and at death was 19.5 (SD 3.5) years. Causes of death were cardiorespiratory (39%), infectious (19%), hemorrhagic (10%), neurologic (9%) and other (19%). In multivariable models, residence in the U.S. Northeast, compared to the South, was associated with increased rates of kidney transplantation. Five year rates of both kidney transplantation and overall survival were less than half among Black compared to white children. Sex, ethnicity, medical insurance and clinical factors were not independent predictors of outcomes in these children.

Table 1. Multivariable-adjusted* Five Year Hazard Ratios (HRs) according to Sociodemographic Factors for Children ages 5–19 years with End-Stage Renal Disease (ESRD) due to Lupus Nephritis in the U.S., 1995–2006

Sociodemographic factor (n)	Renal Transplantation** (95% CI***)	Survival** (95% CI***)
Sex		
Female (442)	1.0 (ref.)	1.0 (ref.)
Male (141)	0.99 (0.68, 1.43)	0.68 (0.45, 1.03)
Race		
White (219)	1.0 (ref.)	1.0 (ref.)
Black (287)	0.48 (0.32, 0.71)	0.44 (0.24, 0.80)
Asian (46)	0.85 (0.49, 1.48)	1.01 (0.36, 2.86)
Other (14)	0.66 (0.20, 2.17)	0.39 (0.13, 1.2)
Ethnicity		
Non-Hispanic (441)	1.0 (ref.)	1.0 (ref.)
Hispanic (142)	0.65 (0.41, 1.01)	1.1 (0.55, 2.22)
Region		
South (247)	1.0 (ref.)	1.0 (ref.)
Northeast (82)	1.84 (1.21, 2.80)	1.56 (0.53, 2.94)
MidWest (97)	1.04 (0.66, 1.64)	1.56 (0.9, 2.78)
West (146)	1.2 (0.80, 1.81)	1.12 (0.66, 1.92)
Medical Insurance		
Private (224)	1.0 (ref.)	1.0 (ref.)
Medicaid (285)	0.79 (0.57, 1.09)	1.01 (0.66, 1.52)
None (52)	0.71 (0.38, 1.32)	0.78 (0.41, 1.45)
Other (14)	1.33 (0.47, 3.75)	0.78 (0.18, 3.33)

*Multivariable model: Age, sex, race, ethnicity, medical insurance, region, diabetes mellitus, hypertension, erythropoietin use, body mass index (kg/m^2), and initial ESRD therapy (hemodialysis, peritoneal dialysis or pre-emptive transplant)
**Renal transplantation among all incident *dialysis* patients (n = 579) and survival among all incident ESRD patients (including pre-emptively transplanted, n = 583)
***95% Confidence Interval by Wald method

Conclusions: Among children with ESRD due to lupus nephritis in the U.S., geographic region and race were the most important predictors of five year kidney transplantation and survival rates. Although these analyses do not account for WHO class of nephritis or lupus disease activity, the results suggest that important disparities in access to care and outcomes exist by region and race in the U.S.

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2105

The Clinical Significance of a Single *MVK* Mutation in HIDS. Karyl S. Barron[2], Amanda K. Ombrello[4], Donald P. Goldsmith[1], Ivona Aksentijevich[4], Anne Jones[5], Beverly K. Barham[6] and Daniel L. Kastner[3]. [1]Drexel Univ College Med, Philadelphia, PA, [2]NIAID/NIH, Bethesda, MD, [3]NIAMS, NIH, Bethesda, MD, [4]NIAMS/NIH, [5]NIH, NIAMS, Damascus, MD, [6]Ntl Inst of Arthritis & MSK SD, Bethesda, MD

Background: HyperIgD syndrome (HIDS) is an autoinflammatory disorder caused by mutations in the *MVK* gene that encodes mevalonate kinase. Traditionally it is considered to be transmitted as an autosomal recessive disorder. As a large referral center for children with periodic fever syndromes, we have seen a cohort of symptomatic patients with only 1 mutation in the *MVK* gene. Since there are no defined diagnostic criteria for HIDS, we compared these patients with our cohort of HIDS patients with 2 *MVK* mutations.

Methods: Patients were evaluated in the Periodic Fever Clinic at the National Institutes of Health. Clinical and laboratory information were collected at each visit. CHI square and Mann-Whitney U tests were performed to compare patients with 2 *MVK* mutations and those with only 1 *MVK* mutation.

Summary: 22 patients with mutations in *MVK* were evaluated in our clinic; 15 patients were found to have 2 mutations (V377I and 1 other mutation). 7 patients were found to have only 1 mutation, V377I. All *MVK* coding regions were screened in these patients and we were unable to identify a second mutation. The carrier frequency of V377I in our control Caucasian population was 0.3% (2/739). In contrast, in 344 independent cases of recurrent fever submitted for *MVK* testing, 8 bore a single copy of V377I for a frequency of 2.3%.

Clinical presentation at the time of a flare was compared between the 2 groups:

	2 mutations	1 mutation
Age of onset (mo)	5.4	5.9
Duration (d)	5.1	5.3
Frequency (wks)	3.6	4.5
T max	104.8	105.1
	n (%)	n (%)
Flare with immunizations	12/13 (92.3)	5/7 (71.4)
Abdominal pain	15/15 (100)	6/7 (85.7)
Diarrhea	14/15 (93.3)	6/7 (85.7)
Oral ulcers	11/15 (73.3)	4/7 (57.1)
Sore throat	13/15 (86.7)	5/7 (71.4)
Arthralgia	13/15 (86.7)	5/7 (71.4)
Arthritis	4/15 (26.7)	2/7 (28.6)
Myalgia	8/15 (53.3)	5/7 (71.4)
Rash	11/15 (73.3)	5/7 (71.4)
Cervical adenopathy	15/15 (100)	6/7 (85.7)
Conjunctivitis	7/15 (46.7)	1/7 (14.3)
Headache	11/14 (78.6)	4/6 (66.7)
Developmental delay	4/15 (26.7)	2/7 (28.6)

There was no significant difference in clinical presentation between the 2 groups of patients.

The two groups were similar in percentage with documented elevations of acute phase reactants with flares and mild elevations of IgA. Mean serum IgD levels for those with 2 *MVK* mutations was 103 mg/dl vs. 31 mg/dl for those with 1 mutation ($p=0.03$).

Conclusions: Aside from the higher IgD levels in those children with 2 *MVK* mutations, there does not appear to be any significant clinical differences between these 2 groups. Prior studies in children with 2 mutations have not correlated IgD levels with disease severity. The relatively small number of children with 1 mutation in our cohort may influence the analyses, but thus far there are no clear trends to offer the clinician in the identification or predictability of the disease course in children with either 1 or 2 mutations. Given the higher frequency of V377I heterozygotes in our patient cohort as opposed to the general population, our data suggests that under some circumstances this could be associated with clinical HIDS, although clearly other factors must play a role given the 0.3% frequency in the general population.

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2106

Biomarkers for Global and Renal Disease Activity in Juvenile Systemic Lupus Erythematosus (jSLE). Rina Mina[4], Michael Bennett[3], Joseph M. Ahearn[1], Joshua Pendl[3], Jamie Eaton[3], Nicole Wilson[5], Prasad Devarajan[3] and Hermine Brunner[2]. [1]Wexford, PA, [2]Cincinnati Child Hosp Med Ctr, Cincinnati, OH, [3]Cincinnati Children's Hospital Medical Center, [4]Cincinnati Children's Med Ctr, Cincinnati, OH, [5]Univerisity of Pittsburgh

Background: Preliminary data suggest that the Lupus Nephritis Renal Panel (LNRP), composed of transferrin, ceruloplasmin, acid-1-glycoprotein, neutrophil gelatinase-associated lipocalin, prostaglandin-D synthethase and monocyte chemotactic protein1, is associated with worsening lupus nephritis in jSLE. Cell-bound complement activated products (CB-CAP) which consist of erythrocyte, reticulocyte and platelet-bound complement components (E-C4d, E-C3d E-fBb, E-CR1, R-C4d, R-C3d, R-fBb and P-C4d) have been shown to reflect ongoing global disease activity in studies limited to adults with SLE.

Objectives: Evaluate the association of the LNRP and CB-CAP with global and renal disease activity in jSLE.

Methods: Clinical, laboratory and biomarker data were collected from 12 jSLE patients during initial and follow-up visits. Levels of LNRP standardized to urine creatinine and CB-CAP were measured by enzyme-linked immunosorbent assay and flow cytometry respectively. Physician-rated change in patient's disease course between visits (global/renal disease worsening: yes/no) served as the criterion standard.

Results: Using Wilcoxon Rank Sum Test and Spearman's correlation, statistically significant association was seen between levels of specific urine biomarkers and the renal domains of disease activity indices and the criterion standard *(see Table 1)*. Levels of urine biomarkers were seen to be elevated three months prior to renal worsening with the change in the biomarker level associated with the change in the renal disease activity scores. No significant correlation between extra-renal disease activity and urine biomarkers was seen. Of the CB-CAP, E-CR1, P-C4d and R-C4d were associated with current global/extra-renal disease activity. Traditional biomarkers for global and renal worsening correlated poorly with disease course and activity.

Correlation of Biomarkers with Disease Variables¶

		Concurrent validity			Predictive validity	
Biomarker¶¶	Disease variable	ρ	p-value	Disease variable	ρ	p-value
Ceruloplasmin	Renal BILAG	0.61	0.02	Renal SLAM	0.70	0.02
	Renal SLEDAI	0.60	0.01	Renal BILAG	0.69	0.02
Monocyte chemotactic protein1	Renal SLAM	0.60	0.01	Extra renal BILAG	−0.60	0.05
	Renal SLEDAI	0.75	0.0008			
Transferrin	Renal SLAM	0.56	0.02	Renal SLAM	0.78	0.01
	Renal BILAG	0.72	0.003	Renal BILAG	0.75	0.01
Prostaglandin-D synthethase	Renal SLEDAI	0.75	0.0005	Renal SLEDAI	0.64	0.05
	Renal BILAG	0.66	0.01	Renal BILAG	0.66	0.03
Acid-1-glycoprotein	Renal BILAG	0.61	0.02	Renal BILAG	0.62	0.04
Erythrocyte complement receptor1	Total/Extra-renal BILAG	−0.53	0.02	Urine protein/creatinine	−0.30	0.04
Erythrocyte-factor Bb	Renal BILAG	−0.52	0.04	Creatinine clearance	0.62	0.03
Reticulocyte bound-C4d	Total/Extra-renal BILAG	0.72	0.04			
Platelet bound C4d	Total/Extra-renal BILAG	0.89	<0.0001			

Legend: ¶Only significant correlation shown ¶¶Urine biomarkers standardized to urine creatinine

Conclusions: LNRP is associated with renal disease activity and CB-CAP with extra-renal disease activity in jSLE. Further studies assessing the predictive properties of combining these biomarkers are in progress.

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2107

Childhood Primary Angiitis of the CNS: Identifying Disease Trajectories and Early Risk Factors for Persistently Higher Disease Activity. Tania Cellucci, Pascal N. Tyrrell, Suzanne Laughlin, Derek Armstrong, William Halliday, Shehla Sheikh and Susanne M. Benseler. The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

Purpose: Childhood Primary Angiitis of the CNS (cPACNS) is a devastating inflammatory brain disease. cPACNS comprises of distinct clinical subtypes at presentation. Disease courses of cPACNS have never been systematically studied. The aim of the study was to characterize and compare distinct disease activity trajectories in cPACNS and to identify early risk factors for persistently higher disease activity over time.

Methods: A single centre cohort study was performed including consecutive children diagnosed with cPACNS based on Calabrese criteria between December 1998 and June 2010. Patients had to be <18 years of age at diagnosis and have serial measures of disease activity as defined by physician global assessment (10 cm Visual Analogue Scale). Standardized clinical assessments, Pediatric Stroke Outcome Measures, inflammatory markers, and

neuroimaging characteristics were collected serially. Longitudinal data were analyzed using mixed effects models accounting for repeated measures and linear regression of slope parameter estimates over time.

Results: The study cohort consisted of 45 children: 21 males, 24 females, median age at diagnosis 9.8 years, and median follow-up 21 months. Diagnoses: 26 (57%) had angiography-negative cPACNS, and 19 (43%) had angiography-positive cPACNS. At diagnosis, children with angiography-negative cPACNS were more likely to be female (81% vs. 16%, $p<0.001$), present with seizures (85% vs. 10%, $p<0.001$), and have elevated levels of ESR ($p=0.036$) and CRP ($p=0.046$). Disease activity decreased significantly over time in all cPACNS patients ($p<0.001$). Distinct trajectories of disease activity over time were identified for each cPACNS subtype. Children with angiography-negative cPACNS had persistently higher disease activity and required a longer time to remission ($p=0.046$). Female sex and elevated inflammatory markers at diagnosis were not predictive of delayed remission. Seizures at diagnosis of cPACNS were found to be an early risk factor for persistently higher disease activity over time ($p=0.016$).

Conclusions: Distinct subtypes of cPACNS were found to have unique disease activity trajectories. In all children, disease activity improved significantly over time. However, children diagnosed with angiography-negative cPACNS and those presenting with seizures were at the highest risk for persistently higher disease activity. Early recognition of this high-risk cohort may enable physician to initiate targeted therapies and prevent long-term brain injury in children with cPACNS.

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ACR Concurrent Abstract Sessions
Quality Measures and Innovation in Practice Management and Care Delivery
Wednesday, November 10, 2010, 2:30 PM–4:00 PM

2108

Predictive Validity of the New Preliminary ACR/EULAR Definitions for Remission in Rheumatoid Arthritis. David T. Felson[2], Josef S. Smolen[3], George A. Wells[5], Bin Zhang[1], Lilian H. D. van Tuyl[7], Julia Funovits[4], Maarten Boers[6] and for the ACR/EULAR Commission To Redefine Remission in Rheumatoid Arthritis. [1]Boston Univ Schl of Medicine, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]Krankenhaus Lainz, Vienna, Austria, [4]Medical University of Vienna, [5]Univ of Ottawa Faculty of Med, Ottawa, ON, Canada, [6]VU University Medical Center, Amsterdam, The Netherlands, [7]VU University Medical Center, Amsterdam

Background: With remission in rheumatoid arthritis (RA) an increasingly attainable goal, there is no widely used definition of remission that is stringent but achievable and could be applied uniformly as an outcome in clinical trials.

Methods: A committee constituted from members of the American College of Rheumatology, the European League Against Rheumatism and the Outcome Measures in Rheumatology (OMERACT) Initiative guided the process and reviewed prespecified analyses from clinical trials of patients with RA. A stringent definition was requested including at least joint counts and an acute phase reactant, but excluding duration of state. As part of the search for a remission definition, trial data were analyzed to examine the ability of candidate measures to predict later good x-ray and functional outcomes (defined as change ≤0 in van der Heijde/Sharp scores and Health Assessment Questionnaire (HAQ) change ≤0 and HAQ score consistently ≤0.5 both during the 2nd year of respective trials). Likelihood ratios compared the proportion of patients in remission having the good outcome to the proportion of patients *not* in remission having the good outcome. To rank candidate definitions of remission, the *p* value from the logistic regression chi square test were used.

Candidate definitions of remission were downgraded when they led to values of core set measures which suggested disease activity incompatible with remission.

Results: Patients in a state of remission by several of the Boolean candidate definitions, as well as by traditional SDAI (≤3.3) and CDAI (≤2.8) definitions had an increased likelihood of both x-ray and HAQ stability (see Table 1).

Table 1. Predictive validity of candidate remission definitions for a good outcome in both x-ray and health assessment questionnaire

Candidate remission definition	Prevalence of good outcome in patients: *in* remission	*not in* remission	LR(+)	P
TJC28, SJC28, CRP ≤1	46%	17%	3.2	***
TJC28, SJC28, CRP, PhGA ≤1	55%	17%	4.5	***
TJC28, SJC28, CRP, PtGA ≤1§	66%	17%	7.2	***
TJC28, SJC28, CRP, Pain ≤1	60%	17%	5.7	***
TJC28, SJC28, CRP, PhGA, PtGA ≤1	68%	17%	8.0	***
TJC28, SJC28, CRP, PhGA, Pain ≤1	64%	18%	6.7	***
TJC28, SJC28, CRP, PtGA, Pain ≤1	64%	17%	6.8	***
TJC28, SJC28, CRP, PhGA, PtGA, Pain ≤1	67%	18%	7.5	***
SDAI ≤3.3§	56%	17%	4.8	***
DAS28 <2.6	38%	18%	2.2	**
DAS28 <2.0	56%	20%	4.5	*
Definitions without CRP (for clinical practice)				
TJC28, SJC28, PhGA, PtGA ≤1	68%	17%	7.9	***
TJC28, SJC28, PtGA ≤1	66%	16%	7.2	***
CDAI ≤2.8	63%	16%	6.4	***

*P-value < 0.02; **P-value ≤ 0.01; ***P-value < 0.001
§New preliminary ACR/EULAR definitions for remission in RA

However, reaching remission according to DAS28, both at the traditional (<2.6) and a more stringent cut point (<2.0), was associated only with the likelihood of HAQ stability but not x-ray stability. Additional definitions were tested, including definitions that incorporated pain or patient global at remission levels and other variations, and results were similar. Apart from the DAS28 result, the analyses did not help to distinguish between definitions.

Conclusion: Based on these and other considerations, we propose that a patient be defined as in remission based on one of two definitions of remission: 1: When their scores on the following measures are all ≤1: tender joint count, swollen joint count, CRP (in mg/dL) and patient global assessment (0–10 scale), OR 2: when their score on the SDAI ≤3.3.

These new definitions can be uniformly applied and widely used in RA clinical trials. We recommend that one of these be prespecified in each trial as an outcome and that the results of both be reported. These definitions are currently 'preliminary' and are pending approval from the ACR and EULAR boards.

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2109

Three Physician-Assigned Global Estimates for Inflammation, Damage and Non-Inflammatory Symptoms/Fibromyalgia Help To Clarify Overall Physician Global Estimates of Status in Patients with Different Rheumatic Diseases. Martin J. Bergman[1] and Theodore Pincus[2]. [1]Arthritis and Rheumatology, Ridley Park, PA, [2]New York University Hospital for Joint Disease, Hastings-on-Hudson, NY

Purpose: To analyze the capacity of three physician-assigned global estimates for inflammation, damage and non-inflammatory symptoms/fibromyalgia to clarify the overall physician global estimate of status in patients with various rheumatic diseases, and for these global estimates to serve as surrogates for a quantitative physical examination.

Methods: All consecutive patients in a rheumatology setting in Pennsylvania, with any diagnosis, were assigned four global estimates by a rheumatologist, including overall global status, and 3 additional global estimates for inflammation, damage to any organ (e.g., joint, kidney) and non-inflammatory/fibromyalgia symptoms. The overall estimate was on a scale of 0–10, while the other 3 scales were scored 0–3, which were recoded to 0–10 for comparison with the overall global score. Consecutive patients were classified at first visit in 7 categories: rheumatoid arthritis (RA) (n=40), osteoarthritis (OA) (n=56), fibromyalgia (FM) (n=14), systemic lupus erythematosus (SLE) (n=9), spondyloarthropathy (n=21), gout (n=26) and other (n=64). Mean scores were compiled in the 6 specific disease categories; the "other" patients were not analyzed.

Results: The overall physician global estimate ranged from 2.00 to 4.36, highest for patients with FM (4.36), followed by RA, spondyloarthropathy, OA, gout, and SLE. Physician global estimates for **inflammation** ranged from 0.50 to 4.53, highest for RA, followed by spondyloarthropathy, gout, SLE, and <1.0 (on the recoded 0–10 scale) for OA and FM. Physician global estimates for joint **damage** ranged from 0.37 to 3.83, highest for OA, followed by RA, spondyloarthropathy, and <1.0 for gout, SLE and FM. Physician global estimates for **non-inflammatory/fibromyalgia symptoms** ranged from 0.37 to 5.13, highest for FM (5.13), followed by spondyloarthropathy and RA, and <1.0 for OA, gout, and SLE. One of the 3 more-detailed global estimates was within 1 unit of the overall global estimate for all 6 diseases studied: for **inflammation** in RA, SLE, spondyloarthropathy, and gout; for **damage** in OA; and for **non-inflammatory symptoms/ fibromyalgia** in FM.

Mean physician-estimated scores for overall global status, inflammation, damage, and non-inflammatory symptoms/fibromyalgia at first visit, in consecutive patients in 6 diagnostic categories

Variable	RA	OA	Fibromyalgia	SLE	Spondyloarthropathy	Gout
Number of patients	40	56	14	9	21	26
Overall Physician global (0–10)	4.03	3.25	4.36	2.00	3.33	2.23
Inflammation (0–10)	**4.53**	0.57	0.50	**2.23**	**4.17**	**2.27**
Damage (0–10)	2.40	**3.83**	0.77	0.37	1.58	0.43
Non-inflammatory/fibromyalgia symptoms (0–10)	1.03	0.83	**5.13**	0.37	1.17	0.43

Conclusion: Physician global estimate scales for inflammation, joint/organ damage and non-inflammatory symptoms/fibromyalgia can clarify an overall physician global estimate. These detailed physician global estimates may be regarded as a quantitative summary of the physical examination. Limitations include the absence of longitudinal data, including disease flares. Nonetheless, in view of the importance of physical examination in clinical decisions in rheumatic diseases, these scales may supplement laboratory tests, which often are the only quantitative data in patient records, to assess and monitor patients with rheumatic diseases over long periods.

Disclosure: M. J. Bergman: Bristol-Myers Squibb, 2, 5; **T. Pincus:** Bristol-Myers Squibb, 2, 5.

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Rheumatologists on the Road: A Subspecialist's Role in Caring for the Homebound. Ruchi Jain[1], Suma Dasari[2], Theresa Soriano[2], Linda DeCherrie[2] and Leslie Dubin Kerr[2]. [1]Mount Sinai Medical Center, New York, NY, [2]Mount Sinai Medical Center

Background: In the next 20 years, the number of permanently homebound individuals in the United States will increase by 50% to reach 2 million. To address this problem, the Mount Sinai Visiting Doctors Program has proven to be a successful model as the largest primary care academic home visit program in the nation, serving over 1000 patients in New York City. Currently, there are no medicine subspecialty consult services in place for this rising subset of the population.

Our purpose in establishing a Rheumatology consult service within the Mount Sinai Visiting Doctors program was to provide a remedy to the unmet need for homebound patients with Rheumatologic diseases, and also to provide an educational opportunity for Residents and Fellows in community Rheumatology. Many of these patients were homebound by the very nature of their disease and social environment, and many had no care under a Rheumatologist.

Methods: Through electronic medical record, home-based primary care physicians sent consult requests to the Rheumatology Division. Initial assessments were made through the Routine Assessment of Patient Index Data 3 (RAPID 3) questionnaire.

Results: Over 6 months, 33 home visits were made; 25 as new consults and 8 as follow up visits. Reasons for referral included: medical management of a known connective tissue disease; a question of inflammatory arthritis; procedures including intra-articular injections, arthrocentesis and bursa drainage.

Demographics of patients (as of June 2010): 100% of consults were women, 40% of patients were Hispanic and 76% of patients were between the ages of 60–101. Twenty patients lived alone or with a home health aide, 5 patients lived with other family members. Fifty percent of patients had rheumatoid arthritis (RA). Osteoarthritis comprised 30% of patients seen. Treatment interventions included the following: addition of a disease modifying anti-rheumatic drug (DMARD) in 10 patients, 8 procedures, counseling in 7 patients and a change in the dose of existing medication in 4 patients. At initial evaluation, the average RAPID 3 score for patients with RA was 22.4, reflecting high severity of disease. One patient with psoriatic arthritis (PsA) on initial evaluation had a RAPID 3 score of 21 (high severity); after intervention the RAPID 3 score was 11 (moderate severity). One patient with diffuse scleroderma had a RAPID 3 score of 20.3 (high severity).

Conclusions: The ongoing, increasing number of consults and extent of disease on initial evaluation of these homebound individuals highlights the importance of a Rheumatologist's role in the community. This initiative underscores a hidden, but growing population with current unmet needs. It also defines our role in patient advocacy consistent with our goals and beliefs as Rheumatologists, and as physicians.

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Validation of Electronic Audiovisual Media Assessments of Patients with Rheumatic Diseases. Sarah McNamara[1], Lorraine O' Neill[3], John J. Carey[2] and Robert J. Coughlan[1]. [1]N.U.I Galway University Hospitals, Galway, Ireland, [2]N.U.I Galway University Hospitals, Galway, Ireland, [3]N.U.I. Galway University Hospitals, Galway, Ireland

Purpose: Rheumatology centres often service remote or geographically dispersed areas where patients have significant access issues because of poor transport service or inclement climate. Our centre services such an area including inhabitants of several islands. The extensive availability of audiovisual communication via the Internet has introduced the possibility of 'virtual' assessment of patients living remote from their rheumatology centre. Studies in other diseases show such technology offers promise with obvious advantages for the patient such as saved travel time and cost. There are no published studies comparing the quality of information gained through remote contact to that gained in conventional face to face clinical encounters for patients with rheumatic diseases. The purpose of this study was to assess the validity of the information collected from a virtual patient visit (e-clinic) using "off the shelf" web based technology.

Methods: This study was approved by the local I.R.B. We planned to evaluate 20 patients referred to our centre with 'possible early arthritis' from different primary care centres (PCC) in our region for this pilot programme. An initial assessment using 'Skype®' or 'iChat®' was performed using 'laptop' computers by an experienced rheumatologist (RJC). A follow-up assessment was scheduled within 2 weeks for a face to face encounter in the rheumatology clinic by the same rheumatologist (RJC). Clinical features and diagnosis were compared using both methods.

Results: 5 PCC agreed to participate. 19 (95%) of subjects completed both assessments. Diagnostic agreement was 100% for both assessments (Rheumatoid Arthritis, Osteoarthritis, Tendonitis, Carpal Tunnel Syndrome). Agreement was ≥90% between both assessments for the following clinical features: joint swelling, restricted motion, Heberden's nodes, tendonitis.

Conclusion: Web-based "off the shelf" technology can be used to accurately assess patients referred with 'possible arthritis' to rheumatologists. Support for further studies and development of audiovisual media for assessment of patients with rheumatic complaints is warranted.

Disclosure: S. McNamara: None; **L. O' Neill:** None; **J. J. Carey:** None; **R. J. Coughlan:** None.

2112 WITHDRAWN

2113

Quality of Care in Patients with Systemic Lupus Erythematosus.
Jinoos Yazdany[4], Laura Trupin[5], Chris Tonner[5], Gabriela Schmajuk[3], Joann Z. Gillis[2], Pantelis Panopalis[1], Laura J. Julian[5], Lindsey A. Criswell[5], Patricia Katz[5] and Edward Yelin[5]. [1]McGill University, [2]National Jewish Medical Center, [3]Stanford University, [4]UCSF, San Francisco, CA, [5]UCSF

Objective: We applied newly developed quality indicators (Qis) for systemic lupus erythematosus (SLE) to a large, community-based cohort of individuals to detect areas where health care quality is suboptimal and to identify groups at risk for lower quality care.

Methods: Data derive from a prospective study of individuals with SLE, the Lupus Outcomes Study (LOS). In 2009, 814 individuals participated in the eighth annual survey. Respondents were queried by telephone regarding receipt of care recommended in 13 (of 20) SLE Qis amenable to self-report, as well as their sociodemographic characteristics, health care utilization, disease activity and medication use. For each QI, we calculated the proportion of eligible participants who received recommended care. In addition, we conducted multivariate analyses in which the primary outcome was a global pass rate, defined as the percentage of times recommended care was received among all eligible individuals. In these analyses, respondents contributed one observation for each eligible service, and thus there were between two and twelve observations per respondent. We accounted for these repeated measures in our regression models through generalized estimating equations, adjusting for age, sex, race/ethnicity, education, and poverty status. After eliminating observations with missing data, a total of 794 (98%) participants remained.

Results: The 794 LOS participants were mostly women (92%); 48% were <55 years old; 36% were non-white; 14% had poverty level incomes; 42% had college degrees. They were eligible for 4,054 quality indicators (mean 5 ± 2 Qis/person, range 2–12 Qis). Qis with the highest rates of receipt included counseling regarding sun avoidance (90%), influenza vaccination in those receiving immunosuppressant medications (80%), and calcium and vitamin D supplementation in those taking glucocorticoids (84%) [Table]. Participants were less likely to report receiving care consistent with other Qis, including assessment of traditional cardiovascular risk factors (smoking, lipids, body-mass index, blood pressure, diabetes; 29%), and counseling regarding medication risks and contraception in women at risk for pregnancy initiating potentially teratogenic medications (40%). The global pass rate was 65%; younger age, nonwhite race/ethnicity, and low income were associated with lower global pass rates. In multivariate analysis, only younger age remained statistically significant.

Discussion: In this community-based cohort of individuals with SLE, receipt of recommended care varied significantly depending on the QI assessed. For some Qis, rates of receipt of recommended care were low, suggesting the need for targeted quality improvement. Younger individuals appear to be at risk for lower quality care.

Quality Indicator summary[1], time frame (*in last year unless noted*)	Number Eligible	% Rec'd
Sun avoidance counseling, ever	814	90%
Influenza vaccination if taking immunosuppressive medications	508	80%
Pneumococcal vaccination if taking immunosuppressive medications, ever	508	69%
Bone mineral density testing if receiving prednisone ≥7.5 mg/day	145	56%
Calcium and vitamin D if receiving prednisone ≥7.5 mg/day	145	83%
Antiresorptive or anabolic agent in patients with osteoporosis receiving prednisone ≥7.5 mg/day	98	61%
Counseling regarding risks if initiating new medication	148	68%
Appropriate drug monitoring for NSAID, DMARD or glucocorticoid, varies	683	69%
Glucocorticoid management plan if receiving prednisone ≥10 mg/day for ≥3 months	51	65%
Management of hypertension if renal disease and consecutively elevated blood pressures	26	54%
ACE inhibitor or ARB if renal disease	180	49%
Assessment of traditional cardiovascular risk factors	814	29%
Counseling regarding risks and contraception if reproductive age woman initiating potentially teratogenic medication	25	40%

NSAID = non-steroidal anti-inflammatory drug. DMARD = disease-modifying anti-rheumatic drug.
ACE = angiotensin-converting enzyme. ARB = angiotensin receptor blocker.
[1] See Yazdany J. et al., Arthritis Rheum 2009; 61: 370–377, for more detailed description of SLE quality indicators.

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ACR Concurrent Abstract Sessions
Rheumatoid Arthritis - Human Etiology and Pathogenesis: Anti-CCP in RA Etiology and Pathogenesis
Wednesday, November 10, 2010, 2:30 PM–4:00 PM

2114

The Gene-Environment Interaction between HLA-SE and Smoking Plays an Important Role in Shaping the Reactivity of the ACPA Response to Several Citrullinated Antigens.
Annemiek Willemze[2], Diane van der Woude[3], Wendim Ghidey Alemayehu[1], René R. P de Vries[4], Tom W. J. Huizinga[3], Leendert A. Trouw[3] and René E. M Toes[3]. [1]Leiden University Medical Center, Department of Medical Statistics, [2]Leiden University Medical Center, Department of Rheumatology, Leiden, The Netherlands, [3]Leiden University Medical Center, Department of Rheumatology, [4]Leiden University Medical Center. Department of Immunohematology and Blood Transfusion

Objective: Rheumatoid arthritis is a complex genetic disorder. Human leucocyte antigen shared epitope (HLA SE) alleles are the strongest genetic risk factor for anti-citrullinated protein antibodies (ACPA) positive rheumatoid arthritis (RA). It has recently been postulated that a specific interaction exists between genotype, smoking and autoimmunity to a peptide from enolase. We showed recently that this is not specific for citrullinated α-enolase, but also for a peptide derived from citrullinated vimentin. The aim of this study was to further expand these findings by investigating if gene-environment interactions affect the reactivity pattern to other citrullinated antigens as well.

Methods: The reactivity of 766 RA patients to cyclic citrullinated peptide (CCP) and to four citrullinated peptides derived from vimentin (cVim), fibrinogen (cFib), linear Enolase (cEnolase=C6lin) and Myelin Basic Protein (cMBP=anti-SA) was determined by enzyme-linked immunosorbent assay (ELISA). The separate effects of the HLA SE alleles and smoking were assessed by logistic regression analysis. Biologic interaction was analyzed by investigating if the effects of the risk factors combined exhibited departure from additivity.

Results: The ACPA reactivity profile was affected by a significant biological interaction between the HLA SE alleles and smoking. Both the separate effects of HLA SE alleles and smoking, as well as their combined effects were present for anti-cVim, anti-cEnolase, anti-cMBP and anti-cFib. This effect was strongest for anti-cVim with an odds ratio (OR) of 41 (95% CI 14.7–118.5) in the anti-cVim-positive subset for smokers who were homozygous for the HLA SE alleles, compared to an OR of 6.2 (95% CI 2.4–16.1) in the anti-cVim-negative subset. For anti-enolase, this resulted in an OR of 40.0 (95% CI 11.4–135.2) in the positive subset and an OR of 10.1 (95% CI 4.2–24.2) in the negative group. Anti-MBP and Anti-cFib resulted in a more modest effect in interaction for smokers who were homozygous for SE (see table 1). Combining anti-cVim positive and anti-cEnolase positive patients that were homozygous for HLA SE and smokers, resulted in an even higher OR of 160.0 (95% CI 18.6–1373.0) compared to the anti-cVim negative and anti-cEnolase negative subset with an OR of 5.4 (95% CI 1.9–15.3).

Table 1. Interaction between HLA SE alleles, smoking and autoimmunity to various citrullinated peptides in RA patients

	HLA SE positive and smoker		HLA SE homozygous and smoker	
	OR	(95% CI)	OR	(95% CI)
CCP2−	1.0	(ref)	1.0	(ref)
CCP2+	7.7	(4.7–12.4)	14.5	(6.4–33.0)
CCP2+cVim+	18.0	(8.2–39.7)	41.7	(14.7–118.5)
CCP2+cVim−	4.5	(2.6–7.8)	6.2	(2.4–16.1)
CCP2+cEnolase+	20.6	(7.9–54.1)	40.0	(11.8–135.2)
CCP2+cEnolase−	5.4	(3.2–9.1)	10.1	(4.2–24.2)
CCP2+cMBP+	11.7	(6.4–21.5)	23.3	(9.3–58.3)
CCP2+cMBP−	4.1	(2.2–7.7)	6.7	(2.3–19.0)
CCP2+cFib+	8.4	(4.8–14.7)	17.6	(7.3–42.7)
CCP2+cFib−	6.0	(3.0–12.0)	9.2	(3.1–27.2)
CCP2+cVim+cEnolase+	73.1	(9.8–544.8)	160.0	(18.6–1373.0)
CCP2+cVim−cEnolase−	3.9	(2.2–7.1)	5.5	(1.9–15.3)

Conclusion: The gene-environment interaction between the HLA SE alleles and smoking is not specific for citrullinated α-enolase or citrullinated vimentin, but rather extends to other citrullinated antigens as well. These findings indicate that gene-environment interactions play an important role in shaping the reactivity of the ACPA response by broadening the ACPA-recognition profile.

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2115

Antibodies of IgG, IgA and IgM Isotypes Against Cyclic Citrullinated Peptide Precede the Development of Rheumatoid Arthritis. Heidi Kokkonen[2], Mohammed Mullazehi[4], Ewa Berglin[2], Göran Hallmans[1], Göran Wadell[3], Johan Rönnelid[4] and Solbritt Rantapää-Dahlqvist[2]. [1]Department of Nutritional Research, Umeå University, Umeå, [2]Department of Public Health and Clinical Medicine/Rheumatology, Umeå University, Umeå, [3]Department of Virology, Umeå University, Umeå, [4]Division of Clinical Immunology, Uppsala University, Uppsala

Background and Statement of Purpose: We have previously shown that the presence of anti-cyclic citrullinated peptide (CCP) antibodies precedes the development of rheumatoid arthritis (RA) by several years. In a recent study we also showed that individuals who later developed RA had significantly increased levels of several cytokines, cytokine-related factors, and chemokines. In this study we aimed firstly to investigate the presence and predictive value of isotypes, IgG, IgA and IgM, of anti-CCP antibodies in individuals before onset of symptoms of RA and to assess their relation to rheumatoid factors (RF), cytokines and chemokines, genetic factors, and smoking habits, and secondly to evaluate the predictive effect of these predating antibodies for radiological score after disease onset.

Methods: A case-control study was nested within the Medical Biobank and the Maternity cohorts of Northern Sweden. Patients with RA were identified amongst blood donors antedating onset of their disease by years by co-analyzing the registers of the patients and for the biobanks. Controls, matched for age, sex, date of sampling and residential area, were selected randomly from the same cohorts. Anti-CCP antibody isotypes were determined using EliA anti-CCP assay on ImmunoCAP 250 (Phadia AB, Uppsala, Sweden)

Results: Eighty-six individuals with RA were identified as being blood donors prior to onset of symptoms of joint disease, median (IQR), 2.5 (1.1–5.9) years before onset, with 71 available samples. The prevalence of anti-CCP antibodies in the pre-patient samples was 35.2% of IgG, 23.9% of IgA, and 11.8% of IgM with a specificity of 98.9%, 97.1% and 93.9%, respectively. IgG- and IgA anti-CCP antibodies were highly significant compared with controls, whereas the IgM isotype did not reach statistical significance compared with controls. Anti-CCP antibody of the IgG and IgA isotype predicted RA significantly in conditional logistic regression models (OR=98.1, 95% CI (13.3–723.8) and OR=13.3, 95% CI (4.9–36.0), respectively), whereas the IgM isotype showed borderline significance (OR=2.5 95% CI (0.9–6.3)). The mean antedating time was longest for IgA isotype, 2.2 years, followed by IgG, 2.1 years and for IgM, shortest, 1.4 years. The concentrations of the antibodies increased significantly and the frequencies of the isotypes increased significantly until disease onset and where at diagnosis of RA 70%, 40% and 30%, respectively. IgA antibodies but not IgG were significantly associated with up-regulated chemokines. In smokers IgA anti-CCP antibodies appeared much earlier before onset of symptoms of RA vs. in non-smokers. Patients positive for all three anti-CCP antibody isotypes already before onset of symptoms had a higher radiographic score both at baseline and after 24 months of disease compared with pre-RA individuals with fewer or no anti-CCP2 isotypes before onset.

Conclusions: Anti-CCP antibodies of both the IgG and IgA isotypes pre-dated the onset of RA by several years, also, anti-CCP antibodies of both IgG and IgA isotypes predicted the development of RA, with the highest predictive value for IgG antibodies.

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2116

Epitope Spreading of the Autoantibody Response in the Pre-Clinical Phase Predicts Progression to Rheumatoid Arthritis (RA). Jeremy Sokolove[2], Reuven Bromberg[3], Kevin D. Deane[5], Piyanka Chandra[3], Leslie Derber[6], Jess D. Edison[7], William R. Gilliland[8], Jill Norris[5], V. Michael Holers[4] and William Robinson[1]. [1]Stanford Univ School of Med, Stanford, CA, [2]Stanford University, Mountain View, CA, [3]Stanford University, [4]Univ of Colorado School of Med, Aurora, CO, [5]University of Colorado Denver, Aurora, CO, [6]University of Colorado Denver, [7]Walter Reed Army Med Ctr, Washington, DC, [8]Walter Reed Army Med Ctr, Potomac, MD

Purpose: Anti-CCP antibodies have been demonstrated in the preclinical phase of RA, however, the fine specificity of antigens targeted by these anti-citrullinated protein antibodies (ACPA) has not been well defined. Similarly, elevations in serum cytokines have been demonstrated in the preclinical phase of RA. We sought to determine the fine specificity of the ACPA response in the preclinical phase of RA, to demonstrate a pattern of epitope spreading, to correlate this spreading with the development of cytokine elevations, and to a derive profile of ACPA fine specificity which can predict the imminent onset of clinical RA.

Methods: We performed multiplex bead arrays using the Bio-Plex system to evaluate a panel of 36 putative RA associated autoantibodies and 48 cytokines/chemokines in serial serum samples collected prior to the development of clinical RA. Serum collected prior to clinical diagnosis of RA was obtained from the US Department of Defense Serum Repository. 81 subjects and matched controls were evaluated. Average number of specimens was 2.9 (range 1–4) with first sample obtained an average of 6.6 yrs before diagnosis (range 0.1–13.7 yrs). Results for antibodies or cytokines with a value 3 SD above the median value of matched controls controls were considered positive. Kaplan-Meier survival analysis was performed based on time to first positive test for each subject and hazard ratios calculated compared to controls. Significance Analysis of Microarrays was applied to compare paired samples pre- and post-anti-CCP seroconversion (CCP2 ELISA) and to compare all samples at the earliest and later timepoints. We evaluated the accumulation of ACPA subtypes over time and correlate this accumulation with (i) anti-CCP titer and (ii) cytokine elevations. We performed logistic regression analysis to identify markers which could predict imminent onset of clinical RA (defined as within 2 years of testing).

Results: Pre-clinical RA subjects displayed a time-dependent expansion of ACPA fine specificity. The timing of appearance of ACPA subtypes was similar to that of anti-CCP antibodies and there was a parallel rise in anti-CCP titer and number of ACPA subtypes during the preclinical period. A rise in several RA-related inflammatory cytokines was strongly associated with the expansion of the ACPA response. Finally, we identify a panel of markers

consisting of autoantibodies alone, or autoantibodies in combination with serum cytokines, which is able to identify those subjects most proximate to onset of clinical RA.

Conclusion: The preclinical phase of RA is characterized by an accumulation of multiple autoantibody specificities targeting a variety of citrullinated epitopes. The pattern of accumulation likely reflects epitope spreading and is correlated with rise in anti-CCP titer and ultimately, preclinical inflammation as reflected by rise in RA-associated cytokines. Characterization of the breadth and fine specificity of ACPA enabled identification of individuals within 2 years of RA diagnosis. Identification of such individuals may provide the opportunity for preclinical interventions in imminent RA not previously possible with use of anti-CCP testing alone.

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Citrullinated Epitopes within the Atherosclerotic Plaque: A Target for Anti-Citrulline Protein Antibodies? Jeremy Sokolove[2], Orr Sharpe[3], Matthew Brennan[3], Andrew J. Connolly[3] and William Robinson[1]. [1]Stanford Univ School of Med, Stanford, CA, [2]Stanford University, Mountain View, CA, [3]Stanford University

Purpose: Patients with rheumatoid arthritis have a significantly increased risk for cardiovascular disease (CVD) due to accelerated atherosclerosis. Atherosclerosis is an inflammatory process similar to that observed within the RA synovium. Notably, elevated risk of CVD is mainly limited to anti-citrullinated protein antibody (ACPA) positive patients. Given our recent observation that citrullinated fibrinogen (cFb) immune complexes co-stimulate macrophage TNF production we sought to determine if citrullinated epitopes, specifically cFb, are present in the atherosclerotic plaque where they could be targeted to form immune complexes thus inducing inflammation and accelerating atherosclerosis.

Methods: We performed a series of proteomic and immunohistochemical studies of atherosclerotic lesions obtained from non-RA patients at time of autopsy to evaluate for the presence and identification of citrullinated proteins. Lysates were prepared from atherosclerotic segments of human aortic arch and subjected to 1 and 2-D polyacrylamide gel electrophoresis (PAGE). Parallel gels were transferred to nitrocellulose and probed for the presence of citrulline modified proteins using an anti-modified citrulline antibody (Millipore) and fibrinogen. Spots from 2D gel corresponding to citrullinated peptides were identified by mass spectroscopy. Atherosclerotic plaque and pulmonary artery lysates were immunoprecipitated with anti-fibrinogen antibody and subjected to immunoblot with IgG purified purified from anti-cFb RA patients. Paraffin sections of human coronary plaque were examined by immunohistochemistry for the presence of citrullinated proteins, fibrinogen, human PAD4, and fibrinogen.

Results: Western analysis of 1 and 2-D PAGE demonstrated several citrulline modified proteins within atherosclerotic plaque lysate. Mass spectroscopy as well as re-probing of the western blot membrane for fibrinogen confirmed the presence of cFb. Fibrinogen immunoprecipitated from atherosclerotic plaque lysate, but not pulmonary artery lysate, stained strongly with IgG purified from anti-cFb positive RA patients. Interestingly, several additional ACPA targets were identified from pre-cleared atherosclerotic lysates probed with ACPA+ IgG. Finally, immunohistochemistry demonstrated co-localization of (i) citrullinated proteins, (ii) PAD4, and (iii) fibrinogen within the coronary artery atherosclerotic plaque.

Conclusion: Citrulline modified proteins are prevalent within the atherosclerotic plaque. Specifically, the presence of citrullinated fibrinogen is confirmed to be present and targeted by RA patient derived IgG. This observation suggests that humeral targeting of citrullinated epitopes, specifically cFb, by ACPA within the atherosclerotic plaque could provide a mechanism for accelerated atherosclerosis observed in ACPA+ RA.

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2118

Risk Factors in Different Subsets of Rheumatoid Arthritis. Karin Lundberg[3], Camilla Bengtsson[1], Lena Israelsson[4], Iskra Pollak-Dorocic[4], Leonid Padyukov[4], Lars Alfredsson[1], Vivianne Malmström[4] and Lars Klareskog[2]. [1]Institute for Environmental Medicine, Karolinska Institutet, [2]Karolinska University Hospital, Stockholm, Sweden, [3]Reumatology Unit, Karolinska Institutet, Stockholm, Sweden, [4]Reumatology Unit, Karolinska Institutet

Background: Risk factors for rheumatoid arthritis (RA), such as *HLA-DRB1* 'shared epitope' (SE) alleles, *PTPN22* and cigarette smoking, associate with anti-CCP positive disease. By subdividing CCP positive patients based on reactivity to CEP-1, the immunodominant B cell epitope on citrullinated alpha-enolase, we have previously shown that SE, *PTPN22* and smoking mainly constitute risk factors for CEP-1 positive, rather than CCP positive RA. Here, we investigate 5 RA subsets, grouped based on reactivity to CCP, CEP-1 and a citrullinated vimentin peptide (CitVim), representing another anti-citrullinated protein/peptide antibody (ACPA)-specificity.

Methods: Antibodies were analysed in serum from 1027 RA patients from the Epidemiological Investigation of RA (EIRA), a Swedish population-based case-control study. An ELISA was set up for detection of anti-CitVim antibodies, using a biotinylated CitVim peptide (amino acid 60–75). One hundred and fifty healthy controls were used to determine the 95th percentile cut-off. A positive and a negative control and a standard of pooled anti-CitVim positive serum were included on each plate. Anti-CCP was measured using the Immunoscan CCPlus kit (Euro-Diagnostica) and anti-CEP-1, using an in-house ELISA previously described (Mahdi et al, Nature Genetics, 2009). Different RA subsets were compared with regard to risk factors by calculating odds ratios (OR) with 95% confidence interval by means of logistic regression.

Results: Patients were divided into 5 subsets: CEP-1+/CitVim+ (41%); CEP-1+/CitVim− (15%); CEP-1−/CitVim+ (11%) (the majority of patients in these subsets were anti-CCP positive and not divided further based on CCP status); CEP-1−/CitVim−/CCP+ (18%) and CEP-1−/CitVim−/CCP− (15%). SE, *PTPN22* and smoking each showed strongest association in the CEP-1+/CitVim+ subset, intermediate association in the single positive subsets and low association in the ACPA negative subset. The combined effect of risk factors showed a similar pattern, with an OR of 52 in the double positive subset, 16 in the CEP-1 single positive, 5 in the CitVim single positive, 6 in the CCP single positive, and 2 in the triple negative. Additionally, antibody levels were higher in CEP-1+/CitVim+ patients compared to single positive patients.

Conclusion: Our data show that the anti-CEP-1 and the anti-CitVim antibody response only partly overlap, and that SE, *PTPN22* and smoking predispose to the development of ACPA with multiple reactivities, rather than one single specificity. Interestingly, the CEP-1-/CitVim-/CCP+ subset still showed a strong association with SE (OR: 12), suggesting that other ACPA fine-specificities, for example citrullinated fibrinogen or collagen type II, could be found in this subset.

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2119

Anti-CCP Positivity in Patients with Lung Disease but No Apparent Articular RA: A Pre-RA State? Joshua J. Solomon[1], Allen Stevens[1], Mary Gill[1], Jennifer Brandorff[1], Jeffrey J. Swigris[1], Kevin Deane[2], Richard Martin[1], Roland M. du Bois[1] and Aryeh Fischer[1]. [1]National Jewish Health, [2]University of Colorado

Background and Objectives: Anti-CCP positivity is highly specific for RA, and can be identified in patients prior to the development of articular manifestations of RA. Also, lung disease may be the initial clinical manifestation of RA, and as such patients with lung disease but no articular RA may have anti-CCP positivity, reflecting early RA-related immune dysregulation. For this study, we sought to identify and describe a patient cohort characterized by lung disease, with moderate-to-high anti-CCP positivity, in the absence of articular manifestations of RA.

Methods: Between January 2008 and January 2010, 2393 patients had an anti-CCP antibody test at our center using the INOVA CCP3.1 IgG/IgA ELISA kit. 312 patients had a positive anti-CCP (≥ 20 IU). Of these, we excluded those with a low-titer positive anti-CCP (20 IU–39 IU) (n=63), patients in whom the anti-CCP was assessed due to joint disease (either with a pre-existing diagnosis of RA, or due to presence of joint symptoms of inflammation or synovitis on examination as determined by the treating physician) (n=214), patients younger than 18 (n=1), those without lung disease (n=2) and all patients with other defined connective tissue diseases (CTD) (n=8). Thus, the study cohort was comprised of 52 patients with a positive anti-CCP of at least moderate titer (≥ 40 IU) along with symptoms of respiratory impairment—without a prior diagnosis of RA, any other CTD, or presence of joint inflammation at initial testing for anti-CCP. All data were extracted by retrospective chart review.

Results:

Clinical characteristics of anti-CCP positive subjects with lung disease	
Number of patients	52
Median follow-up duration (d)	458 (114–755)
Median age (y)	68 (36–84)
Male gender	22 (42%)
Smokers-Past	29 (57%)
Smokers-Current	0 (0)
First degree relative with RA	7 (17.5%)
Dyspnea/cough at presentation	52 (100%)
Synovitis by history or exam at presentation	0 (0%)
Median anti-CCP (IU)	86.5 (40–235)
RF positivity	18 (37%)
Median RF (IU)	148 (20–3650)
Development of articular RA during follow-up	1 (2%)
High-Resolution Computed Tomographic Findings	
Airways disease	17 (33%)
Parenchymal lung disease	18 (35%)
Airways + Parenchymal disease	13 (24%)
*Miscellaneous patterns	4 (8%)

*Includes one each of emphysema, vasculitis, sarcoidosis, and non-tuberculous mycobacterial infection

Conclusions: We have identified a cohort of patients, predominately former smokers, with lung disease, a moderate-to-high positive anti-CCP and no articular manifestations of RA. Within a median follow-up of 15 months, 2% of this cohort has already developed inflammatory arthritis. These findings suggest i) the lung is the site of initial RA-related immune dysregulation, and that such patients represent a 'pre-articular RA' phenotype, ii) the lung in some cases is a pre-articular target of RA-related autoimmunity, or iii) in cases who never develop articular RA, anti-CCP generation may be a non-RA specific immune response, or that some factor prevents these patients from later developing RA-related articular disease. Prospective assessments of this unique cohort should help further our understanding of the etio-pathogenesis of RA.

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ACR Concurrent Abstract Sessions
Systemic Lupus Enrythematosus - Clinical Aspects and Treatment: SLE and Cardiovascular Disease
Wednesday, November 10, 2010, 2:30 PM–4:00 PM

2120

Prevalence of Flow Mediated Dilatation and Its Association with Framingham Risk Score in a Population of Women with Systemic Lupus Erythematosus. Valentina Peeva[4], Paula Harvey[3], Jiandong Su[3], Ellie Aghdassi[3], Ali Al-Dhanhani[3], Stacey Morrison[3], Christian Pineau[2], Janet Pope[1], Debbie Da Costa[2] and Paul R. Fortin[3]. [1]London, ON, Canada, [2]Montreal, QC, Canada, [3]Toronto, ON, Canada, [4]University Health Network, Toronto Western Hospital, Toronto, ON, Canada

Background: Patients with SLE have an increased risk for cardiovascular disease (CVD).Traditional assessment of CVD risk profile is measured using Framingham Risk Score (FRS), but this may not capture all CVD risk factors in patients with SLE. An alternative tool to assess CVD risk is the Flow Mediated Dilation (FMD)

Objective: 1) To perform CVD risk assessment using FRS and endothelial flow mediated dilatation (FMD) using high-resolution brachial artery ultrasound and 2) To determine association between endothelial function and FRS in women with SLE.

Methods: Our cohort consists of 173 females, ≥4 ACR criteria for SLE in whom the FRS and FMD were assessed as part of a study. Ten-year FRS was calculated on the basis of patients: age, smoking, systolic blood pressure (SBP), total cholesterol (TC) and HDL-cholesterol. Smoking, family history, SBP>130mmHg, serum TC>5.5 mmol/l and HDL<1.3mmol/l, were considered as risk factors for CVD. Normal FMD was defined as a 6% to 15% increase in the post-cuff inflation diameter change of the artery. Abnormal FMD was defined as <6% increase in the post-cuff inflation diameter. Associations between FMD and FRS were assessed using linear regression analysis.

Results: The mean (SD) age was 43.6 (12.7) years, SLE duration was 8.9 (2.4, 18.6) and 23% (n=77) were smokers. The mean SBP was at 121.9 mmHg (14.7) and. 22.5% had elevated SBP. The mean (SD) serum profile were as follows; triglycerides: 1.2 (0.6) mmol/l, total cholesterol: 4.7 (1.1) mmol/l, LDL-cholesterol 2.6 (0.8) mmol/L, HDL-cholesterol: 1.7 (0.6) mmol/L, TC/HDL ratio: 3.0(1.0), homocysteine:10.7 (4.3) μmol/L and CRP: 3.2 (6.2) mg/l. Abnormal serum levels were seen in 14.2 % for TG, 21.2% for TC, 50.8% for LDL, 18.4% for HDL,16.7% for homocysteine and 62.7% for CRP. The distribution of total CVD risk factors were as follows: 31% had 1, 44 % had 2 – 4 and 25 % had ≥5 risk factors. 44% (n=76) were at low risk (FRS=1–5 %), 24% (n=42) intermediate risk (FRS=6–10%), 20% (n=35) at high risk (FRS=11–20%) and 12% (n=20) at very high risk (FRS> 20%). For each FRS risk the equivalent % FMD change and proportion of patients with abnormal FMD are reported in Table 1. Adjusted linear regression showed that for each increase of 1% in FRS one observes an average 0.24% decrease in FMD cuff change.

Table 1. FRS, FMD cuff change (%) and proportion of abnormal FMD.

Framingham Risk Score	Mean %FMD +/− SD (cuff change)	No of abnormal FMD/No of patients
<5%	10.1 +/− 8.2	30/76 (40%)
6–10%	9.4 +/− 6.7	14/42 (33%)
11–20%	8.8 +/− 8.9	17/35 (49%)
>20%	7.0 +/− 5.7	10/20 (50%)

Conclusion: FRS explains only a subgroup of patients with abnormal FMD, with approximately 40% of SLE patients with low FRS having abnormal FMD. Assessment of FMD in SLE may identify a subgroup of patients with endothelial dysfunction not identified by FRS. Following these patients prospectively may help to determine their actual CVS risk.

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2121

Protection from Cardiovascular Events and Nephritis in SLE Correlates with Levels of IgM Natural Autoantibodies to Different Apoptosis-Associated Antigens. Caroline Gronwall[3], Ehtisham Akhter[2], Michelle A. Petri[1] and Gregg J. Silverman[3]. [1]Johns Hopkins University School of Medicine, Timonium, MD, [2]Johns Hopkins University School of Medicine, Baltimore, MD, [3]Univ of California San Diego, La Jolla, CA

Background: In murine models, we have reported that induction of high levels of IgM antibodies to phosphorylcholine (PC), a phospholipid neo-determinant on apoptotic cells but not healthy cells, halts the progression of atherosclerosis in hypercholesterolemic mice (1), and can block in vivo and in vivo inflammatory responses to diverse agonists to TLR 3, 4, 7 and 9 (2) that is linked to the inhibition of central inflammatory signaling pathways.

Methods: To investigate for relationships between IgM antibodies to PC and other apoptosis-associated antigens with the clinical and laboratory features of SLE disease, we used standard ELISA to perform

serologic surveys to PC, malondialdehyde (MDA) as well as cardiolipin (CL) and β2 glycoprotein I (β2 gp I) in 95 SLE patients from the well characterized Hopkins Lupus cohort.

Results: In a pre-set series of analyses, for overall disease activity we found only modest inverse correlations with levels of IgM anti-MDA antibodies and the SLEDAI clinical disease activity index and Physicians global estimate (Pearson, P=0.01), but not with other IgM antibodies. Yet, patients without a history of past atherosclerotic cardiovascular (ASCVD) events (i.e., MI, CVA or TIA) had significantly higher IgM anti-PC levels (P= 0.00024, two-tailed t test) compared with those with past events, while there was no relationship with a history of documented lupus nephritis. In contrast, patients without lupus nephritis had higher levels of IgM anti-β2 gp I (P=0.003) and IgM anti-CL (P=0.0001) than in those with lupus nephritis, while there was no association between levels of IgM anti-β2 gp I with history of ASCVD events (P=0.46) and only a trend for IgM anti-CL (P=0.051). IgM anti-β2 gp I levels by themselves did not correlate with other thrombotic events (P=0.3). Patients with higher levels of IgM anti-MDA had modest associations with the absence of past ASCVD events (P=0.04) and the absence of lupus nephritis (P=0.04). Higher IgM anti-β2 gp I levels also correlated with lower C4 levels (Pearson, P=0.006), and a trend toward lower C3 levels (P=0.057). Otherwise there were no other significant associations with IgG anti-dsDNA or anti-C1q, or with C3 or C4, or ESR.

Conclusions: These findings support our hypothesis, based on murine studies and multiplex autoantibody microarray surveys of lupus twins (3), that some IgM autoantibodies are part of an evolutionarily conserved immune repertoire that provide homeostatic functions, which may protect from certain clinical features of autoimmune disease. Future studies will need to address whether these differences in antibody levels are present at earlier stages of disease development, which could provide valuable prognostic tools.

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2. Chen et al. J Immunol. 183:1346 (2009)
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2122

Non-Calcified Coronary Plaque (NCP) in Systemic Lupus Erythematosus (SLE): Quantitative Analysis. Adnan N. Kiani[2], Jens Vogel-Claussen[2], Margaret Yew[2], Laurence S. Magder[3] and Michelle A. Petri[1]. [1]Timonium, MD, [2]Johns Hopkins University, School of Medicine, Baltimore, MD, [3]University of Maryland, School of Medicine

Purpose: Coronary calcium (CC) is increased in SLE. New technology (CTA) can measure non-calcified plaque (NCP). Noncalcified plaque is less stable and more prone to rupture. We report on the largest study of quantified non-calcified coronary plaque in SLE.

Methods: 64 slice coronary multidetector computed tomography (MDCT) was performed in 106 patients with SLE. The MDCT scans were evaluated quantitatively by a radiologist, using dedicated software.

Results: The 106 SLE pts were 88% female, 67% Caucasian, 29% African-American, 4% other; mean age 51±11yrs. Significant results are shown in Table 1. Obesity was the major traditional CVRF associated with NCP. NCP did increase with age. NCP was increased with low complement, particularly with low C3. Anticardiolipin (but not lupus anticoagulant) was associated with increased NCP. Prednisone and Plaquenil therapy had no effect, but methotrexate use had increased NCP (table 1). In the best multivariate model (table 2) age, obesity, and MTX remained significant.

Table 1.

	Group	Mean NCP Score	p-value	p-value for trend, controlling for age
Age			0.011	
	<45 (n = 30)	0.16		
	45–55 (n = 39)	0.21		
	55+ (n = 36)	0.33		
Body Mass Index (BMI)			0.20	0.015
	<25 (n = 34)	0.18		
	25–29 (n = 36)	0.21		
Anticardiolipin antibodies (aCL)			0.027	0.048
	No (n = 37)	0.17		
	Yes (n = 69)	0.28		
Low C3			0.29	0.068
	No (n = 51)	0.21		
	Yes (n = 55)	0.26		
Low C4			0.58	0.090
	No (n = 63)	0.23		
	Yes (n = 43)	0.25		
Current Prednisone			0.24	0.92
	No (n = 69)	0.25		
	Yes (n = 36)	0.22		
Current Plaquenol			0.54	0.91
	No (n = 21)	0.21		
	Yes (n = 84)	0.25		
Current Imuran			0.16	0.29
	No (n = 98)	0.25		
	Yes (n = 8)	0.12		
Current Methotrexate (MTX)			0.011	0.0029
	No (n = 101)	0.22		
	Yes (n = 5)	0.51		
Current Cellcept			0.24	0.58
	No (n = 96)	0.24		
	Yes (n = 10)	0.20		
Current Non-steroidal anti-inflammatory drugs (NSAIDS)			0.95	0.74
	No (n = 62)	0.24		
	Yes (n = 43)	0.24		

Table 2. Multivariable regression model to assess the joint association of predictors and the mean level of NCP

Variable	Effect on mean NCP score (95% CI)	p-value
Age (per 10 years)	0.08 (0.05, 0.12)	<.0001
BMI (per 5 unit change)	0.03 (0.00, 0.07)	.049
History of Anticardiolipin	0.089 (−0.01, 0.17)	.097
Hypertension	0.03 (−0.07, 0.13)	.54
MTX ever	0.27 (0.07, 0.47)	.0076

Conclusion: NCP is a better marker of immediate atherosclerotic risk than is calcified plaque. In our univariate analysis, low complement was associated with NCP. This is the only association with a marker of active lupus. Of the traditional CVRF- obesity- rather than hypertension- is strongly associated with NCP. Our results suggest that both active SLE (serologically) and traditional CVRF (obesity) contribute to NCP in SLE. The association with MTX is of concern, but should be replicated in larger studies and in multiple centers.

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2123

Aspirin Response Is Impaired in Patients with Systemic Lupus Erythematosus. Vivian K. Kawai[1], Ingrid B. Avalos[2], Annette M. Oeser[5], John Oates[4], Ginger Milne[4], Cecilia P. Chung[3] and C. Michael Stein[1]. [1]Vanderbilt University, Nashville, TN, [2]Vanderbilt University, Brookline, MA, [3]Vanderbilt University, Baltimore, MD, [4]Vanderbilt University, [5]VUMC 23rd Ave South Pierce, Nashville, TN

Background: Patients with systemic lupus erythematosus (SLE) have an increased risk of myocardial infarction, stroke and other thrombotic events. Low-dose aspirin, used to prevent thrombotic events, irreversibly acetylates the platelet cyclooxygenase-1 (COX-1) enzyme and thus inhibits thromboxane A_2 (TxA_2) formation and platelet aggregation. However, some individuals do not respond adequately to aspirin—sometimes termed "aspirin resistance". Although many lupus patients receive aspirin to prevent thrombosis, there is no information about platelet responses in this population. We examined the hypothesis that response to aspirin is impaired in SLE.

Material and Methods: We prospectively studied 34 patients with SLE and 36 age and sex-matched controls who received immediate-release aspirin 81 mg /day for 7 days with monitoring of adherence. Subjects did not take NSAIDs for 7 days before the study. As a measure of aspirin's effect on its pharmacologic target, platelet COX-1, we measured concentrations of serum TxB_2, the stable metabolite of TxA_2, by mass spectrometry in whole blood allowed to clot at 37°C, before and after 7 days of aspirin treatment. We compared concentrations of serum TxB_2 in patients and controls who were not receiving aspirin therapy at baseline, and after a week of aspirin therapy. Failure to suppress serumTxB_2 below 10 ng/ml is widely reported as a threshold for defining aspirin resistance; we compared the proportion of patients and controls with aspirin resistance. Continuous variables were expressed as median and interquartile range [IQR]. McNemar and Wilcoxon rank sum tests were used to compare categorical and continuous data.

Results: The demographic characteristics of patients with SLE (n = 34, 82% female, age 41 [29–47 years] and controls (n = 36, 72% female, age 45 [33–50 years]) were similar. At baseline, median serum TxB_2 was similar in SLE (76.8 [39.0–134.8 ng/ml]) and controls (103.3, [30.6–130.3 ng/ml]) (P=0.84). Aspirin suppressed serum TxB_2 production almost completely in controls to 1.5 [0.8–2.7 ng/ml] but had significantly less effect in SLE (3.1 [2.2–5.3 ng/ml]) (P=0.002) (Figure). Aspirin resistance was present in 5/34 (15%) SLE patients and 0/36 controls (P<0.001). Compared to those that were aspirin sensitive, the 5 aspirin resistant patients were more likely to have diabetes (P=0.034), hypertension (P=0.007), a history of smoking (P=0.056), and a higher BMI (p=0.055), but measures of disease activity (SLEDAI) (P=0.96) and damage (SLICC) (P=0.43) did not differ.

Conclusions: Patients with SLE are less responsive to aspirin than controls and resistance to the effect of aspirin on platelet COX-1 occurs. Obesity, diabetes, hypertension and a history of smoking were more common among lupus patients with aspirin resistance.

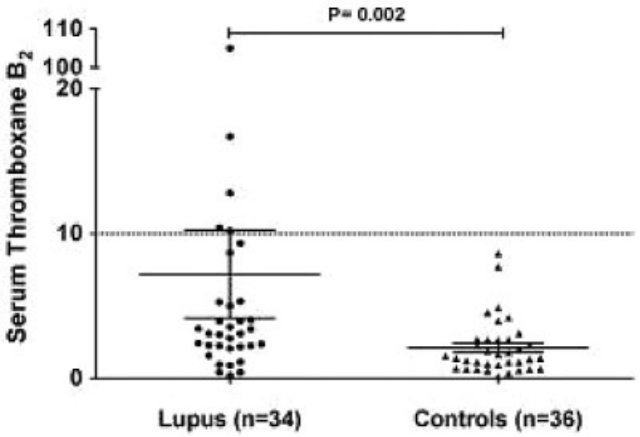

Figure. Serum Thromboxane B_2 in patients with lupus and controls after aspirin treatment.

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2124

Rates of Adverse Cardiovascular Events among SLE Patients Are Higher during Episodes of Disease Activity. Laurence S. Magder[2] and Michelle A. Petri[1]. [1]Timonium, MD, [2]Department of Epidemiology and Preventive Medicine, University of Maryland, School of Medicine, Baltimore, MD

Background: SLE patients are at higher risk of cardiovascular events (CVE) than non-SLE patients, even after accounting for traditional cardiovascular risk factors. We investigated whether CVE risk was associated with SLE disease activity, and whether past history of activity or current activity incurred a greater risk.

Methods: The CVE experience of patients in a large clinical cohort was analyzed. CVE was defined as myocardial infarction (MI), stroke, coronary procedure, incident angina, or claudication. SLE disease activity was defined using SLEDAI, the Physicians Global Assessment (PGA), and various disease components. The analysis was based on a data set with one record per patient-month of cohort participation. Each record contained data regarding the patient's clinical history up until that time, the most recently measured levels of disease activity, medications taken at that time, and whether a CVE occurred during that month. This file was analyzed using pooled logistic regression.

Results: 134 CVE events were observed from among 1874 patients who were followed for 9485 person-years. Events included 65 strokes, 27 MI, 29 cases of angina or coronary procedures, and 13 cases of claudication. The table shows rates of CVE in subgroups.

Table. CVE rates, in subgroups defined by SLE clinical characteristics

Subgroup	# CVE	Rate per 1000 person-yrs	Age-adjusted Rate Ratios (95% CI)	P-value
Duration of SLE				
0–6 years	43	11.4	1.0 (Ref. Group)	
6+ 10 years	29	13.4	1.5 (0.7, 1.7)	.83
10–15 years	24	13.9	1.0 (0.6, 1.7)	.97
15+	38	21.0	1.3 (0.8, 2.0)	.28
Recent SLEDAI				
0	36	9.5	1.0 (Ref. Group)	
1 or 2	30	12.4	1.4 (0.9, 2.4)	.14
3 or 4	31	17.3	2.1 (1.3, 3.4)	.0027
5+	37	24.9	3.4 (2.1, 5.3)	<.0001
Mean SLEDAI in cohort				
0–1	23	10.8	1.0 (Ref. Group)	
1–2.5	35	12.2	1.2 (0.7, 2.1)	.44
2.5–5	49	15.9	1.8 (1.1, 2.9)	.023
5+	27	19.4	2.8 (1.6, 4.9)	.0004
Recent PGA (3 point scale)				
0	36	11.2	1.0 (Ref. Group)	
0.1 to 0.9	29	10.6	1.0 (0.6, 1.6)	.89
1.0 to 1.4	30	14.8	1.4 (0.9, 2.3)	.17
1.5+	39	25.7	2.6 (1.7, 4.1)	<.0001
Mean PGA in cohort				
0–.9	97	12.9	1.0 (Ref. Group)	
1+	37	18.6	1.8 (1.2, 2.6)	.0040
Recent low C3				
No	34	19.3	1.0 (Ref Group)	
Yes	99	12.8	0.5 (0.4, 0.8)	.0019
History of low C3				
No	47	12.3	1.0 (Ref Group)	
Yes	87	15.4	1.6 (1.1, 2.3)	.0082
Recent anti-dsDNA				
No	83	11.9	1.0 (Ref. Group)	
Yes	50	20.1	2.1 (1.5, 3.1)	<.0001
History of anti-dsDNA				
No	48	13.4	1.0 (Ref Group)	
Yes	96	14.6	1.3 (0.9, 2.0)	.15

CVE were not associated with duration of SLE, after age-adjustment. In general, CVE were more strongly related to recent disease activity than to past or average disease activity. A moderate association between recent disease activity (SLEDAI) and CVE persisted after adjustment for cortico-steroids and other risk factors (RR=1.8, p=.054 comparing those with SLEDAI of 5 or more to those with SLEDAI of 0).

Conclusion: CVE rates are elevated during episodes of SLE activity, both in terms of clinical activity (SLEDAI) and serologic activity (low C3, anti-dsDNA). This might be explained by the acute effects of SLE activity on the endothelium, or conditions that cause both SLE activity and CVE.

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2125

Atherosclerosis Is Associated with Low 25(OH) Vitamin D Levels, Lack of Angiotensin Converting Enzyme Inhibitor Use, and Hyperlipidemia in African-American Lupus Patients. Roneka L. Ravenell[3], Diane L. Kamen[4], Spence David[5], Hollis Bruce[2], Almeida Jonas[1] and Jim C. Oates[3]. [1]Department of Bioinformatics and Computational Biology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, [2]Department of Pediatrics, Medical University of South Carolina, Charleston, SC, [3]MUSC, Charleston, SC, [4]MUSC PO Box 250637, Charleston, SC, [5]Robarts Research Stroke Prevention and Atherosclerosis Research Centre, London, ON, Canada

Purpose: Patients with systemic lupus erythematosus (SLE) have a greater prevalence of atherosclerosis than the general population. This study was designed to identify risk factors for preclinical atherosclerosis in a predominantly African-American group of SLE patients.

Methods: Subjects with SLE but without a history of clinical cardiovascular events were enrolled. At entry, a Framingham risk factor history and medication list were recorded. Sera and plasma samples were analyzed for lipids, lupus activity markers, and total 25(OH) vitamin D (25(OH)D) levels. SLE Disease Activity Index (SLEDAI) and SLICC Damage Index scores were calculated. Carotid ultrasound measurements were performed to determine total plaque area (TPA) in both carotids as a validated measure of preclinical atherosclerosis that associates longitudinally with major cardiovascular events. Cases were defined as those with TPA values above that of age-matched controls from a population of 4272 patients in stroke and hypertension clinic. Descriptive analysis was performed on all variables between cases and controls. Associations between TPA and continuous variables were determined by correlation. Chi-square analysis was performed for ordinal variables against case or control status. Logistic regression analysis was performed to explore predictive modeling. P values < 0.05 were considered significant. A nearest related neighbor machine learning model (NRN) to explore variables associating with elevated TPA in a nonlinear or collinear fashion.

Results: Fourteen of 51 subjects (27%) enrolled had elevated TPA compared to age-matched controls. 25(OH)D levels (16.6 ± 3.2 vs. 22.6 ± 1.8 ng/dl), SLEDAI scores (2.3 ± 0.5 vs. 4.3 ± 0.5), and anti-dsDNA antibody levels (34 ± 18 vs. 136 ± 59 IU) were significantly lower, while SLE disease duration (11.9 ± 1.6 vs. 8.7 ± 13 years) was significantly higher in cases. Age ($r=0.58$), C4 ($r=0.36$), and SLE disease duration ($r=0.37$) significantly correlated with TPA, while 25(OH)D levels significantly inversely correlated with age-adjusted TPA ($r=-0.33$). ACE-inhibitor use and a history of hypercholesterolemia were significantly associated with case status. Logistic regression models containing ACE-inhibitor use, 25(OH)D levels, and LDL levels had a diagnostic accuracy of 84%. Season of enrollment was not significant in the model. An NRN model was trained. Variables retained in the model as associating with abnormal TPA were hydroxychloroquine, ACE-inhibitor, and statin use as well as 25(OH)D levels. This model resulted in a receiver operating characteristics area under the curve of 0.75 for discriminating cases.

Conclusions: This study demonstrates in SLE patients novel and previously described associations between lower atherosclerotic burden and factors that are known to restore endothelial function and reduce plaque in non-SLE populations. These associations provide a rational basis for studying the effect of these therapies on endothelial function and vascular outcomes in patients with SLE.

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ACR Concurrent Abstract Sessions
T Cell Biology and Targets in Autoimmune Disease
Wednesday, November 10, 2010, 2:30 PM–4:00 PM

2126

Dipyridamole Inhibits SLE T Cell Activation and Alleviates Nephritis in Lupus-Prone Mice. Vasileios C. Kyttaris, Zheng Zhang, Ourania Kampagianni and George C. Tsokos. Beth Israel Deaconess Medical Center

Background: SLE T cells provide help to B cells to produce autoantibodies and infiltrate tissues orchestrating local inflammatory responses. We have previously shown that SLE T cells are characterized by a robust calcineurin-mediated dephosphorylation of the transcription factor NFAT. Dephosphorylated (activated) NFAT tranlsocates to the nucleus and activates a host of genes, including the co-stimulatory molecule CD154 that enhances antibody production by B cells, and several pro-inflammatory cytokines.

NFAT/calcineurin inhibition represents an attractive option for the treatment of various inflammatory diseases. Yet calcineurin inhibitors (cyclosporine A, tacrolimus) have significant side effects including nephrotoxicity. It was shown recently that dipyridamole inhibits the activation of NFAT without affecting total calcineurin phosphatase activity, potentially causing fewer side effects.

Methods: T and B cells were isolated from the peripheral blood of patients with SLE and healthy individuals. The cells were incubated in the presence of dipyridamole (20μM or 50μM), or tartaric acid as control. T cells were activated with anti-CD3 and anti-CD28 antibodies. MRL/lpr lupus-prone mice were injected intraperitoneally with dipyridamole 50 mg/kg three times a week for 4 weeks. CD154 and cytokine production was measured with flowcytometry.

Results: Dipyridamole treatment of SLE T cells inhibited NFAT activation and decreased the expression of CD154 by $66\pm21\%$ ($p<0.0001$, $N=9$). The production of IFN-γ decreased by $96\pm3\%$ ($p<0.0001$, $N=9$), that of IL-17 by $74\pm29\%$ ($p<0.0001$, $N=9$), and of IL-6 by $57\pm22\%$ ($p<0.0001$, $N=9$). Moreover, dipyridamole inhibited the T cell directed production of immunoglobulin, including anti-dsDNA antibodies, in T:B cell mixed cultures. Activation of isolated B cells by anti-IgM was not affected by dipyridamole. Dipyridamole decreased significantly the expansion of T cells in vitro as assessed by CFSE staining.

Next, we treated MRL/lpr mice with dipyridamole. MRL/lpr mice have a very large number of CD3+CD4-CD8- T cells (double negative T cells, DNT) that express high levels of NFAT. Treatment of these mice with dipyridamole decreased proteinuria by 33% and prevented the emergence of pyuria. The dipyridamole treated mice did not develop skin lesions and were protected from early death (3/5 control-treated mice died by the fourth week of the trial as opposed to 0/5 in the dipyridamole treated group).

Dipyridamole treatment decreased the concentration of IL-6 in the serum (dipyridamole vs. control treated mice$=364\pm52$ vs. $5{,}280\pm206$ pg/mL, $p<0.0001$). The percentage of CD3+ cells in the spleen decreased in the dipyridamole treated animals, primarily due to a decrease in DNT subpopulation (splenic DNT cells in dipyridamole vs. control treated mice$=47\pm2\%$ vs. $67\pm4\%$, $p=0.0045$).

Conclusions: Inhibition of NFAT with dipyridamole results in decreased activation and expansion of lupus T cells, blocking at the same time T cell directed autoantibody production. Dipyridamole alleviates nephritis and prolongs survival of lupus-prone mice. Therefore we propose that dipyridamole is an attractive NFAT inhibitor that can be used in the treatment of SLE.

Disclosure: V. C. Kyttaris: None; **Z. Zhang:** None; **O. Kampagianni:** None; **G. C. Tsokos:** None.

2127

Defective T Cell Tolerance in Rheumatoid Arthritis Due to Increased B-Raf and K-Ras Expression. Pratima Deshpande[2], Karnail Singh[1], Mingcan Yu[2], Guangjin Li[2], Cornelia M. Weyand[3] and Jorg J. Goronzy[3]. [1]Emory University, Atlanta, GA, [2]Stanford University, Stanford, CA, [3]Stanford University School of Medicine, Stanford, CA

Background/Purpose: Autoantibodies to common auto- and neoantigens such as IgG Fc and citrullinated peptides are immunological hallmarks of rheumatoid arthritis (RA). Identified disease risk genes suggest that signaling pathways abnormalities are involved in RA pathogenesis. We have examined the hypothesis that defects in T cell receptor (TCR) signaling lower the activation threshold of RA T cells predisposing for a failure in maintaining tolerance.

Methods: TCR-induced signaling was compared in 65 patients with seropositive RA and 54 healthy controls by phosphoepitope flow cytometry. The MAP Kinase Signaling Pathway PCR Array was used to screen for differentially expressed genes. SOS1, RasGRP1, DUSP5, DUSP6, K-Ras and B-Raf transcription was quantified by qPCR. Protein expression of B-Raf, C-Raf, K-Ras and N-Ras were compared by Western blotting and by flow cytometry. siRNA for K-Ras and B-Raf from Qiagen was used in silencing experiments. Co-localization of B-Raf or C-Raf with K-Ras or N-Ras in T cells from control and RA patients was examined by confocal microscopy. CD4 T cells from healthy HLA-DR4+ individuals were transfected with K-Ras or B-Raf cloned into the pIRES2-AcGFP1 vector. Cells were stimulated with 1 μM aa 65–77 native or R70Cit vimentin peptides.

Summary of Results: RA T cells responded to TCR stimulation with increased ERK phosphorylation compared to healthy controls of the same age

($p<0.0001$). Increased ERK responsiveness was a feature of all functional T cell subsets including naive T cells and did not correlate with disease activity. Increased expression of K-Ras and B-Raf in RA T cells, first identified in gene expression arrays of ERK pathway members, was confirmed by qPCR, Western blotting and flow cytometry ($p<0.01$). None of the RA-implicated cytokines TNF-α, IL-1, IL-6, IL-15 or IL-21 induced B-Raf or K-Ras gene expression in vitro. Partial silencing of K-Ras and B-Raf significantly lowered activation-induced p-ERK levels ($p<0.01$). In individual cells, B-Raf and K-Ras baseline levels correlated with activation-induced ERK phosphorylation ($p<0.001$) confirming that B-Raf and K-Ras are rate-limiting in T cells and concentration differences of these signaling molecules in RA are functionally important. In confocal studies, B-Raf/K-Ras clustering was significantly increased in RA T cells two minutes after TCR stimulation ($p<0.001$). Increased ERK activity was sustained by activation of a positive feedback loop involving p-ERK dependent RKIP phosphorylation and release of sequestered C-Raf. Overexpression of transfected B-Raf or K-Ras lowered the TCR threshold and enabled responses to citrullinated vimentin in healthy HLA-DR4+ individuals.

Conclusions: Restricting ERK activity, in part by Rap-1 mediated inactivation of C-Raf is an important mechanism to maintain anergy to self-antigens or in the absence of costimulation. Expression of B-Raf that can bypass this pathway is low in T cells from healthy individuals. Naive and memory T cells from RA patients have increased B-Raf and K-Ras expressions that enable T cell responses to low affinity and autoantigens. Our data suggest that B-Raf and K-Ras are promising targets to treat autoimmunity.

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2128

SLAP Deficiency Enhances Both Number and Function of FoxP3$^+$ Regulatory T Cells and Inhibits Chronic Arthritis in SKG Mice. Lisa K. Peterson[2], Laura A. Shaw[2], Anthony Joetham[3], Shimon Sakaguchi[1], Erwin W. Gelfand[5] and Leonard Dragone[4]. [1]Kyoto University; Osaka University, [2]National Jewish Health, Denver, CO, [3]National Jewish Health, [4]National Jewish Health; University of Colorado Denver; The Children's Hospital, Denver, CO, [5]National Jewish Health; University of Colorado Denver; The Children's Hospital

Background: Intrinsic defects in lymphocyte signaling have been implicated in the pathogenesis of rheumatoid arthritis. Manipulation of T cell function by altering TCR complex-mediated signaling could be a viable strategy to treat autoimmune disease. However, the signaling networks initiated or regulated by the TCR signaling complex that are required to eliminate or modulate the function of autoreactive T cells are not known, which is an obstacle in our capacity to manipulate autoreactive T cells. SKG mice have a point mutation in zeta-associated protein of 70kDa (ZAP-70) rendering it hypomorphic. Decreased signaling through the TCR complex in developing thymocytes results in selection of highly autoreactive Th17 cells and autoimmune arthritis upon exposure to inflammatory triggers. We hypothesized that increasing signal strength through the TCR complex in SKG mice will prevent autoimmunity. To enhance TCR signal strength, we crossed SKG mice with Src-like adaptor protein (SLAP)-deficient mice. SLAP targets the zeta chain of the TCR (TCRz) for degradation. The same signaling chain of the TCR complex to which ZAP-70 binds. Thus, we specifically chose to create the Double SKG SLAP KnockOut (DSSKO) model because ZAP-70 and SLAP have opposing functions on the regulation of TCR complex mediated signaling. The combination of these two mutations provides a unique opportunity to determine how alterations in TCR complex-mediated signaling can modulate autoimmune disease in the context of a defined genetic background, uniform environmental conditions, and a well-characterized signaling disruption.

Methods: SKG mice were crossed with SLAP-deficient mice to generate Double SKG SLAP KnockOut (DSSKO) mice.

Results: DSSKO mice do not develop zymosan-induced chronic autoimmune arthritis. This prevention of arthritis development is not due to significant alteration in thymocyte development or repertoire selection. Instead, regulatory T cells (Tregs), known to be critical in suppression of autoreactive T cells and prevention of autoimmunity, are increased in both the thymus and spleen of DSSKO mice. This was accompanied by inhibition of differentiation and/or expansion of Th17 cells, upon zymosan exposure, and suppression of chronic arthritis. Treg depletion and/or functional blockade unleashed the autoreactive Th17 cells and arthritis developed in DSSKO mice. *In vitro* suppression of effector T cell proliferation was also enhanced which demonstrated that DSSKO mice have increased numbers of Tregs with improved function.

Conclusions: These data show that DSSKO mice have enhanced development and function of Tregs, preventing the development of arthritis. Understanding how TCR complex-mediated signals influence Treg development, expansion, and function will advance our capacity to manipulate Treg biology. The long-term goal of these studies is to apply our findings to patients in a way that enhances Treg number and/or function to treat autoimmune disease.

Disclosure: L. K. Peterson: None; **L. A. Shaw:** None; **A. Joetham:** None; **S. Sakaguchi:** None; **E. W. Gelfand:** None; **L. Dragone:** None.

2129

The Role of BAFF in Promoting the Development of IL-17-Producing Cells and Th17-Mediated Disease. Xiaohui Zhou[2], Julie Wang[4], Zhongmin Liu[1], William Stohl[3] and Song Guo Zheng[4]. [1]Tongji University Medical School, [2]Univ S Calif Keek Schl of Med, Los Angeles, CA, [3]Univ Southern California, Los Angeles, CA, [4]USC Keck School of Medicine, Los Angeles, CA

Background: B cell-activating factor belonging to the TNF family (BAFF; BLyS) plays a critical role in promoting B cell maturation and survival and the development of autoimmune disorders. BAFF also affects T cell function through binding to one of the BAFF receptors, BAFF-R. BAFF arguments the Th1- but suppresses Th2-mediated inflammatory responses. It is less clear whether BAFF affects the development and Th17 cells-mediated autoimmune diseases.

Methods, Materials: Freshly isolated splenocytes and lymph node cells in BAFF knock out (KO), BAFF transgenic and wild type mice were analyzed ex vivo for the surface staining of CD19, CD4, CD8, CD69, CD44, CD62L, CCR-6, CD25 and intracellular staining of ROR-γt, IL-17, IFN-γ, IL-4 and Foxp3. IL-17A and IL-17F mRNA was determined by qPCR. The effect of BAFF on in vitro differentiation of naïve CD4+ T cells into Th17 cells was assessed through stimulation with soluble anti-CD3/CD28 in the presence of IL-6 and TGF-β plus irradiated APC. We further detected the frequencies of Th1, Th2 and Treg cells in these mice. In addition, we evaluated the role of BAFF in the Th17 development in vivo using a Th17-mediated disease model, EAE.

Results: In comparison to WT mice, the frequencies and total numbers of Th1 and Th17 cells in BAFF KO mice decreased, while that of these cells increased significantly in BAFF Tg mice. IL-17A and IL-17F mRNA in BAFF KO mice decreased compared to WT and Tg mice. In vitro induction of Th17 cells was also down regulated significantly in BAFF KO T cells. In addition, different origins of APC do not affect the induction of Th17 cells. There is no significant difference of Treg induction in these mice. Lack of BAFF delayed the appearance and attenuated the severity of Th17-mediated EAE symptoms. Conversely, the excessive expression of BAFF promoted Th17 cell development and persistent EAE symptoms. Increased IL-6R expression and function by CD4+ cells in BAFF Tg may be responsible for the increased Th17 cell production.

Conclusions: This study suggests that BAFF may promote the development of autoimmune diseases through Th17 cell development and function in addition to its direct effect on B cell maturation and survival. These results implicate that manipulation of BAFF pathways has a beneficial role in treating Th17- and/or Th1-mediated inflammatory diseases.

Disclosure: X. Zhou: None; **J. Wang:** None; **Z. Liu:** None; **W. Stohl:** Genentech and Biogen IDEC Inc, 9, Human Genome Sciences, Inc., 9, Xencor, 2; **S. G. Zheng:** None.

2130

Activated Th17 Cells Drive Rheumatoid Inflammation and Are Resistant to Inhibition by Natural Antagonists of Their Development. Jan Leipe[2], Mathias Grunke[2], Claudia Dechant[2], Christiane Reindl[2], Hendrik Schulze-Koops[1] and Alla Skapenko[2]. [1]University of Munich, Munich, Germany, [2]University of Munich, Germany

Background: IL-17 has been identified as a new pro-inflammatory cytokine contributing to autoimmune inflammation in several animal models. Since the major source of IL-17 in human autoimmune diseases

is still elusive, we analyzed Th17 cells, defined as a cell type producing IL-17, but not IFN-γ or IL-4, in patients with the prototypic autoimmune diseases, rheumatoid arthritis (RA) and psoriatic arthritis (PsA).

Methods: Th17 cells were analyzed *ex vivo* and *in vitro* by various methods e.g. multi-color flow cytometry, enzyme-linked immunosorbent assay (ELISA) and real-time PCR in well-defined cohorts of patients: active treatment-naive RA (n = 36) and PsA (n = 20) with very early disease (disease duration < 3 months), and patients with established RA (n = 21; mean disease duration 68 months) responding or not responding to therapy. For control, patients with osteoarthritis (n=20) and age-matched healthy individuals (n=25) were analyzed.

Summary of the Results: Th17 cell frequencies and IL-17 production of CD4 T cells from the peripheral blood of RA and PsA patients were significantly increased compared to controls. Importantly, Th17 cells frequencies strongly correlated with systemic disease activity in early ($r = 0.91$, $p < 0.0001$) and established ($r = 0.72$, $p < 0.001$) RA, and were reduced to control levels in response to clinically effective treatment. Th17 cells were specifically enriched in the inflamed joints of RA and PsA patients, and increased frequencies of synovial Th17 cells expressed the chemokine receptors CCR4 and CCR6 required for selective migration of Th17 cells into the joints. As molecular mechanisms underlying the pathophysiological Th17 cell activity in autoimmune arthritis, we identified an intrinsically elevated expression of the master transcription factor for Th17 cells, RORC, accompanied by increased Th17 cell differentiation, and a resistance of Th17 cells from the RA and PsA patients to the natural antagonists of their development, e.g. IL-4 and IFN-γ.

Conclusion: Together the data indicate an important role of Th17 cells and their effector functions in the pathogenesis of autoimmune arthritides and provide the scientific basis for treatment approaches targeting Th17 cell functions.

Disclosure: J. Leipe: None; **M. Grunke:** None; **C. Dechant:** None; **C. Reindl:** None; **H. Schulze-Koops:** None; **A. Skapenko:** None.

2131

Regulatory T Cell Recovery in HCV-Related Autoimmunity through IL-2 Treatment. David Saadoun[2], Michelle Rosenzwajg[1], Lucile Musset[1], Fabrice Carrat[1], David Klatzmann[1] and Patrice Cacoub[1]. [1]Internal Medicine Department, [2]Internal Medicine Department and Immunology Laboratory Pitie Salpetriere Hospital

Background: Twenty to 30% of hepatitis C virus (HCV)-related vasculitis patients are resistant to conventional therapy (i.e. antiviral therapy and/or immunosppressors) and still have an active disease. We recently described a $CD4^+$ $CD25^{++}$ regulatory T cell (Treg) deficiency in HCV-related vasculitis patients. Immunomodulatory effects of interleukin-2 (IL-2) are well established, notably the preferential expansion of Treg able to suppress inflammatory responses mediated by $CD4^+$ and $CD8^+$ T cells.

Objective: To evaluate the cellular immune response after IL-2 therapy in HCV-MC Vasculitis patients, resistant to conventional therapy.

Patients: HCV+ patients with cryoglobulinemia vasculitis (n=10), resistant to conventional therapy (i.e. antiviral therapy and/or immunosppressors). Vasculitis was defined according to international criteria: chronic HCV infection (HCV RNA+), serum cryoglobulin ≥ 0.05g/l in at least two determinations, presence of the triad purpura-arthralgia-asthenia and/or biopsy proven vasculitis (kidney, nerve or skin).

Methods: This is an open prospective phase I/II trial. Four cycle of subcutaneous IL-2 therapy (3 millions IU/day from day 1 to 5 every 21 days were carried out at W1, W3, W6, and W9). All patients were followed after IL-2 therapy (W11 to W37). The end points were the immunologic follow-up of Treg and of HCV cellular immune response before, during and after IL-2 therapy and the clinical tolerance.

Results: The percentage of Tregs (CD4+CD25hiCD127-FoxP3+) dramatically increased following IL-2 therapy (3.5 ± 0.25% to 14.5 ± 2.89%, $p<0.001$) with a similar trend between naïve and memory Tregs. This was associated with an increased expression of molecules associated with suppression of Tregs (i.e. GITR, CD152 and LAP). Suppressive function of Tregs was confirmed by suppression tests. At a 1/1 and 1/8 ratio (between effector and tregs cells) the suppression was 97±1% and 66 ± 7%, respectively. A decrease in CD4+CD25+ effector Tcells (41.4 ± 4% to 24 ± 4%, $p<0.01$) and in CD27+IgM+ marginal zone B cells (11 ± 2% to 4.5 ± 0.6%, $p<0.01$) was observed following IL-2 therapy. After IL-2 therapy serum level of IL-2 and IL-2RA were still higher than before therapy. IL-2 therapy was safe with no vasculitis flare.

Conclusion: This is the first study to report the use of IL-2 in human autoimmune disease to modulate the homeostasis of Tregs. IL-2 therapy dramatically increase the percentage of Treg in HCV-vasculitis and was well tolerated.

Disclosure: D. Saadoun: None; **M. Rosenzwajg:** None; **L. Musset:** None; **F. Carrat:** None; **D. Klatzmann:** None; **P. Cacoub:** None.

ACR/ARHP Combined Abstract Session

ACR/ARHP Combined Orthopedics, Low Back Pain and Rehabilitation Abstracts: Hips and Knees: Focus on Function

Wednesday, November 10, 2010, 2:30 PM–4:00 PM

2132

Progressive Resistance Exercise in Women with Knee Osteoarthritis. Renata Jorge[1], Marcelo Souza[2], Aline Chiari[2], Anamaria Jones[2], Império Lombardi, Jr[2], Artur Fernandes[2] and Jamil Natour[2]. [1]UNIFESP, Sao Paulo, SP, Brazil, [2]UNIFESP

Background: Knee osteoarthritis (OA) is a common musculoskeletal disorder. Recent guidelines for the management of knee OA emphasize the role of strengthening exercises. While most studies focus on the benefits of quadriceps strengthening, little is known about hip strengthening exercises in knee OA and also, about prescription in terms of intensity, duration, frequency and load.

Objectives: To assess pain, function, quality of life, walking endurance and muscular strength in women with knee OA who participated in a progressive resistance exercise program (PREP).

Methods: Eligible patients included women, age 40–70 years old with pain between 3 and 8 on a 10-cm pain scale. Of the 144 patients screened, 60 met the eligibility criteria and were randomized to the Experimental Group (EG) or Control Group (CG). Patients in EG participated in a 12-week PREP twice a week and CG remained on a waiting list for physiotherapy. The PREP consisted of strengthening exercises for knee extensors, knee flexors, hip abductors and hip adductors, all performed with 50% and 70% of the maximum amount of weight that can be tolerated for a given exercise (1 repetition maximum-1RM) using machines with free weights. The resistance was reevaluated every 2 weeks. Assessment for pain (VAS), muscle strength (RM), walking endurance (6MWT), function (WOMAC) and quality of life (SF-36) were done at baseline, 6 weeks and 12 weeks by a blinded assessor.

Results: 29 female patients were randomly assigned to the EG and 31 to the CG. In the comparison between groups using ANOVA for repeated measures, we found better results for the EG with statistical difference for VAS ($p<0.001$), WOMAC (pain: $p < 0{,}001$; function: $p < 0{,}001$ and aggregate score: $p<0.001$), some domains of SF-36 (physical function: $p=0.002$; physical role limitation: $p=0.002$ and pain: $p = 0{,}044$) and on muscular strength (extensors: $p<0.001$; flexors: $p=0{,}002$ and abductors muscles: $p<0.001$). At 6 weeks, there was a significant statistical difference in the pain VAS (EG: 5.9; CG:7.0; $p=0.022$); the WOMAC (EG: 30.9; CG:39.1; $p=0.017$); SF-36 physical component summary (EG:39.1; CG: 30.3; $p=0.045$) as well on muscular strength of knee extensors (EG:10.4; CG:5.7; $p<0.001$); knee flexors (EG:7.4; CG:5.2; $p=0.003$) and hip abductors (EG:29.2; CG:21.0; $p<0.001$). At 12 weeks, there was a statistically significant difference in the pain VAS (EG: 4.3; CG: 6.6; $p<0.001$); the WOMAC (EG:24.1; CG: 38.3; $p<0.001$); SF-36 physical component summary (EG: 49.8; CG: 30.8; $p=0.000$); physical role limitation (EG: 48.3; CG: 16.9; $p=0.001$) and pain (EG: 58.6; CG: 41.7; 0,006); as well on muscular strength of knee extensors (EG: 11.8; CG: 5.7; $p=0.000$), knee flexors (EG: 8.6; CG: 5.3; $p=0{,}000$) and hip abductors (EG: 32.7; CG: 19.5; $p=0.000$).

Conclusion: A progressive resistance exercise program was effective in reducing pain and improving function, some domains of quality of life and strength in women with knee osteoarthritis at 6 weeks and 12 weeks after the intervention.

Disclosure: R. Jorge: None; **M. Souza:** None; **A. Chiari:** None; **A. Jones:** None; **I. Lombardi, Jr:** None; **A. Fernandes:** None; **J. Natour:** None.

2133

Reasons for Decline in Walking Despite Improvements in Knee Pain: The MOST Study. Daniel K. White[2], David T. Felson[4], Jingbo Niu[3], Michael C. Nevitt[5], C. Elizabeth Lewis[6], James Torner[7] and Tuhina Neogi[1]. [1]Boston Univ Schl of Med, Boston, MA, [2]Boston Univ School of Med, Boston, MA, [3]Boston University, Boston, MA, [4]Boston University School of Medicine, Boston, MA, [5]UCSF, San Francisco, CA, [6]University of Alabama, [7]University of Iowa

Purpose: Reducing knee pain in persons with knee osteoarthritis (OA) is a key therapeutic goal of rehabilitation. However, recent studies have shown that improvements in pain do not necessarily result in improvements in function, and it's not clear as to why this might be. We therefore evaluated factors associated with substantial declines in walking speed among persons who had meaningful improvements in knee pain.

Methods: The Multicenter Osteoarthritis Study (MOST) is a NIH funded longitudinal study of people who have or are at high risk for knee osteoarthritis. We included subjects who had meaningful improvement over 30 months in pain in either knee, defined as a 41% decrease in VAS pain with an absolute change of 20/100. We defined meaningful decline in walking speed as a decrease of 0.1 meters per second (m/s) during a 20 meter walk. Both values are based on previously published sources. We assessed changes in radiographic OA, comorbidities, widespread pain, and depressive symptoms over 30 months, and baseline knee strength as risk factors for decline in walking speed. To examine the association of risk factors with meaningful decline in walking speed we calculated risk ratios adjusted for age, sex, BMI, race, and baseline knee pain.

Results: Of the 465 persons with meaningful improvement in knee pain (mean (sd) age=63.3 (7.8), 67% female, BMI= 31.3 (6.3), 82% White), 20% (91/465) had a meaningful decline in walking speed. More persons with a new onset of comorbidity had a decline in walking speed (32% (15/47)) compared with those with no comorbidity at baseline or follow up (17% (46/267)). Similarly, more persons with widespread pain at baseline and follow up had a decline in walking speed (24% (40 /165) compared with those with no widespread pain at baseline or follow up (16% (22/139)). Adjusting for confounders, persons with new comorbidities and those with widespread pain had 1.8 and 1.7 times the risk of decline compared with those without comorbidities and widespread pain, respectively (RR 1.8 95% CI [1.1,2.9], 1.7 [1.0,2.9], respectively).

Conclusions: Improvements in knee pain do not guarantee positive changes in walking speed. Health providers should consider that onset of new comorbidities and pain in areas other than knee pain may increase risk of decline in walking speed despite improvement of pain in one or both knees.

Table. Association of risk factors for meaningful decline in walking speed among persons with meaningful improvement in knee pain.

	% (# decline/total #)	Adj Risk Ratio* [95% CI]
ROA		
None at 0 or 30m	20 (32/161)	1.0 [Ref]
Present at 0 and 30m	20 (55/275)	1.0 [0.6, 1.5]
None at 0m, present at 30m	18 (4/22)	1.0 [0.3, 2.9]
Comorbidities		
None at 0 or 30m	17 (46/267)	1.0 [Ref]
Present at 0 and 30m	20 (31/148)	1.1 [0.7, 1.7]
None at 0m, present at 30m	32 (15/47)	1.8 [1.1, 2.9]
Wide spread pain		
None at 0 or 30m	16 (22/139)	1.0 [Ref]
Present 0m, none at 30m	20 (24/119)	1.1 [0.7, 1.7]
Present at 0m and 30m	24 (40/165)	1.8 [1.1, 2.9]
None at 0m present 30m	12 (4/34)	1.0 [Ref]
Strength		
1: High	22 (31/141)	1.0 [Ref]
2	18 (19/106)	0.8 [0.5, 1.4]
3	19 (22/116)	1.0 [0.6, 1.6]
4: Low	18 (10/56)	1.0 [0.5, 1.9]

*Mutually adjusted for age, sex, BMI, race, baseline knee pain, and depressive symptoms. Higher risk ratios indicate greater risk of meaningful decline in walking speed.

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2134

Reduction of the Foot Plantar Maximum Vertical Force Using Medial-Wedge Insoles in Valgus Knee Osteoarthritis. Priscilla Teixeira Rodrigues[2], Rosa M. R. Pereira[2], Julia M. D. Greve[1] and Ricardo Fuller[2]. [1]Rheabilitation Division, Faculdade de Medicina da Universidade de São Paulo, [2]Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo

Introduction: The use of medial-wedge insole associated with ankle support produces a clinical improvement in osteoarthritis of the knee valgus, as described in our previously study [Arthritis Rheum 59(5): 603–608]. However, there are no data regarding the biomechanics effect of these orthoses.

Objective: To evaluate the foot plantar maximum vertical force in patients with OA in the lateral compartment of the valgus knee using medial-wedge insole associated with ankle support.

Method: A total of 42 feet of 21 women with bilateral knee osteoarthritis (ACR criteria), with valgus deformity ≥ 8 degrees were evaluated regarding clinical and biometrics data. Patients were assessed with: 1. standard shoes without the insoles (control); 2. with the medial-wedge insoles (with 8 mm medial elevation at rearfoot) and 3. with these insoles and neoprene ankle support. The system FSCANR 3.816 version, with flexible soles and 960 load sensors on the surface, was used to obtain the foot plantar vertical force. The acquisition of the measures took 8 seconds and the data was collected between seconds 2 and 6. The values were given in Newtons (N).

Results: The patients were 65.14 +10.24 years old; the mean disease duration was 9.3 years, the body mass index was 29.4 ± 4.1. The pain at rest was 5.57 ± 2.18 (range 2–8) by visual analogue scale, the degree of radiographic OA (Kellgren-Lawrence) was 2.62 ± 0.82, WOMAC index was 70.8 ± 11.2 and Lequesne 14.55 ± 3.19. The femorotibial angle was 169.38 ± 4.32 degrees. The maximum vertical force was significantly lower in in the patients with the use of medial-wedge insoles compared to control (287.30 ± 89.28 vs. 347.42 ± 87.14 N, p= 0.003). Likewise, patients with the use of medial-wedge insoles and ankle support had a diminished vertical force compared to control (248.15 ± 99.77 vs. 347.42 ± 87.14 N, p<0.0001). The support promoted a further reduction in strength compared to the isolated use of the insole (248.15 ± 99.77 vs. 287.30 ± 89.28 N, p=0.03).

Conclusion: The use of medial-wedges insoles promotes a reduction in the maximum vertical force in osteoarthritis of valgus knee. This finding may explain the clinical improvement observed in our previous study probably by a more homogenous load distribution in the involved ankle and knee.

Disclosure: P. T. Rodrigues: Centro de Estudos em Reumatologia, 2; **R. M. R. Pereira:** None; **J. M. D. Greve:** None; **R. Fuller:** None.

2135

Functional Benefits Following Dynamic Exercise in Patients with RA Taking Anti-TNFα Therapy Reflected in Lower Limb Function Tests but Not the HAQ. Angela Reid[1], Audrey Brady[2], Tara Cusack[5], Catherine Blake[5], Anne Barbara Mongey[3], Douglas J. Veale[4] and Oliver FitzGerald[3]. [1]Our Lady's Hospice, Dublin, Ireland, [2]Our Lady's Hospice, [3]St. Vincent's University Hospital, [4]St. Vincent's University Hospital, [5]University College Dublin, Ireland

Background: The medical management of rheumatoid arthritis (RA) has advanced with the introduction of biologic drugs including anti-TNFα therapy medication. Dynamic exercise is an important non-pharmacological therapy in RA and has been shown to improve function. The effect of dynamic exercise on function for people with RA on anti-TNFα medication has not yet been described. The purpose of this study was to investigate the effect of dynamic exercise, either on land or in water, on function in people with RA taking anti-TNFα medication.

Methods: A convenience sample of people with RA on anti-TNFα medication was recruited. Participants were randomised into one of 3 groups: a gym, a hydrotherapy or a control group. The gym and hydrotherapy interventions consisted of flexibility, strengthening and aerobic exercises. Exercise classes were undertaken for 1 hour, twice weekly for 8 weeks. The control group received no intervention. Participants were assessed by a blind assessor at baseline, 8 and 24 weeks. The primary outcome measure used was the HAQ. Secondary measures of outcome included the 50ft Walk Test (50ftWT) and the Timed Chair Stand Test (TCST). Semi-structured interviews were conducted at 24 weeks to ascertain the exercise participation levels of individuals following completion of the study.

Results: Fifty one people (12 male / 39 female) with a mean age of 56 (± 10) years were recruited. The mean length of diagnosis was 14.1 (± 10.5) years and the mean length of time taking anti-TNFa medication was 2.9 (± 2.1) years. The 50ftWT improved significantly in both the gym and hydrotherapy groups at 8 weeks compared to the control group (gym p=0.02, hydrotherapy p=0.01). The TCST significantly improved in the gym group (p=0.02) when compared to the control group at 8 weeks. These improvements were not maintained at 24 weeks. No significant change was noted in HAQ scores. Of the 17 exercise group participants interviewed post-study, 3 had continued the exercise programmes between the eight and 24 week time-points. Reasons identified for failing to continue to exercise included lack of access to facilities and reduced motivation.

Table 1. Results

	Group (n = 17)*	Baseline	8 weeks	24 weeks
HAQ (0–3) mean ± SD	Gym	0.79 (0.51)	0.63 (0.48)	0.79 (0.61)
	Hydro	1.07 (0.85)	0.99 (0.85)	1.03 (0.85)
	Control	0.83 (0.55)	0.83 (0.59)	0.79 (0.56)
50ft Walk test (s) mean ± SD	Gym	9.35 (1.97)	8.21 (1.86)†	8.6 (2.62)
	Hydro	11.53 (3.87)	10.07 (2.05)†	10.24 (2.17)
	Control	10.10 (3.36)	10.56 (3.34)	10.35 (2.60)
Timed Chair Stand Test (reps) median (range)	Gym	13 (5–19)	16 (10–32)‡	16 (6–32)
	Hydro	9 (6–23)	12 (8–23)	12 (8–29)
	Control	11 (5–20)	13 (6–22)	13 (0–22)

*Hydro Group n = 16 at 24 weeks. †p ≤ 0.05 one-way Anova, ‡p ≤ 0.05 Mann-Whitney U Test.

Conclusion: Participating in 8 weeks of dynamic exercise, either on land or in a hydrotherapy pool, improved function in this sample of people with RA on anti-TNFα medication as evidenced by the significant improvements in lower limb function tests at 8 weeks. This was not reflected by changes in HAQ scores. Access to facilities and support in terms of organised, suitable, supervised exercise classes may be necessary to enable this population to continue to engage in long term exercise.

Disclosure: A. Reid: None; **A. Brady:** None; **T. Cusack:** None; **C. Blake:** None; **A. B. Mongey:** None; **D. J. Veale:** None; **O. FitzGerald:** None.

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Co-Morbid Pain in Hips, Low Back, and Non-Operative Knee Associated with Physical Function before and after TKR. Patricia D. Franklin[2], Wenjun Li[2], David C. Ayers[2] and Carol A. Oatis[1]. [1]Arcadia University, Glenside, PA, [2]Univ of MA Med Schl, Worcester, MA

Introduction: Older age, female gender, obesity, and poor emotional health are associated with poorer function before and after total knee replacement (TKR). In addition, medical co-morbidities are related to peri-operative adverse events. However, no research has documented the role of co-morbid pain in the low back, hips, and the non-operative knee on physical function before and after TKR. We evaluated the association of co-morbid low back, hip, and bi-lateral knee pain with function in TKR patients.

Methods: A prospective cohort of 130 consecutive, primary, unilateral TKR patients enrolled in a clinical trial reported demographic, pain, and function data before and at 6 months after TKR. Descriptive and multivariate analyses evaluated the associations among age, gender, BMI, emotional health (SF36, MCS), WOMAC pain score in both hips and both knees, and Oswestry low back pain and associations with (1) pre-op function (SF36, PCS) and (2) pre-post functional gain.

Results: Patients were 60% women with mean age=65, BMI=32.6, pre-TKR PCS=32.7. Before TKR, 52% reported mild or no pain in the non-operative knee, hips, and low back. Twenty (20) percent reported moderate/severe pain in one other joint or back, 13% in two locations, and 10% in 3 or 4 locations. Women reported moderate/severe pain more than men in the non-operative knee (34.5% vs. 11%); ipsilateral hip (28% vs. 15%); and low back (33% vs. 20%). After adjusting for age, gender, BMI, and MCS, greater pain in the surgical knee ($p < 0.000$), contralateral hip ($p < 0.074$), and low back ($p < 0.028$) was associated with poorer function in TKR patients (r2=.39).

Conclusion: In addition to pain in the surgical knee, co-morbid pain in the non-operative knee, hips, and low back explain much variation in peri-TKR function. Women report more non-operative joint pain than men at the time of TKR. These data suggest a need for a musculoskeletal co-morbidity score to assess total pain burden when evaluating TKR patient function before and after surgery.

Disclosure: P. D. Franklin: NIAMS-NIH, 2; **W. Li:** NIAMS-NIH, 2; **D. C. Ayers:** NIAMS-NIH, 2, Zimmer, 2; **C. A. Oatis:** NIAMS-NIH, 2.

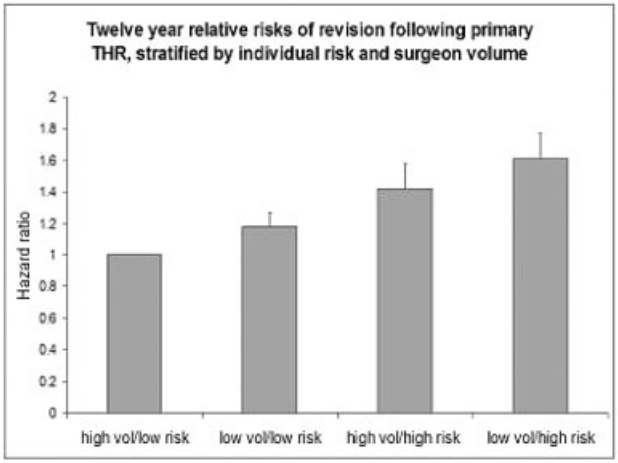
2137

Predictors of 12 Year Revision Risk Following Primary THR for Osteoarthritis in the US Medicare Population. Jeffrey N. Katz[1], Elizabeth A. Wright[1], Akosua A. Nti[1], John Wright[2], Henrik Malchau[5], John A. Baron[4] and Elena Losina[3]. [1]Brigham and Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital, [3]Brigham and Womens Hospital, Boston, MA, [4]Dartmouth Medical School, [5]Massachusetts General Hospital

Introduction: There have been no prior US national population-based studies of the risk of revision following primary total hip replacement (THR) for osteoarthritis (OA) with 12 year follow up and complete ascertainment of revision and mortality.

Methods: We used Medicare claims data to assemble a cohort of 51,347 patients ≥65 years old who had primary THR for OA in 1995–96. We followed this cohort in claims through 2008 and identified patients who had claims with ICD-9 codes indicating revision THR. We used Cox proportional hazard models to examine the association of age, sex, race, Medicaid eligibility (proxy for low income), comorbidity, surgeon and hospital Medicare THR volume on the risk of revision. We aggregated individual risk factors into a risk score and examined the effects of high individual risk score and THR volume in a Cox model.

Results: At the time of primary THR, the cohort had mean age 74, 63% were female, and 53% were operated upon by surgeons who performed fewer than 12 THRs per year in the Medicare population. Over 12 year follow-up, 27,955 patients died and 4,185 underwent revision THR. Factors independently associated with risk of revision THR included younger patient age (65–75 versus > 75; HR 1.47, 95% CI 1.37, 1.57), male sex (HR 1.23, 95% CI 1.16, 1.31) and low annual surgeon THR volume (< 12 cases/year; HR 1.23, 95% CI 1.13, 1.34). After adjusting for these factors, comorbidity, race, Medicaid eligibility and hospital volume were not associated with revision risk. We designated patients with both individual risk factors (male, younger age) as high risk, and those with 0 or 1 of these factors as lower risk. In a Cox regression model, low surgeon volume and high individual risk contributed independently to revision risk (Figure). We found no evidence for an interaction between individual risk and surgeon volume.



Conclusions: These first national, population based estimates of the 12-year risk of revision following primary THR confirm the risk associated with younger age and male sex and demonstrate that low surgeon volume is associated with revision risk in both high- and low-risk patients. The analyses are limited by our inability to adjust for patient weight or activity level with claims data. As THR is performed in increasingly younger patients, these findings underscore the need for further research on the risk of revision in patients < 65 undergoing primary THR.

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ARHP Concurrent Abstract Sessions
Keep Working with Arthritis
Wednesday, November 10, 2010, 2:30 PM–4:00 PM

2138

Too Young? Arthritis Is "Main Cause" of Disability for Millions of Working-Age U.S. Adults. Kristina Theis[3], Charles G. Helmick[1], Jennifer M. Hootman[2] and Matthew Brault. [1]CDC, Atlanta, GA, [2]Centers for Disease Control, Kennesaw, GA, [3]Centers for Disease Control and Prevention

Background: Arthritis is well-established as a cause of disability, particularly among older adults. However, much less is known about its impact on working-age (18–64 years) adults. Using the most recent Survey of

Income and Program Participation (SIPP) data, we describe the prevalence and specific impacts of disability due to arthritis/rheumatism among working-age US adults.

Methods: SIPP is a longitudinal panel survey fielded by the US Census Bureau representing the civilian, non-institutionalized US population. Panel members undergo in-person interviews at 4-month intervals for a period of 2.5–4 years. Data presented here are cross-sectional findings from a disability topic module (fielded June–September 2005) of the 2004 SIPP panel. The disability module was administered to panel adults to identify self-reported disability (difficulty with ≥1 specified functional activities, activities of daily living (ADL), instrumental activities of daily living (IADL), selected impairments, use of an assistive aid, or limitation in ability to work around the house or at a job or business) and ascertain its "main cause." Analyses weighted to population controls and incorporating sampling weights produced estimates and 95% confidence intervals (95% CI) of disability prevalence overall and by specific disability subcomponents for working-age adults overall and by age group (18–44 or 45–64 years) and sex for respondents identifying arthritis as the main cause of their disability. Statistical comparisons by age group and sex were considered significant at the 95% confidence level.

Results: At least 3.6 million working-age adults report arthritis as the main cause of their disability. Of these, 22.4% (95%CI 19.7–25.1) receive federal work disability benefits, 21.0% (95%CI 18.2–23.8) use assistive aids (e.g., cane), 17.7% (95%CI 15.4–20.0) have difficulties with ADLs, 20.9% (95%CI 18.3–23.5) with IADLs, 40.5% (95%CI 37.4–43.6) and 37.8% (95%CI 34.7–40.9) are limited in their ability to work around the house or at a job or business, respectively, and 89.9% (95%CI 88.1–90.7) have difficulty with specified functional activities, e.g., walking 3 city blocks (51.1%), lifting/carrying 10 pounds (32.9%). In absolute numbers, ~1.4 million report limitation in their ability to work at a job, 808,000 receive federal work disability benefits, and 740,000 require the use of cane, crutches, or a walker. The absolute number and % having difficulties with selected specified activities are significantly higher in those 45–64 compared with 18–44 year olds; yet, 743,000 younger adults report that arthritis disables them. Women comprise ¾ of the 3.6 million and ½ to ¾ of those in all specific disability subcomponents.

Conclusion: Respondents in vulnerable pre-retirement years (45–64) and women at all ages, bear a substantial portion of arthritis disability and may be well-served by increasing reach of evidence-based programs that improve pain and physical function. Occupational and physical therapy and increased use of appropriate assistive devices may help mitigate current disability among adults with arthritis.

Disclosure: K. Theis: None; **C. G. Helmick:** None; **J. M. Hootman:** None; **M. Brault:** None.

2139

Arthritis and Labor Force Attachment among Working-Age Australians. Kristina A. Theis, Lucy Busija, Ross Wilkie, Gerald Elsworth and Richard H. Osborne. Deakin University

Background: The impact of arthritis on employment is well-documented in many countries; however, little is known about its extent in working-age (18–64 years) adults in Australia. The aim of this study is to estimate the prevalence of arthritis and explore its links with age, gender, and labor force attachment in working-age Australians.

Methods: Data were obtained from the Household, Income, and Labour Dynamics in Australia (HILDA), a nationally representative survey of community-dwelling adults, with data collected by in-person interview and supplemented by a self-complete questionnaire. Data presented here are cross-sectional findings from HILDA 2007, the most recent time period in which arthritis status was ascertained. Participants reported an arthritis diagnosis by identifying arthritis from a list of conditions following: "Have you ever been told by a doctor or nurse that you have any of the long-term health conditions listed below?" Analysis was restricted to those with known arthritis status (n = 10,940) to estimate arthritis prevalence and the links with age, gender, and labor force attachment (categorized as employed, unemployed (actively seeking employment), or not in the labor force (all other dispositions, including discouraged job seekers). Weighted point estimates and 95% confidence intervals [95% CI], accounting for the complex survey design, were calculated for working-age adults overall and by age group (18–44 or 45–64 years) and sex.

Results: Arthritis affects 14.9% [95% CI 13.8–15.9] of working-age adults in Australia (1.6 million people) and was significantly greater in women (17.5% [16.1–19.0]) compared with men (12.1% [10.8–13.3]. Overall, employment was statistically significantly lower in those with arthritis compared to those without arthritis (57.7% [53.8–61.5] vs. 80.2% [78.9–81.5]). The same pattern of statistically significantly lower employment for those with arthritis vs. no arthritis holds for men (59.8% [53.9–65.8] vs. 86.8% [85.3–88.2]), women (56.2% [51.6–60.8] vs. 73.5% [71.6–75.3]), and both age groups. But the arthritis vs. no arthritis employment gap was much narrower for younger adults (70.9% vs. 81.6%) than for those in the older age group (54.5% vs. 77.5%). More than twice the prevalence of working-age adults with arthritis were not in the labor force compared to those without arthritis (40.6% [36.7–44.5] vs. 17.0% [15.9–18.2]). Unemployment was low and not significantly different between working-age Australians with and without arthritis.

Conclusion: Arthritis is common among working-age Australians, affecting approximately 1 in 7 potential workers. Employment is substantially lower among those with arthritis compared to those without for men and women and across age groups; however, the increase in employment gap between the older versus younger age group suggests that employment is a greater challenge for individuals in middle age. Also, despite lower arthritis prevalence overall, men with arthritis appear to be more affected than women by low employment participation. The application of policy and public health interventions in combination may be needed to reduce the impact of arthritis on employment.

Disclosure: K. A. Theis: None; **L. Busija:** None; **R. Wilkie:** None; **G. Elsworth:** None; **R. H. Osborne:** None.

2140

Association of Depressive Symptoms and Helplessness with Socioeconomic Status in People with Knee Osteoarthritis. Leigh F. Callahan[2], Jack H. Shreffler[4], Kathryn Remmes Martin[3], Britta Schoster[4], Jordan Renner[4] and Joanne M. Jordan[1]. [1]Chapel Hill, NC, [2]Univ of North Carolina, Chapel Hill, NC, [3]University of North Carolina at Chapel Hill, Chapel Hill, NC, [4]University of North Carolina, Chapel HIll

Purpose: Individual and community socioeconomic status (SES) variables have been demonstrated to be associated with psychosocial outcomes in self-report and other types of arthritis, but these associations have not been examined in knee osteoarthritis to date. The purpose of this study is to evaluate associations between educational attainment, occupational status, and community poverty rate with depressive symptoms and perceived helplessness in people with knee OA.

Methods: A cross-sectional analysis was performed using data from 3085 people in the first follow-up evaluation (2000–2003) of the Johnston County Osteoarthritis Project. Depressive symptoms were measured with the 20-item Center for Epidemiologic Studies Depression (CES-D) on a scale of 0–60. Perceived helplessness was measured with the 5-item Rheumatology Attitudes Index (RAI) on a scale of 1–5. Educational attainment was dichotomized as less than high school (HS) diploma or at least a HS diploma. Occupational status was dichotomized as high (e.g. professional, managerial, technical, sales) versus low (labor, service, farm, manufacturing) based on U.S. Census 2000 categories for self-reported occupation. Community poverty was defined from the U.S. Census household poverty rate for the block group in which the participant resided. Poverty rate was trichotomized as <12% (reference), 12–25%, and >25%. Separate analyses were performed for those people having knee radiographic OA (rOA), defined as KL grade>=2 in one or both knees, and for those with symptomatic knee OA (sOA) defined as KL grade >=2 and with symptoms (pain or stiffness) in the same knee. Regression analyses were used to relate CES-D and RAI outcomes to all SES variables while controlling for age, gender, race, and BMI.

Results: Of the sample, 750 people had rOA. The average age was 67 years (45–94), 36% were African American, 58% had BMI ≥ 30, and 64% were female. 37% of the population had less than HS diploma, and 60% were in non-managerial occupations. The average CES-D was 6.9 (8.1), and the average RAI was 2.55 (0.71). Of those with rOA, 488 also met the definition of sOA. For people with knee rOA, CES-D scores were significantly higher for those with low educational attainment (β=2.04, C.I.= [0.77, 3.3]) and, independently, low occupational status (β=1.58 [0.33, 2.8]). RAI scores were significantly associated only with educational attainment (β=0.31 [0.19, 0.43]). Important covariates for CES-D were age ≥ 65 (β=-4.8 [−6.5, −3.2]) and being female (β=3.3 [2.1, 4.4]). Important covariates for RAI are being female (β=0.16 [0.05, 0.27]) and having BMI≥30 (β=0.25 [0.14,

0.37]). For people with knee sOA, results generally paralleled those for rOA, except that CES-D was not independently associated with occupational status. Community poverty was not significantly associated with CES-D or RAI in bivariate or multivariable analyses.

Conclusions: Low educational attainment is associated with higher levels of depression and feelings of helplessness in people with knee OA. Low occupational status may also play an independent role.

Disclosure: L. F. Callahan: None; **J. H. Shreffler:** None; **K. R. Martin:** None; **B. Schoster:** None; **J. Renner:** None; **J. M. Jordan:** None.

2141

The Effect of a 6 Week Walking Program on Work Activity Limitations in Adults with Arthritis. Brian L. Charnock[3], Kathryn Remmes Martin[2], Jack Shreffler[3], Mary Altpeter[3] and Leigh F. Callahan[1]. [1]Univ of North Carolina, Chapel Hill, NC, [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, [3]University of North Carolina at Chapel Hill

Purpose: To evaluate the effect of a revised 6 week walking intervention program, Walk With Ease (WWE), on work limitations among people with self-report arthritis.

Methods: While conducting an evaluation of the Arthritis Foundation's (AF) Walk With Ease (WWE) community based walking program, pretest-posttest physical evaluations and self-report surveys were administered to 462 individuals. Of these, 94 were employed and answered a series of questions using the Workplace Activity Limitation Scale (WALS). This 12-item scale gauges physical activity limitations in working adults with arthritis. Participants answered individual WALS items by marking 0 (no difficulty), 1 (some difficulty), 2 (a lot of difficulty), and 3 (unable to do). Individual item scores were then summed and averaged to yield an overall WALS score which ranged from 0 (good) to 3 (bad) for each participant. At the 1 year WWE follow-up, 67 participants were still employed and retook the WALS. Pre-post t-tests were conducted for each individual WALS item and the overall WALS to determine whether participants significantly improved work limitations. Post-1yr t-tests were also conducted to determine if any improvements were maintained at 1 year.

Results: Employed WWE participants were on average 56 years old, 88% female and 61% Caucasian. Mean Body Mass Index was 32 and 81% had more than a high school education. Overall, 59% of participants improved their WALS during the 6 week program. In pre-post comparisons, the overall WALS significantly improved from a mean of 0.57 (SD $\pm$0.34) to a mean of 0.47 (SD $\pm$0.36), $p<0.001$. Individual WALS items with significant improvement were: "Lifting/Carrying objects" (0.96 ($\pm$0.72) to 0.71 ($\pm$0.78), $p<0.001$), "standing for long periods of time" (0.85 ($\pm$0.77) to 0.6 ($\pm$0.73), $p<0.01$)," maintaining concentration" (0.34 ($\pm$0.50) to 0.19 ($\pm$0.40), $p<0.01$), as well as "using hands" and "reaching" (both $p<0.05$). Improvements shown at 6 weeks were maintained at one year in both the overall WALS (0.45 ($\pm$0.31) to 0.43 ($\pm$0.33)) and the 5 individual WALS items listed above.

Conclusion: After a 6 week walking program, working adults with arthritis showed significant improvement in overall work limitations. Improvements were primarily in lifting/carrying, standing for long periods of time and maintaining concentration while at work. One year after the walking program, work limitation improvements were maintained. Walking intervention programs, such as WWE, should be considered by employers to improve the health and productivity of employees in both the short and long term.

Disclosure: B. L. Charnock: None; **K. R. Martin:** None; **J. Shreffler:** None; **M. Altpeter:** None; **L. F. Callahan:** None.

2142

The Effect of Structural Deformities on Typing Styles of Touch Typists with Rheumatoid Arthritis. Nancy A. Baker[2], Norman P. Gustafson[2], Hyekyoung Shin[3] and Joan C. Rogers[1]. [1]Pittsburgh, PA, [2]University of Pittsburgh, Pittsburgh, PA, [3]University of Pittsburgh

Purpose: Rheumatoid arthritis (RA) may lead to severe fixed structural deformities of the hand and wrist that may change postures/motions during touch typing. Understanding the mechanism of hand motions during touch typing may provide insight into how people with RA can use their computer safely. This cross-sectional study examined the effect of structural deformities on the postures/motions of the hand/wrist during touch typing. We hypothesized that touch typists with RA with structural deformities would have significantly different typing postures/motions and speeds than those without structural deformities.

Method: A total of 33 subjects with RA were recruited from the University of Pittsburgh Medical Center (UPMC). Subjects were adults with RA, aged from 18 to 65 years, who self-reported being touch typists. Subjects' posture/motions during typing were videotaped and rated for visual structural deformities (VSD) by a certified hand therapist. Typing postures/motions were rated by two trained raters using the Keyboard-Personal Computer Style Instrument (K-PeCS). Typing speed was calculated in words per minute. Based on the presence of any VSD, subjects were divided into two groups: 22 subjects with VSD and 11 subjects without VSD. Chi Square statistics and independent t-test were used to compare the K-PeCS items and typing speed between the two groups.

Results: The subjects were primarily female (88%), a mean age of 56.3 $\pm$ 8.8, and white (91%). Touch typists with VSD showed more fixed hand/wrist motions than those without VSD (Figure 1). Significantly more subjects with VSD showed whole hand motions to activate the keys rather than individual finger motions (i.e., no ulna deviation, no MCP hyperextension, straight finger joints, and use of 2 or less fingers). Significantly fewer subjects with VSD also used a wrist support. There was no significant difference for typing speed between the subjects with VSD (25.9 $\pm$ 13.0 wpm) and without VSD (27.7 $\pm$ 11.4 wpm) (p =.70).

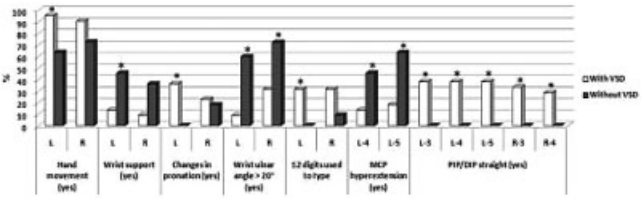

Figure 1. Significantly different postures/motions during touch typing (* $p<.05$).

Conclusion: Structural deformities can affect the typing styles of touch typists with RA. To compensate for inflexible hand movements, touch typists with VSD showed alternative typing strategies, such as "hunt and peck" style: moving whole hands rather than individual joints, floating the wrists, using fewer fingers, and keeping their fingers straight rather than curved. However these strategies may exacerbate existing problems by putting additional stress on already affected joints. Further evaluation by age should be considered.

Possible suggestions to ensure proper working posture include ergonomic keyboard, moveable wrist support, or redesign of computer workstation.

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Disclosure: N. A. Baker: None; **N. P. Gustafson:** None; **H. Shin:** None; **J. C. Rogers:** None.

2143

Formation of Solutions for Rheumatic Condition-Related Work Barriers by Occupational and Physical Therapists (OTs/PTs). Saralynn H. Allaire[2], Julie J. Keysor[1], Nancy A. Baker[5], Jingbo Niu[3] and Michael P. LaValley[4]. [1]Boston Univ Sargent College, Boston, MA, [2]Boston Univ School of Medicine, Boston, MA, [3]Boston University, Boston, MA, [4]BU School of Public Health, Boston, MA, [5]University of Pittsburgh, Pittsburgh, PA

Purpose: Identification of patients' rheumatic condition work barriers along with generation of solutions for barriers can reduce work disability. We have been exploring whether this type of intervention could be effectively provided by OTs/PTs. In a previous study 10 OTs/PTs had difficulty generating solutions for patients' work barriers. To address this finding we used literature and expert opinion to develop an informational booklet containing possible solutions for a wide variety of barriers. In this study, we examined solution generation quality in a large sample of OTs/PTs and tested the effect of providing the solution booklet on quality of solutions generated.

Methods: Subjects were recruited from OT/PT professional associations. We developed and pre-tested 3 patient cases. Case information included a patient's 3 most bothersome barriers. and subjects were asked to provide $\geq$ 1 solution for these 3 barriers. OT and PT subjects were each randomized to either receive (experimental=EXPM) or not receive (control=CTRL) the solution booklet to use as a resource. Three reviewers, blinded on subjects' EXPM/CTRL and OT/PT status, rated the helpfulness of the solutions generated by each subject using a 5-point ordinal scale. Proportions of EXPM

and CTRL subjects giving solutions rated as probably or very likely helpful were calculated. Wilcoxon rank tests were conducted to examine differences in the solution helpfulness scores between the two groups.

Results: 113 subjects provided data, 55 OTs (26 EXPM/ 29 CTRL) and 58 PTs (24 EXPM/ 34 CTRL). To date we have evaluated data from 2 cases. The quality of solutions generated by CTRL subjects was good for 2 physical activity type of work barriers, with ≥ 75% giving probably/very likely helpful solutions. The helpfulness scores of solutions from EXPM subjects for these 2 barriers were not significantly better. For a work/home life barrier the quality of CTRL subject solutions was poor, with only 22% providing helpful solutions. The EXPM subject solution score for this barrier was significantly better (p=.04), but quality was modest with 40% of solutions helpful. The quality of CTRL subject solutions for the remaining 3 barriers was modest with 45% giving helpful solutions for a cognitive barrier, 56% for a company policy barrier and 35% for a vocational direction barrier. However, the quality of solutions given by EXPM subjects for these barriers was good with 86%, 76% and 82% respectively giving helpful solutions (p<.001 for all).

Table. Helpfulness of Solutions Formed by Subjects Who Did and Did Not Receive Information about Possible Solutions

Work barrier	Subjects Who Did Not Receive information (CTRL)* n = 63	Subjects Who Did Receive information (EXPM)* n = 50	p value for comparison of CTRL/EXPM solution quality scores†
Physical job activity barrier: prolonged standing			
Proportion giving helpful solutions‡	75%†	76%	
Median (interquartile range) score§	3.0 (2–4)‡	3.5 (3–4)	0.08
Physical job activity barrier: carrying suit cases			
Proportion giving helpful solutions	87%	90%	
Median (interquartile range) score	4.0 (3–4)	3.5 (3–4)	0.75
Work/home life barrier: attending children's recreational events			
Proportion giving helpful solutions	22%	40%	
Median (interquartile range) score	2.0 (1–2)	2.0 (1–3)	0.04
Cognitive work barrier: concentrating on work activities			
Proportion giving helpful solutions	45%	86%	
Median (interquartile range) score	2.0 (0–3)	4.0 (3–4)	<.0001
Company policy barrier: completing required overtime hours			
Proportion giving helpful solutions	56%	76%	
Median (interquartile range) score	3.0 (0–3)	3.0 (3–4)	0.0002
Vocational direction barrier: change job/career			
Proportion giving helpful solutions	35%	82%	
Median (interquartile range) score	2.0 (1–3)	4.0 (3–4)	<.0001

*CTRL = control group; EXPM = experimental group
†From 0–4 rating of quality (helpfulness) of proposed solutions; 0 = unlikely to be helpful, 4 = very likely to be helpful
‡Subjects giving responses rated as probably (3) or very likely (4) to be helpful
§Wilcoxon rank statistical analyses

Conclusions: OTs/PTs not receiving supplemental information about potential solutions had only a modest ability to form helpful solutions for work barriers not related to physical job activities. However, providing information on ideas for solutions greatly enhanced the quality of solutions for other types of work barriers.

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ACR Concurrent Abstract Sessions
Genetics, Genomics and Proteomics: SLE
Wednesday, November 10, 2010, 4:30 PM–6:00 PM

2144

Exome Resequencing in a Densely Affected Multigenerational SLE Pedigree. Graham Wiley[2], Chee Paul Lin[2], Indra Adrianto[3], Jennifer A. Kelly[3], Kathy L. Moser[2], Kenneth M. Kaufman[3], John B. Harley[4], Courtney Gray-McGuire[2] and Patrick M. Gaffney[1]. [1]Oklahoma Med Research Foundation, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Oklahoma Medical Research Foundation, [4]Univ of OK Hlth Sci Ctr, Oklahoma City, OK

Background: Systemic lupus erythematosus (SLE) is a complex autoimmune disease that has heretofore been the subject of intense genetic scrutiny. While genome-wide association studies in SLE have successfully identified approximately 30 new risk loci the low odds ratios of associated loci leave a substantial portion of the estimated heritability of SLE unexplained. By comparison, the high odds ratios of highly penetrant rare polymorphisms (e.g. *TREX1*, OR=25) suggest the possibility that some of the missing heritability of SLE may exist in the form of rare variants.

Methods: To begin to explore the role of rare variants in SLE susceptibility we resequenced the exome in a unique, densely affected multigenerational SLE pedigree with 7 affected individuals. A densely affected pedigree was specifically chosen with the assumption that rare variations conferring higher SLE risk are more likely to be represented within such a family as opposed to the general population. The entire exonic region for the individuals within this family were captured through the use of the Agilent SureSelect sequence capture system and sequenced to 15x coverage using an Illumina GAIIx second-generation sequencer. Assembly of sequence to reference, variant calling, and other analysis were carried out using the CLC Genomics Workbench bioinformatics suite. Variants were verified with Illumina Omni1 Quad genotyping assays. Identified variants were screened using effect on protein function as determined by the SIFT algorithm.

Summary: Over 1700 coding variations were identified as shared between all case subjects within the family with approximately 40% encoding a nonsynonymous amino acid change. Of these amino acid changes approximately 7% are predicted to be damaging to the encoded protein. We have identified several nonsynonymous changes in proteins previously associated with SLE (*TNIP1*) as well as in loci not previously implicated in SLE including *NFKBIL1* and *NOTCH1*.

Conclusions: We have identified a number of potentially rare variants that appear to preferentially segregate with case samples within a densely affected SLE pedigree. These variants, in some cases, are predicted to cause a nonsynonymous amino acid change which will damage the affected protein. Several of these damaging variants are within genes which have been previously associated with SLE while others are within associated pathways. We believe the identification of these variants may assist in the identification of causal variants as well as shed some light on missing heritability within recent GWAS studies.

Disclosure: G. Wiley: None; **C. P. Lin:** None; **I. Adrianto:** None; **J. A. Kelly:** None; **K. L. Moser:** None; **K. M. Kaufman:** None; **J. B. Harley:** None; **C. Gray-McGuire:** None; **P. M. Gaffney:** None.

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Large-Scale Mapping of Systemic Lupus Erythematosus (SLE) Variants across Different Ethnicities Reveals That the IRF5-TNPO3 Region Is the Strongest Common Risk Factor. Timothy J. Vyse[8], Paula S. Ramos[3], Kenneth M. Kaufman[2], Jennifer A. Kelly[2], Caroline Gallant[7], Angelica Delgado[6], Sharon A. Chung[10], Lindsey A. Criswell[12], Robert P. Kimberly[4], Mary E. Comeau[3], Adrienne H. Williams[3], Laurie P. Russell[3], Chaim O. Jacob[9], Betty P. Tsao[11], Marta E. Alarcon-Riquelme[5], Kathy L. Moser[1], Patrick M. Gaffney[1], John B. Harley[13], Carl D. Langefeld[3] and SLEGEN Consortium. [1]Arthritis and Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Arthritis and Immunology Program, Oklahoma Medical Research Foundation, [3]Dept Biostatistical Sciences, Wake Forest University Health Sciences, [4]Dept Medicine, University of Alabama at Birmingham, Birmingham, AL, [5]Dept of Genetics and Pathology, Uppsala University, Uppsala, Sweden, [6]Dept of Genetics and Pathology, Uppsala University, [7]Dept of Genetics and Pathology, Uppsala University, Sweden, [8]Faculty of Medicine, Imperial College, London, UK, [9]Keck School of Medicine, University of Southern California, Los Angeles, CA, [10]Rosalind Russell Medical Research Center for Arthritis, University of California, San Francisco, San Francisco, CA, [11]UCLA School of Medicine, Los Angeles, CA, [12]UCSF-Box 0500, San Francisco, CA, [13]Univ of OK Hlth Sci Ctr, Oklahoma City, OK

Genome-wide association studies (GWAS) have been extremely successful at identifying important SLE risk factors. Nevertheless, in spite of being more prevalent in African Americans, Hispanics and Asians, the majority of GWAS have been performed in Caucasians. Recent GWAS in Asians have been reported, but there is still a paucity of large-scale data on the genetics of SLE in non-European populations. As such, the specific genetic variants predisposing to SLE and their overlap with European ancestry risk factors are largely unknown. This study is aimed at elucidating the patterns of disease association across different ethnicities. We conducted a trans-ethnic study called Lupus Large Association Study 2 (LLAS2) consisting of 8436 SLE cases and 7554 controls of European (3977 cases and 3538 controls), African American (1679 cases and 1934 controls), Asian (1272 cases and 1270 controls) and Hispanic and Native American ancestries (1508 cases 812 controls). We selected 7069 candidate SNPs from the SLEGEN European

ancestry genome-wide association study (GWAS)(Harley et al, 2008) and genotyped them on an Illumina custom array; approximately 400 ancestry informative markers were included and principal components analysis and admixture estimates were computed. We computed ethnic-specific case-control association analyses adjusting for admixture and trans-ethnic meta-analysis using the weighted inverse normal approach. Analyses were repeated adjusting for ethnic-specific tags for HLA-DR2 and –DR3, and the results were comparable in non-HLA regions. Strongest associated SNP in the region is reported. The most significant trans-ethnic variation is located in the IRF5-TNPO3 region (rs4728142, P=4.77×10–60), followed by STAT4 (rs11889341, P=4.66×10–53), HLA (rs3131379 in MSH5, P=1.17×10–52), ITGAM (rs9888739, P=5.38×10–31), BLK (rs13277113, P=4.79×10–29), PTTG1 (rs2431697, P=6.55×10–24), TNIP1 (rs960709, P=7.22×10–21), UBE2L3 (rs2298429, P=1.98×10–15), NMNAT2 (rs12146097, P=9.64×10–14), and TNFSF4 (rs10798269, P=5.69×10–12). Some regions are dominated by the European association (HLA, ITGAM, PTTG1 and NMNAT2), others by two or more ethnicities (IRF5-TNOP3, STAT4, BLK, TNIP1, UBE2L3, TNFSF4). Some regions share a similar pattern of association between two (IRF5-TNOP3, ITGAM) or more (STAT4, BLK, PTTG1, TNIP1, UBE2L3, NMNAT2) ethnic groups, while in others it is apparently discordant (HLA, TNFSF4). This is the first report of large-scale trans-ethnic mapping in SLE. This study shows that the IRF5-TNPO3 region is the strongest SLE trans-ethnic risk factor, and helps elucidate common versus ethnic-specific risk factors for SLE.

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Targeted Resequencing in Systemic Lupus Erythematosus Genetic Risk Loci: Initial Results from the REVEAL (Resequencing Variants Enhancing Autoimmunity and Lupus) Resource. Patrick M. Gaffney[1], Graham Wiley[2], Jennifer A. Kelly[2], Kenneth M. Kaufman[2], John B. Harley[3], Ekta Rai[4] and Edward K. Wakeland[4]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Univ of OK Hlth Sci Ctr, Oklahoma City, OK, [4]University of Texas Southwestern Medical Center, Dallas, TX

Background: Genetic predisposition is a potent element in susceptibility to SLE. Previous studies by the International Consortium for Systemic Lupus Erythematosus (SLEGEN) and others have associated more than 20 genomic segments with SLE susceptibility. These studies have localized causative genes into small genomic segments, but have not identified the precise genetic variations responsible for the functional changes that cause SLE. To elucidate the genetic lesions that are causative for SLE susceptibility, we have initiated deep sequencing studies of all of the genomic segments exhibiting suggestive or significant association with susceptibility to SLE.

Methods: DNA samples for sequencing were obtained from the Lupus Family Registry and Repository (LFRR) at the Oklahoma Medical Research Foundation. Samples were ranked based on their content of SLE associated SNP haplotypes at defined susceptibility alleles and samples with the highest content of SLE-associated SNP haplotypes were prioritized for sequencing. Isolation of 86 SLE associated genomic segments was performed using either solid-phase microarray capture (Nimblegen) or solution-based capture (Agilent SureSelect) followed by sequencing on the Illumina GAIIx platform. Custom software scripts were used to de-convolute multiplexed samples, eliminate redundant reads and assess for overall sequence coverage. Polished reads were aligned to the human genome reference (hg18) and variants (SNPs and deletion/insertion polymorphisms (DIPs)) were called using CLC Genomics Workbench Software (v4.0).

Results: We have completed sequencing of more than 100 SLE cases. Of the over 40 gigabases of total sequence reads aligning to the human genome in this study, 60–80% mapped to the targeted regions, yielding 35–45-fold average coverage. A comparison of 50 SNP genotypes previously determined in 5 samples with these sequences revealed concordance > 0.95. Further analysis of data from the first 32 European-American samples has revealed more than 2000 novel SNPs or DIPs in 2.9 megabases derived from 25 genomic segments showing significant associations with SLE. Our ongoing analysis of the organization of these polymorphisms, utilizing phylogenetic algorithms to network the SNP haplotypes formed in strong linkage disequilibrium with SNPs associated with SLE, has delineated multiple allele lineages with novel variants in haplotypes that are associated with susceptibility to SLE. These preliminary results suggest that identification of novel, potentially functional variants, in SLE-associated risk haplotypes will significantly improve our understanding of the functional changes that mediate disease susceptibility and ultimately lead to identification the precise causal variants.

Conclusion: We have initiated a large-scale, targeted resequencing resource (REVEAL) to identify and disseminate novel functional variants in 86 regions of SLE susceptibility. Production sequencing is currently underway with a goal of completing 600 subjects (1200 chromosomes) by the end of 2011. Public access to the REVEAL data will parallel policies similar to the ENCODE project.

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Identification of a Novel Systemic Lupus Erythematosus Susceptibility Locus at 11p13 near CD44 in a Multi-Ethnic Study. Christopher J. Lessard[3], Indra Adrianto[1], Jennifer A. Kelly[1], Kenneth M. Kaufman[1], Marta E. Alarcon-Riquelme for the BIOLUPUS Network[2], Juan-Manuel Anaya[4], Sang-Cheol Bae[10], Elizabeth E. Brown for PROFILE[6], Lindsey A. Criswell[14], Jeffrey C. Edberg[8], Barry I. Freedman[7], Chaim O. Jacob[9], Judith A. James[1], Robert P. Kimberly[8], Javier Martin[13], Joan T. Merrill[5], Timothy B. Niewold[16], Bernardo A. Pons-Estel[15], Betty P. Tsao[12], Timothy J. Vyse[11], Courtney G. Montgomery[1], John B. Harley[17], R. Hal Scofield[1], Patrick M. Gaffney[1] and Kathy L. Moser[1]. [1]Arthritis and Immunology Research Program, Oklahoma Medical Research Foundation, [2]Arthritis and Immunology Research Program, Oklahoma Medical Research Foundation and Center for Genomics and Oncological Research (GENyO), Granada, Spain, [3]Arthritis and Immunology Research Program, Oklahoma Medical Research Foundation and Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [4]Center for Autoimmune Diseases Research (CREA), Universidad del Rosario, Bogota, Columbia, [5]Clinical Pharmacology, Oklahoma Medical Research Foundation, [6]Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, [7]Department of Internal Medicine, Wake Forest University Health Sciences, Winston-Salem, NC, [8]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [9]Department of Medicine, University of Southern California, Los Angeles, CA, [10]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Korea, [11]Division of Medicine, Imperial College of London, London, UK, [12]Division of Rheumatology, Department of Medicine, University of California Los Angeles, Los Angeles, CA, [13]Instituto de Parasitologia y Biomedicina Lopez-Neyra, Consejo Superior de Investigaciones Cientificas (CSIC), Granada, Spain, [14]Rosalind Russell Medical Research Center for Arthritis, University of California San Francisco, [15]Sanatorio Parque, Rosario, Argentina, [16]Section of Rheumatology and Gwen Knapp Center for Lupus and Immunology Research, University of Chicago, [17]US Department of Veterans Affairs Medical Center, Department of Medicine, University of Oklahoma Health Sciences Center, and Cincinnati Children's Hospital Medical Center

Background: SLE is a chronic, heterogeneous autoimmune disorder characterized by inflammation, loss of tolerance to self-antigens and dysregulated interferon responses. In this study, we sought to replicate a putative association at 11p13 from a genome-wide association (GWA) study not yet exceeding the stringent threshold for genome-wide significance (typically P<5×10−8).

Methods: Genotyping was performed using Illumina iSelect technology. Stringent quality control measures were applied for Hardy-Weinberg proportions, proportion of missing genotypes and missingness between cases and controls. After quality control filtering, 3562 SLE cases and 3491 controls of European ancestry, 1527 cases and 1811 controls of African-American (AA) descent and 1265 cases and 1260 controls of Asian origin were included in the replication analysis. Logistic regression was implemented using PLINK under dominant, recessive and additive genetic models. Covariates for gender and population admixture were included. Stouffer's weighted Ztrend scores were calculated for a meta-analysis between the GWA and replication results.

Results: Our GWA scan identified two SNPs in strong linkage disequilibrium (LD, r2=0.94) located ~74kb telomeric to CD44 showing suggestive evidence of association with SLE in cases of European descent (rs2732552, P=0.004, OR=0.78, 95%CI=0.690–0.9334; rs387619, P=0.003, OR=0.78, 95%CI=0.675–0.9141). We observed independent replication at both rs2732552 (P=9.03×10−8, OR=0.83, 95%CI =0.77–0.88) and rs387619 (P=7.7×10−7, OR=0.83, 95%CI=0.77–0.90) in the European samples with a Pmeta=1.82×10−9 for rs2732552. The AA and Asian SLE cases also

demonstrated association at rs2732552 (P=5×10−3, OR=0.81, 95%CI=0.70–0.94 and P=4.3×10−4, OR=0.80, 95%CI=0.70–0.91, respectively). The Asian SLE cases were associated with rs387619 (P=0.001, OR=0.8 95%CI=0.70–0.91), but not the AA SLE cases, consistent with differences in the haplotype patterns between racial groups. The meta-analysis at rs2732552 for all 4 ethnic groups produced Pmeta=3.00×10–13.

Conclusion: We have established genetic association with SLE to a haplotype near CD44. Imputation and trans-ethnic mapping focus the effect on a ~14kb haplotype in a region of strong regulatory potential that may influence expression of the centromeric gene CD44. This locus contains multiple regulatory sites that could potentially affect expression and functions of CD44, a cell-surface glycoprotein influencing immunologic, inflammatory and oncologic phenotypes. Further functional studies of this complex locus will be required to determine the precise variant(s) influencing SLE risk and to characterize the contribution to disease.

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Study of Systemic Lupus Erythematosus Susceptibility Genes in a Hispanic Population: Identification of Six New Candidate Susceptibility Loci. Elena Sanchez-Rodriguez[1], Kenneth M. Kaufman[3], Jennifer A. Kelly[1], Adrienne H. Williams[11], Paula S. Ramos[11], Astrid Rasmussen[1], Chaim O. Jacob[9], Patrick M. Gaffney[1], Kathy L. Moser[1], Betty P. Tsao[7], Lindsey A. Criswell[8], Robert P. Kimberly[6], Timothy J. Vyse[4], Carl D. Langefeld[11], John B. Harley[10], Bernardo Pons-Estel[5], Marta E. Alarcon-Riquelme[2] and SLEGEN International Consortium. [1]Arthritis and Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Arthritis and Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK and Center for Genomics and Oncological Research (GENyO), Granada, Spain, [3]Arthritis and Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK and US Department of Veterans Affairs Medical Center, Oklahoma City, OK, [4]Imperial College London, Hammersmith Hospital, London, UK, [5]Sanatorio Parque, Rosario, Argentina, [6]University of Alabama, Birmingham, AL, [7]University of California, Los Angeles, CA, [8]University of California, San Francisco, CA, [9]University of Southern California, Los Angeles, CA, [10]US Department of Veterans Affairs Medical Center, Oklahoma City, OK and University of Oklahoma Health Sciences Center, Oklahoma City, OK, [11]Wake Forest University Health Sciences, NC

Background: Genome-wide association studies (GWAS) have proven highly effective for identifying hundreds of associations across numerous complex diseases. Four GWAS for systemic lupus erythematosus (SLE) in European populations and two in Asian populations have identified more than 20 robustly associated susceptibility genes. Differences in the prevalence and severity of SLE between various ethnicities are well documented, showing the need for further genetics studies in non-European populations.

Objective: The aim of this study was to evaluate and replicate all genes previously associated with SLE with p values <0.05 in the SLEGEN1 study through fine mapping in Hispanic SLE cases and controls.

Material and Methods: Here we evaluated 7069 single nucleotide polymorphisms (SNPs) in a set of 1510 Hispanic SLE patients and 825 Hispanic healthy controls. Tests of association were under a logistic regression model (SNPGWA), adjusting for ancestry proportions (ADMIXMAP) as covariates.

Results: We confirmed 17 previously reported loci in European and Asian populations (BLK, IRF5, TNPO3, STAT4, ITGAM, ITGAX, 1q25, TNIP1, MSH5, HLA-DRA, XKR6, CFB, C2, MICB, PRDM1, ATG5 and LYN). In addition, we identified six new susceptibility loci in Hispanic SLE with a P< 0.0001 (C6orf10, MSRA, SLC44A4, ZBTB12, EHMT2 and CLIC1).

Conclusion: While we replicated the majority of the previous GWAS genes, new candidate genes have been discovered. These findings support the need to perform GWAS and additional fine mapping in Hispanics to locate additional susceptibility loci.

1. Harley JB, Alarcon-Riquelme ME, Criswell LA, et al. Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PXK, KIAA1542 and other loci. Nat Genet 2008; 40:204–10.

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Peripheral Blood Expression Signatures Reflect Current Lupus Activity and Likelihood of Future Flare. Carolyn Meyer[4], Jason W. Bauer[4], Thearith Koeuth[4], Joseph Wilson[4], Michelle A. Petri[1], Peter K. Gregersen[3], Timothy W. Behrens[2] and Emily C. Baechler[4]. [1]Timonium, MD, [2]Genentech Inc, South San Francisco, CA, [3]The Feinstein Institute for Medical Research, Manhasset, Manhasset, NY, [4]University of Minnesota Department of Medicine, Minneapolis, MN

Background: Clinical management of patients with systemic lupus erythematosus (SLE) is complicated by the lack of biomarkers for evaluation of current disease activity and prediction of future flares. Type I interferon (IFN)-regulated genes and proteins are promising biomarkers for disease activity in lupus. However, many other pathways are likely to influence clinical activity. Here we used comprehensive gene expression profiling in blood cells to identify molecular signatures associated with current lupus activity and risk for future flare.

Methods: Illumina WG-6 BeadChips were used to compare expression profiles in blood cells of active SLE (SLEDAI ≥6, n=36) vs. inactive SLE (SLEDAI≤2 and physician's global assessment=0, n=96). Genes with t-test p<0.01 and average difference ≥25 were identified as differentially expressed. Hierarchical clustering was used to identify 10 molecular signatures of activity. Three genes from each signature, plus 16 other genes of interest, were then measured by TaqMan low density arrays (LDA) in longitudinally collected blood samples from additional SLE patients (Phase I, 443 visits from 100 patients). A subset of 23 genes selected from the Phase I study were then measured in 2 additional groups (Phase II, 816 visits from 194 patients; Phase III, single visits from 379 patients). GAPDH was used as a housekeeping control in relative quantification. Wilcoxon's rank sum test identified transcripts that changed in paired visits before and during flare (increase in SLEDAI of ≥3 points; n=62 patients), or before and during attenuation of activity (decrease in SLEDAI of ≥3 points; n=73 patients). Logistic regression analysis identified transcripts associated with future flare (≤1 year).

Results: Among the activity signatures were clusters of translation-related genes, genes encoding MHC proteins, erythrocyte-related genes, granulocyte-related genes, and interferon (IFN)-regulated genes. Of the 23 genes selected for further study, 13 transcripts were differentially expressed between active and inactive SLE in both Caucasians (56% of subjects) and non-Caucasians (44%). However, 7 transcripts were markers for activity only in Caucasians, and 3 transcripts were significant only in non-Caucasians. In longitudinal analyses, 3 genes showed significant changes in expression from pre-flare to flare (CD93, ICAM3, and CXCR3), while HINT1 changed significantly with attenuation of activity. In Phase II, multivariate regression analysis of baseline transcript levels in 139 patients with a year of clinical follow-up (41 patients with flare, 98 with no flare), 3 transcripts showed significant ability to predict future flare: PECAM1 (p=0.0008), MX1 (p=0.01), and GPR183 (0.03) (model p<0.0001). We then tested the same genes in the Phase III validation samples. While GPR183 was not a significant predictor of flare in the Phase III data, both MX1 (p=0.001) and PECAM1 (p=0.07) were significant (model p=0.0008).

Conclusions: These results suggest that gene expression profiles in peripheral blood reflect changes in lupus disease activity and may have utility in predicting future lupus flares.

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The NALP3 Inflammasome Is Activated by Sodium Overload and Water Influx in Gouty Arthritis. Christine Schorn[1], Benjamin Frey[2], Christina Janko[1], Georg Schett[3] and Martin Herrmann[1]. [1]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]Department of Radiation Oncology, Friedrich-Alexander University of Erlangen-Nuremberg, Erlangen, Germany, [3]Friedrich Alexander Univ, Erlangen, Germany

Background: One of the endogenous danger molecules of dying cells generated during apoptosis is monosodium urate (MSU). Precipitated MSU crystals in tissues and joints induce an inflammatory process with IL-1β induction after NALP3 inflammasome activation resulting in gouty arthritis. However, the exact mechanism of NALP3 activation is still elusive.

Purpose: Identification of the mechanism of NALP3 inflammasome dependent IL-1β production induced by MSU crystals.

Methods: The uptake of MSU was analysed by time lapse microscopy and cytofluorometry. The plasma membrane integrity after ingestion of MSU was investigated by propidium iodide staining. Via REM-EDX the morphological and chemical structure of urate crystals was identified. The relative intracellular sodium concentration was analysed by Sodium Green fluorescence. The human IL-1β induction in presence of inhibitors of lysosomal acidification and of aquaporins in culture supernatants was quantified by simplex bead technology. Additionally, in an *in vivo* mice experiment animals were treated i.p. with chloroquine following injection of MSU in generated air pouches. The IL-1β production in the pouch fluid was quantified by ELISA.

Results: Blood borne phagocytes ingest MSU crystals and substantially increase their side scatter (SSc) reflecting increased "granularity". After the uptake of the crystals the cells swell shown by augmented forward scatter (FSc) and time lapse microscopy. Most of the phagocytes show an intact plasma membrane after ingestion of crystals. The treatment of phagocytes with MSU results in an induction of IL-1β production. Needle-shaped MSU crystals release sodium after treatment with acidic milieu and switch into barrel-shaped crystals. In swollen cells the intracellular sodium concentration of phagocytes after the uptake of MSU displays a markedly increased intracellular sodium concentration. Furthermore, the inhibition of lysosomal acidification and of aquaporins results in reduction of IL-1β production in *in vitro* and *in vivo*.

Conclusion(s): We suggest a novel model of NALP3 inflammasome activation after phagocytosis of MSU crystals: the phagocytes ingest crystals into endosomes resulting in fusion with acidic lysosomes. That induces a massive release of sodium from the MSU crystal and enhances the intracellular osmolarity. The hyperosmolarity of the cell is compensated by passive water influx through aquaporins following cell swelling. The latter reduces the intracellular potassium concentration below the threshold of NALP3 inflammasome activation. Finally, the decreased IL-1β production by treatment with inhibitors of lysosomal acidification or inhibitors of aquaporins supports our new model of inflammasome activation by MSU.

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Octacalcium Phosphate (OCP) Crystals Induce Synovial Inflammation and Cartilage. Nathalie Busso[1], Véronique Chobaz[3], Nathaliane Bagnoud[3], Peter Van Lent[5], Christelle Nguyen[4], Frédéric Lioté[4], Alexander So[2] and Hang-Korng Ea[4]. [1]Department of Rheumatology, DAL CHUV, Lausanne, Switzerland, [2]Department of Rheumatology, DAL, CHUV, Lausanne, Switzerland, [3]Department of Rheumatology, DAL, CHUV, Lausanne, Switzerland, [4]INSERM U606, Hospital Lariboisière, University Paris VII, Paris, France, [5]Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Introduction: The presence of intra-articular basic calcium phosphate (BCP) crystals, including OCP, carbonated-apatite, hydroxyapatite and tricalcium phosphate crystals, is associated with severe osteoarthritis and destructive arthropathies such as Milwaukee shoulder. Although BCP crystals displayed, in vitro, mitogenic, anabolic and catabolic responses, their intra-articular effect was never assessed.

Objective: To determine the effects of OCP crystals in joints in vivo.

Methods: OCP crystals (200 ug in 20 μl PBS) were injected into the right knee joint (the contra-lateral knee joint injected with 20 ul of PBS serving as a control) of wild-type mice treated or not by the IL1R antagonist Anakinra or mice deficient for the inflammasome proteins ASC and NALP3. 4 days and 17 days after crystal injection, mice were sacrificed and knee joints dissected. Histological scoring for synovial inflammation and characterisation of macrophages, neutrophils and T cells were performed. Technetium (Tc) uptake was measured at 6h, 1 and 4 days after OCP injection. Cartilage degradation was evaluated by Safranin O staining and VDIPEN immunohistochemistry. Intra-articular localisation of injected OCP crystals was evidenced by Von Kossa staining.

Results: The intra-articular localisation of injected OCP crystals was evidenced by Von Kossa staining performed on non-decalcified samples embedded in methyl-metacrylate. Injection of OCP crystals into knee joints led at day 4 to an inflammatory response with intense macrophage staining and also some neutrophil recruitment in the synovial membrane. This synovitis was not accompanied by increased Tc uptake into the knee joint, Tc uptake being similar in OCP crystal injected knee or control knee at all time points investigated (6h, 1 day, 4 days). The histological modifications persisted over 17 days, with an additional fibrosis evidenced at this later time-point. The OCP crystal-induced synovitis was totally IL-1α and IL-1 independent as shown by the absence of inhibitory effects of anakinra injected into wild-type mice. Accordingly, OCP crystal-induced synovitis was similar in ASC$-/-$ and NALP3$-/-$ mice as no alterations of inflammation were demonstrated between these mice groups. Concerning cartilage matrix degradation, OCP crystals induced a strong breakdown of proteoglycans 4 and 17 days after injection, as measured by loss of red staining from Safranin O-stained sections of cartilage surfaces. In addition, we also measured advanced cartilage matrix destruction mediated by MMPs, as evidenced by VDIPEN staining of cartilage. OCP-mediated cartilage degradation was similar in all experimental conditions tested (WT+Anakinra, or ASC or NALP3 deficient mice).

Conclusion: These data indicate in vivo that the intra-articular presence of OCP crystals is associated with cartilage destruction along with synovial inflammation. This is an interesting and new model of destructive arthropathy related to BCP crystals which will allow to assess new therapies in this disease.

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Quantitative Documentation of Tophus Volume Change Using Dual Energy Computed Tomography Scans. Mohammed Abufayyah[3], Savvas Nicolaou[3], Arash Eftekhari[3], Graham Reid[3], Kamran Shojania[2], Steven Co[3] and Hyon K. Choi[1]. [1]Boston University School of Medicine, Vancouver, BC, Canada, [2]Univ of British Columbia, Vancouver, BC, Canada, [3]University of British Columbia, Vancouver, BC, Canada

Objectives: Dual Energy Computed Tomography (DECT) scans produce obvious color displays for urate deposits and allow quantitative volumetric measurement of urate deposits in the articular and extra-articular structures. This report describes our recent experience on the potential utility of DECT scans to document changes in tophus volume in patients with tophaceous gout receiving urate lowering therapy.

Methods: This study included 12 consecutive patients with tophaceous gout who received urate-lowering therapy agents at our rheumatology clinic and underwent initial and follow-up DECT scans on at least one of the following four peripheral articular regions - elbows, wrists/hands, knees, and ankles/feet. The average interval between the two scans was 19 months (range, 11 – 29 months). Using a computer automated procedure to measure the apparent color-coded information of the urate deposits on DECT scans, we measured volumes of uric acid deposition in cm^3 in initial and follow-up scans. The Wilcoxon rank-sum test was used to compare changes in tophus volume.

Results: All 12 patients (mean age, 67 yrs) with tophaceous gout showed color-coded urate deposits. Ten patients showed clinical improvement due to urate lowering therapy, with lowering serum urate levels (mean follow-up level, 5.9mg/dl) and lower frequency of gout attacks (mean, 1.4/yr), whereas two patients showed clinical deterioration during the follow-up (mean serum uric acid levels=9.1 mg/dl and mean gout attacks 7.5/year). All ten responders showed reduction in tophus volume with a median reduction of 64% (p =

0.002) (See Table and Figure below). Total volumes from 10 patients reduced from 322.1 cm^3 to 107.35 cm^3 (67% reduction). Improvement of individual articular regions in these 10 patients ranged from 41% to 83% (all p-values <0.05). In contrast, the two non-responders showed 36% increase in total tophus volume (total volumes from 157.74 cm^3 to 246.19 cm^3) with similarly increasing volumes in individual articular regions (range, 31% to 38% increase).

Table. Changes in DECT Urate Volume after Urate-Lowering Therapies among Ten Responders*

		Regions of Urate Deposition				
No	Age/Sex	Hands & Wrists	Elbows	Knees	Feet & Ankies	Total Volume (Reduction %)
		Initial Scan → Follow-Up Scan (Volume by DECT, cm^3)				
1	63/M	2.70→0.12	0.05→0	33.37→29.31	3.48→2.69	39.6→32.12 (18%)
2	81/M	2.45→0.33	0.41→0.41	8.44→5.72	12.67→1.93	23.97→8.39 (65%)
3	64/M	0.67→0.1	0.22→0.11	3.3→0.37	0.42→0.09	4.61→0.67 (86%)
4	72/M	0.57→0.24	0.27→0.23	0→0	20.1→6.87	20.94→7.34 (65%)
5	75/M	38.37→6.25	18.58→10.37	57.66→15.29	80.96→14.14	195.57→46.05 (77%)
6	39/M	1.75→0.82	0.37→0.31	6.38→4.19	NA	8.5→5.32 (37%)
7	72/M	1.51→0.22	NA	2.44→1.34	6.91→3.03	9.35→4.37 (53%)
8	84/M	0.02→0.01	0.67→0.57	NA	NA	0.69→0.58 (16%)
9	64/M	NA	NA	0.92→0.35	NA	0.92→0.35 (62%)
10	56/M	NA	NA	17.95→2.16	NA	17.95→2.16 (88%)
Total		48.04→8.09	20.57→12	130.46→58.73	124.54→28.75	322.10→107.35 (67%)
P-values		0.008	0.03	0.008	0.03	0.002

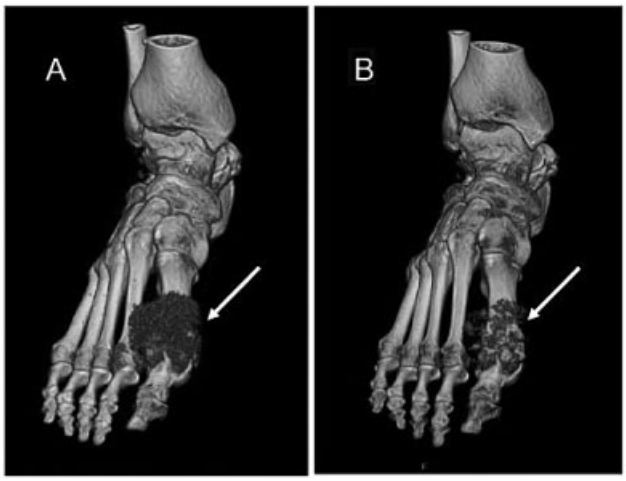

Figure. A. The initial 30-DECT scan image of patient #4 (see Table) showing extensive urate deposits at the first metacarpophalangeal joint. **B.** The follow-up scan showing reduced MSU deposits on after urate-lowering therapy (Arrows denote tophi that appear in red in color display and appear in gray in black/white display).

Conclusion: This study provides a proof of concept for the ability of DECT scan as a potentially sensitive, quantitative imaging tool in assessing urate volume changes in patients with tophaceous gout. These data provide support for further prospective studies to examine the utility of DECT as a reliable imaging tool in following the response to urate-lowering therapy, through measurement of individual tophus volumes and total tophus burden in clinical care and trials.

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Lead and Gout—Going, Going . . . Not Gone! Eswar Krishnan[2], Bharathi Lingala[3], James F. Fries[1] and Vivek Bhalla[3]. [1]Stanford Univ Medical Ctr, Palo Alto, CA, [2]Stanford University, Palo Alto, CA, [3]Stanford University

Background: Saturnine gout, which characteristically follows the onset of chronic kidney disease and hyperuricemia is associated with whole blood lead levels>80microgram (mcg)/dL, and has become rare over time. A whole blood lead level (BLL) ≤25 mcg/dL in adults or ≤10 mcg/dl for children has been considered "not elevated" by several authorities including the Centers for Disease Control. However, it is not known whether such "non-elevated" BLL can still cause hyperuricemia and gout.

Methods: We analyzed data BLL from the NHANES 2005–2007, a series of nationally representative surveys of the US population. We correlated BLL with serum uric acid (SUA) concentration and gout using appropriate sampling weights (SURVEYREG; SAS®). Participants with renal dysfunction were excluded. Geometric means were used to assess BLL due to skewed distribution. Gout was defined as self-reported physician diagnosis and/or use of gout medications (allopurinol and colchicine). Hyperuricemia was defined as SUA≥7.0 mg/dl for men and ≥6.0 mg/dl for women.

Results: Prevalence of gout was 8-fold higher in the highest quartile of blood lead level compared to the lowest.The mean concentration of SUA was 5-fold higher with the highest quartile of lead (3.06 vs 0.57 mcg/dL $p<0.001$). After adjusting for the effects of age, gender, BMI, and ethnicity (variables that emerged statistically significant in bivariate regressions), the highest quartile of lead was associated with a ~2 fold increase in risk for hyperuricemia and gout.

Conclusions: In the era of decreased overt lead intoxication, "non-elevated" BLL remains a significant risk factor for hyperuricemia and gout. Further studies are needed to determine the utility of BLL for evaluating gout in clinical settings.

Table 1.

		Quartile 1	Quartile 2	Quartile 3	Quartile 4
Blood lead level (mcg/dL)	Range	<0.79	0.8–1.26	1.27–2.03	2.04–55.20
	Geometric Mean	0.57 (0.56–.58)	1.01 (1–1.01)	1.59 (1.58–1.6)	3.06 (3.00–3.11)
Hyperuricemia (serum uric acid concentration >7.0 mg/dL)	Mean serum uric acid concentration (mg/dL)	4.89 (4.83–4.95)	5.28 (5.22–5.33)	5.55 (5.48–5.62)	5.77 (5.69–5.85)
	Prevalence (%)	11 (9.54–13.07)	16.47 (14.97–7.97)	19.94 (18.1–21.79)	23.83 (21.13–26.54)
	Results of regression analyses for risk factors for hyperuricemia				
	Bivariate odds ratio	Referent	1.55 (1.27, 1.89)	1.95 (1.61, 2.37)	2.45 (1.95, 3.09)
	Multivariable adjusted	Referent	1.27 (1.02–1.59)	1.55 (1.26–1.89)	1.94 (1.42–2.65)
Gout	Prevalence (%)	0.51 (0.14–0.89)	0.98 (0.43–1.53)	2.98 (2.29–3.66)	4.28 (3.42–5.14)
	Results of regression analyses				
	Bivariate odds ratio	Referent	1.93 (0.70–0.29)	5.94 (2.65–13.33)	8.66 (4.29–17.49)
	Multivariable adjusted odds ratio	Referent	0.94 (0.34–2.60)	1.97 (0.84–4.61)	2.24 (1.03–4.86)

Disclosure: E. Krishnan: Ardea, 2, Savient Pharmaceuticals, 1, Takeda Pharmaceuticals North America, 5; **B. Lingala:** None; **J. F. Fries:** None; **V. Bhalla:** None.

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Increasing Gout Prevalence in the US over the Last Two Decades: The National Health and Nutrition Examination Survey (NHANES). Yanyan Zhu[1], Bhavik Pandya[2] and Hyon Choi[1]. [1]Boston University of School of Medicine, Boston, MA, [2]Takeda Pharmaceuticals International, Inc, Deerfield, IL

Objective: The prevalence of gout in the US more than doubled between the 1960s and 1990s, but it is unknown whether the increasing trend continued over the past 2 decades. To address this issue, we compared the prevalence of gout between National Health and Nutrition Examination Survey (NHANES) III (1988–1994) and NHANES 2007–2008. We also compared the prevalence of hyperuricemia and mean serum urate (sUA) levels between the same time periods.

Methods: Using data from 5,707 participants (2,797 men and 2,910 women) aged 20 years and older in NHANES 2007–2008, we estimated overall, gender-specific, and age-specific prevalence of gout and compared it with data from 18,825 participants (8,816 men and 10,009 women) aged 20 years and older in NHANES III (1988–1994). Using the same data, we compared sUA levels between NHANES III and NHANES 2007–2008. The NHANES definition of hyperuricemia was sUA level >7.0 mg/dL in men and >5.7 mg/dL in women. During the NHANES survey, all participants were asked about a history of health-professional–diagnosed gout.

Results: The overall prevalence of gout among US adults was 3.9% (8.3 million adults) in 2007–2008 (Table). This gout prevalence was significantly higher than that in NHANES III (2.7%), with a difference of 1.2% (95% confidence interval [CI], 0.6 to 1.9). The difference was primarily due to increased prevalence among men and the elderly. Correspondingly, the

prevalence of hyperuricemia in 2007–2008 (21.4%) was significantly higher than that in NHANES III (18.2%), with a difference of 3.2% (95% CI, 1.2% to 5.2%). The mean sUA level significantly increased over the same time period (difference 0.15 mg/dL; 95% CI, 0.07 to 0.24 mg/dL).

Table. Overall, Gender-Specific, and Age-Specific Prevalence of Gout, NHANES III and 2007–2008

	NHANES 2007–2008	NHANES III (1988–1994)	Difference (95% CI)
Overall*	3.9 (3.3 to 4.4)	2.7 (2.3 to 3.0)	**1.2 (0.6 to 1.9)****
Gender			
Male	5.9 (4.7 to 7.1)	3.8 (3.2 to 4.4)	**2.1 (0.8 to 3.4)****
Female	2.0 (1.5 to 2.5)	1.6 (1.3 to 2.0)	0.4 (−0.2 to 0.9)
Age Category (Yrs)			
20–39	0.8 (0.4 to 1.3)	0.7 (0.3 to 1.2)	0.1 (−0.5 to 0.7)
40–59	3.5 (2.5 to 4.5)	2.6 (1.9 to 3.2)	0.9 (−0.2 to 2.1)
60–79	8.5 (6.4 to 10.6)	6.8 (5.8 to 7.9)	1.7 (−0.7 to 4.0)
80+	12.6 (10.1 to 15.1)	5.9 (4.7 to 7.2)	**6.7 (3.9 to 9.4)****

*Adults aged 20 years and above. **$p < 0.05$; bold face type indicates significance.

Conclusions: These findings from 2 separate nationally representative samples of US adults suggest that the prevalence of gout remains substantial and may have increased over the last 2 decades, particularly among men and the elderly. Correspondingly, the prevalence of hyperuricemia increased during the same period.

Disclosure: Y. Zhu: None; **B. Pandya:** Takeda Pharmaceuticals International, Inc., 3; **H. Choi:** Takeda Pharmaceuticals International, Inc., 5.

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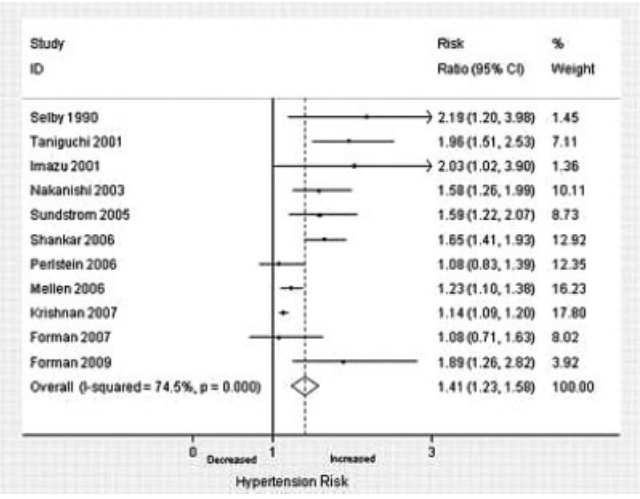
Independent Impact of Hyperuricemia on the Future Risk of Hypertension: A Systematic Review and Meta-Analysis. Peter C. Grayson[1], Seo Young Kim[3], Michael P. LaValley[2] and Hyon K. Choi[4]. [1]Boston University School of Medicine, [2]Boston University School of Public Health, Boston, MA, [3]Brigham & Women's Hospital, Boston, MA, [4]Univ of British Columbia, Vancouver, BC, Canada

Purpose: A novel rodent model and a recent randomized trial of hyperuricemic adolescents with hypertension suggest a pathogenetic role of uric acid in hypertension, but it remains unknown whether these findings apply to adult populations where the larger disease burden exists. We conducted a systematic review and meta-analysis to determine if hyperuricemia was associated with incident hypertension, particularly in demographic subgroups.

Methods: We searched major electronic databases using Medical Subject Headings and keywords without language restrictions (through April 2010). Studies with data on incident hypertension related to serum uric acid levels were eligible for inclusion. We only included (1) prospective cohort studies without age restrictions; (2) at least 1 year of follow-up; (3) sample sizes of at least 100 subjects; and (4) inception cohorts free of hypertension. Hyperuricemia was analyzed both as a categorical and continuous variable, and pooled estimates of both unadjusted and adjusted risk ratios (RRs) for incident hypertension were calculated using a random-effects model. The I^2 - value was calculated to evaluate between-study heterogeneity. We analyzed age, gender, and race subgroups and performed meta-regression to explore any detected heterogeneity.



Results: A total of 18 prospective cohort studies representing data from 55,607 participants and 13,025 incident hypertension cases were included. Hyperuricemia was associated with an increased risk of incident hypertension (unadjusted risk ratio (RR) 1.81, 95% confidence interval (CI): 1.55–2.07). When using adjusted values, the pooled RR was 1.41 (95% CI: 1.23–1.58) and there was high heterogeneity among included studies ($I^2 = 0.75$, $p<0.01$).

For a 1 mg/dl increase in uric acid level, the pooled adjusted RR for incident hypertension was 1.13 (95% CI, 1.06–1.20). These RRs were significantly larger in younger study populations ($p=0.02$) and tended to be larger in women ($p=0.06$). Two studies suggested that the RR may also be larger among black individuals. Furthermore, later publication year and US-based studies were significantly associated with lower RR estimates (p-values <0.02).

Conclusion: Hyperuricemia is associated with an increased risk for incident hypertension, independent of traditional hypertension risk factors. Risk for future hypertension appears more pronounced in hyperuricemic younger individuals and women and appears diminished in US-based studies and studies conducted more recently.

Disclosure: P. C. Grayson: None; **S. Y. Kim:** None; **M. P. LaValley:** None; **H. K. Choi:** None.

ACR Concurrent Abstract Sessions
Osteoporosis and Metabolic Bone Disease: Clinical Aspects and Pathogensis
Wednesday, November 10, 2010, 4:30 PM–6:00 PM

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Effectiveness of Zoledronic Acid in the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis in Men and Premenopausal Women. K. Saag[5], C. Roux[2], J.-P. Devogelaer[3], C.-S. Lau[6], J.-Y. Reginster[7], C. Bucci-Rechtweg[1], G. Su[1], P. N. Sambrook[8] and D. M. Reid[4]. [1]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [2]Paris-Descartes University, Paris, France, [3]Universite Catholique de Louvain, Brussels, Belgium, [4]University of Aberdeen, Aberdeen, UK, [5]University of Alabama at Birmingham, Birmingham, AL, [6]University of Dundee, Dundee, UK, [7]University of Liege, Liege, Belgium, [8]University of Sydney, Sydney, NSW, Australia

Background: Bisphosphonates are effective in increasing bone mineral density (BMD) and reducing vertebral fracture risk in patients beginning or continuing glucocorticoid (GC) treatment. However, there are limited data available on the effect of bisphosphonates in men and premenopausal women receiving GC therapy. We studied 265 men, (mean age 56.4 years, mean femoral neck BMD T-score −0.8) and 195 premenopausal women (mean age 38.1 years, mean femoral neck BMD T-score −0.7) among patients enrolled in two arms of a double-blind, double dummy, 1-year study comparing the effects of zoledronic acid (ZOL) *vs.* risedronate (RIS) in patients either commencing GC treatment at a dose of at least 7.5 mg/day of prednisone or equivalent (prevention arm) or continuing long-term treatment of GC at that dose (treatment arm).

Methods: Patients received either ZOL 5 mg infusion at study entry or RIS 5 mg daily, along with calcium and vitamin D supplementation (1000 mg and 400–1200 IU, respectively). The primary endpoint was difference in BMD at the lumbar spine at 12 months. Secondary endpoints included changes in BMD at other sites (total hip and femoral neck), changes in bone turnover markers (BTM) (β-C-terminal telopeptides of type 1 collagen [β-CTx] and procollagen type 1 aminoterminal propeptide [PINP]), and overall safety.

Results: The percentage change in BMD is listed in Table.

Table. Between-treatment comparison of percentage change from baseline in bone mineral density (BMD) for men and premenopausal women at 12 months (modified ITT population)

Men

	Prevention arm				Treatment arm			
Variable	Zoledronic LS Mean (SE)	Risedronate LS Mean (SE)	Treatment difference (CI)	*p*-value	Zoledronic LS Mean (SE)	Risedronate LS Mean (SE)	Treatment difference [CI]	*p*-value
Lumbar spine BMD	2.46 (0.64) n = 38	−0.24 (0.90) n = 40	2.70 (0.99, 4.42)	0.0024	4.69 (0.52) n = 75	3.27 (0.52) n = 77	1.42 (0.20, 2.64)	0.0232
Total Hip BMD	1.10 (0.64) n = 35	−0.39 (0.66) n = 40	1.49 (0.21, 2.77)	0.0230	1.82 (0.39) n = 74	0.18 (0.38) n = 75	1.60 (0.75, 2.54)	0.0004
Femoral neck BMD	1.37 (0.78) n = 35	−0.02 (0.81) n = 40	1.38 (−0.18, 2.95)	0.0819	1.31 (0.59) n = 74	0.38 (0.58) n = 75	0.94 (−0.42, 2.30)	0.1754

Premenopausal women

	Prevention arm				Treatment arm			
Variable	Zoledronic LS Mean (SE)	Risedronate LS Mean (SE)	Treatment difference (CI)	*p*-value	Zoledronic LS Mean (SE)	Risedronate LS Mean (SE)	Treatment difference (CI)	*p*-value
Lumbar spine BMD	1.76 (0.75) n = 28	0.72 (0.72) n = 29	1.04 (−0.85, 2.92)	0.2746	3.12 (0.56) n = 63	1.74 (0.54) n = 60	1.38 (−0.08, 2.85)	0.0636
Total Hip BMD	0.93 (0.57) n = 28	−0.52 (0.55) n = 29	1.45 (0.01, 2.88)	0.0487	1.41 (0.44) n = 62	0.07 (0.44) n = 57	1.34 (0.17, 2.51)	0.0249
Femoral neck BMD	0.86 (0.72) n = 28	−0.34 (0.70) n = 29	1.20 (−0.62, 3.02)	0.1901	0.96 (0.50) n = 62	−0.40 (0.49) n = 57	1.36 (0.06, 2.67)	0.0411

In the treatment subgroup, ZOL demonstrated a significantly greater reduction in serum β-CTx and PINP relative to RIS at all time-points for men and premenopausal women. In the prevention subgroup, ZOL demonstrated a significantly greater reduction in β-CTx at all time-points for men and premenopausal women, and in PINP at Month 3 ($p=0.0297$) for men and at Month 3 ($p=0.0207$) and Month 12 ($p=0.0160$) for premenopausal women. Both treatments were well tolerated in men and premenopausal women, albeit with a higher incidence of influenza-like illness and pyrexia events post-infusion with ZOL.

Conclusion: In men receiving GC therapy, once-yearly ZOL infusion preserves or increases lumbar spine and total hip BMD within 1 year to a greater extent than daily oral RIS and shows a similar trend for femoral neck BMD compared with RIS in both treatment and prevention arms. In premenopausal women receiving GC therapy, once yearly ZOL or daily oral RIS preserves or increases BMD within 1 year with a significant increase in total hip BMD for ZOL compared with RIS in both treatment and prevention arms.

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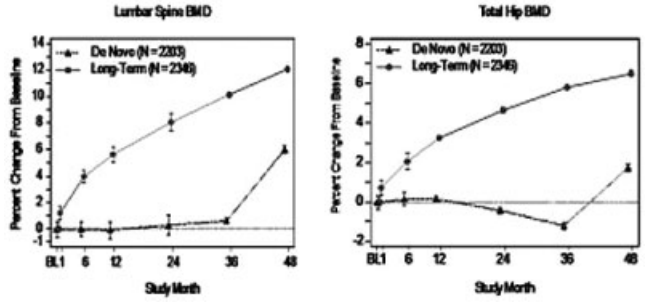
Long-Term Denosumab Treatment of Postmenopausal Women with Osteoporosis: Results from the First Year Extension Study of the FREEDOM Trial.

Roland Chapurlat[6], Socrates Papapoulos[11], Henry G. Bone[12], Maria L. Brandi[16], Jacques Brown[10], Edward Czerwinski[9], Nadia S. Daizadeh[1], Andreas Grauer[1], Christine Haller[2], Marc-Antoine Krieg[4], Cesar Libanati[3], Zulema Man[5], Dan Mellstrom[13], Sebastiao Radominski[7], Jean-Yves Reginster[17], Heinrich Resch[15], Jose A. Roman Ivorra[8] and Steven R. Cummings[14]. [1]Amgen Inc, Thousand Oaks, CA, [2]Amgen Inc., San Francisco, CA, [3]Amgen Inc., Thousand Oaks, CA, [4]Centre Hospitalier Universitaire Vaudois, Lusanne, Switzerland, [5]Centro TIEMPO, Buenos Aires, Argentina, [6]Hopital E. Herriot, Lyon, France, [7]Hospital de Clinicas da Universidade Federal do Parana, Curitiba, Brazil, [8]Jefe Servicio Reumatologia, Valencia, Spain, [9]Krakowskie Centrum Medyczne, Krakow, Poland, [10]Laval University Department of Medicine, Quebec, QC, Canada, [11]Leiden University Medical Center, Leiden, The Netherlands, [12]Michigan Bone and Mineral Clinic, PC, Detroit, MI, [13]Osteoporosis Clinic, Center for Bone Research at the Sahlgrenska, Goteborg, Sweden, [14]SF Coordinating Center, San Francisco, CA, [15]St. Vincent Hospital Medical University, Vienna, Austria, [16]University of Florence, Florence, Italy, [17]University of Leige, Leige, Belgium

Background: FREEDOM was the pivotal 3-year Phase 3 study to establish the efficacy and safety of denosumab for the treatment of osteoporosis in postmenopausal women. The open-label extension of FREEDOM will evaluate the long-term (up to 10 years) efficacy and safety of denosumab. We report here first year results of this extension study, representing up to 48 continuous months of denosumab exposure.

Methods: Subjects enrolled in the extension study previously completed the FREEDOM trial. All subjects received subcutaneous denosumab (60 mg) injection every 6 months during the extension study and continued to take daily calcium (1 g) and vitamin D (≥400 IU) supplements. For those randomized to the denosumab arm in FREEDOM (long-term group), the data reported here reflect a total of up to 8 injections of denosumab. For those previously assigned to placebo (de novo group), the data are from exposure of up to 2 doses of denosumab for 12 months. Changes in bone mineral density (BMD) and bone turnover markers (BTM) over 12 and 48 months are reported for subjects enrolled in the extension. No formal statistical testing was planned for this interim report. *P*-values are descriptive.

Results: A total of 4550 (70.2%) subjects from FREEDOM were enrolled in the extension study: 2343 in the long-term and 2207 in the de novo group. The long-term group had a further 2.0% and 0.8% increase in lumbar spine and total hip BMD, respectively, during the 4th year of denosumab administration ($P<0.0001$ compared to baseline BMD of the extension study; see Figure). The total increase over the 48 months treatment with denosumab in lumbar spine and total hip BMD was 12.1% and a 6.5%, respectively. The de novo group had a 6.0% and 1.7% increase in lumbar spine and total hip BMD, respectively, during their 1st year of treatment with denosumab in the extension study ($P<0.0001$ compared to baseline BMD). The serum C-telopeptide (CTX) reduction profiles after denosumab initiation, and the increase in CTX levels at the end of the dosing period, were similar for the long-term and de novo groups. Adverse events (AEs) were reported by 70.4% and 67.9% of subjects in the long-term and de novo groups, respectively. Serious AEs were reported by 9.8% and 11.2% of subjects in the long-term and de novo group, respectively.



Percentage Change in BMD With Denosumab Treatment for 4 Years (Long-term) or 1 Year (De Novo)

Conclusion: These results suggest that treating postmenopausal women with osteoporosis with denosumab for 48 months continues to significantly reduce bone resorption and further increase BMD. Long-term treatment decreases BTM with a similar pattern and to a similar degree as observed in the first year of treatment.

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IL-3 Inhibits Osteoclast Differentiation by Inducing of ID Expression. Chang Hoon Lee[5], Myeung Su Lee[6], Yun Kyung Hong[3], Jin-Jeong Choi[2], Min-Ho Whang[4], Han-Bok Kwak[1] and Jae Min Oh[1]. [1]Anatomy, Wonkwang University, Iksan, Korea, Republic of, [2]Rheumatology, Cha University Hospital, Sungnam, [3]Rheumatology, Chonbuk University Hospital, [4]Rheumatology, Presbyterian Medical Center, Chonju, [5]Rheumatology, Wonkwang University Hospital, Iksan, Jeollabukdo, Republic of Korea, [6]Rheumatology, Wonkwang University Hospital

Purpose: Interleukin-3 (IL-3) is produced in various pathological conditions and is thought to induce diseases, but it is unclear about its function under normal and disease conditions associated with bone homeostasis. Here we examined the effect of IL-3 on osteoclast differentiation from mouse and human bone marrow macrophages (BMMs).

Methods: Human bone marrow cells were obtained from iliac crest marrow aspirates from healthy donors and multiple myeloma patients. BMMs were used as precursors for RANKL-induced osteoclast differentiation. RT-PCR and Western blotting were used to detect mRNA and protein expression.

Results: Although IL-3 can induce osteoclast differentiation from multiple myeloma bone marrow cells, IL-3 greatly inhibited osteoclast differentiation of mouse BMMs and human BMMs obtained from healthy donors. These effects of IL-3 were determined by treating at early time points (days 0 and 1). IL-3 inhibited the expression of c-Fos and NFATc1, the master transcription factor for osteoclast differentiation, as well as osteoclast-specific genes in BMMs treated with RANKL, but IL-3-mediated inhibition of osteoclast differentiation was partially reversed by ectopic expression of c-Fos and NFATc1. Importantly, IL-3 induced inhibitor of DNA binding/differentiation (Id) 1, Id2, and Id3 expression and Id2 was sustained during course of osteoclast differentiation. Ectopic expression of NFATc1 in Id2-deficient BMMs completely reversed the negative effect of IL-3 on osteoclast differentiation.

Conclusion: We provide evidence that IL-3 inhibited osteoclast differentiation of hBMMs and mBMMs partly by inhibiting c-Fos and NFATc1 expression. Also, IL-3 can induce Ids expressions, which are involved in the inhibitory effect exerted by IL-3.

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Raloxifene for Prevention of Glucocorticoid-Induced Bone Loss: A 12-Month Randomized Double-Placebo-Controlled Trial. Chi Chiu Mok, Chi Hung To, Ling Yin Ho, Ka Lung Yu and Kwok Man Ma. Tuen Mun Hospital

Objectives: To study the efficacy of raloxifene in preventing bone loss in women receiving long-term glucocorticoids.

Methods: Postmenopausal women receiving glucocorticoids were randomized in a double-blind manner to receive either raloxifene (60mg/day) or placebo (one tablet/day) on top of calcium (1000mg/day) and calcitriol (0.25ug/day). Bone mineral density (BMD) and bone turnover markers (urine DPD/Cr, serum osteocalcin, P1NP and CTX) were assessed at baseline, month 6 and 12. New radiological fracture of the spine was assessed at month 12.

Results: 114 patients were recruited (age 55.3±7.7 years; 29% patients naive to calcium and 75% patients naive to calcitriol). The underlying medical diseases were: SLE(51%), rheumatoid arthritis(33%), inflammatory myopathies(4%) and systemic vasculitides(4%). The duration and dose of prednisolone received by the participants was 62.2±64 months and 6.7±5.9mg/day, respectively. The mean duration of menopause was 8.5±7.7 years and the body mass index (BMI) was 23.7±3.5kg/m^2. Pre-existing vertebral fracture was present in 6(5%) patients. Fifty-seven patients were assigned to receive raloxifene whereas the other 57 patients were assigned to receive placebo treatment. Demographic data, osteoporotic risk factors, and BMD at various sites were similar between the two groups of patients. At month 12, a significant gain in the lumbar spine (+1.3±0.4%;p=0.004) and total hip BMD (+1.0±0.4%;p=0.01) was observed in raloxifene-treated patients (N=57). Conversely, BMD of the spine (−0.9±0.4%;p=0.045) and hip (−0.8±0.3%;p=0.01) dropped significantly in the placebo group (N=57). Three new fractures developed exclusively in the placebo-treated patients. All the bone formation and resorption markers dropped significantly in the raloxifene group but did not change significantly in placebo-treated patients. Leg cramps were numerically more frequent in the raloxifene group but none of the participants developed arterial or venous thromboembolism. Other adverse events were not significantly different between the two treatment groups. Nine patients withdrew from the study because non-compliance to treatment (N=5) and adverse events (skin rash N=2, leg cramp N=1 and generalized aching N=1).

Conclusions: In postmenopausal women receiving long-term glucocorticoids, raloxifene is well tolerated and significantly increases spinal and hip BMD after 12 months' treatment.

Disclosure: C. C. Mok: None; **C. H. To:** None; **L. Y. Ho:** None; **K. L. Yu:** None; **K. M. Ma:** None.

2160

Unsuppressed Parathyroid Hormone in Patients with Autoimmune Rheumatic Diseases: Implications for Vitamin D Supplementation. Pier Paolo Sainaghi[1], Mattia Bellan[2], Giuseppina Antonini[3], Giorgio Bellomo[3] and Mario Pirisi[1]. [1]Immuno-Rheumatology Outpatient Unit, DMCS, "A. Avogadro" University and IRCAD (Interdisciplinary Reseach Center of Autoimmune Diseases), Novara, Novara, Italy, [2]Immuno-Rheumatology Outpatient Unit, DMCS, "A. Avogadro" University, Novara, Italy, [3]Laboratory of Chemistry and Clinical Research, DSM, "A. Avogadro" University and "Maggiore della Carità" Hospital, Novara, Italy

Background: Conflicting data have been reported concerning the relationship between vitamin D deficit and autoimmune rheumatic diseases (ARD), but desirable vitamin D concentrations in ARD patients have not been defined taking into consideration calcium homeostasis. In fact, a plasma 25(OH)vitamin D (VITD) concentration should be considered optimal when able to suppress parathyroid hormone (PTH). Therefore, our aim was to verify the hypothesis that ARD patients may be more refractory to PTH suppression by VITD.

Methods: Data from 105 consecutive ARD patients (including rheumatoid arthritis, polymyalgia rheumatica, spondyloarthritis and other connective tissue diseases) attending a tertiary level immuno-rheumatology clinic, and 1542 consecutive adult patients tested at our central laboratory from 2008 to 2010 (controls) were collected. After exclusion of patients with renal failure, known primary hyperparathyroidism, and hypercalcemia (N.=522), plasma VITD, PTH, calcium and phosphorus concentrations were compared between these two groups.

Results: Plasma VITD concentrations were <25 nmol/L in 257 patients (severe deficit, 22.8%), ≥25 but <75 in 661 (mild deficit, 58.8%) and ≥75 in 207 (normal, 18.4%). Despite similar mean age, plasma VITD, calcium and phosphate values (p=n.s.), PTH was higher in ARD (74.8±25.5 pg/ml) than in controls (65.1±24.2, p<0.001). Moreover, mean PTH was always higher in ARD vs controls in all above defined VITD categories.

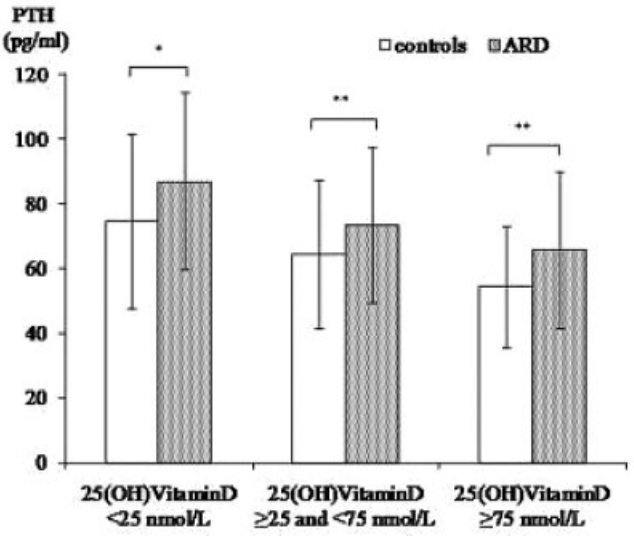


Figure 1.

As expected, the proportion of patients with increased PTH (≥73 pg/ml) was inversely related to VITD; suppressed PTH was observed in 96.9 % [95.8–98.0; 95%CI] of controls with VITD ≥75 nmol/L. However, PTH was increased more frequently in ARD vs controls.

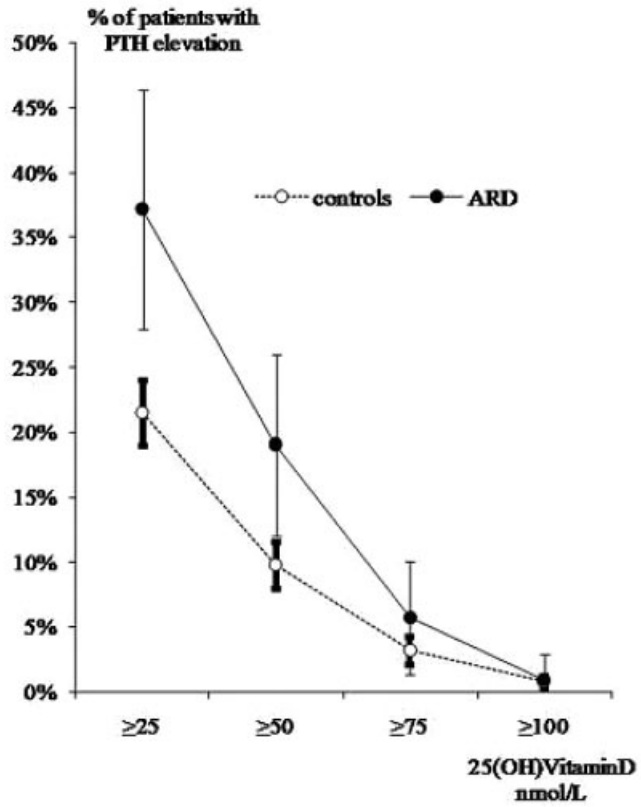


Figure 2.

At multivariate analysis, low VITD values (F: 59.3, $p<0.001$) and the presence of an ARD (14.4, $p<0.0003$) were independent predictors for an increased PTH.

Conclusions: Patients with ARD have an impaired vitamin D metabolism evidenced by an increased PTH concentration for any plasma VITD range. Therefore, vitamin D supplementation to ARD patients should be targeted to reach full PTH suppression and not simply to obtain VITD concentrations considered optimal in other categories of patients.

Disclosure: P. P. Sainaghi: None; **M. Bellan:** None; **G. Antonini:** None; **G. Bellomo:** None; **M. Pirisi:** None.

2161

Bone Remodeling in Postmenopausal Women Who Discontinued Denosumab Treatment. Rachel B. Wagman[1], Jaques Brown[4], David W. Dempster[2], Beiying Ding[1], Ricardo Dent[1], Javier San Martin[1], Andreas Grauer[1] and Jose R. Zanchetta[3]. [1]Amgen Inc., Thousand Oaks, CA, [2]Helen Hayes Hospital, West Haverstraw, NY, [3]Instituto de Ivestigaciones Metabolicas, Buenos Aires, Argentina, [4]Laval University Department of Medicine, Quebec, QC, Canada

Background: Denosumab is a fully human monoclonal antibody to RANKL which increases bone mineral density (BMD), reduces bone resorption, and decreases risk for vertebral, nonvertebral, and hip fractures in postmenopausal women with osteoporosis (Cummings et al. NEJM 2009). Transiliac crest bone biopsies from subjects with osteoporosis treated with denosumab for 1 to 3 years demonstrate low bone remodeling. The effects of denosumab on biochemical bone-turnover markers (BTM) and BMD are reversible upon treatment discontinuation. However, the effects of denosumab discontinuation on bone histology and histomorphometry are not known. This study was designed to characterize the effects of denosumab therapy discontinuation on variables of bone histology and histomorphometry in postmenopausal women with low bone mass or osteoporosis. We report here interim bone remodeling results from a subset of subjects.

Methods: Subjects included in this study completed all denosumab doses in the phase 3 trial they were previously enrolled in, after which they received not more than 1 month of treatment for their osteoporosis. Transiliac crest bone biopsies were obtained for histology and histomorphometry evaluation ≥ 12 and < 36 months after subjects completed the original trial. Fasting serum samples were collected to assess BTM levels at the time of tetracycline (TC) labeling. This study is ongoing with an expected enrollment of approximately 15 subjects. Data from 5 subjects are available and are reported here.

Results: Mean (SD) age for the 5 subjects at enrollment in the biopsy study was 59.6 (4.3) years. The first set of TC labeling occurred after a mean (SD) of 23.4 (2.7) months from denosumab discontinuation. All biopsies showed normal histology without evidence of pathology. Double TC labels were present in all biopsies, suggesting active remodeling. While osteoclast numbers increased, the other bone remodeling parameters were within the reference range. Both bone resorption and formation markers were similar to the subjects' pretreatment baseline BTM levels.

Conclusions: These data demonstrate that bone remodeling returned to pre-treatment levels when postmenopausal women discontinued denosumab treatment. These results confirm that the effects of denosumab on reduction in bone turnover are reversible when therapy is discontinued.

Disclosure: R. B. Wagman: Amgen Inc., 1, 3; **J. Brown:** Abbott Laboratories, 2, 5, Amgen Inc., 2, 5, 8, Bristol-Myers Squibb, 2, Eli Lilly and Company, 2, 5, 8, Merck Pharmaceuticals, 5, 8, Novartis Pharmaceuticals Corporation, 5, 8, Pfizer Inc, 2, Roche, 2, Warner Chilcott, 5, 8; **D. W. Dempster:** Amgen Inc., 2, 5, 8; **B. Ding:** Amgen Inc., 1, 3; **R. Dent:** Amgen Inc., 1, 3; **J. San Martin:** Amgen Inc., 1, 3; **A. Grauer:** Amgen Inc., 1, 3; **J. R. Zanchetta:** Amgen Inc., 5, Eli Lilly and Company, 5, Merck Pharmaceuticals, 5, Pfizer Inc, 5, Sevier, 5.

ACR Concurrent Abstract Sessions
Rheumatoid Arthritis - Clinical Aspects: RA and Cardiovascular Disease
Wednesday, November 10, 2010, 4:30 PM–6:00 PM

2162

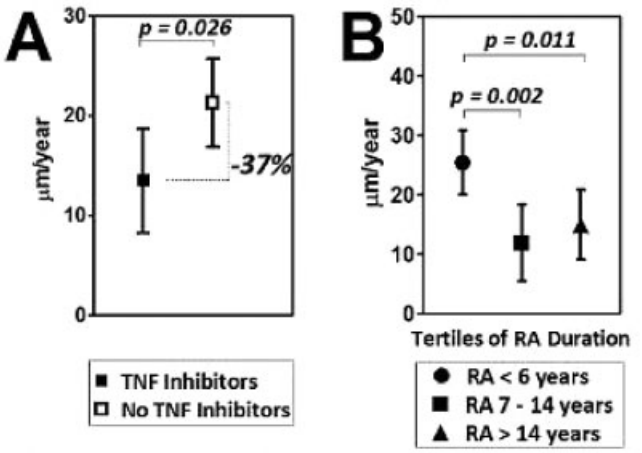
Longitudinal Predictors of Progression of Subclinical Carotid Atherosclerosis in Rheumatoid Arthritis. Jon T. Giles[3], Wendy Post[5], Roger S. Blumenthal[5], Joseph Polak[6], Michelle A. Petri[1], Allan C. Gelber[2], Moyses Szklo[5] and Joan M. Bathon[4]. [1]Timonium, MD, [2]Baltimore, MD, [3]Johns Hopkins Univ, Baltimore, MD, [4]Johns Hopkins University, Baltimore, MD, [5]Johns Hopkins University, [6]Tufts-New England Medical Center

Background: Coronary and extra-coronary atherosclerosis are increased in rheumatoid arthritis (RA) relative to controls; however, few longitudinal studies have explored predictors of change in atherosclerosis in RA patients.

Methods: Men and women with RA enrolled in ESCAPE RA, a cohort study of subclinical cardiovascular (CV) disease in RA, underwent bilateral B-mode ultrasonography of the common (CCA) and internal (ICA) carotid arteries at the first and third study visits, separated by an average of 3.2 ± 0.3 years. Multivariate linear or Poisson regression, as appropriate to the outcome, were used to explore the associations of baseline and cumulative demographic, lifestyle, and RA disease and treatment characteristics with the average yearly change in maximal intima-medial thickness (IMT) of the CCA and ICA, and incident or progressive carotid plaque (defined as newly identified plaque or progression in plaque stenosis). Baseline scans were reanalyzed concurrent with follow-up scans, to control for interpretive drift.

Results: A total of 158 RA patients [36% male; mean baseline age $= 59 \pm 8$ years; median baseline RA duration $= 8.5$ years; median baseline DAS28 $= 3.6$] underwent carotid scanning at both time points. CCA-IMT increased over time in 82% of patients (median yearly increase $= 16$ μm; $p<0.001$) and ICA-IMT increased in 70% of patients (median yearly increase $= 25$ μm; $p<0.001$). After adjusting for demographics, CV risk factors, and baseline IMT, baseline TNF inhibitor use was associated with a 37% lower rate of CCA-IMT progression vs.

non-users (14 vs. 22 μm/year; p=0.026: Figure, Panel A). The adjusted average yearly change in CCA-IMT was significantly higher for patients with earlier RA compared with those with longer duration disease (Figure, Panel B).



Adjusted for age, gender, ethnicity, hypertension, diabetes, hyperlipidemia, exercise, smoking, body surface area, baseline maximum CCA-IMT, RA duration (where appropriate), and TNF inhibitor use (where appropriate).

Figure. Adjusted yearly rate of change in CCA-IMT according to (A) baseline TNF inhibitor use and (B) RA duration.

For ICA-IMT, cumulative prednisone exposure was the only RA feature associated with progression [1.2 μm per year per gram increase in cumulative dose (95% CI 0.1, 2.4)] after adjustment. This rate was significantly lower in patients prescribed statins at baseline. Any plaque was identified in 104 patients (68%), with 13 of these (12%) demonstrating new or progressive plaque during follow-up. After demographic and CV risk factor adjustment, higher average swollen joint count (SJC) and higher average CRP were significantly and independently associated with incident or progressive plaque. Cumulative CRP and SJC were both more strongly associated with plaque progression than cross-sectional levels obtained at the time of scanning. Other RA disease and treatment characteristics were not associated with plaque progression.

Conclusions: These prospective data provide evidence for systemic inflammation and RA disease activity as a contributor to progression of atherosclerosis in RA patients. Further, they suggest that atherosclerosis progression in RA may be modified favorably by TNF inhibitors and detrimentally by glucocorticoids.

Disclosure: J. T. Giles: None; **W. Post:** None; **R. S. Blumenthal:** None; **J. Polak:** None; **M. A. Petri:** None; **A. C. Gelber:** None; **M. Szklo:** None; **J. M. Bathon:** None.

2163

At What Age Is Carotid Ultrasound Most Effective in Predicting Cardiovascular Events and Mortality in Rheumatoid Arthritis? Inmaculada Del Rincon[3], Mrisa Sahai[4], Daniel H. O'Leary[2], Daniel F. Battafarano[1] and Agustin Escalante[3]. [1]Brooke Army Medical Ctr, San Antonio, TX, [2]Tufts School of Medicine, [3]UTHSCSA, San Antonio, TX, [4]UTHSCSA

Introduction: Established cardiovascular (CV) risk factors are limited in their ability to predict CV events and mortality in RA. Carotid ultrasound may improve upon the CV risk factors as a tool to predict CV events in RA. However, because of the strong effect of age on CV disease, the predictive ability of ultrasound may be blunted if it is applied to all age groups. We examined the ability of carotid ultrasound to predict acute coronary syndromes (ACS) and CV mortality in different age groups in an RA cohort.

Patients and Methods: We studied patients with RA who were free of CV disease. We imaged the carotid arteries for plaque and intima-media thickness (IMT) using high-resolution ultrasound and then followed patients prospectively until they either developed an acute coronary syndrome (ACS), died from CV causes, or reached a censoring date. ACS were defined as unstable angina, myocardial infarction, cardiac arrest, or death due to ischemic heart disease. CV death was defined by mention of a CV cause in the death certificate. We used logistic regression to examine the association of carotid ultrasound with ACS or CV death in tertiles of the cohort's age distribution, adjusting for gender, CV risk factors and the erythrocyte sedimentation rate (ESR).

Results: We followed 599 RA patients for 3,085 person-years for ACS, and 6,525 person-years for CV mortality. We observed 66 new ACS, for an incidence of 2.1 per 100 person-years (95% CI 1.7, 2.7) and 120 CV deaths, for a CV mortality rate of 1.8 per 100 person-years (1.5, 2.1). The strength of association between plaque and ACS or CV death varied between cohort's age strata (Table). These findings did not change appreciably with adjustment for gender, CV risk factors or the ESR. Similar results were obtained with the IMT.

		Events		Plaque odds ratio (95% CI)	
Age	Patients	ACS	CV death	For ACS	For CV Death
18 to 53	282	14	8	4.13 (1.72, 9.88)	3.87 (1.32, 11.31)
54 to 64	202	23	28	3.12 (1.02, 9.48)	2.36 (0.91, 6.07)
65 to 91	115	29	84	1.46 (0.38, 5.53)	1.41 (0.44, 4.49)

Conclusion: The ability of carotid ultrasound to predict CV events in RA varies with age. Plaque and IMT are most strongly associated with CV outcomes in younger RA patients. These findings may have implications for the early identification of patients at risk for CV events in RA.

Disclosure: I. Del Rincon: None; **M. Sahai:** None; **D. H. O'Leary:** None; **D. F. Battafarano:** None; **A. Escalante:** None.

2164

Higher Prevalence, Extent and Severity of "Vulnerable" Coronary Plaque in Asymptomatic Patients with Rheumatoid Arthritis (RA). George A. Karpouzas[1], Naser Ahmadi[2], Tae-Young Choi[2], Fereshteh Hajsadeghi[2], Silvia Munoz[2] and Mathew Budoff[2]. [1]Harbor-UCLA, Long Beach, CA, [2]Harbor-UCLA

Background: Higher incidence of myocardial infarctions (MI), sudden cardiac death, and worse survival after MI have all been reported in patients with RA. This risk exceeds traditional risk factors (RF) and insinuates accelerated atherogenesis in RA. We prospectively evaluated the presence, extent, total burden, and differences in the quality of coronary plaque in asymptomatic pts with RA compared to matched controls.

Methods: We report on the first 74 of 150 recruited pts with RA from a single center. Demographic, serologic, metabolic, Disease Activity Score (DAS28-3v-ESR), radiographic parameters and treatments are quarterly recorded. Pts underwent 64+ slice cardiac Computed Tomography Angiography (CTA); this non-invasive modality includes an initial non-contrast phase assessing coronary calcium, followed by a contrast scan that detects plaque with equal accuracy to conventional angiography, and is superior in the assessment of non-calcified, lipid-rich, non-obstructive or "vulnerable" plaque. RA pts were matched for age, gender, hypertension, diabetes, smoking, dyslipidemia and family history with controls undergoing CTA for evaluation of coronary arteriosclerosis. Individual coronary trees were evaluated for plaque volume and composition by standard methods (American Heart Association). Non-parametric tests were used for data analysis; regression models for plaque prevalence ratios (PR) and relative risk for plaque burden in RA vs. controls, adjusted for conventional risk factors were developed.

Results: Asymptomatic RA pts have higher prevalence and more extensive total coronary plaque (table); higher numbers have 2 or 3-vessel disease (p=0.04 for both), and total plaque burden in RA is greater than controls (p=0.01). More importantly, RA pts have higher prevalence, extent and severity of "vulnerable" plaque; 54% of diseased arterial segments in RA pts vs. 21% in controls harbor NC plaque (p=0.0001), and NC plaque burden score is superior in RA (p=0.0001). RA pts have 6-fold the risk and 87% higher burden risk of NC plaque vs. controls adjusted for age, sex and Framingham RF.

Variables	RA=74	Controls=74	p-value
n (%) with plaque	62.2	51.4	0.18
n (%) with Normal atreries	28 (37.8)	36 (48.6)	0.2
1-vessel dz	28 (37.8)	30 (40.5)	0.62
2-vessel dz	14 (18.9)	6 (8.1)	***0.04***
3-vessel dz	4 (5.4)	2 (2.7)	***0.04***
n (%) diseased segments (296)	67 (22.6)	48 (16.2)	0.11
Non-calcified	36 (53.7)	10 (20.8)	***0.0001***
Mixed	15 (22.4)	7 (14.6)	0.06
Calcified	16 (23.9)	31 (64.6)	***0.001***
Total plaque burden score	6.4 ± 4.8	4.3 ± 4.1	***0.01***
Non-calcified	3.2 ± 4.3	1 ± 2.9	***0.0001***
Mixed	1.7 ± 2.9	0.9 ± 2	***0.01***
Calcified	1.5 ± 3.4	2.4 ± 3.3	0.19
Non-calcified	6.06	1 (ref)	***0.0001***
Mixed	2.4	1 (ref)	***0.002***
Calcified	0.38	1 (ref)	***0.009***
Relative Risk-total burden score*	1.38	1 (ref)	***0.02***
Non-calcified	1.87	1 (ref)	***0.001***
Mixed	1.43	1 (ref)	***0.01***
Calcified	0.73	1 (ref)	***0.05***

* Relative risk regression analysis: per standard deviation increase in burden

Conclusion: Asymptomatic RA pts have greater extent, severity and risk of coronary plaque compared to controls matched for all traditional risk factors. More importantly, they have higher prevalence, severity, burden and risk of "vulnerable", rupture-prone plaque that might account for the higher incidence of future MIs.

Disclosure: G. A. Karpouzas: None; **N. Ahmadi:** None; **T.-Y. Choi:** None; **F. Hajsadeghi:** None; **S. Munoz:** None; **M. Budoff:** None.

2165

Anti-b2-Glycoprotein-1 (b2GP1) IgA Ab Are Highly Prevalent and Predict "Vulnerable" Coronary Plaque in Asymptomatic Patients with Rheumatoid Arthritis (RA). George A. Karpouzas[1], Naser Ahmadi[2], Tae-Young Choi[2], Fereshteh Hajsadeghi[2], Silvia Munoz[2] and Mathew Budoff[2]. [1]Harbor-UCLA, Long Beach, CA, [2]Harbor-UCLA

Background: B2GP1 is present in atherosclerotic plaque and b2GP1 IgA Ab have been associated with documented atherosclerosis, including myocardial infarction (MI). RA pts have higher risk of MI; however, the prevalence of b2GP1 IgA Ab in RA and their relevance to plaque characteristics are unknown. We evaluated prospectively the presence of b2GP1 IgA and its associations with coronary plaque prevalence, burden and consistency in asymptomatic pts with RA.

Methods: We report on the first 74 of 150 recruited pts from a single center (table 1). Lupus Anticoagulant (LA), Anticardiolipin (ACL), and b2GP1 IgG, IgM and IgA were assessed by standard methods (DRVVT, Varelisa, and Bindazyme Elisa respectively). Positive (+) tests were confirmed 3 months later. Pts underwent coronary plaque evaluation with 64+ slice cardiac Computed Tomography Angiography (CTA); this non-invasive modality includes an initial non-contrast phase assessing coronary calcium, followed by a contrast scan that detects plaque with equal accuracy to conventional angiography, and is superior in the assessment of non-calcified, lipid-rich, non-obstructive or "vulnerable" plaque. Coronary trees were graded in a standard fashion according to AHA. Non-parametric tests were used for data analysis; linear regressions between disease parameters and plaque, as well as relative risk regression models for plaque burden and consistency were constructed after adjustments for age, sex, classic coronary risk (CRF), RA duration and severity.

Results: B2GP1 IgA was highly prevalent in asymptomatic RA pts, by contrast to all other Ab classes and isotypes ($p<0.0001$). No differences in age, disease duration, or laboratory parameters were seen in (+) vs. negative (−) pts.The number of diseased arterial segments was not different in (+) vs. (−) pts; however, the total plaque burden, and more importantly the NC/mixed plaque was significantly higher in the affected arteries of the b2GP1 IgA (+) ones ($p=0.0001$). In fact, b2GP1 IgA had the strongest correlation with NC/ mixed plaque burden than any other factors tested ($p=0.003$). After adjustments for all CRF, RA duration and severity (DAS28-3v), b2GP1 IgA (+) pts had a 47% higher plaque burden risk for total and 52% higher risk for "vulnerable" plaque ($p=0.01$ and 0.004 respectively).

Conclusions: B2GP1 IgA Ab previously reported in symptomatic pts with documented atherosclerosis, are highly prevalent in asymptomatic RA pts. They independently predict higher total, but more importantly higher vulnerable, NC plaque burden more robustly than the composite of classic CRF. As such, they may represent a useful screening test for "high-risk" plaque in asymptomatic pts with RA.

Table 1. Patient Characteristics

Positive test	X1	X2 (≥3 months later)
Any ACL (%)	1.6	0
LA (%)	7.7	4.6
Any a-b2GP1 (%)	39***	29***
a-b2GP1-IgA (%)	39†	29†
a-b2GP1-IgM (%)	1.4	1.4
a-b2GP1-IgG (%)	1.4	0

*** $p < 0.0001$ for b2GP1 vs. any ACL & LA. † $p<0.0001$ for b2GP1-IgA vs. IgM & IgG.

Variable	b2GP1-IgA (−): 41	b2GP1-IgA (+): 33	p
DAS28-3v-ESR	3.1 ± 1	3.2 ± 0.9	0.5
TNFi-treated (%)	59.6	74.1	0.3
n (%) with plaque	26 (63.3)	20 (60.6)	0.7
n (%) assessed segments	164 (100)	132 (100)	–
n (%) diseased segments	38 (22)	29 (22)	0.9
Non-calcified/mixed	25 (15.2)	23 (17.4)	0.5
Calcified	13 (6.8)	6 (4.6)	0.2
Total plaque burden score	1.5 ± 2.1	4.3 ± 3.8	***0.001***
Non-calcified/mixed	1.4 ± 2.1	3.9 ± 3.7	***0.001***
Calcified	0.7 ± 2.4	1.8 ± 3.1	0.09

Linear Regressions	r (NC plaque burden)	r^2	β (95% CI)	p
Cor Risk F (composite)	0.37	0.14	2.9 (1.04–5.7)	***0.04***
B2 GPI IgA	0.41	0.16	2.5 (1.2–3.9)	***0.003***
DAS28-3v	0.23	0.06	1.2 (1.05–3.7)	***0.04***
CRP (mg/dl)	0.04	0.002	1.04 (0.31–1.2)	0.6
ESR	0.16	0.03	0.03 (−0.01–0.07)	0.16
TNFi therapy	−0.25	−0.07	−1.63 (−3.1–−0.3)	***0.03***

Relative Risk Regression*	b2GP1-IgA (−)	b2GP1-IgA (+)	p
Total plaque burden score	1 (ref)	1.47 (CI=1.06–4.76)	***0.01***
Non-calcified/mixed	1 (ref)	1.52 (CI=1.18–3.34)	***0.004***
Calcified	1 (ref)	1.09 (CI=0.72–3.71)	0.09

* Adjusted for age, gender, all traditional CRF, RA duration and DAS28-3v.

Disclosure: G. A. Karpouzas: None; **N. Ahmadi:** None; **T.-Y. Choi:** None; **F. Hajsadeghi:** None; **S. Munoz:** None; **M. Budoff:** None.

2166

Increased Epicardial and Thoracic Pre-Aortic Fat Depots Predict "Vulnerable" Coronary Plaque in Asymptomatic Patients with Rheumatoid Arthritis (RA). George A. Karpouzas[1], Naser Ahmadi[2], Fereshteh Hajsadeghi[2], Tae-Young Choi[2], Silvia Munoz[2] and Mathew Budoff[2]. [1]Harbor-UCLA, Long Beach, CA, [2]Harbor-UCLA

Background: There is increasing evidence of an association between volume of visceral adipose tissue (VAT) and clinical or subclinical atherosclerosis. Perivascular AT including epicardial (EAT), pericardial (PAT), thoracic pre-aortic (TAT) and subcutaneous (SAT) is metabolically active and a source of pro-inflammatory as well as anti-inflammatory cytokines with both paracrine and systemic effects. VAT volume and associations with coronary plaque burden and features in RA are unknown. We assessed the volume of these AT depots in asymptomatic patients (pts) with RA compared to non-RA matched controls for age, gender and all traditional risk factors undergoing evaluation for coronary artery disease. Additionally, we explored the ability of these diverse AT depots to predict non-calcified (NC), lipid-rich, "vulnerable" coronary plaque burden in RA.

Methods: We report on 74 recruited RA pts from a single center. Pts underwent VAT evaluation with 64+ slice multidetector Computed Tomography Angiography (MDCTA), with advantages of submillimeter collimation, high temporal and spatial resolution, and 3-dimensional

views of the heart and its epicardial surface. Additionally, MDCTA detects coronary plaque with equal accuracy to conventional angiography, and is superior in assessing "vulnerable" plaque. Coronary trees were graded in a standard fashion according to Americn Heart Association (AHA). Non-parametric tests were used for data analysis; linear regressions between different AT depot volumes and vulnerable plaque, as well as relative risk regression models for AT volume risk and prediction of vulnerable plaque burden in RA pts were constructed after adjustments for age, sex, classic coronary risk (CRF), RA duration, and disease activity.

Results: Patients with RA had significantly higher volumes of EAT, PAT, TAT and SAT compared to non-RA matched controls ($p<0.05$ for all, table 1). RA subjects had 44% higher EAT and 49% higher TAT volume risk than non-RA controls after adjustments for age, sex, all CRF, and body mass Index ($p=0.001$ and 0.005 respectively). Additionally, RA pts had significantly higher total coronary plaque burden ($p=0.01$), predominantly accounted for by "vulnerable" NC plaque ($p=0.0001$). EAT and TAT where the strongest predictors of "vulnerable" plaque ($p=0.001$ for both) in asymptomatic RA pts. EAT volume change was the strongest predictor of presence and extent of such friable, high-risk coronary plaque after adjustments for age, sex, all CRF, body mass Index, DAS28-3v and disease duration ($p=0.009$), followed by TAT ($p=0.01$).

Conclusions: VAT tissue depots- especially EAT and TAT- are significantly expanded in asymptomatic RA pts compared to matched controls. They significantly predict the presence of "vulnerable" coronary plaque and remain its strongest determinants after adjustments for traditional CRF, anthropometric, and RA-specific features.

Table 1. Patient Characteristics

Variable	RA (74)	Controls (74)	p
EAT (cc)	109.9 ± 46.5	89.2 ± 38.5	***0.001***
PAT (cc)	47.9 ± 32.4	41.1 ± 29.5	***0.04***
TAT (cc)	157.9 ± 67.8	130.3 ± 56.1	***0.01***
SAT (cc)	53.9 ± 24	45.3 ± 29.5	***0.04***
Relative Risk Regressions*			
EAT (cc)	1.44 (1.09–1.96)	1.0 (Ref)	***0.001***
PAT (cc)	1.31 (1.07–2.15)	1.0 (Ref)	***0.008***
TAT (cc)	1.49 (1.11–2.03)	1.0 (Ref)	***0.005***
SC (cc)	1.22 (1.03–2.21)	1.0 (Ref)	***0.03***
* Adjusted for age, gender, all conventional risk factors, and BMI.			
Total plaque burden score	6.4 ± 4.8	4.3 ± 4.1	***0.01***
Non-calcified	3.2 ± 4.3	1 ± 2.9	***0.0001***
Mixed	1.7 ± 2.9	0.9 ± 2	***0.01***
Calcified	1.5 ± 3.4	2.4 ± 3.3	0.19

RA cohort (n = 74) Linear Regressions	r (NC plaque burden)	r^2	β (95% CI)	p
EAT	0.42	0.18	1.72 (1.11–2.48)	***0.001***
PAT	0.27	0.08	1.41 (1.09–3.51)	***0.03***
TAT	0.46	0.21	2.18 (1.34–8.56)	***0.001***
SAT	0.19	0.04	1.25 (1.03–5.54)	***0.03***

RA cohort (n = 74)** Relative Risk Regressions	NC/Mixed Plaque Score 0	NC/Mixed Plaque Score >0	p
EAT (cc)	1.0 (Ref)	2.68 (1.35–3.24)	***0.009***
PAT (cc)	1.0 (Ref)	1.54 (1.09–1.91)	***0.01***
TAT (cc)	1.0 (Ref)	2.36 (1.19–2.56)	***0.01***
SC (cc)	1.0 (Ref)	1.29 (1.01–1.93)	***0.04***

** Adjusted for age, gender, all CRF, BMI, DAS28-3v and RF duration.

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2167

Citrullination Is Present in the Perivascular Interstitium of the Myocardium and Is Increased in Rheumatoid Arthritis Compared to Controls.

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Background: Myocardial dysfunction is increased among rheumatoid arthritis (RA) patients relative to controls. Autoimmunity against post-translationally modified (citrullinated) myocardial proteins may represent a pathophysiological link to both myocardial structural and functional abnormalities in RA patients.

Methods: Archived myocardial samples obtained during autopsy between 1995 and 2009 were assembled into four groups: RA; scleroderma; fatal myocarditis with no underlying rheumatic disease; and non-rheumatic disease controls. Records were adjudicated to confirm diagnosis. Samples were examined by immunohistochemistry for the presence and localization of citrullination using a commercial anti-modified citrulline antibody. A blinded cardiovascular pathologist graded average citrullination intensity, peak intensity, and average fibrosis for each case on a 0–3 scale. RA and control samples were further examined for the presence of peptidyl argenine deiminase enzymes (PADs 2 and 4) by immunohistochemistry.

Results: Myocardial samples from 17 RA patients were compared to those from 14 controls, 5 fatal myocarditis patients, and 9 scleroderma patients. The RA and control groups did not significantly differ by age, gender, race, or post-mortem interval. Citrullination was detected in the perivascular myocardial interstitium in each of the groups. Citrullination was not detected in the cardiomyocytes or endothelium. Average and peak citrullination were significantly higher in the RA group compared to the other groups, among which citrullination was equivalent (Figure, panels A and B). Myocardial fibrosis did not differ between the groups (Figure, panel C).

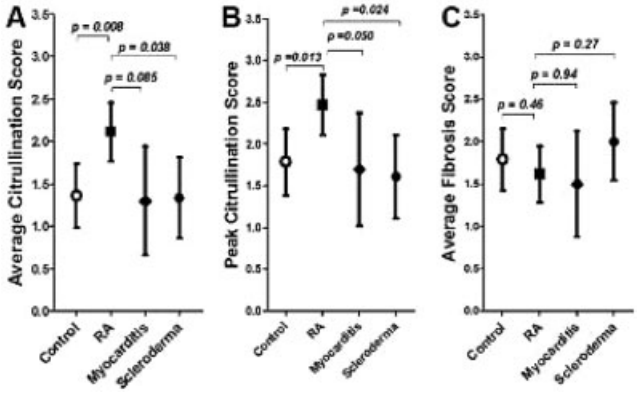

Figure. Average semiquantitative scores for immunohistochemical assessments of average citrullination (A), peak citrullination (B), and average myocardial fibrosis (C), according to group. Means and 95% confidence intervals are depicted. *P*-values were calculated using the Kruskal-Wallis test.

Myocarditis did not differ between the RA and control groups, and did not co-localize with citrullination. Rare, scattered PAD2 and PAD4 staining leukocytes were observed in both the RA and control samples. PAD2 and PAD4 staining was negligible within the cardiomyocytes and endothelium in both groups.

Conclusions: These data provided evidence for the first time that: 1) Citrullinated proteins are present in the myocardium, in general, 2) Higher levels of myocardial interstitial citrullination appear to be specific to RA, 3) differences in demographics, post-mortem interval, and histologic features did not account for higher citrullination in RA, and 4) While myocardial leukocytes were potential sources of PAD2 and PAD4 within the myocardial interstitium, these cells were not increased in RA at the time of death. Further investigation is centered on identifying the specific myocardial proteins that are targets for citrullination, determining whether citrullinated myocardial proteins are recognized by RA sera, and elucidating the consequences of interstitial citrullination on myocardial structure and function in RA patients.

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ALD518 (BMS945429), a High Affinity Monoclonal Antibody Directed Against Interleukin-6, Reduces Disease Activity and Achieves Remission in Patients with Rheumatoid Arthritis and Inadequate Response to Methotrexate. Philip Mease[5], Vibeke Strand[4], Levan Shalamberidze[6], Aleksandar Dimic[3], Richard Aranda[2] and Jeff Smith[1]. [1]Alder Biopharmaceuticals Inc., Bothell, WA, [2]Bristol-Myers Squibb, Princeton, NJ, [3]Institute of Rehabilitation and Treatment, Niska Banja, Serbia, [4]Stanford University, Palo Alto, CA, [5]Swedish Medical Center and University of Washington, Seattle, WA, [6]V. Tsitlanadze Scientific Practical Centre of Rheumatology, Tbilisi, Georgia

Background: Interleukin-6 (IL-6) plays a key role in the inflammatory cascade in rheumatoid arthritis (RA). ALD518 (BMS945429) is an asialated, humanized, anti-IL-6 monoclonal antibody with a half-life of ~30 days. ALD518 binds to IL-6 with high affinity, preventing interaction and signaling mediated via soluble and membrane-bound IL-6R. Here, we report the impact of ALD518 on disease activity and DAS28 remission over 16 weeks.

Methods: Patients with active RA and an inadequate response to MTX were randomized 1:1:1:1 to intravenous ALD518 80, 160 or 320 mg or placebo during this 16-week, double-blind, placebo-controlled Phase II study. Patients received two IV infusions of ALD518 (Day 1 and Week 8), while continuing on stable doses of MTX. The primary efficacy endpoint was ACR 20 responders at Week 12. Disease activity was assessed via DAS28 (CRP) as a secondary endpoint, including mean change from baseline and DAS28-defined remission (score <2.6). Efficacy data were assessed for the modified intent-to-treat population. Safety was monitored throughout. P values for ACR responses are based on Fisher's exact test and for DAS28 classes are based on chi-square tests.

Results: Of 127 randomized and treated patients, 116 completed the trial. At baseline, mean age was 52.3 years and RA duration was 6.8 years. Mean baseline DAS28 (CRP) scores were 6.3, 6.2, 6.2 and 6.1 in the ALD518 80, 160, 320 mg and placebo groups, respectively. Reductions in DAS28 score and the proportion of patients achieving Low Disease Activity State (LDAS; DAS28 [CRP] ≤3.2), remission and ACR 20, 50 and 70 responses were rapidly achieved and greater than placebo for all ALD518 doses at each time point (Table). For all assessments, there was a trend toward greater responses with higher ALD518 doses.

	Time point	ALD518 80 mg (N=32)	ALD518 160 mg (N=34)	ALD518 320 mg (N=28)	Placebo (N=33)
DAS28, mean reduction from baseline (see text)	Week 4	−2.0 (1.2)	−2.0 (0.8)	−2.4 (1.1)	−0.6 (1.0)
	Week 12	−2.7 (1.2)	−2.5 (1.0)	−2.9 (1.3)	−0.9 (1.3)
	Week 16	−2.7 (1.2)	−2.7 (1.0)	−3.2 (1.2)	−1.1 (1.1)
LDAS (%)	Week 4	10.0	23.5*	28.6*	0
	Week 12	20.6*	33.3*	46.1*	6.6
	Week 16	20.7*	50.0*	52.0*	3.4
DAS28-defined remission (%)	Week 4	10.0	8.8*	17.9*	0
	Week 12	17.2*	21.2*	34.6*	3.3
	Week 16	13.8*	28.1*	44.0*	0
ACR 20 (%)	Week 4	50.0*	55.9*	71.4*	24.2
	Week 12	81.3*	70.6*	82.1*	27.3
	Week 16	75.0*	64.7*	82.1*	36.4
ACR 50 (%)	Week 4	9.4	14.7	28.6*	3.0
	Week 12	34.4*	26.5*	50.0*	9.1
	Week 16	40.6*	41.2*	50.0*	15.2
ACR 70 (%)	Week 4	6.3	0	10.7	0
	Week 12	12.5	11.8	25.0*	3.0
	Week 16	21.9	17.6	42.9*	6.1

* $p<0.05$ vs placebo.

Through 16 weeks, serious AEs were reported in two ALD518 patients (both had significant increases in liver enzymes, and discontinued treatment). Increases in ALT >3x upper limit of normal occurred in 12, 6 and 29% of patients in the ALD518 80, 160 and 320 mg groups, respectively. Modest increases in total cholesterol were observed; mean levels at Week 16 were 6.5, 6.4 and 6.0 mmol/L in the ALD518 80, 160 and 320 mg groups, versus 5.4 mmol/L in the placebo group. Nine ALD518 patients had transient Grade II (five in the ALD518 80 mg group and four in the 160 mg group) and two had transient Grade III neutropenia (both in the 80 mg group). There were no serious infections or infusion reactions in any treatment group, and no evident immunogenicity.

Conclusions: In this Phase II study, the IL-6 inhibitor ALD518 resulted in rapid and significant improvements in disease activity sustained over 16 weeks of assessment in patients with RA and an inadequate response to MTX. ALD518 was well tolerated, with a safety profile consistent with the biology of IL-6 blockade.

Reference:
1. Mease P, et al. *Ann Rheum Dis* 2010;**69**(Suppl3):98. Abstract OP013

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Efficacy and Safety of Ocrelizumab in Patients with Active Rheumatoid Arthritis Who Have an Inadequate Response to at Least One TNF Inhibitor: Results from the Phase III SCRIPT Trial. Paul P. Tak[1], Philip J. Mease[7], Mark C. Genovese[8], Joel M. Kremer[9], Boulos Haraoui[4], Yoshiya Tanaka[10], Clifton O. Bingham[5], Ali Ashrafzadeh[2], Helen Travers[6], Simon Safa-Leathers[6], Sanjeev Kumar[6] and Wolfgang Dummer[3]. [1]Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, [2]Genentech, San Francisco, CA, [3]Genentech, [4]Institut de Rhumatologie, Montreal, QC, Canada, [5]Johns Hopkins University, Baltimore, MD, [6]Roche, [7]Seattle Rheumatology Associate, Seattle, WA, [8]Stanford Univ, Sunnyvale, CA, [9]The Center for Rheumatology, Albany, NY, [10]U Occupa & Environ Hlth, Kitakyushu, Japan

Purpose: Treatment with rituximab has demonstrated clinical benefit in patients (pts) with rheumatoid arthritis (RA). This phase III study evaluated efficacy and safety of Ocrelizumab (OCR, a humanized anti-CD20 antibody) plus methotrexate (MTX) or leflunomide (LEF), in pts with active RA who had an inadequate response to ≥1 TNF inhibitor.

Methods: SCRIPT was a randomized, double-blind and placebo (PBO)-controlled (DBPC) study. 840 pts with active RA (1987 ACR criteria; SJC ≥4, TJC ≥4, CRP ≥0.6 mg/dL and RF+ and/or anti-CCP+) and on stable MTX (7.5–25 mg/wk) or LEF (10–20 mg/day), were randomized (1:1:1; 277 PBO, 278 OCR 2 × 200 mg, 285 OCR 2 × 500 mg). Pt baseline (BL) characteristics were well balanced between treatment groups (mean: age ~54 yrs, SJC ~17, TJC ~26, CRP ~2.8, DAS28 ~6.5 and RA duration 11.8 to 12.7 yrs). The DBPC period (48 wks) was comprised of 2 courses of 2 treatments each (Days 1, 15 and Wks 24, 26). All pts received 100 mg IV methylprednisolone premedication. Co-primary endpoints were ACR20 responses at Wks 24 and 48. Secondary endpoints included the change from BL in the total modified (van der Heijde) Sharp score (mTSS) at 48 wks and ACR50/70 responses at 24 and 48 wks.

Results: Key efficacy and safety data are shown in Table 1. Both OCR doses showed statistically significant ($p<0.0001$) improvements (vs PBO) in ACR20/50/70 at Wks 24 and 48. At Wk 48, statistically significant slowing of progression of joint damage (PJD) (change from BL in mTSS) was seen in OCR 500 mg dose group (62% inhibition, $p=0.0020$) but not in OCR 200 mg dose group (30% inhibition, $p= 0.2153$) vs PBO. Frequencies of AEs, SAEs, and overall infections were comparable among the 3 treatment arms. Serious infections (SIEs) were observed more

frequently in OCR dose groups (5.1% and 4.3%) compared to PBO (2.5%). SIE rates were similar in both OCR and PBO groups outside Japan. Most common SIEs included pneumonias, cellulitis and urinary tract infections. Opportunistic infections in OCR-treated groups included 1 suspected Pneumocystis jiroveci, 2 de novo pulmonary tuberculosis, and 1 hepatitis B reactivation and none in PBO. There were no fatal infections during the DBPC period in any treatment groups.

Table 1. Efficacy, radiologic, and safety summary

	Placebo (n=277)	OCR 2 × 200 mg (n=277)	OCR 2 × 500 mg (n=282)
Week 24[a]			
ACR20	24.5	43.0*	48.2*
ACR50	9.0	21.3*	25.2*
ACR70	2.9	7.6***	10.3**
Week 48[a]			
ACR20	21.7	49.5*	50.7*
ACR50	10.1	29.2*	30.9*
ACR70	5.1	11.2***	18.1*
X-ray radiographic[b]			
Mean change in mTSS Score, 24 wks	1.30	1.11	0.67
Mean change in mTSS Score, 48 wks	2.61	1.83	1.00**
Safety, %			
AEs	227 (81.9)	232 (83.8)	238 (84.4)
SAEs	32 (11.6)	40 (14.4)	32 (11.3)
Infections	143 (51.6)	150 (54.2)	164 (58.2)
Serious infections (SIEs)	7 (2.5)	14 (5.1)	12 (4.3)
Infusion-related reactions, %			
1st infusion	5.1	13.0	18.4
2nd infusion	5.8	4.1	4.0
3rd infusion	2.3	6.4	6.7
4th infusion	2.3	3.3	1.6
Serious AE disorder			
Musculoskeletal	12 (4.3)	7 (2.5)	7 (2.5)
Cardiac	4 (1.4)	5 (1.8)	3 (1.1)
Injury	6 (2.2)	4 (1.4)	1 (0.4)
GI	1 (0.4)	5 (1.8)	2 (0.7)
Neoplasms	4 (1.4)	2 (0.7)	1 (0.4)
Blood/lymphatic	3 (1.1)	1 (0.4)	1 (0.4)
Serious infection rates			
Total patient-years	246.03	247.63	254.92
Infections	9	17	16
Infections/100 pt-yrs	3.66	6.87	6.28
95% CI	1.67–6.94	4.00–10.99	3.59–10.19
Safety sub-analysis	**Placebo (n=37/240)**	**OCR 200 mg (n=36/241)**	**OCR 500 mg (n=38/244)**
Total patient-years	Asia†/RoW 33.67/212.36	Asia†/RoW 33.16/214.47	Asia†/RoW 35.10/219.82
Serious Infections	0/9	5/12	5/11
Serious Infections/100 pt-yrs	0/4.24	15.08/5.60	14.25/5.00
95% CI	0–10.96/ 1.94–8.05	4.90–35.19/ 2.89–9.77	4.63–33.25/ 2.50–8.95

* p<0.0001; ** p<0.005; *** p<0.05 vs PBO.
Notes: aCochran-Mantel-Haenszel, stratified for DMARD (MTX/LEF) and region (US/RoW).
Missing data set to Non Responder.
bVan Elteren test, stratified for DMARD (MTX/LEF) and region (US/RoW).
mITT (pts 1 BL and at least 1 post BL X-ray) n=265 for PBO, n=261 for OCR 2 × 200 mg.
and n=266 for OCR 2 × 500 mg groups. Missing data was extrapolated/ interpolated.
†Asian pts mostly recruited in Japan.
CI=confidence interval, RoW=rest of world

Conclusions: Both OCR doses met the clinical primary efficacy endpoints. The reduction in PJD was statistically significant for 500 mg dose but not for 200 mg dose at 48 wks. The rate of SIEs was higher in both OCR doses compared to PBO; the increased rates appeared to be primarily driven by pts in Japan.

Disclosure: P. P. Tak: Genentech and Biogen IDEC Inc, 2, 5, Roche, 2, 5; **P. J. Mease:** Genentech and Biogen IDEC Inc, 2, 5, 8, Roche, 2, 5, 8; **M. C. Genovese:** Genentech and Biogen IDEC Inc, 2, 5, Roche, 2, 5; **J. M. Kremer:** Genentech and Biogen IDEC Inc, 2, 5, 8, Roche, 5, 8, Roche Diagnostics, 2; **B. Haraoui:** None; **Y. Tanaka:** None; **C. O. Bingham:** None; **A. Ashrafzadeh:** Genentech and Biogen IDEC Inc, 3, Roche, 1; **H. Travers:** Roche, 1, 3; **S. Safa-Leathers:** Roche, 1, 3; **S. Kumar:** Roche, 1, 3; **W. Dummer:** Genentech and Biogen IDEC Inc, 3, Roche, 1.

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Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of the Monoclonal Antibody ASK8007 Blocking Osteopontin in Patients with Rheumatoid Arthritis in a Randomized, Placebo-Controlled, Combined First-in-Man and Proof-of-Concept Study.

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Background: Osteopontin (OPN) is an extracellular matrix protein that is constitutively expressed in bone and epithelial tissues and upregulated in activated T cells, macrophages, synoviocytes and chondrocytes. OPN has diverse functions including chemotaxis, immunomodulation and activation of osteoclasts. High levels of OPN in serum, synovial fluid and tissue have been reported in rheumatoid arthritis (RA) patients. OPN-blockade improves arthritis in animal models of RA. In this study we assessed the safety, tolerability, pharmacokinetics, pharmacodynamics and initial efficacy of the humanized monoclonal antibody ASK8007 which binds to the SVVYGRL epitope of OPN in patients with active RA receiving methotrexate (MTX), leflunomide (LEF) or sulfasalazine (SSZ).

Methods: In this combined first-in-man single dose escalation study (part A) and multiple dose proof-of-concept study (part B), patients meeting the American College of Rheumatology (ACR) criteria for RA who had been taking MTX, LEF or SSZ for 4 months with active disease were randomly assigned to receive either ASK8007 or matching placebo intravenously while continuing to receive MTX, LEF or SSZ. In Part A, patients were treated with a single dose of 0.3, 1.25, 5 or 20 mg/kg ASK8007 intravenously in four consecutive dose cohorts of 8 patients each. In part B, patients received 3 consecutive infusions of 20 mg/kg ASK8007 or matching placebo on day 1, day 8 and day 29. Safety monitoring, pharmacokinetic and pharmacodynamic analyses and clinical assessments were performed throughout the study. Synovial tissue was obtained at baseline and after 43 days of treatment, and was analyzed by immunohistochemistry and digital image analysis. The two co-primary efficacy endpoints were the change from baseline in the disease activity score evaluated in 28 joints (DAS28) and the change from baseline in the number of CD68 positive sublining macrophages in the synovium as assessed on day 43.

Results: ASK8007 was well tolerated up to the highest studied dose of 20 mg/kg in both parts of the study. No anti-ASK8007 antibodies were detected and no renal clearance of ASK8007 was observed. In part B, in the intention-to-treat population, no difference was observed in the delta DAS28 between the ASK8007 treated patients (n=33) and the placebo-treated patients (n=16, $P = 0.95$). Results were similar for the per protocol population. In addition, no difference was observed in the delta CD68 positive sublining macrophages between the ASK8007-treated patients (n=9) and the placebo-treated patients (n=4, $P = 0.61$). Paired analysis also did not show a clear cut decrease in sublining macrophages within the ASK8007 treatment group. Although quantifiable ASK8007 concentrations were obtained in synovial fluid samples which indicates that it reaches the target site, there was also no effect of multiple doses of ASK8007 on the biomarkers for bone and cartilage metabolism and for inflammation in any of the matrices tested (blood, urine, synovial fluid and synovial tissue).

Conclusion: The results of this trial consistently show that blocking the extracellular matrix protein osteopontin is unlikely to be a feasible strategy for the treatment of RA.

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Tasocitinib (CP-690,550) Appears To Be Effective and Tolerated When Administered Either as Long-Term Monotherapy or on Background Methotrexate in Patients with Rheumatoid Arthritis. Carol A. Connell[1], Richard Riese[2], Susan Wood[2], John Bradley[2] and Samuel H. Zwillich[2]. [1]Pfizer Inc, New London, CT, [2]Pfizer Inc

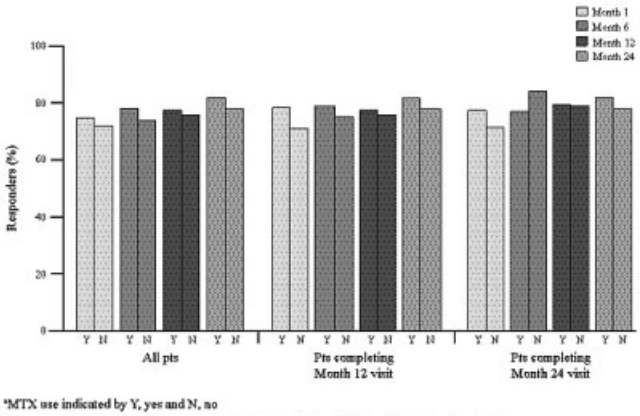
Background: Tasocitinib (CP-690,550) is an oral, selective Janus kinase inhibitor that has previously demonstrated efficacy in treating rheumatoid arthritis (RA) and a manageable safety profile in randomized studies. Patients were enrolled in this long-term follow-up study upon completion of participation in a prior randomized study of tasocitinib (PRST). Here safety and efficacy is compared between patients who received tasocitinib monotherapy and those on background methotrexate (MTX).

Methods: In this Phase 2/3 open label study of 1070 patients who had participated in a PRST, treatment was initiated with either 5 or 10 mg tasocitinib twice daily. Key outcome measures included safety and ACR20 response rates. Results are presented for all patients (ALL, n=1070), patients who completed Month 12 (M12, n=648), and patients who completed Month 24 (M24, n=207) visits. The baseline is that of the PRST for patients who enrolled within 14 days of PRST participation; if enrollment was >14 days after PRST participation, baseline was the start of this study. Some PRSTs required background MTX; others were conducted as monotherapy.

Results: Background MTX use was reported in 422/1070 (39.4%, ALL MTX), 332/648 (51.2%, M12 MTX), and 162/207 (78.3%, M24 MTX). Treatment-related adverse events (TRAEs) were generally manageable and infrequently led to discontinuation (70/1070). The most frequently reported TRAEs were infections and infestations for both MTX and non-MTX treatment groups. The most common TRAEs reported by MTX patients were urinary tract infection (4.7%), bronchitis (4.0%), and sinusitis (3.6%); in non-MTX patients, the most common TRAEs were upper respiratory tract infection (2.5%), bronchitis (2.3%), and herpes zoster (2.2%). These TRAEs and TRAEs of abnormal liver laboratory tests are presented by treatment group in the table below.

	Tasocitinib monotherapy (n=639)			Tasocitinib + MTX (n=422)		
Treatment-related AEs, n	**Mild**	**Mod**	**Severe**	**Mild**	**Mod**	**Severe**
Infections and Infestations, n (%)	**49 (7.7%)**	**38 (6.0%)**	**4 (0.6%)**	**47 (11.1%)**	**45 (10.7%)**	**14 (3.3%)**
Bronchitis	9	6	0	6	11	0
Herpes zoster	7	6	1	6	5	2
Nasopharyngitis	6	5	0	9	1	0
Sinusitis	2	1	0	7	8	0
Upper respiratory tract infection	13	3	0	8	5	0
Urinary tract infection	4	3	1	10	8	2
Liver Laboratory Test AEs, n (%)	**3 (0.5%)**	**5 (0.8%)**	**0**	**15 (3.6%)**	**11 (2.6%)**	**0**
Alanine aminotransferase increased	0	1	0	6	3	0
Aspartate aminotransferase increased	0	1	0	5	2	0
Gamma-glutamyl transferase increased	0	0	0	1	2	0
Hepatic enzyme increased	3	2	0	1	3	0
Liver function test abnormal	0	1	0	2	1	0

ACR20 response rates demonstrated similar efficacy of tasocitinib between ALL MTX and non-MTX patients, as well as M12 and M24 patients (Figure 1). ACR20 response rates at Month 24 were 81.8% and 77.8% for M24 MTX and non-MTX patients, respectively.



[a]MTX use indicated by Y, yes and N, no

ACR, American College of Rheumatology; BID, twice daily; MTX, methotrexate; pts, patients

Figure 1. % responders for ACR20[a] by MTX use for pts initially treated with tasocitinib 5 or 10 mg BID.

Conclusion: The safety profile of tasocitinib, regardless of background MTX use, was generally tolerable and manageable. Tasocitinib demonstrated sustained efficacy over 24 months in the treatment of RA. ACR response rates were similar in patients receiving tasocitinib monotherapy compared with patients on background MTX therapy.

Disclosure: C. A. Connell: Pfizer Inc, 3; **R. Riese:** Pfizer Inc, 3; **S. Wood:** Pfizer Inc, 3; **J. Bradley:** Pfizer Inc, 3; **S. H. Zwillich:** Pfizer Inc, 3.

2172

A Randomized Dose-Ranging, Placebo-Controlled Study of INCB028050, a Selective JAK1 and JAK2 Inhibitor in Subjects with Active Rheumatoid Arthritis. Maria W. Greenwald[1], Rosanne Fidelus-Gort[4], Rich Levy[4], Jinjin Liang[4], Kris Vaddi[4], William V. Williams[3], Robert Newton[4], Swamy Yeleswaram[4], Robert Flores[4], Edward McKeever[4], James Rodgers[4], Stacey Shepard[4], Pierre-Yves Berclaz[2], Chin Hyok Lee[2] and Monica E. Luchi[3]. [1]Desert Medical, Palm Desert, CA, [2]Eli Lilly & Company, [3]Incyte Corporation, Wilmington, DE, [4]Incyte Corporation

Purpose: To characterize safety and efficacy of INCB028050 (050) in RA in subjects who have had an inadequate response to any DMARD therapy including biologics.

Methods: Subjects with active RA(≥6 tender>/4 swollen joints of 28), ESR≥28mm or CRP ≥ 7mg/L) despite DMARD therapy were randomized to placebo (PBO)or 050 at once daily oral doses of 4mg, 7 mg or 10 mg with background DMARDs (excluding biologics). After 12 weeks subjects randomized to placebo were re-randomized to 7mg or 10mg for an additional 12 weeks (wks). The primary analysis was at the end of the 12-week PBO-controlled period. Subjects remained blinded to treatment assignment during the 24-wk treatment period. Subjects could be on stable doses of methotrexate (MTX), hydroxychloroquine, leflunomide, corticosteroids (<10 mg/day) and/or sulfasalazine. Results below are at Wk 12. The study was not designed to test for statistically significant differences between individual dose groups and placebo; p-values and significance levels are not displayed.

Results: The study enrolled 127 subjects, eighty percent women. Two subjects were randomized but not treated. One subject had no post-baseline assessments. Mean ages across treatment groups 54–58yrs. Mean disease duration ranged from 7–9 yrs. The proportion of subjects on background MTX ranged from 72–77%. The proportion of subjects who failed biologics in the past was 13%, 38%, 6% and 20% for the PBO, 4mg, 7mg and 10mg groups respectively. Of the subjects who had failed biologics, 30% failed multiple biologics.

Response rates are expressed as mean % (also percent change from baseline for DAS28).

Wk 12 results	PBO n=31	4 mg 050 n=31	7 mg 050 N=32	10 mg 050 N=30
ACR20 (%)	32	52	59	53
ACR50 (%)	13	35	31	30
ACR70 (%)	3	16	9	10
DAS28 CRP Mean (%change)	5 (−19)	4 (−34)	4 (−32)	4 (−33)
DAS28 <=2.6 (%)	16	23	25	17

Responses were observed as early as the first assessment (Wk2), demonstrating a rapid onset of action. Similar ACR responses were achieved with 050 regardless of background therapy or previous biologic experience. ACR20 responses for biologic experienced subjects was 33% for PBO and 53%, 73% and 43% for 4mg, 7mg and 10mg, respectively. ACR50 responses for biologic experienced subjects was 11% for PBO and 33%, 45% and 29% for 4mg, 7mg and 10mg, respectively.

The nature of treatment-emergent adverse events (TEAEs) was similar across groups. The frequency of TEAEs in PBO, 4mg, 7 mg and 10 mg 050 groups was 61.3%, 48.4%, 59.4% and 74.2%, respectively. One subject reported an unrelated serious AE (GI bleed). The most frequently reported TEAEs were headache (active 10.6% vs. 6.5% PBO), URI (active 5.3% vs. 9.7% for PBO) and diarrhea (active 5.3% vs. 6.5% PBO). At Wk 12, two cases of herpes zoster were reported (2.1% active vs. 0% PBO). Increases were observed in HDL and LDL, and HDL:LDL ratios tended to increase with therapy (active 10.06% vs. 0.41% PBO).

Conclusion: In this study, INCB028050 given once a day over 12 weeks was well tolerated and demonstrated clinically meaningful responses in subjects with inadequate response to DMARDs including biologics over 12 wks of treatment. All three doses tested were effective.

Disclosure: M. W. Greenwald: None; **R. Fidelus-Gort:** Incyte, 1, 3; **R. Levy:** Incyte, 1, Infinity, 3; **J. Liang:** Incyte, 1, 3; **K. Vaddi:** Incyte, 1, 3; **W. V. Williams:** Incyte, 1, 3; **R. Newton:** Incyte, 1, 3; **S. Yeleswaram:** Incyte, 1, 3; **R. Flores:** Incyte, 1, 3; **E. McKeever:** Incyte, 1, 3; **J. Rodgers:** Incyte, 1, 3; **S. Shepard:** Incyte, 1, 3; **P.-Y. Berclaz:** Eli Lilly and Company, 1, 3; **C. H. Lee:** Eli Lilly and Company, 1, 3; **M. E. Luchi:** Incyte, 1, 3.

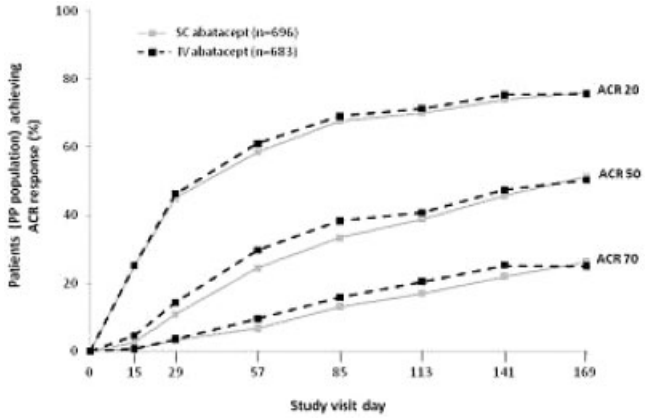
2173

A Large, Phase IIIb Non-Inferiority Trial of Subcutaneous (SC) Abatacept Compared with Intravenous (IV) Abatacept, in Patients with Rheumatoid Arthritis (RA). Mark C. Genovese[13], Jose Arturo Covarrubias[3], Gustavo Leon[5], Eduardo F. Mysler[8], Mauro W. Keiserman[10], Robert M. Valente[9], Peter Nash[15], J. Abraham Simon[2], Wieslawa Porawska[11], Jane H. Box[14], Clarence W. Legerton[6], Evgeny Nasonov[7], Patrick Durez[4], Richard Aranda[1], Ramesh Pappu[1], Ingrid Delaet[1], Julie Teng[1] and Rieke Alten[12]. [1]Bristol-Myers Squibb Co, Princeton, NJ, [2]Centro de Especialidades Médicas, Merida, Mexico, [3]Centro Medico de Las Americas, Merida, Yucatan, Mexico, [4]Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium, [5]De Ginecologia Y Reproduccion, Lima, Peru, [6]Department of Medicine, Medical University of South Carolina, Charleston, SC, [7]Institute of Rheumatology, Moscow, Russia, [8]Organización Médica de Investigación, Buenos Aires, Argentina, [9]Physician Research Collaboration, Lincoln, Lincoln, NE, [10]Pontificial Catholic University, School of Medicine, Porto Alegre, Brazil, [11]Poznanski Osrodek Medyczny Novamed, Ponzan, Poland, [12]Schlosspark-Klinik, Charité, University Medicine Berlin, Department of Internal Medicine II Rheumatology, Berlin, Germany, [13]Stanford University, Palo Alto, Sunnyvale, CA, [14]The Arthritis Clinic & Carolina Bone & Joint, Charlotte, NC, [15]University of Queensland, Brisbane, Australia

Background: The efficacy and safety of IV abatacept has been well established in patients with RA;[1,2] an SC abatacept formulation will provide additional treatment options. Here we compare the efficacy and safety of SC and IV abatacept.

Methods: This was a Phase IIIb, double-blind, double dummy study of patients with active RA (≥10 swollen and ≥12 tender joints, CRP ≥0.8 mg/dL) and inadequate response to MTX. Patients were randomized to weekly SC abatacept (125 mg) injections with added IV loading (~10 mg/kg) on Day 1, or IV abatacept (~10 mg/kg) on Days 1, 15, 29 and every 4 weeks thereafter, plus MTX (≤15 mg/week), for 6 months. The primary objective was to determine non-inferiority of SC to IV abatacept, by difference in ACR 20 response at Month 6. Secondary endpoints included ACR 50 and 70 responses, physical function (HAQ-DI response; improvement from baseline of ≥0.3) and immunogenicity (ELISA). Efficacy was assessed for both per protocol (PP) and intent to treat (ITT) populations. Patients who received ≥1 dose of abatacept were monitored for safety.

Results: Of 1457 randomized and treated patients, 693/736 (94.2%) SC and 676/721 (93.8%) IV patients remained on treatment at Month 6; 78 patients deviated protocol. Mean baseline characteristics were similar between groups (PP population): RA duration was 7.7 years; tender and swollen joint counts were 29.6 and 20.0; HAQ-DI was 1.7. At Month 6, 76.1% (95% CI: 73.0, 79.3) of SC vs 75.7% (72.5, 78.9) of IV patients achieved ACR 20, with an estimated difference (95% CI) of 0.3 (–4.2, 4.8) confirming non-inferiority of SC abatacept to IV abatacept. ACR responses over time were comparable (Figure). At Month 6, similar proportions of SC and IV patients achieved HAQ-DI response; 69.8 (66.4, 73.2) and 65.0% (61.4, 68.6), respectively. Results were consistent for PP and ITT populations. Frequencies of AEs and serious AEs over 6 months were comparable for SC versus IV (67.0 vs 65.2% and 4.2 vs 4.9%, respectively). Events of interest were comparable in the SC versus IV groups, respectively (serious infections in 5 [0.7%] vs 10 [1.4%], most common being pneumonia [1 vs 3]; malignancies in 3 [0.4%] vs 5 [0.7%], most common being basal cell carcinoma [2 vs 1]; pre-specified autoimmune events in 7 [1.0%] vs 6 [0.8%], most common being psoriasis [2 vs 4]). Local injection site reactions occurred in 19 (2.6%) SC and 18 (2.5%) IV patients; most were mild. Abatacept-induced antibodies were observed in 1.1 and 2.3% of SC and IV patients, respectively, and did not affect safety, efficacy or pharmacokinetics.



Conclusions: Consistent with the established IV abatacept profile, SC abatacept provides comparable efficacy and safety, with low immunogenicity and high retention rates; injection site reactions were few and mild. SC abatacept will provide additional treatment options for RA patients.

[1]Genovese MC, et al. *N Engl J Med* 2005;**353:**1114–23
[2]Kremer JM, et al. *Ann Intern Med* 2006;**144:**865–76

Disclosure: M. C. Genovese: Bristol-Myers Squibb, 2, 5, 8; **J. A. Covarrubias:** Bristol-Myers Squibb, 9, Lilly USA, LLC., 9, Pfizer Inc, 9, UNIDAD REUMATOLOGICA LAS AMERICAS SCP, 4; **G. Leon:** None; **E. F. Mysler:** Bristol-Myers Squibb, 6, Novartis Pharmaceuticals Corporation, 6, Roche, 6; **M. W. Keiserman:** Abbott Laboratories, 2, 5, Biogen Idec, 2, Bristol-Myers Squibb, 2, 5, Eli Lilly and Company, 2, Human Genome Sciences, Inc., 2, MSD, 2, 5, Pfizer Inc, 2, Roche, 2, UCB, Inc., 2; **R. M. Valente:** None; **P. Nash:** Centocor, Inc., 2, Schering-Plough, 8; **J. A. Simon:** None; **W. Porawska:** None; **J. H. Box:** Box Arthritis and Rheumatology of the Carolinas PLLC, 4, Bristol-Myers Squibb, 5, 8; **C. W. Leggerton:** Bristol-Myers Squibb, 5; **E. Nasonov:** None; **P. Durez:** Bristol-Myers Squibb, 8, Schering, 8, Wyeth Pharmaceuticals, 8; **R. Aranda:** Bristol-Myers Squibb, 1, 3; **R. Pappu:** Bristol-Myers Squibb, 3; **I. Delaet:** Bristol-Myers Squibb, 1, 3; **J. Teng:** Bristol-Myers Squibb, 1, 3; **R. Alten:** Bristol-Myers Squibb, 2, 8.

ACR Concurrent Abstract Sessions
Sjögren's Syndrome
Wednesday, November 10, 2010, 4:30 PM–6:00 PM

2174

Receptor-Mediated Small Interfering RNA Delivery in Sjögren's Syndrome. Kaleb M. Pauley, Adrienne E. Gauna and Seunghee Cha. University of Florida, Gainesville, FL

Background: Sjögren's syndrome (SjS) is characterized by xerophthalmia and xerostomia resulting from loss of secretory function due to immune cell infiltration in lacrimal and salivary glands. Current SjS therapeutic strategies employ secretagogues to induce secretion via muscarinic receptor stimulation. Based on our expertise on muscarinic type-3-receptor (M3R), we are utilizing ligands specific for MR to deliver siRNA into cells via receptor-mediated endocytosis, thereby altering epithelial cell responses to external cues such as pro-inflammatory or death signals while simultaneously stimulating secretion.

Methods: MR agonist carbachol was conjugated with siRNA targeting caspase-3. To test siRNA efficacy after conjugation, HSG cells were transfected with conjugate. To test conjugate efficacy, conjugate was added to HSG cells in culture. Quantitative RT-PCR and immunofluorescence were used to detect caspase-3 gene and protein expression, respectively. Carbachol functionality was assessed using intracellular calcium release assays. A FAM-labeled DNA probe was designed to target the antisense strand of caspase-3 siRNA and in situ hybridization was utilized to detect conjugate entry into cells.

Results: Transfection of conjugate into cells resulted in 80%-reduction in caspase-3 gene expression, confirming retained function of siRNA after conjugation. External conjugate treatment of HSG cells resulted in similar intracellular calcium release and induction of endocytosis as carbachol stimulation indicating that the carbachol portion of conjugate also retained function after conjugation. Using the FAM-labeled probe, conjugate uptake was visualized in HSG cells, indicating that the conjugate binds M3R and is taken into cells via receptor-mediated endocytosis as expected. In conjugate-treated HSG cells caspase-3 mRNA and protein expression was reduced 50% demonstrating the efficacy of our conjugate in siRNA delivery.

Conclusion: Both siRNA and carbachol portions of the conjugate were shown to retain function after conjugation, and external treatment of HSG cells with conjugate shows promising results. Further in vitro/in vivo studies are needed to optimize conjugate entry and test efficacy of conjugate in the prevention of cytokine-induced apoptosis. This therapeutic strategy can easily be manipulated to target different genes of interest while maintaining cell-type specificity, and has many potential clinical applications in the treatment of SjS. Supported by NIH grant T32DE007200 and Sjögren's Syndrome Foundation Research Grant

Disclosure: K. M. Pauley: None; **A. E. Gauna:** None; **S. Cha:** None.

2175

Structure and Antigenicity of the Ro/La RNP Particle. hY1 RNA Differentiates the Recognition of Epitopes in Systemic Lupus Erythematosus and Sjogren's Syndrome. John G. Routsias[1], Nikos C. Kyriakidis[1], Stathis Kotsakis[1] and Athanasios G. Tzioufas[2]. [1]Department of Pathophysiology, Medical School, University of Athens, Athens, Greece, [2]Medical School-Univ of Athens, Athens, Greece

Background: Ro/La RNP particle is targeted by autoantibodies in patients with Sjögren's syndrome (SS) and systemic lupus erythematosus (SLE). Although the antigenicity of the components of the complex has been extensively studied, its overall 3D structure remains unknown. In contrast to Xenopus laevis, human Ro60 structure has not been solved. Two parts of the human La structure have been solved till now, one comprising the conserved La motif and its adjacent RNA recognition motif (RRM1) and another holding the C-terminal RNA recognition motif (RRM2), followed by a C-terminal nuclear retention element (NRE). For hY1 RNA, only its secondary structure has been experimentally defined. The aim of this study was to determine the 3D structure of Ro/La RNP complex, evaluate the modeled structure experimentally and define its antigenicity

Methods: Human Ro60 protein model was built by homology modelling from Xenopus Ro. 81% of human La was constructed by the assembly of its 3 parts: (i) 5–202 aa (La motif +RRM1), (ii) 203–224aa (linker region), (iii) 225–334 aa (RRM2 + NRE). hY1 RNA was built on the basis of its known secondary structure by a stepwise fashion. The whole Ro/La RNP complex was assembled and the structure was refined using extensive molecular dynamics. EMSA was performed using synthetic hY1RNA and recombinant Ro60 and La antigens. ELISA experiments were performed using immobilized biotinylated synthetic hY1RNA analogue, recombinant Ro60 and La antigens and purified antibodies against specific epitopes or Ro60 and La autoantigens.

Results: Electrostatic analysis of the Ro/La RNP complex revealed that adjacent Ro and La autoantigens form a consecutive positively charged patch, interacting with the negatively charged hY1 RNA molecule. More specifically, hY1 RNA binds to conserved amino acid residues located on the outside domain of the Ro60 doughnut and within the cleft formed between the La motif and an edge of the adjacent RRM1 of La. At this orientation, hY1-RNA completely masks epitopes 169–190aa of Ro60 and 145–164aa of La that were previously associated with SLE but not the SS related epitopes 211–232aa of Ro60 and 349–364aa of La. EMSA experiments demonstrated that the synthetic hY1-RNA analogue could form a complex with Ro60 and La autoantigens. In this regard, an ELISA assay was carried out, based on competition between synthetic-hY1 RNA and purified antibodies against specific epitopes on Ro and La autoantigens. It was found that Ro60 – hY1-RNA interaction was inhibited by anti-443–454, anti anti-211–232 and anti 169–190 antibodies by 13%, 45% and 76%, respectively while La-hY1-RNA interaction was inhibited by purified anti-349–364, anti-301–320 and anti-145–164 antibodies by 10%, 43% and 97%, respectively. Moreover, EMSA experiments demonstrated that Ro60 and La interactions with hY1 RNA can also be inhibited by peptides corresponding to regions 169–190aa and 145–164aa of Ro60 and La autoantigens.

Conclusions: Our study demonstrates that the SLE related epitopes on Ro and La autoantigens are actually cryptotopes in Ro/La RNP three-dimentional structure masked by hY1 RNA. On the other hand, SS related epitopes are directly accessible by autoantibodies in Ro/La RNP structure.

Disclosure: J. G. Routsias: None; **N. C. Kyriakidis:** None; **S. Kotsakis:** None; **A. G. Tzioufas:** None.

2176

A Role of Autoimmune Response to M3 Muscarinic Acethylcholine Receptor in the Pathogenesis of Sjogren's Syndrome Like Autoimmune Sialoadenitis. Mana Iizuka[2], Hiroto Tsuboi[2], Yumi Nakamura[2], Naomi Matsuo[2], Isao Matsumoto[2] and Takayuki Sumida[1]. [1]Univ of Tsukuba/Inst Clin Med, Tsukuba City, Japan, [2]Univ of Tsukuba/Inst Clin Med

Objective: Sjögren's syndrome (SS) is a chronic autoimmune disease characterized by lymphocytic infiltration of salivary glands, in which $CD4^+$ T cells are predominant. These infiltrating T cells play a crucial role in the generation of SS. Previous studies showed that autoantibodies and autoreactive T cells against M3 muscarinic acethylcholine receptor (M3R) were detected in patients with SS. In this study, to reveal the pathological role of M3R immune response in SS, we tried to induce SS like sialoadenitis by autoimmune response to M3R.

Methods: (1) C57BL/6J ($M3R^{+/+}$) mice and M3R knockout ($M3R^{-/-}$) mice were immunized intradermaly with synthesized peptides encoding the extracellular domains of murine M3R (N-terminus, 1st, 2nd, and 3rd extracellular loops) in CFA. On day 10, these mice were boosted with intradermal injection. Ten days after booster immunization, spleens were isolated, the immune response to M3R was examined in vitro, and then the splenocytes were transferred to Rag1 knockout mice ($Rag1^{-/-}$) ($M3R^{-/-} \rightarrow Rag1^{-/-}$). (2) Anti-M3R antibodies and the amount of saliva flow $M3R^{-/-} \rightarrow Rag1^{-/-}$ were measured on day 0, 15, 45. (3) In $M3R^{-/-} \rightarrow Rag1^{-/-}$ mice, salivary glands were investigated histologically by H&E staining and evaluated immunohistochemically using anti-Thy1, anti-B220, anti-CD4 and anti-CD8 antibodies. Infiltrating lymphocytes derived from salivary glands were cocultured with M3R peptides in vitro and cytokine (IFN-g, IL-17, IL-4) in the supernatant was measured by ELISA. (4) $CD3^+$ T cells purified from $M3R^{-/-}$ mice immunized with M3R were transferred to $Rag1^{-/-}$ mice ($M3R^{-/-}CD3^+ \rightarrow Rag1^{-/-}$) and salivary glands were examined by histological analysis. (5) The splenocytes from IFN- $g^{-/-}/M3R^{-/-}$ mice immunized with M3R were transferred to $Rag1^{-/-}$ mice (IFN- $g^{-/-}/M3R^{-/-} \rightarrow Rag1^{-/-}$).

Results: (1) IL-17 and IFN- g were highly produced in splenocytes of immunized $M3R^{-/-}$ mice compared with $M3R^{+/+}$ mice. (2) In $M3R^{-/-} \rightarrow Rag1^{-/-}$ mice, anti-M3R antibodies was significantly increased and saliva flow were decreased. (3) On day 45, the sialoadenitis with remarkable mononuclear infiltration was observed and $Thy1^+CD4^+$ cells predominantly infiltrated in salivary glands of $M3R^{-/-} \rightarrow Rag1^{-/-}$ mice. IL-17 was preferentially produced from M3R reactive infiltrated T cells. (4) The moderate sialoadenitis with T cell infiltration was also detected in $M3R^{-/-}CD3^+ \rightarrow Rag1^{-/-}$ mice. (5) The obvious sialoadenitis was also observed in IFN- $g^{-/-}/M3R^{-/-} \rightarrow Rag1^{-/-}$ mice as well as $M3R^{-/-} \rightarrow Rag1^{-/-}$ mice.

Conclusion: These findings support the notion that M3R reactive Th17 cells might play a crucial role in the generation of autoimmune sialoadenitis such as SS.

Disclosure: M. Iizuka: None; **H. Tsuboi:** None; **Y. Nakamura:** None; **N. Matsuo:** None; **I. Matsumoto:** None; **T. Sumida:** None.

2177

Δ4BAFF, an Alternate-Splice Isoform That Acts as a Transcription Factor To Enhance BAFF Production in Primary Sjögren's Syndrome. Jacques-Olivier Pers, Gabriel J. Tobon, Laëtitia Le Pottier and Pierre Youinou. Brest University, Brest, France

Background: Elevated expression of 'B cell activating factor belonging to the tumor necrosis factor family' (BAFF), a potent B cell survival factor contributes to the expansion of low-affinity self-reactive B cells during the establishment of tolerance. However, mechanisms leading to BAFF overexpression in autoimmune settings, such as primary Sjögren's syndrome (SS) or rheumatoid arthritis (RA) and in lymphoproliferation such as chronic lymphocytic leukemia (CLL) are not understood. To date, 3 transcriptional variants of the BAFF gene have been described, including Δ3BAFF, a truncated form that negatively regulates BAFF, by forming non-functional heterotrimers with full-length (FL) BAFF. Herein, we report the discovery and the role of a new transcript for BAFF due to the fact that exon 4 is spliced out.

Methods and Results: A 3' RACE-PCR was performed in B cells from SS patients and revealed another transcript with deletion of nucleotides 749 to 861 encoding the predicted exon 4. A new in-frame stop codon was artificially generated resulting in a truncated protein. A same alternate splice isoform was detected in mice. To assess the biochemical properties of the new variant of BAFF, RAMOS B cells were transiently transfected with pIRES2-EGFP-Δ4BAFF. Two bands at 21 and 17-kD prove to belong to Δ4BAFF, which is very telling of a post-translational modification. Incubation with PNGase F showed that Δ4BAFF was glycosylated and led to the predicted mobility of Δ4BAFF at 17kD. Interestingly, Δ4BAFF was located in the nucleus and, contrary to FL BAFF, absent from the cytoplasm. Because BAFF was up-regulated after Δ4BAFF transfection in RAMOS cells, we asked the question as to whether Δ4BAFF might function as a transcriptional regulator of BAFF. A ChIP analysis revealed that the Δ4BAFF protein bound to the BAFF promoter. To confirm the role of Δ4BAFF as a transcription factor that activates its own gene to increase BAFF production, we synthesized a digoxigenin-labeled consensus NFkB binding probe within the BAFF promoter and performed an EMSA. When nuclear extracts from Δ4BAFF transfected RAMOS B cells were incubated with this probe, a protein/DNA complex was seen. A supershift was only detected when the anti-BAFF mAb was added. Finally, we observed the presence of the Δ4BAFF protein in B

cells from patients with CLL, in synoviocytes from patients with RA or in epithelial cells from patients with SS.

Conclusion: We thus expand the view of BAFF gene regulation, which should contribute a better understanding of complex physiologic mechanisms involved in normal B cell survival, as well as in pathophysiology of autoreactive B cells. Our work introduces for the first time an entirely novel concept in biology suggesting that a human cytokine gene can be transcriptionally regulated by the activity of one of its own splice variants.

Disclosure: J.-O. Pers: None; **G. J. Tobon:** None; **L. Le Pottier:** None; **P. Youinou:** None.

2178

Local TACI-Ig Gene Therapy of the Salivary Gland of NOD Mice Reduces Auto-Immune Inflammation by Affecting the B Cell Compartment. Nienke Roescher[2], Jelle L. Vosters[2], Marco Guadagnoli[2], Jan P. Medema[2], Gabor G. Illei[4], John A. Chiorini[3] and Paul P. Tak[1]. [1]Academic Med Ctr/Univ of Amsterdam, Amsterdam, The Netherlands, [2]Academic Medical Center-University of Amsterdam, [3]National Insitutes of Health-National Institute of Dental and Craniofacial Research, [4]NIDCR, NIH #10 1N114, Bethesda, MD

Background: Sjögren's syndrome (SjS) is characterized by inflammatory autoimmune exocrinopathy in which B cells and B cell-related factors are important. Some patients have benefited from the use of the pan B cell depleting agent rituximab, validating the B cell compartment as a therapeutic target. An alternative therapeutic approach could be to use the soluble receptor TACI, which binds BAFF and APRIL, factors important in B cell survival and activation. Overexpression of BAFF in mice leads to a SjS-like syndrome and BAFF and APRIL are aberrantly expressed in salivary glands (SG) of patients with SjS. Therefore, we evaluated the effect of blockade of APRIL and BAFF using local gene transfer of a gene encoding for a TACI-Ig fusion protein in the SG of Non-Obese Diabetic (NOD) mice that spontaneously develop a SjS-like disease.

Material and Methods: An adeno-associated virus serotype 2 (AAV2) vector encoding the TACI fusion protein was constructed by cloning of the extra-cellular domain of mouse TACI coupled to the Fc-part of mouse immunoglobulin (Ig) G1. Expression of this gene was driven by the CMV promoter. The TACI-Ig vector or a control vector expressing beta galactosidase (LacZ) was administered once locally into the SG of NOD mice at the age of 10 weeks. Stimulated saliva flow was determined 10 weeks post-vector delivery. Gene transfer was measured by QPCR and protein analysis of the transduced SG. Inflammation was assessed by quantitative immunohistochemisty as well as by analysis of Ig and cytokine levels in the SG and in serum.

Results: TACI-Ig was highly expressed following transduction of 293T cells, and media from transduced cells could block BAFF induced B cell proliferation in vitro. In vivo, retrograde canulation of mouse SG also resulted in stable transduction and expression of TACI-Ig as determined by QPCR and ELISA. No change in stimulated saliva flow was observed between TACI treated and control mice. However, TACI-Ig treated mice had reduced SG inflammation as determined by the number of inflammatory foci per cross sectional surface area of the SG (LacZ 3.8 vs TACI-Ig 2.6, $p < 0.01$) and pro-inflammatory cytokines levels (IL-2, IL1β, IFN gamma) in the SG tended to be lower compared with control mice. Moreover, the numbers of B and plasma cells, were significantly lower ($p<0.05$) in the SG of treated mice, as well as IgG and IgM levels (50% and 41% reduction respectively, $p<0.05$). IgA levels did not change resulting in a significant improvement of the IgG/IgA ratio for the treated mice. Systemically, no significant changes in Ig-subtypes or cytokine levels were observed.

Discussion: The results presented here suggest that local B-cell targeted therapies may be beneficial in the treatment of SjS. The expression of a soluble TACI-Ig fusion protein in SG of NOD mice decreased autoimmune inflammation by reducing the number of B and plasma cells locally. The observed changes in IgG and IgM and the reduced IgG/IgA ratio levels suggest restoration of the balance of the mucosal immune system. When tested in patients with SjS, the timing of administration of the gene construct in the disease process may be critical in determining the outcome for salivary flow.

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2179

EBV-mir-Bart13 Downregulates Stim1, a Protein Involved in Calcium Signaling, in Human Salivary Gland Cells and May Contribute to the Pathogenesis of Sjogren's Syndrome. Alessia Gallo[1], Mayank Tandon[1], Gabor G. Illei[2] and Ilias Alevizos[1]. [1]National Insitutes of Health-National Institute of Dental and Craniofacial Research, [2]NIDCR, NIH #10 1N114, Bethesda, MD

Background: Loss of secretory function of salivary glands is one of the most important functional effects of Sjogren's syndrome (SS), a chronic systemic autoimmune disease. Previous studies have reported the presence of Epstein Barr Virus (EBV) DNA in salivary glands of SS patients. MicroRNA profiling studies in our laboratory have identified an EBV microRNA (ebv-mir-BART13) as significantly over-expressed in minor salivary gland biopsies of SS patients, when compared to the expression in minor salivary glands from non-Sjogren's controls.

Methods: Using the RNA22 target prediction algorithm, we identified STIM1 3'UTR as a target of ebv-mir-BART13. Store-operated calcium entry (SOCE) and calcium release-activated calcium current (CRAC) are critical events for the replenishment of intracellular calcium stores and have indispensable roles in various cellular functions, including salivary secretion. SOCE is activated by the depletion of calcium in the endoplasmic reticulum (ER). STIM1, is a protein that has recently been identified as a critical molecular component of CRAC channels. STIM1, is suggested to be the ER-Ca2+ sensor protein regulating SOCE in a number of different cell types. Attenuation of SOCE current underlies salivary gland dysfunction in mice lacking transient receptor potential 1 (TRPC1). We hypothesized that ebv-miR-BART13 may contribute to the salivary gland dysfunction by down-regulating STIM-1 and decreasing cacium influx in salivary gland epithelial cells.

Summary of the Results: To test this hypothesis, an expression plasmid was generated containing the 3'UTR of STIM1 downstream of the firefly luciferase coding sequence. The plasmid was co-transfected with ebv-mir-BART13 analogues and antagonists in HSG cells (human submandibular salivary gland cells). A 40% decrease in the intensity of the luciferase activity was observed 48 hrs after transfections, compared to controls, suggesting that ebv-mir-BART13 binds directly to the 3'UTR of STIM1.

HSG cells were transfected for 24 and 48hrs, with ebv-miR-BART13 analog and the mRNA and protein levels of STIM1 were measured. The mRNA level was not affected by the presence of this viral miRNA. However, the protein level was dramatically decreased (over 70% decrease) both 24 and 48hrs after transfection, suggesting that the ebv-mir-Bart13 exerts its effects on STIM1 not by degrading its transcript, but by repressing STIM1 translation. Functional Ca2+ assays through Thapsigargin-mediated depletion of the ER calcium in the ebv-mir-BART13 transfected cells showed a significant delay in the influx of calcium in the cytosol compared to controls.

Conclusions: Together, these functional measurements suggest that the presence of ebv-miR-BART13 in the salivary glands of SS patients might be, at least partially, responsible for the salivary gland dysfunction in those patients, by reducing the expression of STIM1, a critical member of the saliva secretion mechanism.

Disclosure: A. Gallo: None; **M. Tandon:** None; **G. G. Illei:** None; **I. Alevizos:** None.

ACR Concurrent Abstract Sessions

Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment - Biomarkers

Wednesday, November 10, 2010, 4:30 PM–6:00 PM

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Striking Prevalence of Axial Spondyloarthritis in Primary Care Patients with Chronic Low Back Pain; a Cross-Sectional Study. Lonneke van Hoeven[3], Jolanda Luime[1], Huub Han[2] and Angelique Weel[4]. [1]Erasmus Medical Centre, [2]Maasstadziekenhuis, [3]Maasstadziekenhuis/Erasmus Medical Centre, Rotterdam, The Netherlands, [4]Maasstadziekenhuis Rotterdam, Rotterdam, The Netherlands

Background: Chronic low back pain (CLBP) is one of the most common pain syndromes with unknown cause. Few studies however report that 5–7 % is caused by Ankylosing Spondylitis (AS), a disease that until recently could be diagnosed 7–10 years after first presentation of symptoms. Since treatment of AS is most successfully in an early stage of the disease, the ASAS group[1]

developed new criteria to diagnose axial Spondyloarthritis (aSpA) early. Early treatment requires early recognition and should therfore be done in primary care. Until now however, prevalences of aSpA in primary care patients with CLBP are missing.

Purpose: To determine the prevalence of aSpA in primary care patients with CLPB classified by ASAS criteria. To assess the diagnostic value of clinical tests commonly available to GPs and inflammatory back pain (IBP) questionnaires completed by patients themselves.

Method: In this cross-sectional study primary care patients with CLBP aged 19–45 years were identified from GP records by the International Classification of Primary Care code L03. All patients completed IBP questionnaires, (ASAS, Calin and Berlin) and underwent a complete history and physical examination by rheumatologist. Blood was drawn to assess HLAB27 and CRP. Sacroiliac joints (SIJ) were imaged by conventional radiography and MRI (Siemens Essenza). All images were scored by two experienced MSD radiologist, without any clinical information. Radiographic sacroiliitis was defined by Modified New York criteria and MRI (T1, T2 and fat suppression series) evaluation followed ASAS recommendations.[1] Definite aSpA was defined by the ASAS criteria of aSpA.[1] Statistics were performed by using chi-square and logistic regression analysis.

Results: 364 patients (43% male, 36.3 yrs(sd 6.8), 9 yrs (sd 7.44) of symptoms) were evaluated. The overall point prevalence of aSpA was 21.5 % (n= 77;) using the ASAS criteria, n=52 were diagnosed by the MRI criteria with one other SpA feature and n=12 were diagnosed by a positive HLA B 27 and two other SpA features. Based on the modified New York criteria we identified 6.6% (n = 24) of which 75% also fulfilled the ASAS criteria. Figure 1 shows the diagnostic value of characteristics available to GPs and IBP questionnaires. Highest post probability test were achieved for the diagnostic test HLA-B27 and X-SIJ with respectively 68.3% and 75%.

[1] Sleper J, Rudwaleit M et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis 2009;68;ii1ii44.

Diagnostic value of clinical available tests in GP practice; Pretest 21.5%

Determinant	Sensitivity %	Specificity %	Post test** %
History			
Male	**36.4**	**55.8**	**18.1**
BMI <=25	**31.2**	**61.3**	**17.8**
Uveïtis*	**3.9**	**98.6**	**42.9**
Crohn's/colitis*	**3.9**	**99.0**	**50.0**
Positive family history*	**22.1**	**92.0**	**42.5**
Good response to NSAID's*	**76.5**	**52.5**	**33.1**
Inflammatory back pain*	**29.9**	**86.0**	**36.5**
Peripheral arthritis*	**13.0**	**93.7**	**35.7**
Dactylitis*	**5.2**	**96.9**	**30.8**
Enthesitis*	**10.4**	**85.0**	**15.7**
Psoriasis*	**6.5**	**95.5**	**27.8**
Any of*	**40.3**	**77.4**	**32.3**
Diagnostics			
CRP >10 mg/l	**11.7**	**95.8**	**42.9**
HLA-B27 pos	**19.5**	**98.3**	**75.0**
X-SIJ	**36.4**	**95.5**	**68.3**
IBP Questionnaire			
Calin	**85.7**	**27.2**	**24.0**
ASAS	**55.8**	**67.2**	**31.4**
Berlin	**79.2**	**34.1**	**24.4**

** **Post test probability;** probability of having the disease after a positive test. This could be compared to the pre test probability to assess information gain by the test.

Conclusion: In this cross-sectional study of primary care patients with CLBP the prevalence of aSpA based on the ASAS criteria is strikingly high. Additional 'red flag' symptoms determined by medical history and IBP questionnaires have modest diagnostic value. However, determine HLA-B27 and X-ray of SIJ could help physicians in primary care identifying patients that should have accelerated referral to rheumatologist to start accurate treatment as early as possible.

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2181

Screening for Axial Spondyloarthritis in a Primary Care: Comparison of Two Strategies in a Multicenter Prospective Study. Denis Poddubnyy[1], Janis Vahldiek[1], Inge Spiller[1], Beate Buss[1], Martin Rudwaleit[1] and Joachim Sieper[2]. [1]Charité - Campus Benjamin Franklin, Berlin, Germany, [2]Charite Campus Benjamin Frankl, Berlin, Germany

Background: The delay between first symptoms of axial spondyloarthritis (SpA) and the final diagnosis has been reported in different surveys to be still between 5 and 10 years. A major reason for such a delay in the diagnosis is the difficulty in identifying axial SpA patients among the large group of patients with chronic back pain in primary care. The current prospective randomized study was designed 1) to confirm the applicability of the established referral strategy [1, 2] in a multicenter study with rheumatologists not specialized in SpA and with primary care physicians, 2) to investigate whether this strategy can be improved by comparing it with a second strategy including additional screening parameters and asking for at least two parameters to be positive in case of referral.

Methods: Primary care physicians (n=259) were randomly assigned either to strategy 1 or strategy 2 for referral of patients with chronic back pain (duration of more than 3 months), age of back pain onset <45 years and no diagnosis of axial SpA to a cooperating rheumatologist (n=43) for further diagnostic workup. According to strategy 1 suitable patients were referred if at least one of the following 3 screening parameters was present: HLA-B27, inflammatory back pain (IBP), or sacroiliitis detected by imaging. According to strategy 2, patients were referred if 2 out of 5 parameters were positive: the same 3 parameters from strategy 1 and additionally a positive family history of ankylosing spondylitis (AS) or a good treatment response to non-steroidal anti-inflammatory drugs. The final diagnosis of the rheumatologist was used as the gold standard.

Results: 560 consecutively referred patients were included in this analysis. Among 318 patients referred via the 1st strategy 41.8% (n=133) were diagnosed with definite axial SpA: AS in 61.7% (n=82) and non-radiographic axial SpA in 38.3% (n=51) of all axial SpA cases. Among 242 patients referred via the 2nd strategy, 36.8% (n=89, p>0.05 vs strategy 1) were diagnosed with definite axial SpA: similarly, AS in 61.8% (n=55) and non-radiographic axial SpA in 38.2% (n=34) of the SpA cases. The probability of the axial SpA diagnosis was clearly increased with the increase of the number of positive referral parameters. The most common referral parameter in both strategies was IBP but the best performance demonstrated HLA-B27 in strategy 1 (with 57.7% of the referred with this parameter patients diagnosed as axial SpA) and sacroiliitis by imaging in strategy 2 (axial SpA was diagnosed in 53.3% of the patients). The best combination of two referral parameters in both strategies was the combination of HLA-B27 with sacroiliitis by imaging with about 70% of the patients diagnosed as axial SpA.

Conclusion: The simpler referral strategy 1 confirmed it's applicability in a multicenter study and demonstrated a slightly better performance in comparison to strategy 2. Therefore, strategy 1 can be recommended as an easy and reliable screening method for axial SpA on the primary care level.

References

1. Sieper J, Rudwaleit M. Ann Rheum Dis. 2005;64:659–63.
2. Brandt HC, et al. Ann Rheum Dis. 2007;66:1479–84.

Disclosure: D. Poddubnyy: None; **J. Vahldiek:** None; **I. Spiller:** None; **B. Buss:** None; **M. Rudwaleit:** None; **J. Sieper:** None.

2182

Do the New EULAR/ACR Rheumatoid Arthritis Classification Criteria Identify Early Psoriatic Arthritis Patients? Laura C. Coates[2], Philip G. Conaghan[2], Paul Emery[2], Michael J. Green[3], Gamal Ibrahim[1], Helen MakIver[1] and Philip S. Helliwell[2]. [1]Bradford Hospitals NHS Trust, UK, Bradford, United Kingdom, [2]LIMM, Section of Musculoskeletal Disease, University of Leeds, Leeds, UK, [3]York Hospitals NHS Trust, York, UK

Background: The new ACR-EULAR classification criteria for rheumatoid arthritis (RA) have been developed to enable an early identification of patients with RA. They were tested during development in undifferentiated arthritis populations. The aim of this study was to investigate whether the new ACR/EULAR criteria for early RA are robust in excluding PsA and whether any patients would meet both these criteria and PsA classification criteria.

Methods: The new ACR/EULAR criteria for early RA and the Moll&Wright and CASPAR criteria for PsA were applied to cases of early PsA (less than 24 months symptom duration) early RA and other forms of

early inflammatory arthritis who were all disease-modifying anti-rheumatic drug naive. Gold standard diagnosis was confirmed by a consultant rheumatologist. All joints required for the ACR/EULAR criteria were assessed.

Results: 111 early PsA cases, 82 early RA cases and 29 other early arthritis controls (undifferentiated arthritis n=13, spondyloarthritis n=9, inflamm OA n=4, crystal arthritis n=3) were recruited. The sensitivity of the ACR/EULAR criteria (score ≥6) in classifying early RA was 91%. The specificity for the criteria when considering all other diagnoses was 53%. When considering the specificity only for PsA, it was lower at 48%. When comparing classification criteria for RA and PsA, none of the RA patients met the PsA criteria (either Moll&Wright or CASPAR), and only 1 of the other inflammatory arthritis patients fulfilled these criteria. The majority of PsA patients who met the RA classification criteria also met a PsA classification criteria.

ACR/EULAR criteria components (%)	Early PsA (n=111)	Early RA (n=82)	Other controls (n=29)
Synovitis of at least 1 joint	92	96	83
1 large joint only	46	50	45
2–10 large joints	53	46	59
1–3 small joints	23	11	28
4–10 small joints	41	37	35
>10 joints including 1 small	30	60	7
Neg RF and ACPA	94	20	79
Low positive RF or ACPA	4	10	14
High positive RF or ACPA	3	71	7
Duration ≥6 weeks	99	98	83
Raised CRP or ESR	48	77	63
	Early PsA (n=111)	**Early RA (n=82)**	**Other controls (n=29)**
Met ACR/EULAR criteria	52	92	28
Met CASPAR criteria	87	0	3
Met Moll&Wright criteria	80	0	3
Met ACR/EULAR criteria AND Moll&Wright criteria	39	0	0
Met ACR/EULAR criteria AND CASPAR criteria	43	0	0

Conclusion: The new ACR/EULAR criteria are sensitive at identifying early RA but are not specific when considering psoriatic arthritis. The majority of PsA patients met the criteria due to high joint counts despite having negative immunology. The ACR/EULAR criteria must be used with caution in an early arthritis population particularly when patients have evidence of skin or nail psoriasis.

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The CASPAR Criteria Can Be Used To Identify Early Psoriatic Arthritis. Laura C. Coates[2], Philip G. Conaghan[3], Paul Emery[3], Michael J. Green[4], Gamal Ibrahim[1], Helen MakIver[1] and Philip S. Helliwell[3]. [1]Bradford Hospitals NHS Trust, UK, Bradford, United Kingdom, [2]LIMM, Section of Musculoskeletal Disease, University of Leeds, Leeds, United Kingdom, [3]LIMM, Section of Musculoskeletal Disease, University of Leeds, UK, [4]York Hospital NHS Trust, York, UK

Background: The classification of psoriatic arthritis (CASPAR) criteria were derived from a large patient dataset and have been shown to be valid in classifying established PsA (sensitivity 91.4%, specificity 98.7%). However in the original study, only 5% of the cohort had early disease (less than 12 months disease duration). The aim of this study was to assess the sensitivity and specificity of the CASPAR criteria in classifying early psoriatic arthritis and to compare the results to that of the Moll & Wright criteria.

Methods: The CASPAR criteria were applied to cases of early PsA (less than 24 months symptom duration) and controls with other forms of early inflammatory arthritis who were all disease-modifying anti-rheumatic drug naive. Gold standard diagnosis was confirmed by a consultant rheumatologist. Proportions of cases and controls meeting the criteria were compared using McNemars test. Receiver operator characteristic (ROC) curve analysis was performed to identify the area under the curve (AUC) and optimal cut point in the CASPAR criteria for a diagnosis of early PsA. Logistic regression was performed to identify which features were associated with PsA.

Results: 111 early PsA cases and 111 early arthritis controls (RA n=82, undifferentiated arthritis n=13, spondyloarthritis n=9, inflamm OA n=4, crystal arthritis n=3) were recruited. The sensitivity of the CASPAR criteria (score ≥3) in classifying early PsA was 87.4% compared to 80.2% for the Moll and Wright criteria. The specificity for both criteria was 99.1%, with only 1 control patient fulfilling both criteria for PsA. The AUC for the CASPAR criteria was 0.991 compared to 0.896 for the Moll & Wright criteria. When considering different cut-points for the CASPAR criteria, the best cut-point for classification remained a score of ≥3 as in the original CASPAR analysis. Considering a score of ≥2 gave a higher sensitivity of 99.1% but resulted in a drop in specificity to 94.6%.

When considering the individual components of the CASPAR criteria, 96.4% of cases had current, previous or a family history of psoriasis with 84% having current psoriasis. Dactylitis and nail psoriasis were highly discriminatory as only 1 control patient each had these features. Regression analysis identified that psoriasis and a negative RF were the most important features to differentiate PsA, followed by nail psoriasis and the presence of dactylitis.

CASPAR Features of PsA	Cases (n=111)	Controls (n=111)
Current psoriasis (%)	84	4
Previous psoriasis (%)	6	1
Family history of psoriasis (%)	18	8
Nail psoriasis (%)	38	1
Negative Rheumatoid factor (%)	96	47
Dactylitis (%)	28	1
New bone formation (%)	2	0

Conclusion: The CASPAR criteria are more sensitive than the Moll & Wright criteria in classifying early PsA. Although the sensitivity is slightly lower than that in established disease, the CASPAR criteria are valid for use as inclusion criteria for early psoriatic arthritis trials.

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Supppression of Both DKK-1 and SOST in a Mouse Model of Ankylosing Spondylitis Implicates the WNT-Signalling Pathway in the Linkage of Inflammation and Bony Ankylosis in Spondyloarthritis. Gethin P. Thomas[2], Ran Duan[3], Allison Pettit[4], Tibor Glant[1] and Matthew A. Brown[2]. [1]Rush University Medical Center, [2]The University of Queensland Diamantina Institute, [3]The University of Queensland Diamantina Institute, [4]University of Queensland Centre for Clinical Research

Ankylosing spondylitis (AS) is characterised by inflammation at entheses particularly in the spine and pelvis. Unlike in seropositive arthropathies in which erosion is the usual consequence of uncontrolled arthritis, in AS inflammation is followed by bony ankylosis. Although the inflammatory stages can be controlled medically, very little is known about the progression to the uncontrolled bone formation and no therapies are available that can slow this progression.

The proteoglycan-induced spondylitis model (PGISp) is a well-characterised mouse model of AS. Disease is induced by injections of a human proteoglycan extract, with axial inflammation evident after 9-weeks in the spine and sacroiliac joints. The resultant intervertebral disc destruction is followed by massive ectopic cartilage formation that eventually ossifies resulting in ankylosis, as demonstrated by toluidine blue staining and immunohistochemistry for collagen type I and osteocalcin.

To investigate the role of the Wnt-signalling pathway in this process, we studied the expression of two inhibitors of bone formation which act through the Wnt pathway, DKK-1 and SOST. Expression levels of both genes were significantly down-regulated in the spine and knee joints of PGISp mice. By week 12, DKK1 and SOST expression levels were reduced by 49% and 63% respectively in the spine, and by week 24 by 59% and 62% in peripheral joints, in PGISp compared with control mice ($P<0.05$).

We then undertook a microarray study comparing joints from control and PGISp mice. Unsupervised clustering clearly delineated between control and PGISp mice with 2600 genes being significantly differentially expressed between the two groups with 125 genes upregulated > 2-fold and 18 downregulated > 2-fold. In addition to genes involved in inflammation, and immune regulation, a significant over-representation of genes specifically involved in bone regulation including other members of the Wnt pathway was observed.

This study implicates the Wnt pathway as a likely mediator of the mechanism by which inflammation induces bony ankylosis in spondyloarthritis, raising the potential that therapies targeting this pathway may be effective in preventing this process.

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2185

Genetic and Clinical Correlates in African Americans with Ankylosing Spondylitis. Shervin Assassi[4], Julie T. Dang[3], Michael M. Ward[2], Joel D. Taurog[6], Michael H. Weisman[1] and John D. Reveille[5]. [1]Cedars-Sinai Medical Center, Los Angeles, CA, [2]NIH, NIAMS, IRP, Bethesda, MD, [3]Univ of Texas Health Science Center at Houston, [4]Univ of Texas Health Science Center at Houston, Houston, TX, [5]Univ Texas Health Sci Ctr, Houston, TX, [6]U-Texas SW Med Ctr, Dallas, TX

Background: There are few studies investigating disease characteristics of ankylosing spondylitis (AS) in African Americans (AA) because of the low prevalence of AS in this population. Furthermore, there are no previous studies, comparing disease severity between AA and white patients with AS.

The goal of this study was to compare clinical parameters in AA patients with AS to white patients and to examine associations of HLA-B, DRB1 and DQB1 alleles with AS in African Americans.

Method: Clinical data of 50 AA AS patients were derived from a cohort of 342 unrelated patients with AS. HLA class I and II alleles ascertained by DNA typing was performed on the AA AS patients as well as on 243 AA unaffected controls.

Results: AA AS patients had higher ESR, CRP, BASDAI, BASFI, and BASRI scores than white patients (Table). The difference in ESR, BASFI and BASRI remained significant despite correcting for disease duration, HLA-B27 status, gender, educational level and use of biologics. Despite higher disease burden, AA AS patients were less likely to be using biologic agents. This was especially pronounced in AA men with AS.

HLA-B27 negative African Americans with AS were older at disease onset, and had less frequently anterior uveitis compared to HLA-B27 positive AA patients.

HLA-B27 was present in 60% of AA patients, compared with 2% of AA controls. *HLA-B*4001* (B60) was the only other HLA-B allele significantly increased among patients. Marginally significant increases were also seen in *HLA-DRB1*1302* and *DQB1*0501*.

	AA-AS patients N=50	White-AS patients N=292	P-value	AA Controls N=263	P-value	OR
Education, college degree (%)	27.8	61.5	<0.001	NA	NA	NA
BASDAI(0–10)	4.85	3.48	0.009	NA	NA	NA
BASFI(0–100)	50.94	31.2	0.006	NA	NA	NA
BASRI (1.5–16)	9.26	6.56	<0.001	NA	NA	NA
CRP (mg/dl)	1.75	0.78	<0.001	NA	NA	NA
ESR (mm/hr)	32.8	14.5	<0.001	NA	NA	NA
Biologic use (%)	23	50.7	0.001	NA	NA	NA
HLA-B27 positivity (%)	62	84	<0.001	2	2.6×10^{-4}	71
B*4001 (%)	8	NA	NA	1	0.008	10
DRB1*1302 (%)	27	NA	NA	11	0.006	3
DQB1*0501 (%)	34	NA	NA	23	0.003	2.8

Conclusions: These data suggest that AA AS patients have more severe disease than whites as well as a lower frequency of HLA-B27. Also, the association with *HLA-B*4001* (B60) is seen in yet another ethnic group, in addition to whites and Asians.

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2186

Neutrophil Gelatinase Associated Lipocalin (NGAL) and Its Role in the Pathogenesis of Nephritis Induced by Pathogenic Antibodies. Rahul Pawar[4], Simona Gindea[4], Arlene T. Tieng[3], MIlena Pitashny[4], Leal Herlitz[5], Benjamin E. Levine[2], Thorsten Berger[6], Tak W. Mak[6] and Chaim Putterman[1]. [1]Albert Einstein College of Med, Bronx, NY, [2]Albert Einstein College of Medicine, Woodmere, NY, [3]Albert Einstein College of Medicine, Bronx, NY, [4]Albert Einstein College of Medicine, [5]Columbia-Presbyterian School of Medicine, [6]The Campbell Family Institute for Breast Cancer Research, Toronto, ON, Canada

Background: Anti-dsDNA antibodies are instrumental in the pathogenesis of lupus nephritis, although the mechanism by which these antibodies contribute to kidney damage has yet to be determined conclusively. We had found that treatment of mesangial cells with pathogenic anti-dsDNA antibodies induced the expression of multiple proinflammatory mediators known to be associated with lupus nephritis. One of the most highly induced genes was NGAL (AKA Lipocalin-2). NGAL is upregulated in response to a variety of inflammatory, ischemic, and other insults to the kidney, and in fact is a sensitive and early urine biomarker in several types of human disease.

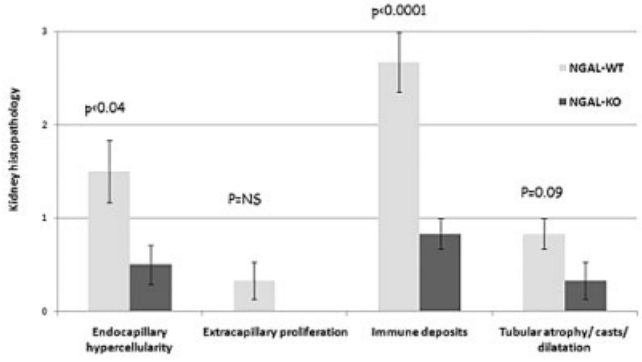
Purpose: To determine whether NGAL is expressed in the context of lupus nephritis, and investigate its role in the pathogenesis of renal injury induced by nephritogenic antibodies.

Methods: NGAL expression in serum, urine, and kidneys was analyzed serially in the MRL/lpr mouse lupus model. Nephrotoxic serum nephritis (NTS) was induced by passive transfer of preformed rabbit anti-mouse glomerular antibodies to C57Bl/6 wild type and NGAL deficient mice.

Results: With development of disease, MRL/lpr lupus mice displayed higher kidney NGAL expression than age-matched non-autoimmune mice. In addition, serum NGAL was significantly elevated in old MRL/lpr mice, as compared to young MRL/lpr, old MRL/+ and old BALB/c mice. Importantly, NGAL kidney expression in lupus mice significantly correlated with anti-dsDNA antibody titers and the renal pathology score. Significant elevations of kidney, serum and urine NGAL were observed as well in non-autoimmune mice following passive tranfer of rabbit anti-mouse glomerular antibodies and induction of NTS.

To determine if NGAL upregulation is instrumental in antibody mediated nephritis, we compared the severity of renal damage in C57Bl/6 NGAL knockout and wild type mice following induction of NTS. We found that NGAL deficient mice had significantly attenuated proteinuria, and improved renal histopathology (decreased endocapillarly proliferation and immune deposits) as compared to NGAL sufficient mice.

NGAL deficient mice display less kidney pathology following induction of NTS



Similarly, following NTS induction in non-autoimmune mice, NGAL injection significantly exacerbated nephritis (as assessed by increased proteinuria and more severe renal histopathology) and decreased survival. NGAL induced apoptosis via activation of caspase 3 and promoted the expression of inflammatory genes, in kidney cells in vitro and when injected to mice in vivo.

Conclusions: Nephritogenic antibodies upregulate kidney NGAL, which then appears to be instrumental in the pathogenesis of antibody mediated nephritis via promotion of inflammation and/or apoptosis. We are currently studying whether blocking NGAL may be a novel therapeutic approach for lupus nephritis.

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Dependence of IFNα-Exaggerated Immunopathology and Clinical Disease on B Cells and BAFF in SLE-Prone NZM 2328 Mice. Noam Jacob[6], Shunhua Guo[6], Alexis Mathian[3], Michael N. Koss[6], Simona Gindea[2], Chaim Putterman[1], Chaim O. Jacob[5] and William Stohl[4]. [1]Albert Einstein College of Med, Bronx, NY, [2]Albert Einstein College of Medicine, [3]Hôpital de la Pitié-Salpêtrière, [4]Univ Southern California, Los Angeles, CA, [5]University of Southern California Keck School of Medicine, Los Angeles, CA, [6]University of Southern California Keck School of Medicine

Purpose: IFNα is a potent activator of innate and adaptive immunity, and it has been ascribed an important contributory role in SLE pathogenesis. It has previously been shown that administration of IFNα to pre-autoimmune (NZBxNZW)F1 (BWF1) mice promotes rapid development of virulent SLE, whereas identical administration to non-SLE-prone BALB/c mice has no deleterious effect. Given the known importance of B cells and BAFF to SLE, we evaluated the dependence of IFNα-exaggerated disease on B cells and on BAFF in the BWF1-derived SLE-prone NZM 2328 (NZM) mouse model.

Methods: Fully congenic B cell-deficient NZM.JHD mice and BAFF-deficient NZM.BAFFKO mice were generated through "speed congenics". At 2–3 months of age (when autoimmunity had not yet developed in wild-type [WT] NZM mice), NZM WT, NZM.JHD, and NZM.BAFFKO mice were injected i.v. with $1–1.5 \times 10^9$ viral particles of either a recombinant adenovirus (Adv) vector containing murine IFNα subtype 5 under the control of the CMV promoter/enhancer (Adv-IFN) or the identical Adv vector lacking the IFNα insert (Adv-control). Mice were assessed for serum levels of SLE-associated IgG autoantibodies by ELISA; spleen lymphocyte phenotype by flow cytometry; renal immunopathology by routine histology, immunofluorescence, and immunohistology; severe proteinuria (≥3+) by urine dipstick; and mortality.

Results: In response to Adv-IFN, NZM WT mice developed virulent disease, characterized by rapid development of proliferative GN (with wire loops and crescents), glomerular deposition of all IgG isotypes (IgG1, IgG2a, IgG2b, IgG3) and C3, and severe proteinuria followed shortly thereafter by death. In contrast, NZM.JHD mice developed neither renal immunopathology nor clinical disease, and NZM.BAFFKO mice, despite developing limited glomerular IgG and C3 deposition, also remained free of histological GN and clinical disease. Strikingly, similar T cell expansion and serum IgG responses were observed in WT and BAFF-deficient mice despite their disparate pathological and clinical responses, whereas numbers of activated B cells increased in WT mice but not in BAFF-deficient mice. Nonetheless, B cell, plasma cell, and T cell infiltration of the kidneys in Adv-IFN-treated WT mice was similar to that in WT mice treated with Adv-control. Its ability to promote SLE disease in WT mice notwithstanding, IFNα administration failed to drive the preferential expansion of CD4+ memory T cells that occurs during the natural course of disease, and glomerular infiltration of macrophages failed to associate with development of clinical disease.

Conclusions: Therapeutic targeting in SLE of BAFF and/or B cells in SLE could be successful even in states of IFNα overexpression. Moreover, our results document potentially important biological differences between IFNα-driven and spontaneous "natural" SLE disease.

Disclosure: N. Jacob: None; **S. Guo:** None; **A. Mathian:** None; **M. N. Koss:** None; **S. Gindea:** None; **C. Putterman:** None; **C. O. Jacob:** None; **W. Stohl:** Genentech and Biogen IDEC Inc, 2, Human Genome Sciences, 2, Xencor, 2.

2188

IFNα Induced SLE in NZB/W Mice Is T Cell Dependent but Blockade of T_{FH} Does Not Prevent Disease. Zheng Liu[1], Ramalingam Bethunaickan[1], Weiqing Huang[1] and Anne Davidson[2]. [1]Feinstein Institute, [2]Feinstein Institute for Medical Research, Manhasset, NY

Background: IFNα accelerates SLE in several different murine models. The goal of these experiments was to investigate the mechanism for acceleration of lupus by interferon alpha (IFNα) in NZB/W F1 mice and to determine how excess IFNα influences the response to therapeutic agents.

Methods: Female NZB/W mice were given a single dose of IFNα adenovirus at 12 weeks of age. Starting the day of adenovirus injection, separate groups of mice were treated continuously with depleting anti-CD4 antibody, CTLA4Ig, anti-IL21, TACI-Ig or agonistic anti-4-1BB. Mice were monitored for autoantibodies and for proteinuria and some were sacrificed for analysis 50 days after adenovirus injection. Separate groups of mice received either anti-CD4 or combination CTX/costimulatory blockade at proteinuria onset and were sacrificed 4–6 weeks later.

Results: IFNα accelerated lupus in NZB/W F1 mice is associated with elevated serum levels of IgG2a and IgG3 anti-dsDNA antibodies, robust germinal center formation and accumulation of large numbers of short-lived plasma cells in the spleen. SLE onset is associated with an increase in B cell TLR7 expression, increased levels of BAFF and IL-6, and induction of T cells expressing IL-21. Although IFNα drives IL-6 production and a polyclonal increase in serum levels of IgG in a T-independent fashion, autoantibody induction and the development of nephritis are both completely dependent on CD4 T cell help. However, neither CTLA4Ig nor anti-IL-21 prevented proteinuria onset despite inhibiting T cell activation, germinal center formation, and production of IgG2a autoantibodies. This was due to failure to inhibit the generation of pathogenic IgG3 autoantibodies. In contrast, anti-4-1BB inhibited both IgG2a and IgG3 autoantibodies and prevented proteinuria onset. TACI-Ig did not prevent autoantibody formation, T cell activation or Ig deposition in the kidneys but still effectively delayed proteinuria onset by inhibiting renal chemokine production and preventing the activation of renal mononuclear cells. Remission could be induced with combination CTX/costimulatory blockade that depleted both IgG2a and IgG3 autoantibody producing short-lived plasma cells thereby decreasing autoantibody deposition in the kidneys.

Conclusions: IFNα induces short-lived plasma cells that produce autoantibodies in a T cell dependent manner through both germinal center and extrafollicular mechanisms. Prevention of germinal center formation is not sufficient to prevent SLE onset. Anti-4-1BB prevents both germinal center (IgG2a) and extrafollicular (IgG3) autoantibody formation and prevents SLE onset. Depletion of short-lived plasma cells producing the autoantibodies induces remission of disease. Surprisingly BAFF/APRIL blockade delays SLE onset without altering either autoantibodies or T cell activation; this is mediated via inhibition of the renal response to immune complex deposition but disease eventually ensues despite continuous treatment. These findings are relevant to interpreting results of recent clinical trials of biologic agents in SLE and suggest that the IFN signature confers a higher bar for therapeutic intervention.

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2189

Type I IFN-Dependent $CD86^{high}$ Marginal Zone-Precursor B Cells Are Potent T Cell Costimulators in the BXD2 Mouse Model of Lupus. John S. Wang[3], Qi Wu[3], PingAr Yang[1], Hao Li[1], Jun Li[1], John D. Mountz[2] and Hui-Chen Hsu[1]. [1]Univ Alabama at Birmingham, [2]Univ Alabama at Birmingham and VA Medical Center, Birmingham, AL, [3]Univ of Alabama at Birmingham

Background: We previously showed that type I-IFN producing plasmacytoid dendritic cells (pDCs) upregulated the expression of CD69 on $CD1d^{hi}CD21^{hi}IgM^{hi}CD23^{hi}$ marginal zone precursor (MZ-P) B cells in the spleens of lupus prone BXD2 mice. This action promotes the follicular migration of antigen delivering MZ-P B cells directly to the germinal centers (GC) in BXD2 spleen. In the present study, we determined if type I IFN can promote T-dependent antibody responses in BXD2 mice via its augmentation of the costimulatory function of MZ-P B cells.

Methods: Confocal imaging was used to determine the location of pDCs, MZ-Ps and CD4 T cells in the spleens of BXD2 and BXD2-*Ifnar*$^{-/-}$ mice. H&E staining of spleen and kidney was used to determine the presence of IgG^{bright} cells in BXD2 and BXD2-*Cd86*$^{-/-}$ mice. ELISA was used to determine serum levels of IFN-α, autoantibody, and NP-CGG- or NP-Ficoll-induced anti-NP_2 antibody titers. The level of type I IFN transcripts in the peripheral blood was determined by quantitative real-time PCR. [^{3}H]-thymidine was used to measure T cell proliferation.

Summary of the Results: There was increased clustering of pDCs located in the marginal sinus in the spleens of BXD2 mice, compared with B6 spleens. Consistent with this, RNA isolated from the peripheral blood of 3–6-mo-old BXD2 mice expressed >5-fold higher levels of *Ifna1*, *Ifna4*, and *Ifna11*, compared with those from B6 mice. Type I IFN receptor (IFNAR) deletion abrogated development of IgG^{bright} cell formation and suppressed a T-dependent but not T-independent antibody response in BXD2 mice. Type I IFN signaling induced the expression of CD86, but not CD80, on $CD1d^{lo}CD21^{lo}IgM^{lo}CD23^{hi}$ follicular (FO), $CD1d^{hi}CD21^{hi}IgM^{hi}CD23^{lo}$ marginal zone, and MZ-P B cells. However, MZ-P B cells demonstrated the highest expression of CD86 and the highest capacity for T-cell costimulation with intact IFNAR. In BXD2, but not BXD2-*Ifnar*$^{-/-}$ mice, MZ-P B cells clustered at the intra-follicular T-B border, an important immunological junction where GC formation is initiated. Both IFNAR and CD86 deletion

suppressed GC formation, autoantibody production, and IgG deposits in the kidney.

Conclusions Reached: Our study proposes that type I IFN can offer a new avenue by which T-dependent autoantibody responses are generated in BXD2 mice. First, type I IFN is critical in bringing MZ-Ps to the T-B border in the FO interior at the pre-GC stage. Second, type I IFN significantly increases the levels of CD86 on MZ-Ps, providing potent costimulation to CD4 T cells. Because pDCs are systemically circulated between the peripheral blood and the spleen, the present study exhibit important pathogenic and mechanistic implication for the IFN signature in the peripheral blood of human lupus patients.

Disclosure: J. S. Wang: None; **Q. Wu:** None; **P. Yang:** None; **H. Li:** None; **J. Li:** None; **J. D. Mountz:** None; **H.-C. Hsu:** None.

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Identification of a Genetic Locus on New Zealand Black Chromosome 1 Congenic Mice That Leads to Increased Generation of T Follicular Helper and TH17 Cells. Nafiseh Talaei[4], Yui-Ho Cheung[3], Carolina Landolt-Marticorena[4], Babak Noamani[1] and Joan E. Wither[2]. [1]Toronto Western Research Institute, [2]University Health Network, Toronto, ON, Canada, [3]University of Toronto, [4]University of Toronto, Toronto, ON, Canada

Purpose: Genetic loci on the New Zealand Black mouse chromosome 1 have been linked to the development of glomerulonephritis (GN) and production of anti-nuclear antibodies. Congenic mice in which a NZB chromosome 1 (c1) interval, extending from 35–106 cM, produce anti-nuclear antibodies and develop mild glomerulonephritis (GN). By creating mice with smaller overlapping NZB c1 intervals, we found that at least 5 genetic loci modulate autoimmunity in this interval. Notably, mice with a 70–100cM interval (c1(70–100cM)) developed high titre anti-dsDNA antibodies and severe GN resulting in death of ~40% of mice by 8 months of age, whereas those with a smaller 96–100 interval (c1(96–100)) produced lower levels of anti-nuclear antibodies and lacked renal disease. A prominent feature of c1(70–100) mice was increased numbers of large germinal centers, which can be seen in mice with expansion of T follicular helper cells (T_{FH}). The current study was undertaken to determine whether genetic loci on NZB c1 lead to expansion of T_{FH} and determine the cytokine profile of these cells.

Methods: c1(35–106cM), c1(70–100cM), and c1(96–100cM) congenic and B6 control mice were aged to 4 months. The proportion and number of splenic T_{FH} cells was determined by flow cytometry. To evaluate cytokine production, splenocytes were stimulated with PMA/ionomycin for 24 h and the supernatant assayed by Cytometric Bead Array or ELISA. IL-4, IFN-γ, or IL-17 producing cells were quantified by stimulating splenocytes with PMA/ionomycin for 4 h and examining intracellular cytokine expression by flow cytometry. Splenic sections were used to visualize the presence of T_{FH} and IL-17-producing $CD4^+$ T cells in the germinal centers using immunofluorescence microscopy.

Results: The proportion of T_{FH} ($CD4^+CD44^{high}CD62L^{low}CXCR5^+$) was significantly increased in c1(70–100) and c1(35–106) mice, with the highest levels seen in c1(70–100) mice. Splenocytes from all c1 congenic mouse strains demonstrated increased production of IL-21 and IL-17 following stimulation of PMA and ionomycin with the greatest increase seen in c1(70–100) mice and intermediate levels in c1(35–106) mice. Similar findings were observed for the proportion of IL-17-producing $CD4^+$ cells. No differences were seen for production of IL-4 and IFNγ between B6 controls and congenic mouse strains, although c1(70–100) and c1(35–106) mice had increased proportions of IFNγ-producing $CD4^+$ cells. Immunofluorescence microscopy confirmed the presences of increased numbers of T_{FH} cells in c1(70–100) and c1(35–106) mice, and revealed that the majority of IL-17 producing cells in c1(70–100) mice were located in the T cell zone and not the germinal center.

Conclusion: The findings suggest that a genetic polymorphism(s) on NZB c1 leads to expansion of T_{FH} and IL-17-producing T cells and that the levels of these cell populations are closely associated with the severity of disease.

Disclosure: N. Talaei: None; **Y.-H. Cheung:** None; **C. Landolt-Marticorena:** None; **B. Noamani:** None; **J. E. Wither:** None.

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Histone Deacetylase 9 Acts as an Epigenetic Switch in Aberrant CD4 T Cell Plasticity and PPAR-g Regulation in Systemic Lupus Erythematosus. Nilamadhab Mishra[3], Kailin Yan[5], Qiang Cao[6], Christopher M. Reilly[2], Jennifer Cann[4] and Benjamin A. Garcia[1]. [1]Princeton University, [2]Virginia Polytechnic Institute and State University and Edward Via College of Osteopathic Medicine, [3]Wake Forest Univ Health Scienc, Winston-Salem, NC, [4]Wake Forest University School of Medicine, [5]Wake Forest Unv Health Sciences, [6]Wake Forest UnvHealth Sciences

Pharmacological inhibition of histone deacetylase (HDAC) activity provides a therapeutic benefit in murine model of SLE, but clinical efficacy remains to be established. Understanding the role of individual HDAC that plays in lupus pathogenesis may lead to development of isoform specific HDAC inhibitors for better tolerability and efficacy in lupus. To identify which HDAC play significant role in lupus disease we first surveyed HDACs in splenocytes, T cells, kidneys in MRL/lpr mice and human lupus CD4+T cells. In this study, we report that HDAC9 is overexpressed in lupus prone MRL/lpr mice and human lupus CD4+T cells compared to controls. To explore the role of HDAC9 in pathogenesis of lupus, we generated MRL/lpr mice with systemic HDAC9 deficiency by genetic deletion approach. We demonstrated that MRL/lpr mice deficient with HDAC9 have decreased lymphadenopathy, splenomegaly, serum levels of high-affinity dsDNA autoantibodies, proteinuria, immunocomplex deposit in kidney, glomerulonephritis and increased survival. HDAC9 deficiency resulted Th2 polarization, decreased DNT cells, ICOS positive T effector cells, plasma cells and increased regulatory T cells in MRL/lpr mice. This epigenetic switch of CD4+T cells as a result of HDAC9 deletion are due to changes in lineage specific master regulator transcription factors of CD4+T effector and regulatory cells. HDAC9 deficient MRL/lpr mice have increased Foxp3, GATA3, and decreased Bcl6 expression. Increased expression of roquin, and miRNA101 contributed to the decrease expression of ICOS in HDAC9 deficient MRL/lpr mice. Upregulation of PPAR-g resulted decreased IFN-g, IL-12, iNOS, MCP1, CXCR3, CXCR4, CXCR5,CXCR6, and CXCR9 which resulted decreased inflammatory cells in kidney and peripheral tissues in HDAC9 deficient MRL/lpr mice. HDAC9 deficiency created changes in chromatin landscape selectively by increased site specific lysine histone acetylation in H3 (H3K9, H3K14 and H3K18) globally and locally in gene specific manner (IL-4, Foxp3, roquin and PPAR-γ genes). Together, our results unveil a epigenetic switch regulatory role of HDAC9 in aberrant CD4+ T cell plasticity in MRL/lpr mice. Therefore, targeting HDAC9 by a specific inhibitor may provide therapeutic benefit in lupus, possibly, with fewer side effects.Finally, measurement of levels of different histone modifications particularly site specific histone acetylations (H3k9, K14 and K18) may provide a biomarker for selecting lupus patients most likely to benefit from HDAC9 inhibitors.

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ACR Concurrent Abstract Sessions
Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's - Clinical Aspects and Therapeutics
Wednesday, November 10, 2010, 4:30 PM–6:00 PM

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Long-Term Benefit of Mycophenolate Mofetil for Treatment of Diffuse Cutaneous Systemic Sclerosis. Elizabeth Le[3], Fredrick M. Wigley[1], Ami A. Shah[2], Francesco Boin[2] and Laura K. Hummers[2]. [1]Johns Hopkins University, Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD, [3]Johns Hopkins University

Background: No drug has been demonstrated to successfully control active diffuse cutaneous scleroderma, but immunosuppressive therapy, particularly if given at the early inflammatory phase of diffuse skin disease, could alter the natural course of the disease. In this observational study, we analyzed our Scleroderma Center's experience using mycophenolate mofetil (MMF) for treatment of diffuse skin disease and compared changes in skin score with data from historical controls.

Methods: Scleroderma patients in our Center's database started on MMF primarily for active skin disease were included in the analysis. Historical controls were obtained from 3 large multicenter randomized clinical trials (RCTs) of other medications (D-penicillamine (D-pen), Recombinant Human

Relaxin (Relaxin), and Oral Bovine Type I Collagen (Collagen) Trials). Data from these 3 RCTs were pooled and analyzed irrespective of treatment assignments because none of the primary and secondary outcomes differed in the active agent groups compared with the placebo or control groups. The overall mean change in modified Rodnan skin scores (mRSS) at 6 months for the Relaxin group, and at 12 months for the D-pen and Collagen groups were compared to those of our MMF cohort at 6 and 12 months, respectively, using Student's t-tests.

Results: Of 2571 patients in our database, 99 patients satisfied our inclusion criteria and were included in the primary analysis. Patients were mostly female (82%) of white (76%) or black (14%) race. The mean age at MMF initiation was 48.2 ± 11.2 years, and the mean scleroderma duration at MMF initiation was 21.8 ± 77.5 months with a median of 12 months (IQR 8–23). The median MMF dose was 3 grams daily (range 0.5–3 gm daily). The mean baseline mRSS of the MMF cohort (24.2 ± 9.5) was not significantly different from that of the Collagen group (26.1 ± 7.8, p= 0.08), but was significantly higher than the D-pen group (21.0 ± 8, p=0.006) and lower than the Relaxin group (27.3 ± 6.9, p=0.001). The mean mRSS of the MMF cohort progressively decreased over time and was statistically significant compared to baseline at 6 months (21.4 ± 10.6, p=0.0003), 9 months (17.5 ± 10.3, p<0.0001), and 12 months (17.3 ± 10.5, p<0.0001), but not at 3 months (23.4 +/− 10.1). Although the change in mean mRSS between the control population (Relaxin: −4.83 ± 6.99) and the MMF cohort (−3.07 ± 7.4) at 6 months was similar (p=0.06), a statistically significant improvement in mRSS was detected at 12 months in the MMF cohort (−7.55 ± 10.0) compared to controls (D-pen: −2.47 ± 8.6, p 0.0009; Collagen: −3.4 ± 7.12, p 0.001). Compared to baseline, at 12 months there was also a statistically significant improvement in quality of life (p<0.0001) as indicated by the Health Assessment Questionnaire disability index and in the general (p=0.006) and muscle (p=0.01) Medsger severity scores. Forced vital capacity and diffusing capacity remained stable at 1 year.

Conclusions: This study suggests that mycophenolate mofetil can be an effective therapy for active diffuse skin disease in scleroderma, but the full benefits of the drug may be evident after long-term therapy.

Disclosure: E. Le: None; **F. M. Wigley:** None; **A. A. Shah:** None; **F. Boin:** None; **L. K. Hummers:** None.

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Imatinib Mesylate (Gleevec™) in the Treatment of Diffuse Cutaneous Systemic Sclerosis: Results of a One Year, Phase IIa, Single Arm, Open Label Clinical Trial. Robert F. Spiera[1], Jessica K. Gordon[2], Jamie Mersten[2], Cynthia Magro[3], Mansi Mehta[2], Horatio Wildman[3], Stacey Kloiber[2], Kyriakos A. Kirou[2], Stephen Lyman[2] and Mary K. Crow[2]. [1]Hospital for Special Surgery, New York, NY, [2]Hospital for Special Surgery, [3]Weill-Cornell Medical College

Purpose: To assess the safety and effectiveness of imatinib mesylate in the treatment of diffuse cutaneous systemic sclerosis (dcSSc.)

Methods: In this phase IIa, open-label, single-arm clinical trial, 30 patients with dcSSc were treated with imatinib 400 mg daily. Patients were monitored monthly. Modified Rodnan Skin Scores (MRSS) were assessed every three months. Pulmonary function testing, chest-radiography, echocardiography, and skin biopsies were performed at baseline and after 12 months of treatment. Paired t-tests were performed to compare before and after treatment.

Results: Twenty-four of 30 patients completed 12 months of therapy. At baseline median age was 48 (range 18 to 71.) Eighty percent were female. Race/ethnicity: 73% white, non-Hispanic, 13% Hispanic, 13% African-American. Average disease duration was 3.4 ± 2.3 years. 53% had interstitial lung disease (ILD.) 30% were anti-Scl70 positive.

171 adverse events (AEs) with possible relation to imatinib were identified; 97.6% were grade 1 or 2. Twenty-four serious AEs were identified, occurring in 8 patients. Two SAEs were attributed as at least possibly related to study medication. There was one death during the course of the trial due to pneumonia with respiratory failure in a patient with severe ILD and pulmonary artery hypertension which was not felt to be medication related. The most common AEs were edema (80%), nausea (73%), myalgia (67%), and creatine kinase elevations (43%).

MRSS decreased by 6.6±4.7 points at 12 months (p=0.001.) This change was not evident at 3 months (Δ=−0.5, p=0.43), but was seen at 6 months (Δ=−4.5, p<0.001) and 9 months (Δ=−5.3, p<0.001.) This decline in MRSS was seen regardless of duration of disease. In the subgroup of early patients with <18 months from disease onset there was an improvement in the MRSS of 7.9±5.2 (p=0.006) at 12 months. The Forced Vital Capacity (FVC) improved from 82.9±21.1% predicted to 89.3±25.2%, (p = 0.008). The diffusion capacity (DLCO) remained stable from 78.0±22.9% to 83.5±29.2% predicted (p = 0.12.) Improvement in FVC was significantly greater in patients without ILD, 10.7% predicted v. 2.1% predicted (p=0.01.) Improvements were seen in the VAS global (Δ=−9.6, p<0.046), shortness of breath (Δ=−6.7, p=0.006), and pain (Δ=−18.7, p<0.001) as well as in the SF-36 mental component (Δ=−6.6, p=0.03.) Other health related quality of life measures remained stable. Physician global assessment improved from 6.3±1.6 to 4.1±2.3 (p<0.001.) Blinded dermatopathologic analysis demonstrated a significant decrease in skin thickness and improvement in skin morphology with decreased thickness of collagen bundles and increased interstitial space.

Conclusions: Patients with dcSSc treated for one year with imatinib demonstrated improvements in skin thickening and FVC in this single-group study. Although adverse events were common, most were mild to moderate in severity. The conclusions that can be drawn from this study regarding efficacy and safety are limited by the uncontrolled study-design. Further investigation of imatinib to treat dcSSc in a double-blind randomized placebo controlled trial is warranted. (ClinicalTrials.gov number, NCT00555581.)

Disclosure: R. F. Spiera: Bristol-Myers Squibb, 2, Novartis Pharmaceuticals Corporation, 2, United Therapeutics, 2; **J. K. Gordon:** None; **J. Mersten:** None; **C. Magro:** None; **M. Mehta:** None; **H. Wildman:** None; **S. Kloiber:** None; **K. A. Kirou:** NovoNordisk, 2; **S. Lyman:** None; **M. K. Crow:** None.

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Serious Complications and Mortality among 158 Patients with Systemic Sclerosis (SSc) in the Scleroderma Lung Study (SLS) Followed for up to 9 Years. Daniel E. Furst[4], Dinesh Khanna[3], Philip J. Clements[5], Keith Sullivan[1] and Donald P. Tashkin[2]. [1]Duke, Durham, NC, [2]UCLA, [3]University of California Los Angeles, Los Angeles, CA, [4]University of California Los Angeles Medical School, Los Angeles, CA, [5]University of California Los Angeles School of Medicine, Los Angeles, CA

Objectives: To examine the mortality and serious complications of SSc in SLS patients, in up to 9 yrs f/u.

Methods: Pt's: In 158 SSc patients(59% diffuse,41% limited), age: 47.9(1.0) yrs; dis dur:3.2(0.2)yrs;mRSS:14.7(0.9),All had alveolitis by lung HRCT of the lungs and/or BAL. FVC: 68(1.0) (SD) % pred;DLCO 47.2(1.1) % pred. Renal function was normal.They had entered the 1 yr, double-blind, study of cyclophosphamide vs. plac and then underwent usual clinical care for the ensuing 4.7(1.8) yrs, thru 11/2009 or until death or loss to f/u.

Methods: 12/08 to 11/09, all centers were repeatedly contacted regarding pt outcomes, to get complete data.Data requested were: mortality (date, cause),cancer (type, outcome), renal dialysis (dates),renal or lung transplantation (date, outcome),TPN (date, duration) and/ or requirement for oxygen (duration, continuous or intermittent use).Where needed, IRB approval and re-consenting was undertaken.

Results: 72% of pt's had complete or nearly complete data. Mortality data was available on 134 patients but complete date were available in 52 pt's.5 yr mortality was 31.4- and 23.2%-Plac(p=0.92).Cancer caused death in 2 pt's (colon and angiosarcoma) and occurred in 5 others (still alive) (breast, prostate, vulva, 2 unknown primary). 2 pts required total parenteral nutrition (2/108,1.8%),2 required dialysis(2/109,1.8%) and no pt's underwent renal transplantation. 22 pt's(32/109,20.3%) required at least intermittent oxygen therapy and 2 underwent lung transplantation (2/108, 1.9 %).

Conclusion: Among SSc pt's with alveolitis but generally moderate disease of moderate duration, mortality was surprisingly high over 9 yrs (27%). The need for oxygen occurred commonly (20.3%). Renal dialysis,TPN and lung transplantation were noted(1.8–1.9%).Cancers were not those usually associated with cyclophopsphamide or immunosuppressive therapy, despite f/u for up to 9 yrs.

Table 1. Demographics

Diffuse SSc	59%	mRSS (max: 51)	14.7 (1.5)
Age (yrs)	47.9 (1.4)	Alveolitis	100%
Disease Duration (yrs)	3.2 (0.3)	FVC (% predicted)	68.1 (1.5)
		DLCO (% predicted)	47.2 (1.6)

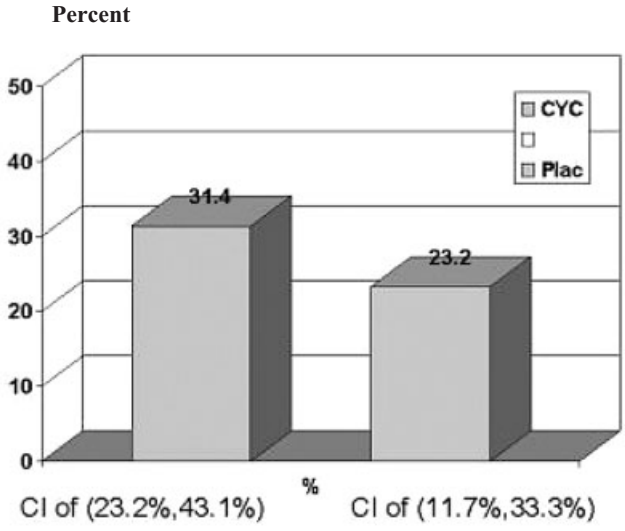

Figure 1. Mortality at 5 years.

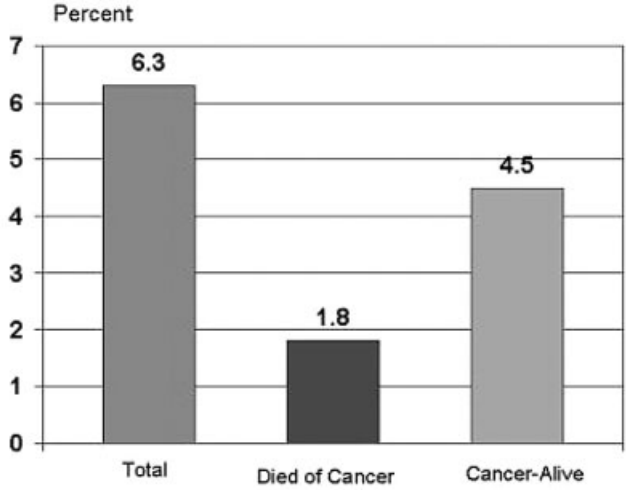

Figure 2. Cancers.

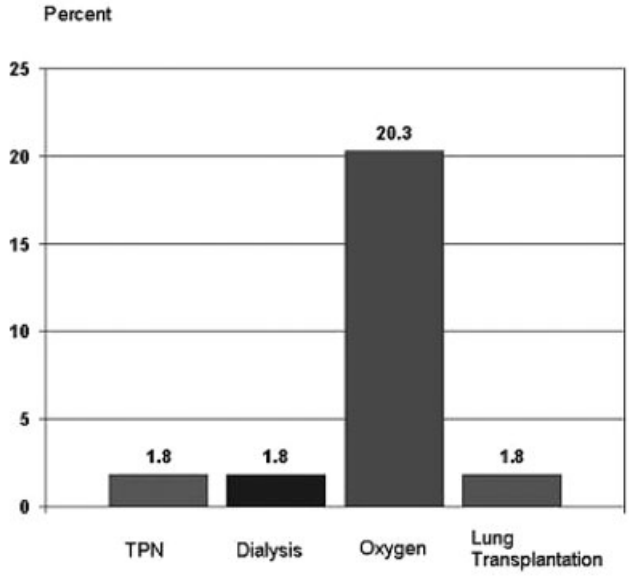

Figure 3. Other serious complications.

Disclosure: D. E. Furst: Abbott Laboratories, 2, 5, 8, 9, Actelion Pharmaceuticals US, 2, 5, 8, 9, Amgen Inc., 2, 5, 9, Biogen Idec, 5, 9, Bristol-Myers Squibb, 2, 5, 9, Centocor, Inc., 5, 9, Corrona, 3, Genentech and Biogen IDEC Inc, 2, 5, 9, Gilead Sci; **D. Khanna:** Actelion Pharmaceuticals US, 2, 8, Encysive Pharmaceuticals, 2, Gilead Sciences, Inc., 2, 8, NIAMS-NIH, 2; **P. J. Clements:** None; **K. Sullivan:** None; **D. P. Tashkin:** None.

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Productivity at Home and Work Place in Scleroderma—Analysis from the UCLA Scleroderma Quality of Life Study. Manjit K. Singh, Philip J. Clements, Daniel Furst, Paul Maranian and Dinesh Khanna. UCLA, Los Angeles, CA

Objective: Scleroderma (SSc) is associated with functional disability and poor quality of life. This study examines the productivity of SSc outside and within the home in a large observational cohort.

Methods: 162 patients completed the Work Productivity Survey (Osterhaus, J., Arthritis Research and Therapy 2009) at baseline. Patients indicated whether or not they were employed outside of the home, how many days /month they missed work (employment or household work) due to SSc, how many days/month productivity was decreased ≥ 50%, and how many days per month where SSc interfered with work. Patients also completed other patient-reported outcome (PRO) measures (HAQ-DI, Functional Assessment of Chronic Illness Therapy (FACIT), and CESD). We developed binomial regression models to assess the predictors of days missed at home per month or days missed outside the home per month. The covariates included: type of SSc, education, physician global assessment, patient global assessment, HAQ-DI, FACIT-Fatigue and CESD.

Results: The average age of patients was 51.8 years, 81% were female, 69% were Caucasian, 51% had limited SSc, 41% had diffuse SSc, and 7% had overlap syndrome. Sixty patients (37%) were employed outside of the home, with a majority employed in non-manual work (68%). Employed patients reported missing 2.6 days per month of work (absenteeism), had 2.5 days per month productivity reduced by half (presenteeism), and had 2.2 days per month where SSc interfered with their work (Table). Of the 102 patients that were not employed outside of the home, 39.4% were unable to work due to SSc related health problems, 12.1% were homemakers, 28.3% were retired and 5.05% were students. Patients missed an average of 8 days of housework per month, had home productivity reduced by more than 50% in 6 days per month, and had 4 days where SSc interfered with household work.

In the regression models, patients with lower education and greater physician assessment of disease severity were more likely to miss work outside the home. Type of SSc (limited or diffuse) did not influence productivity but those with high HAQ-DI were more likely to miss work at home.

Table 1.

Productivity in the work place†	
Work days missed (absenteeism), mean (SD)	2.6 (6.3)
Days with work productivity reduced by ≥50% (presenteeism), mean (SD)	2.5 (6.1)
Days of SSc interference with work productivity, mean (SD)	2.2 (2.9)
Productivity at home	
Household work days missed, mean (SD)	8 (10.6)
Days with household work productivity reduced by ≥50%, mean (SD)	6 (9.7)
Days with family, social, leisure activities missed, mean (SD)	2.5 (5.5)
Days with outside hired help due to SSc, mean (SD)	2 (5.0)
Days of SSc interference with household work productivity, mean (SD)	4 (3.4)

†Employed patients only. n = 60.

Conclusion: SSc has a major impact on productivity at home and at work. Nearly 40% of patients are disabled due to their SSc. Education, physician assessment and HAQ-DI were independent predictors of low productivity.

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2196

Results of the Delphi for EULAR/ACR Classification Criteria Working Group in Systemic Sclerosis. Jaap Fransen[4], Sindhu R. Johnson[5], Alan Tyndall[6], Murray Baron[1], Marco Matucci-Cerinic[8], Frank van den Hoogen[2], Janet E. Pope[3] and Dinesh Khanna[7]. [1]Jewish General Hospital, Montreal, QC, Canada, [2]Sint Maartenskliniek, [3]St Joseph Health Care London, London, ON, Canada, [4]The Radboud University Nijmegen Medical Centre, [5]Toronto Western Hospital, Toronto, ON, Canada, [6]University of Basel, [7]University of California Los Angeles, Los Angeles, CA, [8]University of Florence, Firenze, Italy

Background: Classification criteria for Systemic Sclerosis (SSc) are being updated as the previous ACR criteria did not regard all patients with limited cutaneous SSc, and did not include autoantibodies or nailfold capillaroscopy as items.

Objective: To select a set of items using Delphi procedures and the Nominal Group Technique (NGT) to be regarded for the classification of SSc.

Methods: Potential items for revising classification criteria for SSc were identified through two independent internet based consensus exercises, performed by the Scleroderma Clinical Trials Consortium (SCTC) and the EULAR scleroderma trials and research group (EUSTAR). The two first-round item lists were collated with removal of redundancies to a list of 168 items. This list was subjected to a Delphi procedure in three rounds using appropriateness scores on a 1–9 scale (1=completely inappropriate and 9=completely appropriate) and a consensus meeting using NGT.

Results: Round 1: 105 experts participated rating each of the 168 items. Items with a median score <3 were removed, resulting in a list of 102 items. Round 2: These items were again rated for appropriateness and subjected to a consensus meeting using NGT by European and North American SSc experts (n=16), resulting in 24 items. Round 3: The participants then individually scored each of the 24 items in a last Delphi round, using an appropriateness score (1–9) and by ranking their 10 favorites (top ranking 1–10). Items scored as relevant (70% of ratings in 7–9) were kept and ranked according to their top ranking while items scored as irrelevant (70% of ratings in 1–3 but less than 30% in 7–9) were discarded. This resulted in a list of 12 items that were kept (Table 1) and 12 'indecisive' items, while no item was scored as irrelevant. The indecisive items were: DLCO, FVC, dysphagia, esophageal dilatation, reflux disease, telangiectasia, finger flexion contracture, tendon friction rubs, ANA, anti-PMSCL autoantibodies, PAH, puffy fingers, finger pulp loss, calcinosis and cardiomyopathy.

Table 1.

Item	Appropriateness score (median)	TOP score	Rank
Positive anti-topoisomerase-1	9	73%	1
Presence of scleroderma	9	70%	2
Abnormal nailfold capillary pattern	9	67%	3
Positive anti-centromere	9	62%	4
Positive antiRNA polymerase III	8	43%	5
Finger tip ulcers or pitting scars	8	34%	6
Raynauds phenomenon	7	33%	7
Interstitial lung disease/pulmonary fibrosis	7	28%	8
Renal crisis	8	27%	9

Conclusion: The Delphi and NGT resulted in a set of items that will be assessed for their discriminative ability in a prospective study. Prospective data on SSc and 'mimickers' will be collected to yield further item reduction and development of new classification criteria for SSc.

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2197

Antinuclear Antibody Screening in Systemic Sclerosis. Donna Rose Swistowski[2], Nicole Saddic[3], Victoria K. Shanmugam[1] and Virginia D. Steen[4]. [1]Georgetown University Division of Rheumatology, Immunology, and Allergy, Great Falls, VA, [2]Georgetown University Division of Rheumatology, Immunology, and Allergy, Bethesda, MD, [3]Georgetown University Hospital Department of Medicine, [4]Georgetown University Medical Center, Washington, DC

Purpose: Scleroderma specific antinuclear antibodies (SScAB) are helpful predictors of disease manifestations, clinical course and outcome in scleroderma. Historically, immunofluorescence (IF) antinuclear antibody (ANA) testing was the gold standard method for ANA detection, and the American College of Rheumatology continues to recommend IF for evaluation of ANA. Many commercial labs have recently adopted newer, automated, non-immunofluorescence methods (NEW ANAs), such as EIA (enzyme immunoassay) or immunobead methods to evaluate for the presence of antinuclear antibodies. These new techniques rely on a limited panel of autoantigens in the assay.

The purpose of this study was to evaluate ANAs and SScAB results performed through commercial labs, using both NEW ANA detection techniques and traditional IF, in a consecutive cohort of scleroderma patients seen in the Georgetown Scleroderma Clinic over a one year period.

Methods: Between June 2008 and June 2009, 241 scleroderma patients were evaluated. Patient charts were reviewed for results of NEW ANA, IF-ANA, isolated nucleolar ANA pattern (NuANA), and the SScAB profile including anticentromere (ACA), anti-topoisomerase (Scl-70), U1 RNP, and RNA polymerase III (Pol III) antibodies.

Results: The results of this study are summarized in table 1. NEW ANA results were available in 58 patients with 28 patients (48%) testing negative. Of these 28 patients, 22 had either positive IF-ANA or a SScAB recorded: IF-ANA only (n=7), NuANA (n=6), Pol III (n=7), SSB (n=1), U1 RNP (n=1). In the patients with a positive NEW ANA (n=30) the NEW ANA successfully detected all patients with ACA (n=4), Scl-70 (n=13), UI RNP (n=6), and SSA (n=1) antibodies. A positive NEW ANA additionally identified Pol III (n=1), NuANA with a + SSA (n=3), and nonspecific ANA (n=2). However, the NEW ANA failed to identify the NuANA, Pol III antibodies, and other IF-ANA patterns in a significant number of patients (20/22 vs. 6/30, $p<0.0001$).

The remaining 183 SSc patients did not have NEW ANA testing available. Of these patients, 156 (85%) had positive SScABs or an IF-ANA. ACA was present in 22.4%, Scl-70 in 25%, and U1 RNP in 9.6%. This accounts for 57% of patients who we predict would be identified with the NEW ANA assay. However, patients with other antibodies including Pol III (10.2%), NuANA (19.2%), and nonspecific ANA patterns (13.5%), account for 40% of the scleroderma patients in our population, and we predict these patients would not be identified using NEW ANA assays.

Conclusions: Immunofluorescence ANA should be performed in all patients in whom there is clinical suspicion for scleroderma. Physicians should remain skeptical of negative ANAs in patients with clinical evidence of scleroderma.

Table 1. NEW ANA test results on 52 patients with corresponding ANA IF data or SScABs

ACA	NEW ANA Positive (n=30)		NEW ANA Negative (n=22)	
	4		0	
Scl-70	13		0	
UI RNP	6		1	
SSA/SSB	1		1 (+SSB)	
NuANA	3 (all+SSA)	20%	6	91%
Pol III	1		7	
ANA IF	2		7	

*$p<0.0001$.

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ACR Concurrent Abstract Sessions
Vasculitis
Wednesday, November 10, 2010, 4:30 PM–6:00 PM

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Association between Vascular Physical Examination Findings and Angiographically-Detected Arterial Lesions in Subjects with Large Vessel Vasculitis. Peter C. Grayson[4], Gunnar Tomasson[3], David Cuthbertson[11], Simon Carette[9], Gary S. Hoffman[6], Nader A. Khalidi[10], Carol A. Langford[5], Carol McAlear[4], Paul A. Monach[1], Philip Seo[7], Kenneth J. Warrington[8], Steven R. Ytterberg[8] and Peter A. Merkel[2]. [1]Boston University, Boston, MA, [2]Boston University School of Medicine, West Newton, MA, [3]Boston University School of Medicine, Boston, MA, [4]Boston University School of Medicine, [5]Cleveland Clinic Foundation, Cleveland, OH, [6]Cleveland Clinic Foundation, Pepper Pike, OH, [7]Johns Hopkins Bayview Medical Center, Baltimore, MD, [8]Mayo Clinic, Rochester, MN, [9]Toronto Western Hospital, Toronto, ON, Canada, [10]University of Hamilton, Hamilton, ON, Canada, [11]University of South Florida

Purpose: The vascular physical examination (PE) to assess for pulses, bruits, and systolic blood pressure (SBP) readings is considered essential in the clinical evaluation of patients with large vessel vasculitis (LVV), including Takaysu's arteritis (TAK) and giant cell arteritis (GCA). This study examined the relationship between findings on PE and angiographic-detected arterial lesions in subjects with established LVV.

Methods: 100 subjects (TAK=68, GCA=32) enrolled in a longitudinal, observational cohort underwent standardized PE and magnetic resonance

angiography of the aorta and its primary branches. Analysis was restricted to bilateral common carotid, subclavian, and axillary arteries. Sensitivity and specificity was calculated for the association between PE findings (absent pulse, bruit, and inter-arm SBP difference) and angiographic lesions defined as stenosis, occlusion, or aneurysm. To determine if PE findings accurately localized arterial lesions, a PE finding (e.g. left carotid bruit) was compared to angiogram findings in both the anatomically correlated vessel (e.g. left carotid artery) and in all vessels within the region (carotid or subclavian or axillary arteries).

Results: Participants were predominantly female (92%), Caucasian (87%), and had mean ages of 40 years (TAK) and 69 years (GCA). 67% had at least one PE abnormality: absent pulse (41%-TAK, 38%-GCA), bruit (54%-TAK, 28%-GCA), or ≥ 15 mmHg SBP difference (52%-TAK, 29%-GCA). Lesions in any of the carotid, subclavian, or axillary arteries were detected in 75% of subjects (82%-TAK, 59%-GCA). Individual PE findings had poor sensitivity (range 14–51%) and good-excellent specificity (range 72–98%) to detect arterial lesions. Sensitivity improved (range 52–71%) and specificity worsened (range 59–86%) if *any* of the 3 different PE maneuvers considered in combination were abnormal. Sensitivity worsened (range 6–30%) and specificity improved (range 88–100%) if *2 or more* of the PE findings were abnormal or if individual PE findings were compared to regional vessels without imposing single vessel anatomic correlation.

Physical Exam Finding	Angiogram Comparison Vessel	No.	Sensitivity	Specificity
Individual Exam Findings with Anatomic Correlated				
Absent Pulse				
Common Carotid	Ipsi CC	179	14	98
Radial	Ipsi SA	193	40	94
Bruit				
Common Carotid	Ispi CC	179	45	82
Subclavian	Ispi S	191	27	91
Blood Pressure				
BP Difference	Bilat SA	96	51	72
Any 1 Abnormal Exam Finding				
Carotid Bruit No Carotid Pulse	Ipsi CC	179	52	80
Subclavian Bruit No Radial Pulse	Ipsi SA	195	54	86
Subclavian Bruit BP Difference	Ipsi SA	195	65	59
No Radial Pulse BP Difference	Ipsi SA	195	63	61
Subclavian Bruit BP Difference No Radial Pulse	Ipsi SA	195	71	59

Physical Exam Finding	Angiogram Comparison Vessel	No.	Sensitivity	Specificity
Individual Exam Findings with Regional Correlated				
Absent Pulse				
Common Carotid	Ipsi CC/SA	195	7	99
Common Carotid	Bilat CC/SA	196	7	100
Bruit				
Common Carotid	Ipsi CC/SA	194	30	88
Common Carotid	Bilat CC/SA	195	27	91
Subclavian	Ipsi CC/SA	195	30	91
Subclavian	Bilat CC/SA	196	29	98
2 or More Combined Abnormal Exam Findings				
Carotid Bruit No Carotid Pulse	Ipsi CC	179	7	100
Subclavian Bruit No Radial Pulse	Ipsi SA	195	14	98
Subclavian Bruit BP Difference	Ipsi SA	195	14	93
No Radial Pulse BP Difference	Ipsi SA	195	25	95
Subclavian Bruit BP Difference No Radial Pulse	Ipsi SA	195	6	99

Key: Ispi=Ispilateral, Bilat=Bilateral, CC=Common Carotid, SA=Subclavian/Axillary, S=Subclavian

Conclusion: In subjects with established LVV, vascular PE findings have low sensitivity but high specificity to detect arterial disease. Abnormal PE findings are highly associated with the presence of arterial lesions, but normal PE findings do not rule out the possibility of arterial disease. Even when considering PE findings in combination, sensitivity is still inadequate to rule out arterial lesions. Specificity improves when PE findings are evaluated in association with a broader region of arterial lesions rather than a specific anatomically correlated vessel, suggesting that PE findings do not always accurately localize disease. While valuable in the assessment of arterial disease in LVV, the PE should not form the sole basis of assessment and should be supplemented by angiography.

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Sex, Age, and Birth Cohort Effects on Incidence of Giant Cell Arteritis.

Maureen Dubreuil[1], Hyon K. Choi[2], Yuqing Zhang[2] and Yanyan Zhu[2]. [1]Boston Medical Center, Boston, MA, [2]Boston University School of Medicine, Boston, MA

Purpose: Giant Cell Arteritis (GCA) is a common vasculitis affecting adults. Studies have shown that incidence of GCA increases with age and is higher among women than men. Several previous studies have also reported a secular trend of increasing GCA incidence. However, these data may be confounded by birth cohort effects. The purpose of this study was to estimate effect of age, birth cohort (birth year) and period (year of diagnosis) on the incidence of GCA in a UK general population cohort.

Methods: Incident cases of GCA between 1990 and 2008 were identified from The Health Improvement Network (THIN), an electronic medical record database of 6.3 million patients from general practices across the United Kingdom. Incident cases of GCA were defined by physician diagnosis of GCA and use of glucocorticoids in 1995–2008. An incident GCA case was defined as a subject aged over 50 years with first diagnosis of GCA following at least one year of enrollment in the database. Glucocorticoid use was defined as two prescriptions for oral glucocorticoids: the first within 6 months of GCA diagnosis date, and the second within 6 months of the first. Crude incidence rates were calculated as the number of new GCA cases divided by total person-years. Age- and gender-specific incidence rates of GCA were plotted, as were relative incidence rates of GCA for age, birth cohort (birth year) and period (year of diagnosis), using age-period-cohort spline curves, based on Poisson-type likelihood. Incidence rate ratios were estimated for women compared with men and for later versus earlier birth cohorts, using proportional hazards models.

Results: Of 1.7 million subjects (men: 47.7% women: 52.3%) aged 50–90 years old in 1995–2008, 2715 subjects developed incident GCA. The crude incidence rate was 1.3 and 3.0 cases per 10,000 person-years in men and women, respectively. The incidence rate of GCA increased with age until age 80, then decreased (Figure). For every 5-year age increment, incidence of GCA increased by 41% (RR: 1.41, 95% CI: 1.38–1.44). Incidence of GCA was 1.98 times higher in women than in men (RR=1.98, 95% CI: 1.82–2.16). Furthermore, the incidence was higher for later birth cohorts, with rate ratio of 1.49 per 10-year interval (95% CI 1.38–1.60). Incidence rate of GCA did not vary materially over the study period.

Conclusion: In this UK general population, there was a significant birth cohort effect on GCA incidence, independent of age and calendar year at diagnosis. After adjusting for the birth cohort effect, incidence rates and age-gender effects remained similar to those reported previously. This is the first study to demonstrate a birth cohort effect on incidence of GCA, suggesting the presence of risk factors to which individuals born more recently were exposed. Further research should aim to identify factors that contribute to these changes in GCA incidence.

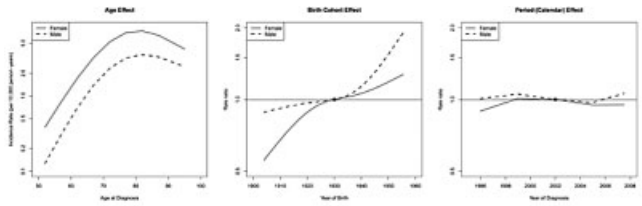

Figure. Age, birth cohort and period effects of giant cell arteritis.

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Identification of JAK1 as a Candidate Inflammatory Signalling Pathway by Genome-Wide Expression Profiling in Monocytes from Patients with Behcet's Disease.

Haner Direskeneli[3], Joseph J. Boyle[1], Filiz T. Ozdemir[3], Vuslat Yilmaz[2], Emel Eksioglu-Demiralp[3], Dorian Haskard[1] and Guher Saruhan-Direskeneli[2]. [1]Cardiovascular Sciences Centre, Imperial College, London, United Kingdom, [2]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [3]Marmara University, School of Medicine, Istanbul, Turkey

Purpose: Both innate and adaptive immune responses are observed in Behcet's Disease (BD). We aimed to obtain a global view of the immune/inflammatory activity in BD compared to Familial Mediterranean Fever (FMF), a classical, autoinflammatory disease.

Method: Twenty-eight patients with BD (F/M: 9/19, mean age: 33.4 years), 13 with FMF (F/M: 9/4, mean age: 30.4 years) and 21 healthy controls (HC) (F/M: 11/10, mean age: 30.6 years) were enrolled to the study. Whole-genome microarray profiling was performed with human U133 (Plus 2.0) microarrays on an Affymetrix platform using CD14+ monocyte and CD4+T lymphocyte subsets isolated by microbeads from peripheral blood mononuclear cells. Data was analysed with Genespring (Version 10.0) software. RT-PCR was performed for the validation of JAK1 expression.

Results: Among 28792 transcripts analysed, in CD14+ monocytes, 1188 transcripts reached a significant difference level with a minimum 2-fold difference observed in 279 genes. In CD4+T-lymphocytes, 2880 transcripts showed significant difference with at least 2-fold difference in 109 genes. In CD14+ monocytes of BD patients, oxysterol binding protein-like-8 (OSBPL8)(3.8 fold), cell-division-cycle-27 homolog (S. cerevisiae) (CDC27)(3.1 fold), myeloid/lymphoid or mixed-lineage leukemia-3 (MLL3)(3.1 fold), PHD finger protein-3 (PHF3)(2.9 fold) and BCL2-associated × protein (BAX)(2.7 fold) had the highest expressions. However,

in principal component analysis, Januse-kinase-1 (JAK1)(2.6 fold) and metallothionein 1X, (MT1X)(2.1 fold) appeared to be the dominant molecules associated with immune/inflammatory signalling pathways. Validation by RT-PCR also showed an increased JAK1 expression (fold increase compared to GAPDH: BD: 9.5 vs FMF: 5.1 vs HC: 7.3, p=0.07, BD vs FMF: p=0.04).

Discussion: Whole-genome microarray analysis demonstrated a selective activation of BD monocytes compared to FMF, suggesting their critical role between innate and adaptive immune responses. Activation of JAK1 through various cytokines such as IL-2, IL-6, IL-15 and interferon-gamma may be one of the dominant signaling pathways driving inflammation in BD.

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2201

A Randomized, Controlled, Multicenter Phase III Study of the Efficacy and Safety of Rituximab (RTX) Monotherapy Versus the Best Available Treatment in Patients with Mixed Cryoglobulinemia Syndrome. Salvatore De Vita[15], Luca Quartuccio[15], Miriam Isola[8], Paola Masolini[16], Stefania Sacco[15], Ginevra De Marchi[15], Cesare Mazzaro[6], Patrizia Scaini[13], Marco Lenzi[4], Mauro Campanini[1], Salvatore Scarpato[21], Antonio Tavoni[20], Maurizio Pietrogrande[9], Clodoveo Ferri[19], Maria Teresa Mascia[18], Dario Roccatello[3], Anna Linda Zignego[2], Paolo Pioltelli[11], Armando Gabrielli[12], Davide Filippini[14], Oreste Perrella[5], Sergio Migliaresi[17], Massimo Galli[7], Giuseppe Monti[10] and Stefano Bombardieri[20]. [1]A.O. Maggiore-Medicina II, Novara, Italy, [2]Center for Systemic Manifestations of Hepatitis Viruses (MaSVE), Department of Internal Medicine, University of Florence, Florence, Italy, [3]Centro di Ricerche di Immunopatologia e Documentazione su Malattie Rare, Struttura Complessa a Direzione Universitaria di Immunologia Clinica, Ospedale S.G. Bosco, Torino, Italy, [4]Department of Clinical Medicine, University of Bologna, S. Orsola-Malpighi Hospital, Bologna, Italy, [5]Department of Infectious Diseases and Immunology, Cotugno Hospital, Naples, Italy, [6]Department of Internal Medicine, Pordenone General Hospital, Pordenone, Italy, [7]Dipartimento di Scienze Cliniche Luigi Sacco, Sezione di Malattie Infettive e Immunopatologia, Università degli Studi, Ospedale Luigi Sacco, Milano, Italy, [8]Institute of Statistics, University of Udine, Udine, Italy, Italy, [9]Internal Medicine Unit, Policlinico San Marco, Bergamo, Italy, Italy, [10]Internal Medicine Unit, Saronno Hospital, Azienda Ospedaliera di Busto Arsizio, Saronno, VA, Italy, Italy, [11]Internal Medicine, Donizetti Hospital, Monza, Italy, Italy, [12]Internal Medicine, Università Politecnica delle Marche, Ancona, Italy, Italy, [13]Nephrology Unit, Spedali Riuniti, Brescia, Italy, Italy, [14]Rheumatology Clinic, A.O. Niguarda Ca' Granda Hospital, Milan, Italy, [15]Rheumatology Clinic, Azienda Ospedaliero-Universitaria "S. Maria della Misericordia", Udine, Italy, [16]Rheumatology Clinic, Azienda Ospedaliero-Universitaria "S. Maria della Misericordia", Udine, Italy, [17]Rheumatology Clinic, University of Naples, Italy, Italy, [18]Rheumatology Unit, Department of Internal Medicine, University of Modena e Reggio Emilia, Italy, Italy, [19]Rheumatology Unit, Department of Internal Medicine, University of Modena, Italy, Italy, [20]Rheumatology Unit, Department of Internal Medicine, University of Pisa, Pisa, Italy, Italy, [21]Rheumatology Unit, M. Scarlato Hospital, Scafati, Salerno, Italy, Italy

Objectives: this is the first randomized controlled trial comparing RTX with the best available treatments (i.e., cyclophosphamide, azathioprine, high-dose steroids, or plasma exchange) in MC patients with glomerulonephritis, or peripheral neuropathy or skin ulcers, where antiviral therapy failed or was contraindicated by the expert clinician. Primary end point was to evaluate the survival on treatment (due to lack of treatment failure) on RTX in comparison with the best available treatment options (as chosen by expert clinicians) on major manifestations of MC.

Patients and Methods: 59 MC patients were enrolled; 30 patients were randomized in the arm A (best available treatments), 10 nephritis, 3 skin ulcers and 17 peripheral neuropathy, while 29 patients were randomized in the arm B (RTX), 7 nephritis, 3 skin ulcers and 17 peripheral neuropathy. RTX 1 g × 2 at day 1 and 15 was administered with standard premedication. Patients were followed for 24 months. Rescue arm with RTX for non-responders to the best available treatment was permitted in any time, while withdrawn due to RTX treatment failure was introduced at the 6th month after RTX, if no response was observed. Finally, RTX retreatment was given at the time of clinical relapse.

Results: Fifty-seven patients were available for data analyses. Patients were HCV positive in 53/57 (93%), they were 46 female and 11 male, and median age was 65 years (range 37–79 years). No differences between the two randomized groups were observed in terms of age and sex distribution.

Treatment chosen in group A were: high-doses of corticosteroids in 17/29 (58.6%), plasmapheresis in 5/29 (17.2%), cyclophosphamide in 4/29 (13.8%) and azathioprine in 3/29 (10.3%).

Average survival time on treatment was (mean±SE) 76.9 ± 24.2 days on group A, while it was 529.1 ± 40.5 days in group B (p<0.0001, log Rank test). Survival rate on treatment in group B vs group A was 93% vs 14% at month +3, 3% vs 71% at month +6, 3% vs 64% at month +12, and 61% vs 3% at month +24.

When considering the following variables in a multivariate regression model (age, sex, baseline BVAS, and the baseline clinical manifestations, as defined as skin ulcers, and/or glomerulonephritis and/or neuropathy, and the treatment group), only the assigned treatment group was selected and significantly associated with the survival time on treatment (p=0.0001, OR: 7.9; 95% CI: 3.6–17.2), thus confirming the association between the survival on treatment and the assignment to the rituximab group.

Conclusion: RTX is the best choice in MC patients with active major involvements (i.e. renal, neurologic or cutaneous), when antiviral therapy failed or is contraindicated. The RTX 1 g × 2 treatment schedule was alternative to the standard hematologic regimen of 4 weekly 375 mg/m^2 infusions.

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2202

A New Polymorphism of the Fibroblast Growth Factor (*FGF*)*23 Gene:* A Promising Predictor of Coronary Damage in Kawasaki Disease (KD). Fernanda Falcini[1], Laura Masi[3], Francesco Franceschelli[3], Gigliola Leoncini[3], Serena Capannini[1], Francesco La Torre[4], Giuseppina Calcagno[4], Marco Matucci Cerinic[2] and Maria Luisa Brandi[3]. [1]Department of BioMedicine, Section of Rheumatology, Transition Clinic, University of Florence, Florence, Italy, [2]Department of BioMedicine, Section of Rheumatology, Transition Clinic, University of Florence, Florence, Italy, [3]Department of Internal Medicine, Metabolic Bone Diseases Unit, University of Florence, Italy, [4]Department of Paediatrics, Rheumatology Unit, University of Messina

Background: Vascular endothelial cell damage is crucial in KD, acute systemic vasculitis complicated by arterial dysfunction. Intimal thickening and fibrosis are reported in KD coronary arteries. Several pts even timely treated with IVIG may develop coronary artery abnormalities (CAA) with risk of ischemic heart disease. Phosphatonins are new hormones involved in phosphate homeostasis and bone mineralization. FGF23, the master phosphatonin, acts through FGFr1 present in vasculature and heart. *Fgf23* knockout mice develop ectopic calcifications and vascular and heart damage assuming that FGF23 contribute to the development of vascular injury.

Aims: 1.To measure the intact FGF23 serum levels in KD pts. 2.To assess the association between FGF23 levels and CAA 3.To screen KD pts for *FGF23* gene mutation looking at a possible role of FGF23 allelic variants in cardiac damage.

Patients: 95 KD pts (58 M,37F, median age 30.5 mths) after informed consent entered the study. 30 age-sex matched healthy children acted as controls All pts had received IVIG and ASA. In all, at baseline and at study entry lipid profile (cholesterol, HDL, LDL, tryglicerides) was evaluated.

Methods: Serum intact FGF23 level was measured, using an ELISA assay (Immunotopics Inc. San Clemente, CA, USA).Genomic DNA was extracted from peripheral blood and the 3 *FGF23* exons, including the intron-exon boundary regions, were PCR-amplified and analyzed on ABI Prism 3100 Genetic Analyzer (Applied Biosystems, Foster City, CA.

Results: KD pts have higher FGF23 serum levels than controls (72+/−40SD vs 12,3+/−3.2SD pg/ml. Student's T Test: p=0.01).DNA analysis shows a new C insertion in the intronic region between −36 and −37 nucleotide close to the exon 2 (rs3832879: NM_020638.2:c.212-37_212-36insC).All pts (18M,10F) with polymorphic allelic variant have CAA (aneurysms, dilatations), and display higher levels of serum FGF23 than pts without polymorphic site (120+/− 40 vs. 38.2+/− 5).

Conclusions: From our preliminary data the segregation of FGF23 genotype with the CAA advocates a possible functional role of the new polymorphism in KD coronary artery injury. These data point to FGF23 gene polymorphism and serum FGF23 levels as two potential predictors of high

risk of CAA. So far, no individual genotype data are available for FGF23 gene polymorphism.

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2203

Mepolizumab, a Humanized Anti-IL-5 Antibody, Has Steroid-Sparing Potential in Churg-Strauss Syndrome. Frank Moosig[1], Kristina Butherus[1], Bernhard Hellmich[2] and Wolfgang L. Gross[1]. [1]University Hospital Schleswig Holstein & Klinikum Bad Bramstedt, [2]University of Tübingen & Kreiskrankenhaus Plochingen

Background: In Churg-Strauss-Syndrome (CSS), a condition closely related to the hypereosinophilic syndrome (HES), high doses of glucocorticoids (GC) are often needed to control activity despite additional immunosuppression. Currently, severe cases demand treatment with cytotoxic agents such as cyclophosphamide and 15–20% of patients are refractory to standard therapy. Therefore, new targeted therapeutic options are needed. Interleukin-5 (IL-5) is the major inductor of hypereosinophilia and eosinophils (EO) are believed to mediate organ damage. In HES, a steroid-sparing effect of mepolizumab has been demonstrated. Therefore, targeting IL-5 in CSS is reasonable.

Methods: In this phase II trial, we included 10 CSS patients with active disease (Birmingham vasculitis activity score [BVAS] >3) under standard therapy. After stopping previous immunosuppressive medication, except GC, 750 mg mepolizumab was administered IV every 4 weeks for a total of 9 infusions. GC were tapered, as feasible, without loss of disease control. Methotrexate was initiated after the last mepolizumab infusion.

Results: The initial median BVAS was 9 (range 4–15), the GC dose 20 mg/d (range 12.5–70 mg/d) and the EO count 205/μl (range 13–4867/μl). One patient was excluded from the study because of non-compliance after 3 infusions. All 9 remaining patients reached remission (BVAS 0 and GC dose <7.5 mg/d prednisolone). GC dose could be reduced in all 9 patients (week 32: 4.5 mg/d [range 4–12.5 mg/d]). BVAS and EO counts improved significantly (week 32: BVAS 0 (0 ± 0), $p=0.0057$; EO 18/μl (range 4–64.8/μl), $p=0.0059$). No severe adverse events attributable to mepolizumab occurred and the overall safety profile was good. After stopping mepolizumab, 2 patients experienced major and 3 minor relapse during a follow up of 10 months (range 4–14 months).

Conclusion: This phase II trial strongly suggests that mepolizumab may be an effective and safe therapeutic option in refractory CSS and might offer benefits beyond its steroid-sparing potential.

ClinicalTrials.gov Identifier: NCT00716651

Disclosure: F. Moosig: None; **K. Butherus:** None; **B. Hellmich:** None; **W. L. Gross:** None.

2204

Periodontal Disease Hampers Anti-TNF Treatment Response in Rheumatoid Arthritis. Cynthia Savioli[1], Gisele Maria Campos Fabri[2], Ana Luisa Calich[5], Ana Cristina Medeiros Ribeiro[5], Julio Cesar Moraes[5], Carla Gonçalves Saad[5], Jozélio Freire Carvalho[5], Clovis Almeida Silva[4], Eloísa Bonfá[5] and José Tadeu Tesseroli Siqueira[3]. [1]Dentistry and Rheumatology Division (CEDMAC), Faculdade de Medicina da Universidade de São Paulo, Osasco, São Paulo, Brazil, [2]Dentistry and Rheumatology Division (CEDMAC), Faculdade de Medicina da Universidade de São Paulo, [3]Dentistry Division, Faculdade de Medicina da Universidade de São Paulo, [4]Paediatric Rheumatology Unit, Rheumatology Division (CEDMAC), Faculdade de Medicina da Universidade de São Paulo, [5]Rheumatology Division (CEDMAC), Faculdade de Medicina da Universidade de São Paulo

Purpose: To evaluate prospectively the effect of anti-TNF therapy in periodontal disease and its possible association with rheumatoid arthritis (RA) treatment response.

Methods: Twenty RA (ACR criteria) patients were assessed before (BL) and after 6 months (6M) of anti-TNF treatment. A dentist performed systematic dental and facial examinations that included: orofacial clinical features, tooth decay (DMFT) index, periodontal assessment [plaque and gingival bleeding index, probing pocket depth (PPD), cementoenamel junction (CEJ) and clinical attachment level (CAL)], Helkimo's index and salivary flow. All patients were examined by a rheumatologist, blinded to dentist assessment, in order to evaluate: demographic data, clinical manifestations, drug use, disease activity (CRP, ESR, DAS 28) and quality of life (HAQ) parameters.

Results: The median age of RA patients was 50(27–70) years and 90% were female. The median disease duration was 11(2–43) years. Infliximab was used in 17(85%) patients, adalimumab in 2 and etanercept in 1. No differences were observed in the median of plaque and gingival bleeding indices, PPD, CEJ and CAL comparing BL and 6M ($p>0.05$) in spite of a significant DAS28 reduction (5.55 vs. 3.98, $p=0.008$) and a trend to ESR (24 vs.13 mm/1st h, $p=0.071$) after 6 months of therapy. Further analysis of the 9(45%) patients with periodontal disease (PD) at study entry revealed a lack of response with no significant differences in the disease activity parameters between BL and 6M ($p>0.05$). In contrast, patients without PD showed a significant improvement in disease activity [DAS 28 (5.5 vs. 3.8, $p=0.01$) and ESR (25 vs.12 mm/1st h, $p=0.05$)] comparing BL and 6M, respectively. No differences were observed in the frequencies of orofacial complaints, alteration of mandibular mobility and clinical dysfunction indices and in the median of salivary flow after 6M in both groups ($p>0.05$). DMARDs use was similar comparing whole group at BL and 6M as well as comparing patients with and those without PD ($p>0.05$).

Conclusions: This study supports the notion that an underlying periodontal disease affects TNF blockers efficacy in RA patients. The possibility that a sustained gingival inflammatory state hampers treatment response in this disease has high clinical interest, since this a treatable condition.

Disclosure: C. Savioli: None; **G. M. C. Fabri:** None; **A. L. Calich:** None; **A. C. M. Ribeiro:** None; **J. C. Moraes:** None; **C. G. Saad:** None; **J. F. Carvalho:** None; **C. A. Silva:** None; **E. Bonfá:** None; **J. T. T. Siqueira:** None.

2205

Safety without Borders: Upper and Lower Gastrointestinal Safety of Celecoxib in a Pooled Analysis of 52 Prospective, Randomised, Double-Blinded, Parallel-Group Clinical Trials. Gurkirpal Singh[3], George Triadafilopoulos[3], Naurang Agrawal[1], Geoff Makinson[2], Chunming Li[2] and Ha Nguyen[2]. [1]KUMC, [2]Pfizer, [3]Stanford University

Objectives: Nonsteroidal anti-inflammatory drug (NSAID)-related serious upper and lower gastrointestinal (UGI/LGI) complications are well-recognized, but most clinical trials of cyclooxygenase (COX)-2 selective NSAIDs have focused on UGI outcomes as their primary endpoints. We used a novel composite endpoint measuring injury in the entire GI tract to study GI outcomes in patients enrolled in celecoxib clinical trials using individual patient-level data.

Aims & Methods: A novel endpoint – clinically-significant upper and lower GI events (CSULGIEs) – was developed. A total of 52 randomized, double-blind, parallel group studies were identified from the Celecoxib Clinical Database and included in this patient-level pooled analysis. All studies had a planned duration of continuous treatment with celecoxib and either a nsNSAID (ibuprofen, naproxen, diclofenac, ketoprofen, loxoprofen), rofecoxib or a placebo comparator arm for ≥ than 4 weeks. All included studies had their final study reports completed by October 1st, 2007. Open-label and cross-over trials, and all healthy volunteer studies were excluded from the analysis. The primary endpoint was the cumulative incidence of CSULGIEs (including perforations, obstructions, clinically significant bleeds) or symptomatic ulcers as adjudicated by an independent blinded committee. Adjudication was based on predefined criteria and available reported adverse events, laboratory data and narratives. The stratified log rank test was used to compare treatments, adjusting for studies. All doses of celecoxib (from <200 to 800 mg total daily dose) and nsNSAIDS were pooled. Asymptomatic hemoglobin or hematocrit drops were not considered as cases for this analysis.

Results: A total of 51,048 patients were included in the study: 28,614 patients were randomized to celecoxib (mean age 60.1 years), 15,278 to nsNSAIDs (mean age 59.3 years), 1,329 to rofecoxib (mean age 70.6 years) and 5,827 to placebo (mean age 57.2 years). A total of 354 cases of serious UGI/LGI complications were reviewed by the adjudication committee who confirmed 92 CSULGIEs. The number of events and the incidence rate per 100 person-years were: celecoxib [40, 0.33%], nsNSAID [38, 0.82%], rofecoxib [0] and placebo [14, 0.37%]). The difference between celecoxib and nsNSAIDs was statistically significant, using Kaplan Meier stratified log-rank test ($p<0.0015$).

Conclusion: The known UGI safety of celecoxib is also associated with a lower risk of all clinically significant GI events throughout the entire GI tract compared to patients treated with nsNSAIDs.

Disclosure: G. Singh: Pfizer Inc, 2; **G. Triadafilopoulos:** Pfizer Inc, 5; **N. Agrawal:** Pfizer Inc, 5; **G. Makinson:** Pfizer Inc, 3; **C. Li:** Pfizer Inc, 3; **H. Nguyen:** Pfizer Inc, 3.

2206

Dose Matters: The Risk of Complicated Gastroduodenal Ulcers with Naproxen Is Dose-Dependent. Gurkirpal Singh[3], Ajitha Mannalithara, Amrita Sehgal[4], Alka Mithal[2], Mark Sostek[1] and George Triadafilopoulos[3]. [1]Astra Zeneca, [2]ICORE, [3]Stanford University, [4]University of California Berkeley

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the management of pain and inflammation associated with osteoarthritis, rheumatoid arthritis and other musculoskeletal disorders but they carry a risk for cardiovascular (CV) and gastrointestinal (GI) toxicity. Large outcome studies have found that high-dose naproxen is associated with GI toxicity but less serious CV toxicity than other NSAIDs and COX-2 selective inhibitors (Kearney *et al*. *BMJ* 2006;332:1302–1308). It is unclear whether lower doses of naproxen present a similar level of GI risk while maintaining a favourable CV safety profile.

Objectives: To examine the prevalence of hospitalisations for complicated gastric and duodenal ulcers (bleeding, perforation, obstruction) in patients treated with varying doses of naproxen, as used in everyday clinical practice, in order to ascertain if lower doses of naproxen are associated with a comparable risk of upper GI (UGI) complications to naproxen 1,000 mg/day.

Methods: We conducted a nested case-control study using data from MediCal, California (the largest Medicaid programme in the US, with more than 7 million participants per year). Patients were aged 18 years or older with physician-diagnosed arthritis and had received treatment with an NSAID or COX-2 selective inhibitor between January 1999 and June 2005. All hospitalisations for complicated gastric and duodenal ulcers were risk-set matched with 4 controls on the basis of age, gender and date of hospitalisation. Analyses were adjusted for potential confounders, co-medications, co-morbidities and over-the-counter use of NSAIDs, including aspirin.

Results: A total of 688,424 patients were included, contributing 2,665,611 person-years of observation time. Of these, 11,303 patients who were hospitalised due to complicated gastric or duodenal ulcers were matched to 45,212 controls (mean age 70.7 years, 35% male). Patient characteristics of users of different NSAIDs were similar, except for COX-2 selective inhibitors being prescribed to older patients with more GI risk factors, as expected. Multivariate-adjusted rate ratios (95% CI) for hospitalisation with different doses of naproxen compared with remote use (≥61 days prior to hospitalisation) were: 500 mg/day, 2.51 (1.61–3.92); 750 mg/day, 2.95 (2.34–3.73); and

1,000 mg/day, 3.1 (2.71–3.61). All rate ratios were significantly higher when compared with remote NSAID or COX-2 selective inhibitor use ($p<0.001$).

Conclusions: Although the risk of hospitalisation for ulcer complications with naproxen is dose-dependent, even low (equivalent to over-the-counter) doses are associated with a significant risk of serious UGI toxicity. Concomitant gastro-protective therapy should be strongly considered for high-risk patients, regardless of naproxen dose, in order to protect against complicated gastric and duodenal ulcers.

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2207

Disappointing Responsiveness of the SF-6D to Improvement in Patients Receiving a First TNF-Blocker: Results of the DREAM Registry. Laurien Buitinga[3], Louise M. A. Braakman-Jansen[4], Erik Taal[4], Wietske Kievit[1], Henk Visser[2], Piet L. C. M. Van Riel[1] and Mart A. F. J. van de Laar[5]. [1]Radboud University Nijmegen Medical Centre, [2]Rijnstate Hospital, Arnhem, [3]University of Twente, Enschede, Overijssel, The Netherlands, [4]University of Twente, Enschede, The Netherlands, [5]University of Twente; Medical Spectrum Twente, Enschede

Background: For reimbursement of innovative but costly treatments results of cost-utility analyses are increasingly important. Preferences for health states (utilities) can be measured with instruments as the EQ-5D or SF-6D. Evidence about which measure can be used best to detect improvement in patients with Rheumatoid Arthritis is inconclusive [1].

Objective: To examine the responsiveness of the EQ-5D and SF-6D in patients with RA receiving a first TNF-blocker.

Methods: Data of 284 RA patients included in the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry starting a first TNF-blocker were used. The Wilcoxon Signed Rank test and standardized response mean (SRM) were calculated to measure internal responsiveness over 12 months and 95% CIs were estimated using bootstrapping. Receiver-operating characteristic (ROC) curves were used to assess external responsiveness and areas under the curves (AUCs) were calculated. Perceived health transition (item SF-36) and change in disease activity (DAS-28) were used as external criteria. For the ROC curves, both criteria were dichotomized. Patients were classified as 'responders' (good and moderate) or 'non-responders', based on the EULAR28 response criteria, which takes into account the individual change in DAS28 and the level of DAS28 reached. Patients were classified 'improved patients' (perceived health much better or somewhat better than a year ago) or 'non-improved patients' (perceived health the same as a year ago, or somewhat worse or much worse than a year ago), based on their health transition score.

Results: According to the EULAR response criteria, 41.2% of the patients were good responders, 36.6% moderate and 22.2% non-responders. The EQ-5D scores slightly improved over 12 months (SRM(CI) 0.46(0.32 to 0.58)), whereas the SF-6D scores did not improve at all (SRM 0.02(−0.10 to 0.13)). The EQ-5D was moderately able to correctly classify patients as 'improved' or 'non-improved' respectively 'responder' or 'non-responder' as the AUCs were 0.67 when using self-reported health transition and 0.72 when using disease activity as external criteria. The AUCs of the SF-6D did not differ from 0.5.

Conclusion: The EQ-5D was more responsive to improvement than the SF-6D. The SF-6D was poorly responsive to improvement in patients with RA receiving a first TNF-Blocker. There is a need to reconsider the SF-6D as a valid utility measure in cost utility analyses in RA.

References:

[1] Harrison et al. (2008). J Rheumatol;35:592–602.

Disclosure: L. Buitinga: None; **L. M. A. Braakman-Jansen:** None; **E. Taal:** None; **W. Kievit:** None; **H. Visser:** None; **P. L. C. M. Van Riel:** None; **M. A. F. J. van de Laar:** None.

ACR Concurrent Abstract Sessions
Epidemiology and Health Services Research: General Interest
Thursday, November 11, 2010, 9:00 AM–10:30 AM

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Multiple Medications Use in Adults with Chronic Disease, with and without a Musculoskeletal Condition. Gillian A. Hawker[3], Ruth Croxford[1] and Elizabeth M. Badley[2]. [1]Institute of Clinical and Evaluative Sciences, Toronot, Canada, [2]Toronto Western Research Institute, Toronto, ON, Canada, [3]Women's College Hospital, Toronto, ON, Canada

Purpose: Musculoskeletal (MSK) conditions, which disproportionately affect older adults, are the most common cause of pain and long term disability. Chronic medication use is central to symptomatic management of MSK conditions and their downstream effects (e.g. sleep disruption and depressed mood). However, their chronic use may increase risk for adverse outcomes. This study evaluated the prevalence and correlates of use of combinations of medications (pain relievers, narcotic medications, and anti-depressants) among people with MSK and non-MSK chronic conditions.

Methods: Data from Ontario respondents to the 2001 Canadian Community Health Survey (CCHS) (Cycle 1.1), a nationally representative cross-sectional survey of the Canadian community-dwelling population, were used. Participants aged 25 years and older who responded to the questions about MSK conditions (physician diagnosed arthritis or rheumatism *and* back pain) and about their medication use in the past month, including the use of *pain relievers* (e.g., aspirin, acetaminophen, arthritis medicine or anti-inflammatories), *narcotic medications* (codeine, Demerol or morphine), and *anti-depressants* (e.g., Prozac, Paxil or Effexor), were included. The age-standardized percentage of Ontario respondents aged 25+ years who reported taking two or more of these types of medications (i.e. ***multiple medication use***) was calculated for those with a MSK condition compared to those with one or more non-MSK chronic conditions (e.g. pulmonary disease, diabetes, heart disease). Among respondents with at least 1 chronic condition, correlates of multiple medication use (yes/no) were evaluated using logistic regression. Correlates considered were: age, gender, MSK condition, number of other chronic conditions, and annual household income.

Results: Among ~ 26,000 respondents, 34.9% reported an MSK condition and 12.1% reported at least one non-MSK chronic condition. The percentage reporting multiple medication use was 16.2% in those with an MSK condition and 9.5% in those with at least one non-MSK chronic condition. Significant independent correlates of multiple medication use were: a greater number of chronic conditions (adj OR for 2 versus 1 condition 1.35; $p=0.003$; adjusted OR for 3+ versus 1 condition is 3.24; $p<0.0001$); lower income ($p=0.004$); and an age-sex interaction ($p=0.02$). Younger women were more likely to be using multiple medications than younger men, but the probabilities were similar among older men and women. Controlling for these factors, the presence of a MSK condition was independently associated with a higher likelihood of multiple medication use (adjusted OR 1.68, $p<0.0001$).

Conclusions: People with MSK conditions are almost twice as likely as adults with other chronic conditions to be using combinations of medications typically used to manage chronic pain, potentially increasing their risk for adverse drug effects leading to hospitalization and death.

Disclosure: G. A. Hawker: None; **R. Croxford:** None; **E. M. Badley:** None.

2209

Population-Based Estimates of Common Comorbidities and Cardiovascular Disease in Ankylosing Spondylitis. Ann B. I. Bremander[2], Ingemar F. Petersson[1], Stefan Bergman[4] and Martin Englund[3]. [1]Lund University Hosp, Lund, Sweden, [2]Musculoskeletal Sciences, Department of Orthopedics, Clinical Sciences Lund, Lund University, Oskarstrom, Sweden, [3]Musculoskeletal Sciences, Department of Orthopedics, Clinical Sciences Lund, Lund University, Lund, Sweden, [4]Research and Development Center, Spenshult Hospital for Rheumatic Diseases, Oskarstrom, Sweden

Background: Comorbidities associated with AS contribute to the burden of the rheumatic disease. However, epidemiologic studies presenting estimates of the increased rate of comorbidities in AS are scarce.

Objective: To study the rate of common comorbidities and cardiovascular disease in ankylosing spondylitis (AS) patients compared with the general population seeking health care.

Methods: Sweden has a publicly funded health care system. All health care utilization is registered by the patients' personal identifier in databases. We studied 1374 subjects (60% men) age ≥20 years, living in the county of Skåne, Sweden, who were registered with an AS diagnosis (ICD-10 code M45) in the Skåne Health Care Register at least once during 4 calendar years (2004 to 2007). We then recorded the occurrence of physicians' diagnostic codes for a select number of comorbidities commonly associated with AS or

cardiovascular disease or its risk factors. To obtain morbidity rates we calculated the person-time from the day after the first occurrence of the AS diagnosis within the study period until the first diagnosis of the disease or another censoring event (death/relocation). We then obtained standardized morbidity ratios (SMRs) by dividing the observed morbidity rate in AS patients by the expected based on the corresponding rate of the disease in the general health care seeking population of the county (761 210 inhabitants aged ≥20); an SMR >1 equals a higher rate of the disease among AS patients than in the general population of corresponding age and sex distribution.

Results: The highest SMRs were found for uveitis 26.06 (95% CI 21.97, 30.70) and inflammatory bowel disease 8.19 (95% CI 6.47, 10.22), Figure 1. Also, we found increased SMRs for ischemic heart diseases 1.83 (95% CI 1.53, 2.18), hypertension 1.70 (95% CI 1.51, 1.91), disorders of lipoprotein metabolism 1.34 (95% CI 1.04, 1.71), and diabetes mellitus 1.34 (95% CI 1.10, 1.62). Within the group of ischemic heart diseases we also evaluated acute myocardial infarction separately and although it is a relatively rare event the SMR was close to be significantly elevated; 1.43 (95% CI 0.97, 2.03), Figure 2. Further, the SMRs for psoriasis, osteoporosis, and atrioventricular blocks were also statistically significantly elevated.

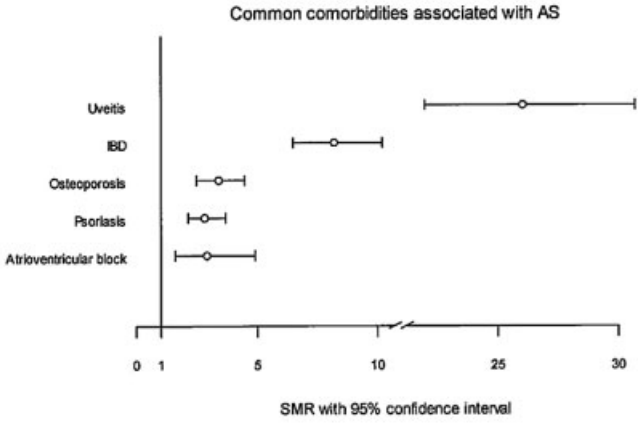

Figure 1.

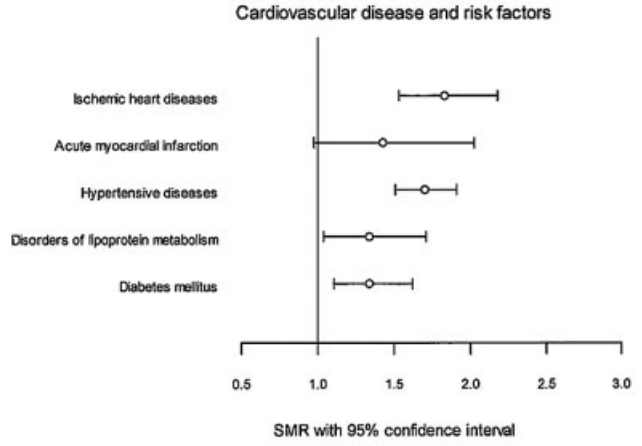

Figure 2.

Conclusion: Inflammatory diseases affecting the eye and the digestive system were the most notable comorbidities in AS patients, but the rate for cardiovascular disease was also higher indicating that AS is a chronic rheumatic disease with strong influence of comorbidities affecting the total burden of the disease.

Disclosure: A. B. I. Bremander: None; **I. F. Petersson:** None; **S. Bergman:** None; **M. Englund:** None.

2210

Elevated Maternal Serum Alpha Fetoprotein Predicts Reduction in RA Disease Symptoms during Pregnancy but Does Not Reduce Risk for Preterm Delivery. Don Nguyen[4], Gretchen Bandoli[1], Diana Johnson[3] and Christina D. Chambers[2]. [1]San Diego State University, [2]University of California San Diego, San Diego, CA, [3]University of California San Diego, [4]University of California SanDiego

Background: Mid-trimester elevated maternal serum alpha fetoprotein (MSAFP), a glycoprotein produced by the fetus, is associated with an approximately 3-fold increased risk of preterm delivery in otherwise normal pregnancies. Pregnant women with RA are at increased risk of preterm delivery, a risk that may be related to inflammatory disease activity or poor symptom control. It is suspected that the immunomodulatory effects of MSAFP represent a mechanism whereby disease symptom remission occurs in at least 2/3 of pregnant RA patients. However, it is not known if elevated MSAFP values in pregnant patients with RA are associated with the same 3-fold risk of preterm delivery as in the general population, or if high MSAFP values may lead to symptom remission and thereby reduce risk of early delivery in these patients.

Methods: The OTIS Autoimmune Diseases in Pregnancy Project, a North American-wide prospective cohort study of pregnancy outcome, enrolled 115 pregnant women with RA between 1999 and 2008 for whom mid-trimester MSAFP values were available from the obstetric record. Of these, 115 had one assessment of symptoms in the first half of gestation and 68 had a second assessment at 32 weeks' gestation, each consisting of 3 likert scale measures of interference with activity, pain, and global impact of disease based on the CLIN-HAQ and collected by maternal report. We examined the relationship between symptom scores at each time point and preterm delivery (<37 weeks' gestation), and symptom scores and elevated MSAFP (>=2.0 multiples of the median) using student's t-tests. We also evaluated elevated MSAFP as a predictor of preterm delivery using logistic regression.

Results: A total of 19.8% of women in the sample delivered preterm and 5.8% of women had a documented elevated MSAFP. All 3 symptom assessments measured in the first half of pregnancy were significant predictors of preterm delivery ($p < 0.05$). However, none of these same measures collected in the third trimester were associated with preterm delivery. Elevated MSAFP was associated with a non-significant 3-fold increased risk of early delivery (OR 3.32, 95% CI 0.69, 15.97). However, elevated MSAFP significantly predicted a reduction in symptom scores from early to late pregnancy on all 3 measures ($p < 0.05$).

Conclusion: Elevated MSAFP does appear to be linked to reduction in symptoms over the course of pregnancy, but the immunomodulatory effect of MSAFP does not appear to contribute to a reduction in risk for preterm delivery, which approximates the increased risk reported for the general population. Women with RA who have poor symptom control in early pregnancy and/or elevated MSAFP are at increased risk of preterm delivery, but those with elevated MSAFP are likely to see remission of symptoms as pregnancy progresses.

Disclosure: D. Nguyen: None; **G. Bandoli:** None; **D. Johnson:** None; **C. D. Chambers:** Abbott Laboratories, 2, Amgen Inc., 2, Apotex, 2, Bristol-Myers Squibb, 2, Parr, 2, Sandoz, 2, sanofi-aventis, 2, Teva Pharmaceuticals, 2.

2211

Cardiovascular Disease Prevalence in a Primary Care Cohort of Individuals with Inflammatory Arthritis, Diabetes, and Osteoarthritis: A Comparative Cross-Sectional Study. Mark M. J. Nielen[4], Alper M. van Sijl[3], Mike J. L. Peters[1], Robert A. Verheij[4], Francois G. Schellevis[4] and Michael T. Nurmohamed[2]. [1]Department of Internal Medicine, VU Medical Centre, Amsterdam, The Netherlands, [2]Department of Rheumatology, Jan van Breemen Institute, Amsterdam, Netherlands, Amsterdam, The Netherlands, [3]Department of Rheumatology, Jan van Breemen Institute, Amsterdam, Netherlands, [4]Netherlands Institute for Health Services Research (NIVEL), Utrecht, The Netherlands

Background: The evidence base for an increased cardiovascular burden in inflammatory arthritis (as in diabetes, an established cardiovascular risk factor) is growing, but data from primary care records are rare. We sought to determine the prevalence of cardiovascular (CV) events in inflammatory arthritis, diabetes, hip- and/or knee osteoarthritis (non-inflammatory comparator) in comparison to the population.

Methods: Data on CV morbidity (ICPC codes K75 (myocardial infarction), K89 (transient ischemic attack), and/or K90 (stroke/cerebrovascular accident) from patients with inflammatory arthritis (n=1.343), diabetes (n=11.784), osteoarthritis (n=3.320) and controls (n=158.439) were used from the Netherlands Information Network of General Practice (LINH), a large primary care cohort. Data were analyzed using multi-level logistic regression analyses and corrected for I: age, gender; and II: age, gender, hypercholesterolemia and hypertension.

Results: Age and gender adjusted CV disease prevalence rates were significantly higher in inflammatory arthritis (OR 1.6 (95%-CI: 1.3–2.0) and in diabetes (OR 1.8 (95%-CI: 1.6–1.9), but not in osteoarthritis (OR 0.9

(95%-CI: 0.8–1.0). These results attenuated - especially in diabetes - but remained statistically significant after adjustment for hypertension and hypercholesterolemia: OR 1.5 (95%-CI: 1.2–1.9) for inflammatory arthritis, OR 1.3 (95%-CI: 1.2–1.4) for diabetes, and OR 0.8 (95%-CI: 0.7–1.0) for osteoarthritis, respectively.

Table 1. Study characteristics

	IA	DM	OA	General population
n	1.343	11.784	3.320	158.439
Mean age, years	59*	66*	69*	51
Female gender, %	64*	52	68*	50
AMI, %	1.6*	2.7*	1.4*	0.7
TIA, %	1.6*	2.1*	1.7*	0.6
CVA, %	2.5*	3.6*	2.5*	0.9
Total CVD, %	5.4*	8*	5.3*	2
Hypertension, %	28*	48*	35*	13
Hypercholesterolemia, %	7.6*	24*	10*	4.8

* $p < 0.001$ (compared to general population). DM, diabetes mellitus; IA, inflammatory arthritis; OA, knee- and/or hip osteoarthritis; AMI, acute myocardial infarction; TIA, transient ischaemic attack; CVA, cerebro vascular accident; CVD, cardiovascular disease

Table 2. Multilevel logistic regression analyses for the association with CVD

	General population	IA	DM	OA
Crude model	1.0	2.1 (1.7–2.7)*	3.7 (3.5–4.0)*	1.9 (1.6–2.2)*
Model 1	1.0	1.6 (1.3–2.0)*	1.8 (1.6–1.9)*	0.9 (0.8–1.0)
Model 2	1.0	1.5 (1.2–1.9)*	1.3 (1.2–1.4)*	0.8 (0.7–1.0)

* $p < 0.001$. Results as odds ratios (95%-confidence interval). DM, diabetes mellitus; IA, inflammatory arthritis; OA, knee and/or hip osteoarthritis.
Model 1: Adjustment for age and gender
Model 2: Adjustment for age, gender, hypertension and hypercholesterolemia

Conclusions: These results confirm an increased CV burden in inflammatory arthritis to levels broadly similar to diabetes. By contrast, lack of excess CV disease in osteoarthritis further suggests that the systemic inflammatory load is critical to the CV disease burden in inflammatory arthritis.

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2212

Impact of Age, Gender, Obesity, and Steroid Use on Quinolone-Associated Tendon Disorders. Barton Wise[3], Christine Peloquin[2], Hyon K. Choi[4], Nancy E. Lane[5] and Yuqing Zhang[1]. [1]Boston Univ School of Medicine, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]Ctr for Healthy Aging-UC Davis, Sacramento, CA, [4]Univ of British Columbia, Vancouver, BC, Canada, [5]Univ of California at Davis, Hillsborough, CA

Background: Quinolone antibiotics are associated with an increased risk of tendinopathy, including tendon rupture. However, it is unknown whether certain characteristics predispose individuals to the adverse effects of quinolones. Identifying individuals who are more susceptible to these detrimental events has important clinical implications.

Methods: Using The Health Improvement Network (THIN) database, an electronic medical record database based on 6.3 million patients from general practices across the UK, we conducted a case-crossover study to assess whether the effects of quinolone use on the risk of tendon disorders vary by age, gender, obesity, and oral glucocorticoid use. For our primary outcomes, we examined Achilles tendonitis and tendon rupture at any site, to help ensure a high level of diagnostic specificity of end points. We identified patients with Achilles tendonitis or tendon rupture between 1986–2009 based on their electronic medical records. Subjects whose Achilles tendonitis or tendon rupture occurred within the first 2 years of entry to the THIN database were excluded. For each patient, we determined whether a quinolone and comparison antibiotic (trimethoprim, amoxicillin, nitrofurantoin) had been prescribed within 30 days prior to diagnosis of Achilles tendonitis and tendon rupture (case period) as well as the prescription of the same medications within 30 days one year prior to disease diagnosis (control period). We examined potential effect modifications according to age (<60 vs. ≥60 years), sex, obesity (BMI<30kg/m^2 vs.BMI ≥30kg/m^2), and concurrent glucocorticoid use (yes vs. no) by adding an interaction term between quinolone use and each potential modifier in the conditional logistic regression model.

Results: We identified 29,312 cases of Achilles tendonitis and 7,740 cases of tendon rupture. Use of quinolone was strongly associated with an increased risk of Achilles tendonitis (OR=4.4, 95% CI: 3.3–5.8) and tendon rupture (OR=2.0, 95% CI: 1.2–3.4). No association was found between the use of other antibiotics and either outcome. The association with Achilles tendonitis was stronger among patients who were older than 60 yrs, non-obese, and who used oral glucocorticoids (p-values for interaction: <0.001, 0.01, and 0.03, respectively). The effect of quinolones appeared to be greater in women than in men although the interaction term was not statistically significant (see table). Similar subgroup effects were observed in the associations with tendon rupture, except for the age group effect.

		Achilles Tendonitis			Tendon Rupture		
Potential modifier	Quinolone use	Case period	Control period	OR (95% CI)	Case period	Control period	OR (95% CI)
Men	Yes	118	38	3.7 (2.4–5.5)	21	18	1.2 (0.6–2.3)
	No	15,605	15,685		5,261	5,264	
Women	Yes	153	39	5.1 (3.4–7.7)	28	7	4.0 (1.7–9.2)
	No	13,435	13,550		2,430	2,451	
<60 yrs	Yes	66	41	1.7 (1.1–2.6)	14	7	2.2 (0.8–5.7)
	No	21,511	21,536		4,451	4,458	
>=60 yrs	Yes	206	36	8.4 (5.4–12.9)	35	18	2.0 (1.1–3.6)
	No	7,529	7,699		3,240	3,257	
No obesity	Yes	111	21	7.9 (4.5–14.1)	23	9	2.7 (1.2–6.2)
	No	6,466	6,556		1,937	1,951	
Obesity	Yes	25	11	2.4 (1.1–5.0)	2	4	0.5 (0.1–2.7)
	No	3,910	3,924		828	826	
Glucocorticoid use	Yes	99	17	10.1 (5.1–20.1)	21	4	5.2 (1.8–15.3)
	No	732	814		364	381	
No glucocorticoid use	Yes	173	60	3.3 (2.4–4.6)	28	21	1.4 (0.8–2.5)
	No	28,308	28,421		7,327	7,334	

Conclusion: These findings from a large primary care population confirmed that quinolone use increases the risk of Achilles tendonitis and tendon rupture. These detrimental effects of quinolones appear to occur more often among women, elderly, non-obese patients, and individuals with concurrent use of glucocorticoids.

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2213

Bisphosphonate (BisP) Use May Be a Risk Factor for Osteonecrosis (ON) in Those Who Have Not Used Glucocorticoids (GCs): Data from the Health Improvement Network (THIN). Steven C. Vlad[2], Hyon K. Choi[3], Christine Peloquin[2] and Yuqing Zhang[1]. [1]Boston Univ School of Medicine, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]Univ of British Columbia, Vancouver, BC, Canada

Background: BisP use has been linked to ON of the jaw in case reports. However, two epidemiologic studies suggested different conclusions about whether BisP use is associated with ON in general: one found that BisP use was associated with ON even after adjusting for GC use; the other found no association after adjusting for GC use and other factors. The latter suggests that GC use could be a strong confounder of any BisP-ON relationship. We therefore used data from THIN to investigate the association between BisP use and ON in persons who have not used GCs.

Methods: THIN collects anonymized patient data on over 3 million patients from a sample of primary care clinics throughout the United Kingdom. As all health information flows through the GP, THIN provides a complete patient record while an individual remains in a practice including medication prescriptions and refills. We created a cohort of subjects who had not been prescribed BisPs within the 1st year of entering a practice (new user population), and who had no recorded ON diagnosis within the 1st year (to exclude prevalent cases). We identified all cases of ON (index date), the diagnosis date, and the date the case entered the practice. We matched each case to 4 controls by gender, age in 10 year bands (< 16, 16–25, 26–35, . . . 86–95, ≥ 96), practice, calendar year of entry into the practice, and continuing enrollment in the practice at the index date. Subjects who used GCs before the index date could not be cases or controls. We defined BisP exposure as 1) current (including the 30 days prior to index date), recent (31–180 days), and past (> 180 days), and 2) total dose (1–180 days, 181–360 days, > 360 days), with no use as the reference in both cases. We used conditional logistic regression, adjusted for heavy alcohol use (ever, never), and tobacco use (current, past, never, missing), to calculate odds ratios for ON.

Results: We identified 608 persons with new ON (310 men, 298 women, mean age 52.7 yrs (sd 21.7)) and matched 2389 controls (51.6 yrs (sd 21.3) — 16 cases had fewer than 4 controls). 33 cases (5.4%) and 35 controls (1.5%) had at least one BisP prescription. Compared to never use the risk of ON was elevated in both current BisP users and recent users, but not in past users (see table). Compared to no use the risk of ON was elevated for all categories of total dose, with the peak from 181–360 days. The risk remained elevated after restricting the analysis to current users.

Table: Association of bisphosphonate use with osteonecrosis

Bisphosphonate use	Cases N (%) (N = 608)	Controls N (%) (N = 2389)	OR	(95% CI)
Never used (reference)	575 (94.6)	2354 (98.5)	1	–
Recency of use				
Current use (within 30 days)	24 (4.0)	21 (0.9)	6.1	(3.1, 12.0)
Recent use (31–180 days)	5 (0.8)	3 (0.1)	9.8	(2.2, 43.3)
Past use (>180 days)	4 (0.7)	11 (0.5)	1.7	(0.5, 5.4)
Duration of use				
1–180 days	10 (1.6)	13 (0.5)	2.5	(1.0, 6.2)
181–360 days	9 (1.5)	4 (0.2)	7.7	(2.3, 26.3)
>360 days	14 (2.3)	18 (0.8)	2.7	(1.1, 6.8)
Duration of use in current users				
1–180 days	9 (1.5)	4 (0.2)	10.0	(3.0, 33.2)
181–360 days	7 (1.2)	3 (0.10)	10.6	(2.7, 42.8)
>360 days	13 (2.1)	17 (0.7)	4.4	(1.9, 10.1)

Odds ratios (ORs) adjusted for heavy alcohol and tobacco use

Conclusions: Though our analysis is limited by small numbers, BisP use appears to be a risk factor for ON even in those who have not used GCs. The risk appears highest with up to 1 year of use, suggesting that those who have not had ON within 1 year may be in less danger. After 6 months off drug, the risk approaches null. Given the high correlation between osteopenia/osteoporosis and BisP use, we cannot exclude that these findings are due to confounding by indication, though no relationship between low bone mass and ON is known.

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ACR Concurrent Abstract Sessions
Genetics, Genomics and Proteomics: RA and Other Rheumatic Diseases
Thursday, November 11, 2010, 9:00 AM–10:30 AM

2214

Genome-Wide Association Study of Systemic Sclerosis Clinical Features Identifies New Disease Risk Variants. Olga Gorlova[16], Jose-Ezequiel Martin[15], Blanca Rueda[15], Bobby P. C. Koeleman[19], Maria Teruel[15], Lina-Marcela Diaz-Gallo[15], Jasper C. Broen[12], Madelon C. Vonk[17], Carmen P. Simeon[14], Behrooz Z. Alizadeh[8], Marieke J. H. Coenen[8], Alexandre E. Voskuyl[9], Annemie J. Schuerwegh[8], Piet L. C. M. van Riel[8], Ruben van 't Slot[8], Annet Italiaander[8], Roel A. Ophoff[8], Nico Hunzelmann[3], Norberto Ortego-Centeno[6], Miguel A. González-Gay[6], María F González-Escribano[6], Paolo Airo[4], Jaap van Laar[1], Jane Worthington[1], Roger Hesselstrand[7], Vanessa Smith[2], Filip de Keyser[2], Fredric Houssiau[2], Meng May Chee[1], Rajan Madhok[1], Paul Shiels[1], Rene Westhovens[2], Alexander Kreuter[3], Hans Kiener[10], Elfride de Baere[2], Torsten Witte[3], Leonid Padykov[7], Lars Klareskog[7], Rafaella Scorza[4], Benedicte A. Lie[5], Anna-Maria Hoffmann-Vold[3], Patricia Carreira[6], John Varga, Monique Hinchcliff, Annette T. Lee, Pravitt Gourh, Christopher I. Amos, Gabriella Riemekasten[11], Ariane Herrick[20], Lorenzo Beretta[21], Peter K. Gregersen[13], Sandeep Agarwal[18], Shervin Assassi[18], Filemon K. Tan[18], Frank C. Arnett[18], Timothy R. D. J. Radstake[17], Maureen D. Mayes[18] and Javier Martin[15]. [1]United Kingdom, [2]Belgium, [3]Germany, [4]Italy, [5]Norway, [6]Spain, [7]Sweden, [8]The Netherlands, [9]The The Netherlands, [10]Austria, [11]Charité University Hospital, Germany, [12]Department of Rheumatology, Radboud University Nijmegen Medical Center, The Netherlands, [13]Feinstein Institute of Medical Research, [14]Hospital Valle de Hebron, Spain, [15]Instituto de Parasitologia y Biomedicina Lopez-Neyra, Spain, [16]MD Anderson, [17]Radboud University Nijmegen Medical Center, The Netherlands, [18]The University of Texas Health Science Center–Houston, [19]University Medical Center Utrecht, The Netherlands, [20]University of Manchester, Manchester Academic Health Science Centre, United Kingdom, [21]University of Milan, Italy

Purpose: Systemic sclerosis (SSc) is a rare and severe rheumatic disease. Different lines of evidence suggest that genetic factors may underlie not only SSc susceptibility but also the predisposition to develop certain specific disease phenotypes or clinical symptoms such as limited (lcSSc) and diffuse (dcSSc) cutaneous subtypes and the presence of auto-antibodies, such as anti-centromere (ACA) and anti-topoisomerase I (ATA). To assess the genetic component involved in the different SSc subtypes we analyzed genome-wide association (GWAS) data and replication cohorts from the US and Europe in a total of 5,471 Caucasian individuals with SSc and 10,143 healthy Caucasian controls.

Methods: After all data was quality filtered, 2,296 individuals with SSc and 5,171 healthy controls were analyzed for genetic associations with lcSSc, dcSSc, ACA positive and ATA positive subgroups. SNPs from each subphenotype with a corrected P value lower than $1\times10-4$ not previously described in the literature were selected for replication. These associations were then analyzed in 9 replication cohorts from US and Europe comprising an additional 3,175 SSc patients and 4971 healthy controls.

Results: Eighteen non-HLA SNPs were selected from the SSc GWAS analysis. Meta-analysis of all the cohorts (5,471 individuals with SSc and 10,143 healthy controls) showed a strong association of rs11642873 in the IRF8 gene ($P = 5.42\times10–12$, OR = 0.75) and a suggestive but consistent association among populations, of rs12540874 in the GRB10 gene ($P = 1.31\times10-6$, OR = 1.15) with the limited subtype of the disease. We also found a strong association of rs11047102 of the SOX5 gene ($P = 1.04\times10-7$, OR = 1.36) with the ACA positive subgroup of patients. In addition to these phenotype dependent associations, we found rs11724804 in the DGKQ gene ($P = 1.79\times10-6$, OR = 1.12), rs1868929 between the AMRC9 and PSMD1 genes ($P = 3.27\times10-6$, OR = 1.27) and rs10275834 in the JAZF1 gene ($P = 9.44\times10-6$, OR = 1.12) to be associated with SSc.

Conclusions: Outside of the HLA region, we have identified 3 new genes (IRF8, GRB10 and SOX5) associated with clinical manifestations of the disease, emphasizing the differential genetic component of each subphenotype of SSc. We also have identified 3 new genes associated overall with the disease: DGKQ (implicated in cell signal transduction), PSMD1 (the immuno-proteosome subunit which loads immunogenic peptides for MHC transfer) and JAZF1 (a transcriptional repressor previously associated with SLE).

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2215

Genetic Markers of Rheumatoid Arthritis Susceptibility in Anti-Citrullinated Peptide Antibody Negative and Shared Epitope Negative Patients. Sebastien Viatte[1], Darren Plant[2], John Bowes[2], Anne Barton[2] and Jane Worthington[1]. [1]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [2]Arthritis Research UK Epidemiology Unit, The University of Manchester

Introduction: Recent genome wide and candidate gene association studies have identified over 30 confirmed single nucleotide polymorphisms (SNPs) predisposing to disease. Many of these studies have been undertaken exclusively or largely in samples from patients with anti-citrullinated peptide antibody (ACPA) (as assessed by anti-CCP status) positive RA and there is evidence that some genetic associations appear stronger in this subgroup than in ACPA negative disease. This differential association of susceptibility markers with ACPA positive/negative RA subsets or shared epitope (SE) positive/negative RA has led researchers to hypothesize that RA comprises a number of different diseases. However, due to the small numbers of seronegative or SE negative RA patients included in these studies, they lack sufficient statistical power to address the question currently. We aimed to

undertake a thorough investigation of confirmed RA susceptibility loci in a large cohort of ACPA negative subjects with RA.

Methods: RA patients from 5 different large cohorts of patients originating from the UK were pooled together to reach a number of over 8,000 cases. The comparison group comprised 7000 healthy UK controls. Serologic data was available for 5300 cases (3000 anti-citrullinated peptide antibody (ACPA) positive and 2300 APCA negative patients) and data on SE carriage was available for 6400 patients (4500 bearing at least one copy, 1900 without any copies). This corresponds to the largest pool of ACPA-negative patients studied, to date. A set of over 40 SNPs mapping to 31 confirmed RA susceptibility loci was tested for association between controls and each of the 4 following subgroups: APCA+, APCA-, SE+, SE-.

Results: As expected, strong associations were observed between RA susceptibility SNPs and APCA positive or SE positive patients. The emerging picture in the APCA negative RA subset shows a differential association. A set of SNPs is associated with RA susceptibility, irrespective of the serologic status (eg. PTPN22, TNFAIP3), whereas other RA susceptibility SNPs do not show significant association with ACPA negative RA (eg. PRDM1, CD40). A similar picture characterizes the SE negative RA subset, though a higher number of RA susceptibility loci seem to be associated irrespective of the carriage of the SE.

Discussion: In the largest sample size studied, to date, we have shown that the strength of association, the effect size and the number of SNPs associated with disease appear to be smaller in SE negative RA patients compared to SE positive patient, and these effect sizes are even smaller in APCA negative patients. This opens the question as to whether unidentified SNPs could preferentially and differentially confer susceptibility to ACPA/SE negative RA.

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2216

A Signature of Aberrant Responsiveness of the Peripheral Immune System Predicts the 6-Month Risk of Infections in Rheumatoid Arthritis. Megan L. Krause, John M. Davis III, Michael A. Strausbauch, Cynthia S. Crowson, Terry M. Therneau, Eric L. Matteson, Keith L. Knutson and Sherine E. Gabriel. Mayo Clinic, Rochester, MN

Purpose: Patients with rheumatoid arthritis (RA) experience a high burden of infectious disease, which is a leading cause of mortality. Currently there are no biomarkers that stratify the risk of infections in these patients. We have recently shown that "signatures" of aberrant functional responsiveness of the peripheral immune system are associated with RA disease severity. We performed a pilot study to assess whether a blood-based immune signature could predict incident infections in patients with RA.

Methods: We designed a prospective, population-based cohort study of patients with RA. Infections were identified first by diagnosis codes and then validated by medical records review using previously published definitions. Peripheral blood mononuclear cells were isolated and stimulated with a panel of stimuli for both the innate and adaptive immune systems. Seventeen cytokine concentrations were measured via multiplex immunoassays. The stimulation panel included anti-CD3/anti-CD28, cytomegalovirus and Epstein Barr virus lysates, CpG oligonucleotides, heat shock protein 60, phytohemagglutinin, phorbol myristate acetate with ionomycin, and Staphylococcal enterotoxins A and B. Mixed models were used to normalize log-transformed cytokine concentrations, adjust for assay effects, and to estimate and test for differences between the groups with and without incident infections. An immune signature score was created by selecting cytokine-stimulation combinations that were significantly different ($p<0.05$) between the groups. Logistic regression was used to test the association of a multi-cytokine prediction score and the risk of incident infections.

Results: In the six-month period following the index blood draw, 28 incident infections occurred among 267 patients with RA, 74.5% female, with mean age of 61 years and mean disease duration of 9.6 years. The only statistically significant variable at baseline that predicted infection was functional status defined by the Health Assessment Questionnaire (HAQ) disability index. Nine cytokine-stimulation combinations were significantly different between those with and without infection, including higher levels of TNFα, IFNγ, IL-17, IL-8, and GM-CSF and lower levels of IL-10 and IL-12 in response to various stimuli. The immune signature score was a statistically significant determinant of the 6-month risk of infections with an odds ratio of 4.0 (95% CI: 1.5 to 11, P=0.007) after adjusting for age, gender, HAQ, and use of disease-modifying medications.

Conclusion: This was one of the first studies to analyze ex vivo cytokine production and derive an immune signature that could help predict infection risk in patients with RA. The ability to predict infection risk could affect the choice of RA medications with their inherent immunosuppressive effects and the use of antibiotic prophylaxis. Reducing infection by preemptively altering therapy based on infection risk would have the potential to reduce morbidity and mortality for patients with RA.

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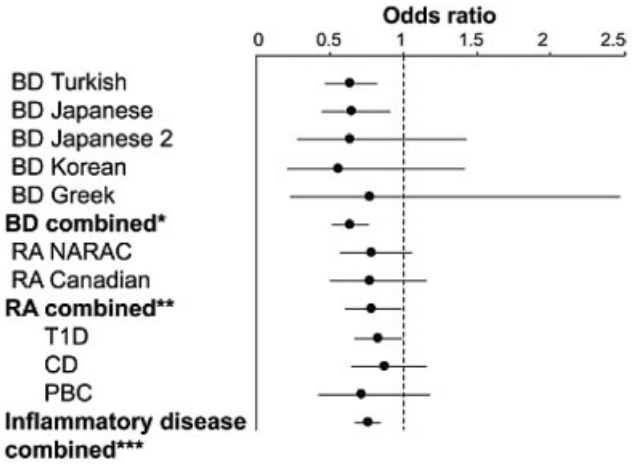
2217

Homozygous 3.2kb Deletion in LEPREL1 (P3H2) Intron 1 Reduces Cytokine Production and Protects from Multiple Inflammatory Diseases. Yohei Kirino[14], Michael J. Ombrello[15], Ahmet Gul[11], Kai Wang[1], Akira Meguro[7], Barbara Yang[14], Massimo Gadina[14], Fulya Cosan[11], Neslihan Abaci[3], Katherine Siminovitch[9], Peter K. Gregersen[12], Phaedon Kaklamanis[8], Young-Hun Cho[10], Dongsik Bang[2], Hong-wei Sun[14], Christopher Amos[16], Massa Hama[4], Mitsuhiro Takeno[4], Nobuhisa Mizuki[7], Hidetoshi Inoko[5], Shigeaki Ohno[6], Yoshiaki Ishigatsubo[17], Hakon Hakonarson[1], Daniel L. Kastner[13] and Elaine Remmers[14]. [1]Center for Applied Genomics, The Children's Hospital of Philadelphia, [2]Department of Dermatology, Yonsei University College of Medicine, [3]Department of Genetics, Institute for Experimental Medicine, [4]Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, [5]Department of Molecular Life Science, Division of Molecular Medical Science and Molecular Medicine, Tokai University School of Medicine, [6]Department of Ocular Inflammation and Immunology, Hokkaido University Graduate School of Medicine, [7]Department of Ophthalmology and Visual Science, Yokohama City University Graduate School of Medicine, [8]Department of Rheumatology, Athens Medical Center, Athens, Greece, [9]Departments of Medicine, Immunology and Molecular Genetics, Department of Medicine, University of Toronto, Mount Sinai Hospital and University Health Network, [10]Graduate School of Medical Science and Engineering, KAIST, [11]Istanbul Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Istanbul University, [12]N Shore Univ Hosp Rsch Ctr, Manhasset, NY, [13]NIAMS, NIH, Bethesda, MD, [14]NIAMS/National Institute of Health, [15]NIAMS/National Institute of Health, Bethesda, MD, [16]University of Texas M. D. Anderson Cancer Center, [17]Yokohama City Grad Sch of Med, Yokohama, Japan

SNP genome-wide association studies (GWAS) are a powerful means to detect disease-associated variants, though it is difficult to detect rare or structural variants. Accumulating evidence has shown an involvement of gene copy number variation (CNV) in inflammatory diseases including systemic lupus erythematosus and psoriasis, suggesting that CNV analysis may be a promising means to identify novel disease-associated loci in rheumatic diseases. SNP marker intensity data from our previous Turkish Behcet's disease (BD) GWAS (1215 cases and 1278 controls) revealed a common 3.2kb deletion in *LEPREL1* intron1 (odds ratio (OR)=0.62, $p=6.5\times10^{-4}$), homozygous deletions of which appeared to protect individuals from disease development. This association of homozygous *LEPREL1* deletion replicated in a Japanese BD collection (382 cases and 410 controls, OR=0.64, p=0.014). Independent BD collections showed trend toward protection from the disease (combined cases n=1821, controls n=2005, OR=0.63, meta analaysis $p=2.9\times10^{-6}$). As the homozygous deletion in *LEPREL1* was found to be common in both Turkish and Japanese populations, we sought to determine whether the deletion influences other inflammatory diseases, or in other ethnicities, as well. We found that patients with rheumatoid arthritis (combined cases n=1351, controls n=1659, OR=0.76, p=0.019), and type 1 diabetes (cases n=2214, controls n=2645, OR=0.82, p=0.038) were also protected from the disease, and trend towards protection in juvenile-onset Crohn's disease and primary biliary cirrhosis was observed. A meta-analysis of these combined inflammatory diseases (cases n=6406, controls n=6309) supports our hypothesis that *LEPREL1* has a role in inflammation ($p=2.4\times10^{-7}$).



LEPREL1, a prolyl 3-hydroxylase which is also called P3H2, is involved in type IV collagen modification. This gene appears to have additional functions. Although the protein is expressed in lymph nodes, there has been no direct evidence linking LEPREL1 to inflammation. We found that *LEPREL1* is primarily expressed in dendritic cells, and peripheral lymphocytes from individuals homozygous for this deleted region produce less LEPREL1 and inflammatory cytokines following exposure to stimulators of innate immunity. Our results offer new insights into the role an intragenic copy number variation plays in repressing development of inflammatory disease and reveal a novel modulatory mechanism for inflammation.

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2218

Association of IL2RB Polymorphisms with Erosive Disease in ACPA Positive Early Rheumatoid Arthritis (RA): Results from the ESPOIR Cohort. Adeline Ruyssen-Witrand[3], Delphine Nigon[4], Alain G. Cantagrel[5], Cédric Lukas[7], Jacques Morel[7], Jean Sibilia[6], Anne Cambon-Thomsen[1] and Arnaud L. Constantin[2]. [1]INSERM, U558, Toulouse, France, [2]Purpan University Hospital, Toulouse, France, [3]Rheumatology Center, Purpan Teaching Hospital, Toulouse, Toulouse, France, [4]Rheumatology Center, Purpan Teaching Hospital, Toulouse, France, [5]Rheumatology Center, Purpan Teaching Hospital, Toulouse, University Paul Sabatier, Toulouse, France, [6]Rheumatology Department, Hautepierre Teaching Hospital, Strasbourg, France, [7]Rheumatology Department, Lapeyronie Teaching Hospital, Montpellier, France

Purpose: RA is a complex disease that leads to joints erosions. The receptor of the Interleukin 2 (IL2R), a cytokine secreted by T lymphocytes implicated in the TH1 differentiation, is a quaternary complex of IL2RA, IL2RB and IL2RG. One SNP of the *IL2RA* gene (rs 2104286) and 2 SNPs of the *IL2RB* gene (rs743777 and rs3218253) were previously associated with RA susceptibility. The aim of this study was to assess the impact of these SNPs on the risk of erosions in early RA patients.

Methods: 813 patients with early arthritis (<6 months) were included in a national multicenter prospective study (ESPOIR cohort). Among Caucasian patients, 439 fulfilled the 1987 ACR criteria for RA, had radiographs at inclusion and after one year of follow-up and the 3 SNPs genotyped. Structural damage was quantified according to the Total van der Heijde modified Sharp score (TSS). Erosive RA was defined on an erosion Sharp score (ESS) >0. The 3 *IL2RA* and *IL2RB* SNPs were genotyped by KBiosciences (Herts,UK). *Statistical analysis*: we compared the proportions of patients with erosive disease at baseline and one year among patients carrying the 3 genotypes or the 2 alleles of each SNP using a chi-square test in the whole sample and after stratification on ACPA status. Crude Odds ratios (OR) with 95% confidence interval (95%CI) were calculated according to allele carriage in univariate and multivariate analyses.

Results: Of the 439 RA patients included (median age: 52 years, 76% of females, median symptom duration: 5 months, median DAS 28: 5.33, rheumatoid factor (RF) positive: 53%, anti-CCP2 positive: 48%), 268 (61%) were erosive at baseline (median TSS=3 [IQR:1–8], median ESS=1 [0–4]) and 287 (65%) at one year (median TSS=4 [1–9], median ESS=2 [0–5]). None genotype of the 3 SNPs was significantly associated with ACPA production.

In the whole RA sample, the IL2RB rs3218253 was significantly associated with erosive status at one year (CC: 69%, CT: 65%, TT:46%, p=0.023) in genotype analysis and at baseline (C allele carriage 63% vs 43%– 0R=2.205 [1.058–4.664]) and one year(C allele carriage 67% vs 46%– 0R=2.406 [1.152–5.059]) in allele carriage analysis.

In ACPA+ patients, the IL2RB rs743777 was significantly associated with erosive status at baseline (AA:71%, AG:71% and GG:36%, p=0.002) and one year (AA:78%, AG:75% and GG:44%, p=0.002) while the IL2RB rs3218253 was significantly associated with erosive status at baseline (CC: 74%, CT:66% and TT:30%, p=0.001) and one year (CC:81%, CT:71% and TT:35%, p<0.0001) in genotype analysis.

The A allele of IL2RB rs743777 was significantly associated with the risk of erosion at baseline (71% vs 36%–OR=4.313 [95%CI: 1.663–11.709]) and one year (77% vs 44%–OR=4.203 [95%CI: 1.625–10.972]). The allele C of IL2RB rs3218253 was significantly associated with the risk of erosions at baseline (71% vs 30%–OR=5.583 [1.881–18.490]) and one year (77% vs 35%–OR=6.162 [2.108–19.231]).

The A allele of the IL2RB rs743777 and the C allele of IL2RB rs3218253 remained independently associated with erosive disease in ACPA+ RA patients in multivariate analysis.

Conclusion: The A allele of the IL2RB rs743777 and the C allele of IL2RB rs3218253 were associated with the risk of erosion in ACPA+ early RA.

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2219

Discovery and Replication of JIA Predisposition Genes by Genome-Wide Association and Validation of Candidates in Fibroblast-Like Synoviocytes. Terri H. Finkel[9], Haitao Zhang[1], Benedicte A. Lie[10], Edward M. Behrens[3], Mara L. Becker[2], Carol Wise[6], Marilynn Punaro[7], Emma Reuschel[8], Debra Shivers[8], Berit Flatø[4], Øystein Førre[4], Jane Munro[11], Justine Ellis[11] and Hakon Hakonarson[5]. [1]Center for Applied Genomics, The Children's Hospital of Philadelphia, [2]Children's Mercy Hospital, Kansas City, MO, [3]Childrens Hospital of Phil, Philadelphia, PA, [4]Department of Rheumatology, Oslo University Hospital, Rikshospitalet, Norway, [5]Division of Genetics, The Children's Hospital of Philadelphia, University of Pennsylvania, [6]Division of Medical Genetics, Texas Scottish Rite Hospital for Children, [7]Division of Rheumatology, Texas Scottish Rite Hospital for Children, [8]Division of Rheumatology, The Children's Hospital of Philadelphia Research Institute, [9]Division of Rheumatology, The Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA, [10]Institute of Immunology, Oslo University Hospital, Rikshospitalet, Norway, [11]Murdoch Childrens Research Institute, Royal Children's Hospital, Melbourne, Australia

Purpose: Juvenile Idiopathic Arthritis (JIA) is the #1 cause of acquired disability in children. We recently identified TRAF1-C5 as a genetic locus associated with JIA, and have undertaken a comprehensive translational approach to elucidate its genetic contribution to this disease. Here, we identify single nucleotide polymorphisms (SNPs) associated with JIA by a genome-wide association (GWA) screen of a large well-phenotyped patient cohort. We validate expression of GW significant candidates in B cells and in synovial lining cells (human fibroblast-like synoviocytes, HFLS), the tissue targeted by inflammatory arthritis. HFLS provide a readily available and renewable source of patient-derived tissues to examine JIA risk alleles/ genotypes and screen drugs that might alter the risk phenotype.

Method: We use a GWA approach to identify risk alleles that associate with JIA in a discovery cohort of 1500 cases (diagnosed by revised ILAR criteria) recruited from greater Philadelphia and internationally (Stage 1). In Stage 2, we genotype an additional 1000 existing samples from well-phenotyped JIA cases recruited by other collaborating sites. This database is leveraged against matched samples from >10,000 genotyped controls. In parallel studies, we study allele-specific gene expression in:

1) genotyped lymphoblastoid cell lines (LCLs) from HapMap-CEU population samples and 2) primary HFLS established from synovial fluid samples obtained from a subset of the >200 JIA patients undergoing arthrocentesis each year at Children's Hospital, obtained after informed consent.

Results: We have completed full genome genotyping of 1166 JIA cases and 8793 matched healthy controls using the Illumina HumanHap610Q BeadChip to track 600,000 polymorphisms, and have demonstrated significant associations of JIA to MHC loci, and to the non-MHC loci, PTPN22, IL2RA, and ANTXR2, as previously reported in inflammatory arthritidies. We have also discovered GW significant associations within a locus encoding a novel chemokine receptor (CKR; discovery p-value = 4.32×10^{-11}; odds ratio = 0.66), for which replication is pending. We have demonstrated allele-specific effects on gene expression for significantly associated loci by assaying total RNA in genotyped LCLs from HapMap-CEU population samples, comparing individuals homozygous for risk vs. non-risk genotypes, and in primary HFLS established from JIA synovial fluid samples, analyzing allele-specific changes for our most significantly associated SNPs.

Conclusion: PTPN22, IL2RA, ANTXR2, and a novel CKR are associated with all forms of JIA, thereby potentially functioning as "master switches" predisposing to arthritis. The functional role of these genes is assessed for the first time in the disease-target tissue, HFLS, from children with JIA. HFLS are quiescent synovial lining cells that become highly proliferative and invasive in arthritis, and provide us with a renewable, druggable source of patient-derived cell types/tissues expressing our gene(s) of interest.

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ACR Concurrent Abstract Sessions
Imaging of Rheumatic Disease: Ultrasound
Thursday, November 11, 2010, 9:00 AM–10:30 AM

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High Frequency of Subclinical Ultrasound-Detected Synovitis in Juvenile Idiopathic Arthritis Patients with Clinically-Defined Inactive Disease. Silvia Magni-Manzoni[1], Carlo A. Scirè[3], Angelo Ravelli[2], Catherine Klersy[4], Silvia Rossi[3], Valentina Muratore[1], Chiara Visconti[1], Stefano Lanni[1], Pietro Merli[1] and Carlomaurizio Montecucco[3]. [1]Dep.Pediatrics, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy, [2]II Pediatric Unit, IRCCS Gaslini, Genova, Italy, [3]Reumatology Unit, Fondazione IRCCS Policlinico S.Matteo, Pavia, Italy, [4]Scientific Dep, Fondazione IRCCS Policlinico S.Matteo, Pavia, Italy

Background: In children with juvenile idiopathic arthritis (JIA), it is unclear whether clinically-defined remission couples with absence of synovitis on imaging studies. Subclinical synovitis, as detected with US, has been found to be common in JIA.

Objectives: To investigate the frequency of US-detected subclinical synovitis in JIA patients with clinically-defined inactive disease (ID) and the role of US abnormalities in predicting a subsequent flare of synovitis.

Methods: The clinician established the presence of ID (active joint count =0, physician's global assessment on a 0–10 cm visual analog scale ≤0.5, and negative acute phase reactants) in 28 consecutive JIA patients. On the same day, a sonographer scanned independently 52 joints in each patient for synovial hyperplasia (SH), synovial fluid (SF), power Doppler signal (PDS), and tenosynovitis (TS). Patients were followed-up for at least 6 months; based on the subsequent disease course, they were classified having persistent ID at the last follow-up visit or a relapse of arthritis during the follow-up period (defined as a recurrence of clinically-defined active synovitis in 1 or more joints).

Results: The frequency of SH, SF, PDS, and TS in the 28 patients with ID was 75%, 71.4%, 32.1%, and 14.3%, respectively. Following the diagnosis of ID, 21 patients had persistent ID after a median of 12 months, whereas 7 patients experienced a relapse of arthritis a after a median of 6 months. The frequency of US abnormalities at the time of the diagnosis of ID in the 7 patients who had a subsequent disease flare was 100% for SH, 87.5% for SF, 14.3% for PDS, and 28.6% for TS. The main joints involved in the baseline US abnormalities were the knee and the wrist.

Conclusion: JIA patients with clinically-defined ID had a high frequency of US-detected synovial abnormalities, namely SH and SF. Of the US features, SH and SF may have a greater role in predicting a future relapse of synovitis, especially when detected in the knee and the wrist.

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2221

Ultrasonography at the Onset of Early Arthritis Predicts Joint Erosions at One Year: Results of the ESPOIR Cohort Ultrasound Study. Thomas Funck-Brentano[4], Fréderique Gandjbakhch[4], Fabien Etchepare[4], Sandrine Jousse[2], Cedric Lukas[3], Violaine Foltz[4], Alain Saraux[2], Philippe Goupille[5], Patrick Boumier[1], Pierre Bourgeois[4] and Bruno Fautrel[4]. [1]Amiens, [2]Brest Universitary Hospital, [3]Immuno-rhumatologie, Hopital Lapeyronie, Montpellier, France, [4]Rheumatology Department, Pitié-Salpetrière Hospital, Paris 6 University, France, [5]Tours Universitary Hospital

Background: Ultrasonography (US) has been shown highly sensitive to detect erosions at baseline, compared to conventional radiography (CR). However, only few longitudinal studies have investigated its capacity to predict future structural damage.

Objective: to assess the predictive value of US for future radiographic erosion on the same joint based on the ESPOIR cohort data.

Methods: ESPOIR is a nationwide early arthritis cohort that included between 2002 and 2005 813 early arthritis patients.

US was performed at baseline on 127 patients from the ESPOIR cohort in 4 centers at baseline. US characteristics: 10–13MHz linear array transducer; Power Doppler (PD): frequency of 8.3MHz and pulse repetition frequency of 750Hz. US was performed blindly from clinical and radiological findings. Targeted joints were MCP2&5 and MTP5 for erosion detection, MCP2 to 5 and MTP5 for synovitis (gray scale and power Doppler). CR of the hands, wrists and feet at baseline and one year were read by one investigator according to the van der Heijde modified Sharp score. Baseline US findings associations with joint erosions on CR at one year were tested in univariate analyses using two-by-two tables and Pearson's chi-square tests. Predictive factors for joint erosion at one year by CR were tested in multivariate analysis including age, DAS28, CRP, ESR, positivity for Rheumatoid factor (RF) and anti-CCP and corticotherapy, using a mixed procedure.

Results: Patients characteristics at baseline were (mean ± sd or %): age 50.3 ± 12.2; Female 77.2%; DAS28 5.1± 1.3; number swollen joints 7.8±5.6; number tender joints 7.4±6.4; ESR 31.2±24.0mm; CRP 19.8±32.9 mg/l; Anti-CCP antibody positive 46.8%; Rheumatoid factor (RF) positive 35.4%. CR data at one year was obtained on 1184 joints that had mode B and PD evaluation and 708 joints for US erosions. CR erosions at one year: 105(8.9%) joints were erosive by CR on the 10 targeted joints. In univariate analysis, baseline PD positive synovitis and US erosions were associated with the presence of a CR erosive joint at one year. After adjustment for the clinical and biological variables, US erosions at baseline remained predictive of the presence of CR erosive joints at one year, independently from CRP and the presence of RF, also significantly associated ($p<0.001$).

Table 1. Baseline US characteristics for the presence of CR erosion at one year:

Prediction of future joint damage on X-ray at 1 year						
			X-Ray findings at year 1			
			Eroded joint	Noneroded joint	OR (unadjusted)	OR (adjusted)*
US findings at baseline	US Synovitis (N = 1184)	Joint with Doppler + synovitis	32/105 (30.4%)	196/1077 (18.2%)	1.97 [1.26–3.07]	1.79 [1.00–3.19]
	US Erosion (N = 708)	Eroded joint	21/71 (29.5%)	57/635 (9.0%)	4.26 [2.39–7.59]	3.12 [1.65–5.87]

* Adjustment for age, DAS28, CRP, ESR, positivity for Rheumatoid factor (RF) and anti-CCP and corticotherapy

When restricted to CR non erosive joints at baseline, these associations were maintained (PD synovitis: OR=5.41[2.09–14.01];$p<0.001$; US erosion: OR=3.93;[1.35–11.43];$p=0.012$). When restricted on non erosive patients on baseline CR, US erosions became borderline significant ($p=0.052$).

Conclusion: At the joint level, baseline US findings are associated with structural damage at one year. US is a reliable and useful technique to predict future erosions in early arthritis patients.

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CRP-Levels and Duration of Morning Stiffness as Predictors of Active Rheumatoid Arthritis as Verified by Ultrasound in Routine Clinical Practice. Christian Dejaco[5], Christina Duftner[2], Edith Wipfler-Freiβmuth[3], Helmut Weiss[4], Winfried B. Graninger[5] and Michael Schirmer[1]. [1]Department of Internal Medicine I, Medical University Innsbruck, Innsbruck, Austria, [2]Department of Internal Medicine, General Hospital of the Elisabethinen Klagenfurt, Klagenfurt, Austria, [3]Department of Internal Medicine, Hospital of the Barmherzige Brüder Marschallgasse Graz, Graz, Austria, [4]Department of Radiology, General Hospital of the Elisabethinen Klagenfurt, Klagenfurt, Austria, [5]Department of Rheumatology, Medical University Graz, Graz, Austria

Objective: To identify clinical and serological parameters predicting active disease as verified by ultrasound in rheumatoid arthritis (RA) patients from routine clinical practice.

Methods: Retrospective analysis of data from 149 consecutive RA-patients subjected to ultrasound (US) examination [mean disease activity score for 28 joints (DAS-28) 4.5 (standard deviation ± 1.3); mean age 63.7 (±13.4) years; 84.6% female; median disease duration 18 months]. Each patient underwent bilateral US assessment of wrists, metacarpo-phalangeal and proximal inter-phalangeal joints (=22 joints) for the assessment of synovial hypertrophy and/or effusion (SH/E) as well as synovial vascularization as determined by power Doppler (PD). According to Balsa A et al. sonographic remission was defined as the absence of PD-signals whereas presence of hypervascularisation indicated active disease[i]. The number of tender (TJ) and swollen joints (SJ), global assessment of disease activity on a visual analogue scale by the physician (VAS-phys) or patient (VAS-pt), C-reactive protein (CRP)-levels, erythrocyte sedimentation rate (ESR), duration of morning stiffness (MS), DAS-28, clinical disease activity index (CDAI), simplified disease activity index (SDAI) and health assessment questionnaires (HAQ) were recorded. This retrospective analysis was accepted by the local ethics committee.

Results: Sonographically detected hypervascularization was observed in 117 (78.5%) of the RA-patients. CRP, ESR and MS were higher in patients with sonographic signs of disease activity than in those with remission [CRP: median 0.8 (inter-quartile range 2.1) vs. 0.3 (0.6) mg/dl, $p=0.01$; ESR: 24 (39) vs. 14 (16) mm/1st hour, $p=0.019$; MS: 30 (115) vs. 12.5 (30) minutes, $p<0.001$, respectively]. TJ- and SJ-count, VAS-phys, VAS-pt, ESR, DAS-28, CDAI, SDAI and HAQ were similar among both groups. None of the parameters differed between those 10 patients without sonographic lesion and the 22 patients showing SH/E but no PD-signals. Using backward logistic regression analysis we found an odds ratio (OR) of 3.8 (1.6–9.1, $p=0.003$) for CRP >5.0mg/L (normal values 0–5.0mg/L) and an OR of 1.6 (1.1–2.5, $p=0.024$) for MS >30min (interaction between these parameters not significant) to predict active disease. The other clinical and serologic parameters showed no association with disease activity.

Conclusion: In routine clinical practice elevated CRP-levels and longer duration of MS alone are predictors of active RA as verified by ultrasound. This observation could be helpful for the development of referring strategies in the management of these patients.

[i] Balsa A, de Miguel E, Castillo C, Peiteado D, Martín-Mola E. Superiority of SDAI over DAS-28 in assessment of remission in rheumatoid arthritis patients using power Doppler ultrasonography as a gold standard. Rheumatology 2010; 49:683–90.

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2223

Resistant Tennis Elbow (RTE) Due to Radial Tunnel Syndrome: Clinical Presentation, Sonographic Findings and Surgical Correlation. David A. Bong[3], Jordi Palau[1], Ingrid Möller[1] and Esperanza Naredo[2]. [1]Barcelona Sonoanatomy Group, [2]Hosptial Universitario Severo Ochoa, Madrid, Spain, [3]Instituto Poal de Reumatologia, Bruce, WI

Background: Tennis elbow is a commonly encountered problem in rheumatologic practice and it is frequently resistant to the standard treatment. The resistance may be related to the misdiagnosis rather than an actual lack of therapeutic response. We present, to our knowledge, the largest series of patients with RTE due to radial nerve entrapment in the radial tunnel. Radial tunnel syndrome is a pain syndrome characterized by point tenderness distal to lateral epicondyle(LE) with radiation distally into the dorsal forearm due to compression of the deep motor branch of the radial nerve (posterior interosseus nerve or PIN) as it courses through the radial tunnel. With longstanding compression these patients may go on to develop motor findings.

Methods: Our study group consist of 23 patients, that were referred for evaluation of ongoing lateral elbow region pain unresponsive to conservative or invasive treatment. Evaluation consisted of thorough history and clinical examination. Ultrasound (US) examination of the elbow was performed by one of two experienced sonographers with a LOGIC E(General Electric, Waukesha, Wisconsin) using a 12-7 MHz linear probe. In addition the radial nerve was examined from its origin to the wrist in both upper extremities. All patients subsequently underwent surgical exploration by the same hand surgeon with release of the compressive structures.

Summary of the Results: US findings included: positive "sonopalpation" in 19/23 patients at the proximal radial(proximal to Arcade of Frohse) and in 4/23 patients at the distal radial tunnel. The nerve was enlarged in relationship with the contralateral nerve, in the proximal tunnel in 9/23 patients and distal to the exit of the tunnel in 3/23 patients. No US changes were observed in 11/23 patients. In the 10 patients that underwent electrophysiologic testing only one was positive and in all 8 patients that had MRI there no evident changes of the PIN. At surgery all patients were found to have enlargement of the radial nerve. In 19/23 the enlargement was noted proximal to the Arcade of Frohse. In 3/23 patients the enlargement was noted distal to the exit of the nerve from the distal radial tunnel. In the final patient enlargement was evident throughout the entire course of the radial nerve between the two heads of the supinator muscle.

Conclusion: High resolution US enables us to visualize the peripheral nervous system and is an important part of the evaluation of entrapment neuropathies. This study is the most extensive report of radial tunnel syndrome and confirms the value of US in the diagnosis of this entity prior to the onset of motor weakness. US was able to localize the precise point of involvement by sonopalpation. US was helpful to the surgeon in localizing the area of entrapment and in planning the most appropriate surgical approach.

We also propose the following classification criteria for Radial Tunnel Syndrome: Type l- Radial nerve involvement in the proximal portion of the tunnel proximal to the arcade of Frohse; Type ll – involvement of the distal portion as it emerges from the supinator heads; Type lll – diffuse enlargement throughout its couse between the supinator heads.

Disclosure: D. A. Bong: None; **J. Palau:** None; **I. Möller:** None; **E. Naredo:** None.

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Clinic Based MSK Ultrasound in the Diagnosis and Treatment of Shoulder Pain—A Randomized Prospective Study. Aamir Saeed[2], Mumtaz Khan, Siobhan Morrissey and Alexander D. Fraser[1]. [1]Castleroberts, County Limerick, Ireland, [2]Mid Western Regional Hospital, Limerick, Ireland, Ireland

Introduction: Local corticosteroid injections are accepted by rheumatologists to be an effective option in the treatment of shoulder pain. Clinic based high frequency ultrasonography has been postulated to have a role in the diagnosis of shoulder pathology and guiding injections.

Aim: This randomized prospective study aims to assess whether clinic based MSK Ultrasound significantly improves the accuracy of diagnosis, treatment choices and positioning of injections in shoulder pain and if so whether this improves outcome.

Methodology: 100 consecutive patients with 125 painful shoulders were selected. Patients were randomized to receive either sonographic assessment and blind subacromial injection of 40 mg depomedrone (Group 1, n = 66) or a sonographic assessment and guided injection of 40 mg depomedrone (Group 2, n = 59). A blinded consultant rheumatologist performed all clinical assessments at baseline, 6 and 12 weeks including the hawkin-kennedy test, supraspinatous tendon tenderness, patient and physician global visual analogue score for pain (0–10). All differences between clinical and ultrasound diagnosis for shoulder pain and incidental ultrasound findings for asymptomatic shoulders were recorded.

Results: 80 patients with 90 symptomatic shoulders (46 blinded and 44 guided groups) completed the study. Mean age 57.7 years, 65% female; mean

shoulder pain duration was 18 weeks (14–22). Shoulder function tests (SFT), improved significantly from baseline in both groups at 6 and 12 weeks. However significantly greater improvements were noted at both time points in the guided versus the blind injection groups (Delta BL $p<0.01$ and $p<0.05$) respectively. Patient VAS scores and PGA for pain also improved significantly in both groups at 6 and 12 weeks but again improvements were significantly greater at both time intervals in the guided group $p<0.05$. 20 patients, 11(19 shoulders) from blinded and 9(16 shoulders) from guided group were excluded from study at 6 weeks either due to repeat injection or surgical referral. About 10% of asymptomatic contra-lateral shoulders significant pathology on ultrasonography ranging from shoulder impingement to full thickness tears. 8% of clinical diagnoses differed significantly from the ultrasound diagnosis and with clinical relevance.

Conclusions: Both blind and guided steroid injections are associated with significant improvements in shoulder function and pain when assessed at 6 and 12 weeks. Guided injections are more effective and should at least be considered in non-responders. 2 Clinically relevant differences between clinical and ultrasonographic diagnosis may occur and significant pathology may be identified in contra-lateral asymptomatic shoulders raising interesting insights into the historical pathophysiology of shoulder pain.

Disclosure: A. Saeed: None; **M. Khan:** None; **S. Morrissey:** None; **A. D. Fraser:** None.

2225

Sonographic Needle Guidance and Cost-Effectiveness of Intraarticular Injections for Osteoarthritis of the Knee. Natalia R. Chavez-Chiang[3], Wilmer L. Sibbitt[4], Suzanne Delea[2], Kye Park[6], Arthur D. Bankhurst[5], Philip A. Band[1] and Hillary Norton[3]. [1]New York University School of Medicine, [2]University of New Mexico, Albuquerque, NM, [3]University of New Mexico, [4]University of New Mexico HSC, Albuquerque, NM, [5]University of NM Med Ctr, Albuquerque, NM, [6]Univresity of New Mexico, Albuquerque, NM

Objective: The present randomized controlled study addressed whether sonographic needle guidance affected the outcomes of intraarticular injection for osteoarthritis of the knee.

Methods: 94 non-effusive knees with osteoarthritis were randomized to injection by conventional palpation-guided anatomic injection or sonographic image-guided injection enhanced with a one-handed RPD (the reciprocating procedure device) syringe. A one needle, two-syringe technique was used. After intraarticular placement and synovial space dilation were confirmed by sonography, a syringe exchange was performed, and 80 mg of triamcinolone acetonide was injected with the second syringe through the indwelling intraarticular needle. Baseline pain, procedural pain, pain at outcome (2 weeks and 6 months), responders, therapeutic duration, reinjection rates, total cost, and cost per responder were determined.

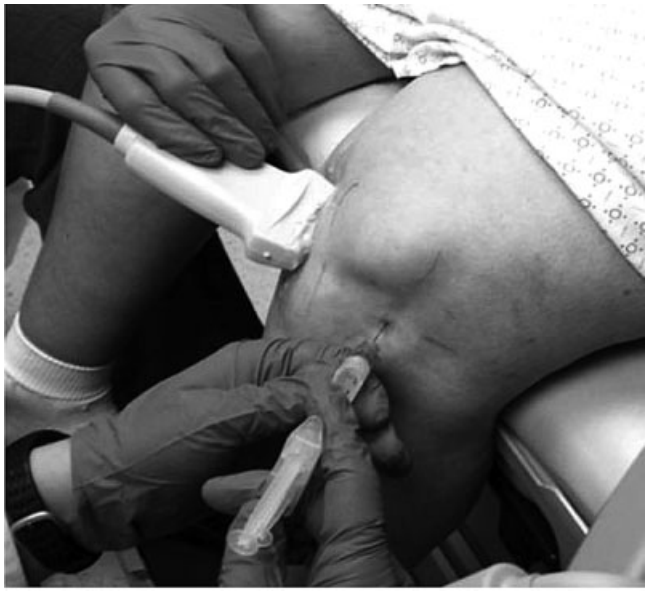


Figure 1.

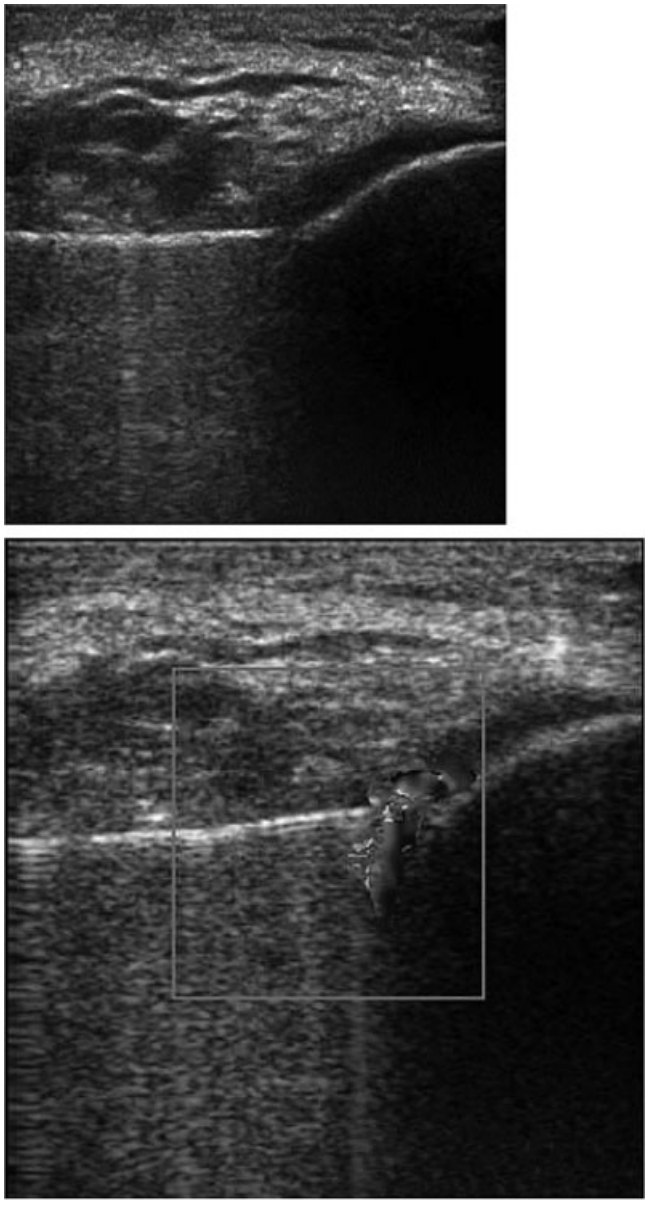


Figure 2.

Results: Relative to conventional palpation-guided methods, sonographic guidance for injection of the knee resulted in 47.7% reduction in procedural pain ($p<0.001$), a 41.7% reduction in pain scores at outcome ($p<0.03$), 107% increase in the responder rate ($p<0.001$), 51.6% reduction in the non-responder rate ($p<0.001$), a 35.5% increase in therapeutic duration ($p=0.01$), a 14.6% reduction ($48) in cost/patient/year, and a 58.8% ($593) reduction in cost/responder/year for a hospital outpatient ($p<0.001$).

Conclusions: Sonographic needle guidance improves the performance, clinical outcomes, and cost-effectiveness of intraarticular injections of the osteoarthritic knee.

Disclosure: N. R. Chavez-Chiang: None; **W. L. Sibbitt:** Apple, Inc, 1, 2, 5, Avanca Inc, 1, 2, 5, Avanca Medical Devices, 1, 2, 5, Avasca inc, 1, 2, 5, Avasca Medical Inc, 1, 2, 5, Becton Dickinson, 5, Celgene, 1, Ferring Pharmaceuticals Inc., 5, Inteligence Managment Solutions, 1; **S. Delea:** None; **K. Park:** None; **A. D. Bankhurst:** None; **P. A. Band:** None; **H. Norton:** None.

2226

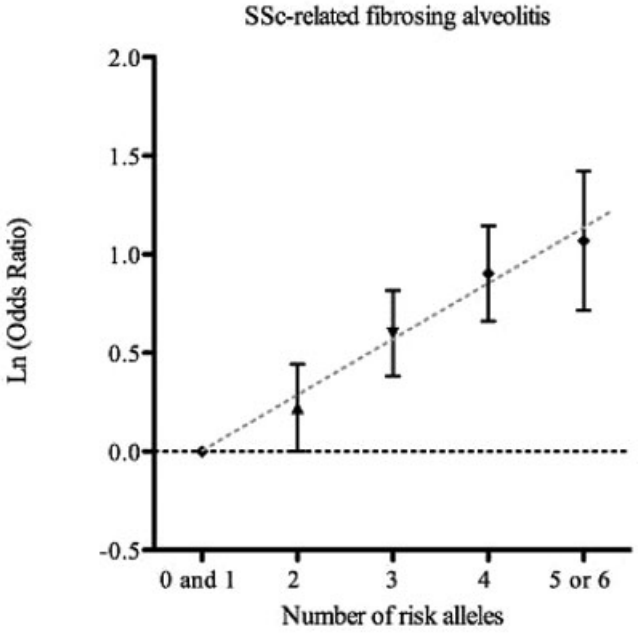
Identification of NLRP1 as a Systemic Sclerosis Susceptibility Gene: A New Clue for the Contribution of Innate Immunity in SSc Pathogenesis. Philippe Dieudé[7], Mickaël Guedj[4], Julien Wipff[6], Gabriela Riemekasten[2], Paolo Airo[8], Inga Melchers[1], Marco Matucci-Cerinic[10], Eric Hachulla[5], Catherine Boileau[9], Yannick Allanore[3] and and the GENESYS Consortium. [1]Clinical Research Unit for Rheumatology, University Medical Center, Freiburg, Germany, [2]Department of Rheumatology and Clinical Immunology, Charité University Hospital, Schumannstr. 20/21, D-10117, Berlin, Germany, [3]Hopitaux de Paris Cochin, Paris, France, [4]Laboratoire Statistique et Génome, UMR CNRS-8071/INRA-1152/Université d'Evry Val d'Essonne, France, [5]National Scleroderma Centre, Lille Cedex, France, [6]Paris Descartes University, Department of Rheumatology A, Cochin Hospital, Paris, France, [7]Paris Diderot University, Department of Rheumatology, Bichat Claude Bernard Hospital, APHP, Paris, France, [8]Rheumatology and Clinical Immunology, Spedali Civili, Brescia, Italy, [9]Saint Quentin Yvelines University, Laboratoire de Biochimie Hormonale et Génétique, Ambroise Paré Hospital, AP-HP, Boulogne, France, [10]University of Florence, Firenze, Italy

Background: Recent evidence has highlighted a potential role of interleukin 1 beta (IL-1β) in systemic sclerosis (SSc). NLRP1 provides a scaffold for the assembly of the inflammasome that promotes the processing and maturation of pro-IL-1β. In addition, NLRP1 variants were found to confer susceptibility to autoimmune disorders.

Objective: To test for association the NLRP1 SNPs rs6502867, rs26706600, rs8182352, rs12150220, rs4790797 with SSc in the European Caucasian population.

Methods: NLRP1 SNPs were genotyped in 3227 individuals comprising a Discovery set (870 SSc patients and 962 controls) and a Replication set including individuals from Germany (532 SSc patients and 324 controls) and Italy (527 SSc patients and 301 controls), all individuals being of European Caucasian origin.

Results: Conditional analyses revealed a significant association only for the NLRP1 rs8182352 variant. Both the NLRP1 rs8182352 C allele variant and the CC genotype were found to be associated with SSc-related fibrosing alveolitis (FA+) in the combined population: OR 1.19 95% CI [1.05–1.36], P=0.0065 and OR 1.43 95% CI [1.10–1.84], P=0.0063, respectively. Significant differences were also found when the FA+ SSc patients were compared to the FA- SSc patients. Linear regression analysis showed an additive effect of IRF5 rs2004640, STAT4 rs7574865 and NLRP1 rs8182352 risk alleles on SSc-related fibrosing alveolitis.



Conclusions: Our results establish NLRP1 as a new genetic susceptibility factor for SSc. This provides new insights into the pathogenesis of SSc, underlining the potential role of innate immunity in particular in the FA+ SSc sub-phenotype, which represents a severe subset of the disease.

Disclosure: P. Dieudé: None; **M. Guedj:** None; **J. Wipff:** None; **G. Riemekasten:** None; **P. Airo:** None; **I. Melchers:** None; **M. Matucci-Cerinic:** None; **E. Hachulla:** None; **C. Boileau:** None; **Y. Allanore:** None; **and the GENESYS Consortium:** None.

2227

MASP-1 and Pro-Factor D Proteins Are Present in Synoviocytes and May Locally Activate the Complement Alternative Pathway To Induce Inflammatory Arthritis in Mice. Nirmal K. Banda[4], Minoru Takahashi[2], Magdalena J. Glogowska[4], Kazue Takahashi[3], Gregory L. Stahl[1], Teizo Fujita[2], William P. Arend[4] and V. Michael Holers[4]. [1]Center for Experimental Therapeutics and Reperfusion Injury, Brigham and Women's Hospital, Boston, MA, [2]Department of Immunology, Fukushima Medical University School of Medicine, Fukushima, Japan, [3]Department of Immunology, Massachusetts General Hospital for Children, Boston, MA, [4]Division of Rheumatology, University of Colorado at Denver, Aurora, CO

Purpose: Mannose-binding lectin-associated serine proteases 1/3 (MASP-1/3) can cleave pro-factor D (pro-Df) into active factor D (Df), which is required for activation of the alternative complement pathway (AP). The AP is both necessary and sufficient for mediation of collagen antibody-induced arthritis (CAIA) in mice. We have recently shown that *MASP1/3*$^{-/-}$ mice are resistant to CAIA due to a defective AP and MASP-1/3 protein is the predominant mechanism to cleave pro-Df in vivo. The objectives of this study were to examine whether MASP-1/3 not bound to mannose-binding lectin (MBL) or ficolins (FCN) can activate the AP, and if MASP-1 and pro-Df proteins are present in the joint.

Methods: Sera from wild type (WT), *MASP-1/3*$^{-/-}$, *MBL*$^{-/-}$*/FCN A*$^{-/-}$ and *FCN A*$^{-/-}$ C57BL/6 mice were used. CAIA was induced in WT and *MASP-1/3*$^{-/-}$ mice by injecting 4 anti-type II collagen (CII) mAb i.p. on day 0 and LPS i.p. on day 3. All mice were sacrificed on day 10. Sera from CAIA mice (with and without disease) and *MBL*$^{-/-}$*/FCN A*$^{-/-}$ mice were analyzed by western blot analysis for the presence of pro-Df and Df. Immunohistochemical (IHC) analysis was performed for the presence of MASP-1/3 and pro-Df proteins in the knee joints of mice with or without CAIA. Sera from *MBL*$^{-/-}$*/FCN A*$^{-/-}$ mice were examined for the presence of MASP-1 using a gel filtration assay followed by western blot analysis. Additionally, sera from *MBL*$^{-/-}$*/FCN A*$^{-/-}$ and *FCN A*$^{-/-}$ mice were examined in vitro for AP activation induced by anti-CII antibodies, zymosan and mannan.

Results: In the sera of WT and *MBL*$^{-/-}$*/FCN A*$^{-/-}$ mice, factor D existed exclusively in its active form, indicating that pro-Df is cleaved by MASP-1 in both sera. Conversely, sera from *MASP1/3*$^{-/-}$ mice contained only pro-Df. There was no conversion of pro-Df to Df between day 0 (without disease) and day 10 (with CAIA) in *MASP1/3*$^{-/-}$ mice. MASP-1/3 proteins are normally bound to MBL or FCN; however, we detected MASP-1/3 in the sera of *MBL*$^{-/-}$*/FCN A*$^{-/-}$ mice which might be bound to an unknown protein. Anti-CII mAb, zymosan and mannan particles all induced C3b deposition and C3a and C5a generation in vitro using sera from *MBL*$^{-/-}$*/FCN A*$^{-/-}$ and *FCN A*$^{-/-}$ mice under conditions where only the AP was active. These results suggest that MASP-1/3 is present in the circulation of *MBL*$^{-/-}$*/FCN A*$^{-/-}$ mice and can initiate the AP of complement in vitro. IHC analysis showed the presence of MASP-1/3 in the synovium, but not on chondrocytes, in the knee joints of WT mice with CAIA. Pro-Df was found by IHC both in the synovium and on chondrocytes in the knee joints of *MASP1/3*$^{-/-}$ mice without CAIA. These results indicate that MASP-1/3 protein is the predominant mechanism for cleavage of pro-Df in vivo and may activate the AP locally. Future studies will examine whether MASP-1 and pro-Df proteins are produced by the same cell in the synovium and whether conversion of pro-Df to Df occurs locally inside the cell or in the microenvironment.

Conclusions: MASP-1/3 protein predominantly cleaves pro-Df *in vivo* in CAIA. This study demonstrated that MASP-1/3, in the absence of MBL or FCN, can act locally in the knee joint and in the circulation to initiate the AP and inflammatory disease.

Disclosure: N. K. Banda: None; **M. Takahashi:** None; **M. J. Glogowska:** None; **K. Takahashi:** None; **G. L. Stahl:** None; **T. Fujita:** None; **W. P. Arend:** None; **V. M. M. Holers:** Taligen Therapeutics Inc., 1.

2228

Mutated NLRP3 in Cryopyrin-Associated Periodic Syndromes Is Released from Restriction by CARD8. Sayaka Ito[2], Yukichi Hara[3], Yukio Shima[1] and Tetsuo Kubota[3]. [1]Kyorin University, [2]Tokyo Medical and Dental University, Tokyo, Japan, [3]Tokyo Medical and Dental University

Purpose: NLRP3 in monocytes and other cell types plays a role in innate immunity as one of the intracellular pathogen recognition receptors, and its mutation is responsible for cryopyrin-associated periodic syndromes (CAPS). Once activated, NLRP3 forms a protein complex called the inflammasome with procaspase-1 and an adaptor protein ASC, leading to activation of caspase-1 and production of mature proinflammatory cytokines IL-1β and IL-18. Some experiments using cells expressing truncated NLRP3 indicated interaction between the NACHT domain of the NLRP3 and the FIIND domain of another adaptor protein CARD8, but involvement of CARD8 in NLRP3 inflammasome remains controversial. We herein aimed to clarify the role of CARD8 in NLRP3 inflammasome and its relevance to the pathophysiology of CAPS.

Methods: HEK 293 cells were transiently transfected with ASC, CARD8, procaspase-1, proIL-1β, and NLRP3 in wildtype or with CAPS-associated mutation. 24h later, whole cell lysates were provided for immunoprecipitation and western blotting. 48h after transfection, IL-1β in the culture supernatant was measured by ELISA.

Results: Wild type full-length NLRP3 was immunoprecipitated with CARD8, but interestingly, this interaction was inhibited by coexpression of ASC in a dose-dependent manner, suggesting that affinity between NLRP3 and ASC is higher than that between NLRP3 and CARD8. In contrast, NLRP3 with CAPS-associated mutation R260W or H312P was unable to interact with CARD8. Cells expressing wildtype NLRP3, ASC, procaspase-1 and proIL-β spontaneously produced IL-β, and it was significantly suppressed by cotransfection with full-length CARD8. Cotransfection of the FIIND domain of CARD8 showed less, but still significant, suppressive effect on the IL-1β production.

Conclusions: CARD8 interacts with full-length wildtype NLRP3, and may prevent the NLRP3 inflammasome from unristricted activation. Disability of CARD8 to interact with mutated NLRP3 may explain continuous release of IL-1β by monocytes from CAPS patients.

Disclosure: S. Ito: None; **Y. Hara:** None; **Y. Shima:** None; **T. Kubota:** None.

2229

Complement Component C5 Plays a Central Role in Osteoarthritis. William Robinson[3], Andrew L. Rozelle[1], Tamsin M. Lindstrom, Reuben Gobezie, V. Michael Holers[4], David M. Lee[2] and Qian Wang. [1]Menlo Park, CA, [2]Brigham and Womens Hospital, Boston, MA, [3]Stanford Univ School of Med, Stanford, CA, [4]Univ of Colorado School of Med, Aurora, CO

Background/Purpose: Osteoarthritis (OA) is characterized by the breakdown of articular cartilage and is generally believed to result from "wear and tear". Although low-grade inflammatory responses are observed in OA, their contribution to its pathogenesis is unclear. We investigated a role for the complement system—and specifically complement component C5 and the membrane attack complex (MAC)—in the pathogenesis of OA.

Methods: Proteins present in synovial fluids derived from OA patients were surveyed by mass spectrometry. ELISA analysis was used to assess activation of the complement cascade in OA synovial fluid and in serum incubated with cartilage proteins. Immunohistochemical staining with antibodies specific for the MAC (comprising complement components C5b-9) was performed on remnant cartilage tissue from patients with OA. Bioinformatic analysis was performed on RNA profile datasets from OA and healthy synovial membrane to determine relative levels of expression of the complement effectors and inhibitors identified by mass spectrometry. A murine model of OA, generated by surgical medial meniscectomy, was used to determine the susceptibility of mice deficient in complement component C5 to OA. Arthritis severity was assessed by histological analysis of toluidine-blue-stained joint sections and by gait analysis performed using the CatWalk System. Finally, qPCR and immunoassays were used to determine the effects of sublytic MAC on chondrocyte gene and protein expression.

Results: Mass spectrometry analysis revealed the presence of multiple complement effectors and inhibitors in the synovial fluid of OA patients. ELISA analysis demonstrated elevations of C3a and C5b-9 in OA synovial fluids, indicating activation of the complement cascade. Further, synovium derived from OA patients was found to express complement components, whereas synovium from healthy individuals expressed complement inhibitors, suggesting that the synovium contributes to a local imbalance in the complement system in OA joints. Using an *in vivo* model of OA, we found that mice deficient in the central complement component C5 are protected against the development of degenerative arthritis, as assessed histologically and by gait analysis. Wild-type mice treated with an anti-C5 antibody were similarly protected. Moreover, the MAC (the cell-bound form of C5b-9) was detected on chondrocytes in cartilage from OA patients, and deposition of sublytic MAC on chondrocytes derived from OA cartilage induced the production of matrix–degrading enzymes, cell cycle regulators, inflammatory mediators, and complement components.

Conclusions: Our results suggest that local dysregulation of complement in synovial joints plays a critical role in the development of OA. Further, we demonstrate a critical role for the complement component C5 in the pathogenesis of experimental OA.

Disclosure: W. Robinson: Synostics, 1; **A. L. Rozelle:** None; **T. M. Lindstrom:** None; **R. Gobezie:** Synostics, 1; **V. Holers:** None; **D. M. Lee:** Synostics, 1; **Q. Wang:** None.

2230

Toll-Like Receptor 2 Negatively Regulates FCg Receptor Response in Macrophages and Inhibits FCgR-Mediated Arthritis. Shahla Abdollahi-Roodsaz[3], Marije I. Koenders[2], Fons A. J. van de Loo[4] and Wim B. Van Den Berg[1]. [1]Radboud Univ Nijmegen Med Cntr, Nijmegen, The Netherlands, [2]Rheumatology Research and Advanced Therapeutics, Radboud University Nijmegen Medical Centre, Nijmegen, [3]Rheumatology Research and Advanced Therapeutics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, Nijmegen, The Netherlands, [4]Rheumatology Research and Advanced Therapeutics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Current evidence indicates that Toll-like receptors (TLRs) and FCg receptors (FCgRs) are involved in the pathogenesis of arthritis and mutual regulatory functions for these innate immune receptors have been suggested as well. In the present study, we investigated the involvement of TLR2 in regulation of FCgR response and assessed the functional consequences for the development of arthritis.

Peritoneal macrophages from naïve wild-type (WT) and TLR2$^{-/-}$ mice were stimulated with heat-aggregated gamma globulins (HAGGs) and immune complexes, and cytokine production was evaluated. Although no clear shift was noticed in the expression pattern of activating and inhibitory FCgRs, macrophages from TLR2$-/-$ mice showed a greatly exaggerated functional response (>6 fold) and produced much more TNFa, IL-1b and IL-6 upon FCgR triggering compared to WT cells.

To assess the functional consequence of enhanced FCgR response in TLR2$^{-/-}$ condition for arthritis, FCgR-driven serum-transfer arthritis was induced by i.p. injection of serum from arthritic K/BxN mice. TLR2$^{-/-}$ mice showed an accelerated onset of arthritis and had a strikingly enhanced disease severity. Marked increase in inflammation was also obvious in the knee joints in addition to the paws. Furthermore, gene expression of several proinflammatory cytokines, including TNF, IL-1 and IL-6, and certain matrix metalloproteinases was enhanced in synovial tissue of TLR2$^{-/-}$ mice compared to WT.

PCR analysis revealed that basal expression of activating and inhibitory FCgRs in peritoneal macrophages, spleen and synovial tissue of arthritic mice was not affected by TLR2 deficiency. Furthermore, regulation of FCgR expression in macrophages upon stimulation with K/BxN serum and HAGGs was not affected. However, macrophages from arthritic TLR2$^{-/-}$ mice released significantly more TNF and IL-6 upon general PMA/ionomycin stimulation, while having similar levels of IL-10 compared to WT cells. This indicates a potentiated M1 and similar M2 profile in macrophages from arthritic mice in the absence of TLR2. Importantly, FCgR triggering of macrophages isolated briefly after disease induction and before appearance of clinical differences using immune complexes resulted in markedly higher levels of TNF and IL-6, but not

IL-10, in TLR2$^{-/-}$ condition. Unaltered response of TLR2$^{-/-}$ macrophages to IL-1 as control excluded a non-specific effect.

These findings indicate an important regulatory function of TLR2 in macrophage FCgR response with remarkable consequences for arthritis expression. A protective role of TLR2 in immune-complex driven arthritis beyond its previously-described role in promoting regulatory T cell function may provide a relevant therapeutic intervention for the future treatment of RA.

Disclosure: S. Abdollahi-Roodsaz: None; **M. I. Koenders:** None; **F. A. J. van de Loo:** None; **W. B. Van Den Berg:** None.

2231

A Novel Role of Endothelin-1 in Linking Ro60-ssRNA Immune Complexes to Cardiac Fibrosis in Congenital Heart Block. David Alvarez-Carbonell[4], Jiri Zavadil[5], Rosanna Abellar[1], Franck Barrat[2], Robert Clancy[3] and Jill Buyon[5]. [1]Columbia University Medical Center, [2]Dynavax Technologies, [3]New York University School of Mediciine, [4]New York University School of Medicine, New York, NY, [5]New York University School of Medicine

Passively acquired anti-Ro associated congenital heart block (CHB) likely results from pathologic crosstalk between inflammatory and fibrosing pathways eventuating in scarring. The target, Ro60, complexed with uridine rich ssRNA induces TLR7-dependent macrophage production of supernatants capable of trans-differentiating human fetal cardiac fibroblasts. This study addressed the molecular components responsible for the TLR-dependent profibrosing effects. In seeking the link between an inflammatory response of macrophages and the profibrotic effect on fibroblasts, a microarray analysis comparing the mRNA expression profile of macrophages stimulated with hY3 (ssRNA associated with Ro60) or immune complexes consisting of Ro60-hY3-IgG fraction containing anti-Ro60 antibodies (IC) in the presence or absence of IRS661 (antagonist of TLR7) was performed. Gene expression of the vasoconstrictor endothelin-1 (ET-1), recently shown to promote dermal fibrosis, was significantly up-regulated by $\sim$ 4 fold and confirmed by RT-PCR. Incubation of macrophages with either hY3 or IC increased secretion of ET-1 from 2.64 pg/mL (baseline) to 9.67 pg/mL ($p < .0001$) and 7.52 pg/mL ($p = .0003$) respectively. Pre-treatment with IRS661 decreased hY3-induced secretion to 3.83 pg/mL and IC to 3.98 pg/mL. The direct effect of ET-1 (100 nM) on these fibroblasts (shown to express both ETa and ETb receptors) resulted in a profibrosing phenotype as demonstrated by a) TGFbeta secretion (13 pg/mL vs. 772 pg/mL, $p = .03$), b) increased collagen release (18 ng/mL baseline vs. 772 ng/mL, $p = .05$, and c) expression of α-smooth muscle actin (α-smac). ET-1-induced TGFbeta secretion was significantly decreased ($p = .03$) by each of the following: BQ-123, an ETa antagonist (119 pg/mL), BQ-788, an ETb antagonist (145 pg/mL), and anti-ET-1 antibody (211 pg/mL), but not isotype control antibody (691 pg/mL). Similarly, ET-1-induced collagen secretion was significantly decreased ($p = .05$) by BQ-123 (147 ng/mL collagen), BQ-788 (247 ng/mL), anti-ET-1 antibody (253 ng/mL), and anti-TGFbeta antibody (239 ng/ml), but not isotype control (815 ng/mL). Predictably, pretreatment of fibroblasts with either BQ-123, BQ-788 or incubation of supernatants with anti-ET-1 antibody, but not isotype control, significantly inhibited the profibrosing readouts (increased TGFbeta, collagen and α-smac) induced by supernatants from macrophages stimulated with either hY3 or IC. Additionally, fibroblasts transfected with either ETa or ETb siRNA, but not scrambled siRNA, also significantly inhibited the profibrosing readouts induced stimulated macrophages. Immuno-histochemistry of a heart from a fetus dying with CHB revealed ET-1/2/3 antibody staining but not isotype IgG control in the septal region in areas showing calcification, fibrosis, and mononuclear cell infiltrates (not seen in an age-matched fetal heart). In conclusion, these data suggest that macrophage secretion of ET-1 may be one mechanism linking TLR inflammatory signaling to subsequent fibrosis and provide new insight in considering therapeutics for CHB.

Disclosure: D. Alvarez-Carbonell: None; **J. Zavadil:** None; **R. Abellar:** None; **F. Barrat:** Dynavax Technologies, 3; **R. Clancy:** None; **J. Buyon:** NIAMS-NIH, 2, NIH, 2.

ACR Concurrent Abstract Sessions
Rheumatoid Arthritis - Animal Models: T cell Pathogenesis an Novel Therapeutic Targets
Thursday, November 11, 2010, 9:00 AM–10:30 AM

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Mucosal Associated Invariant T Cells Contribute to the Pathogenesis of Arthritis. Asako Chiba, Ryohsuke Tajima, Yusei Miyazaki, Takashi Yamamura and Sachiko Miyake. Department of Immunology, National Institute of Neuroscience, NCNP

Background: MR1-restricted mucosal associated invariant T (MAIT) cells are a subset of innate lymphocytes which express an invariant TCRα chain (Vα 19-Jα 33 in mouse and Vα 7.2-Jα 33 in human) with a limited set of TCRβ chains. We previously reported the regulatory role of MAIT cells in experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis. To understand their role in animal models of arthritis, we generated MR1$^{-/-}$ DBA1/J mice and analyzed their disease susceptibility to collagen-induced arthritis(CIA). We also investigated if MAIT cells are involved in the effector phase of arthritis by using two animal models of antibody-induced arthritis (AIA). Finally we studied mechanisms by which MAIT cells modulate autoimmune responses.

Methods: To obtain MR1$^{-/-}$ DBA1/J mice, MR1$^{-/-}$C57BL/6 mice were backcroosed to DBA1/J mice for ten generations. To induce CIA, MR1$^{-/-}$ DBA/1J mice or WT littermates were immunized intradermally with bovine type II collagen (CII) (150μg) in Freund's complete adjuvant containing 250μg of H37Ra *Mycobacterium tuberculosis* on day 0 and CII in IFA on day 21. AIA was induced in MR1$^{-/-}$ C57BL/6 mice and WT littermates by injecting either K/BxN serum i.p. or a mixture of anti-type II collagen antibodies i.v. followed by lipopolysaccharide i.p. Vα 19i T cells (mouse MAIT cells) were sorted from liver or spleen cells of Vα19iTCR-Transgenic (Vα 19iTg) CD1d$^{-/-}$ mice by using anti-TCRβ and anti-NK1.1 monoclonal antibodies. In adoptive transfer studies, NK1.1^{+} TCRβ^{+} Vα19i T cells sorted from Vα19iTg CD1d$^{-/-}$ mice were injected i.v. into MR1$^{-/-}$ mice on one day before the induction of arthritis. Cytokine producing capacity of MAIT cells stimulated with or without anti-CD3mAb in the presence of various types of cytokines was evaluated by ELISA or cytokine bead assay kit.

Results: MR1$^{-/-}$ DBA/1J mice were more resistant to CIA compared to WT littermates, as demonstrated by clinical and histological scores of arthritis. CII specific antibody levels in the serum were reduced in MR1$^{-/-}$DBA/1J mice compared to WT controls. The severity of clinical and pathological features of AIA was reduced in MR1$^{-/-}$ mice compared to control WT mice. MR1$^{-/-}$ mice reconstituted with MAIT cells developed severe forms of arthritis to the similar level of arthritis in WT mice. IL-17 production by anti-CD3mAb-stimulated MAIT cells was highly augmented in the presence of IL-23. In addition, MAIT cells were activated and produced IL-17 upon IL-23 stimulation even without TCR stimulation.

Conclusions: MAIT cells contribute to the pathogenesis of arthritis. MAIT cells may be activated by cytokines which are abundant in inflammatory arthritis, and this may in turn amplify autoimmune responses.

Disclosure: A. Chiba: None; **R. Tajima:** None; **Y. Miyazaki:** None; **T. Yamamura:** None; **S. Miyake:** None.

2233 WITHDRAWN

2234

An Endothelium-Specific NF-kappaB Inhibitor Ameliorates Inflammatory Joint Diseases. Bettina Sehnert[4], Harald Burkhardt[2], Falk Nimmerjahn[5], Johannes Wessels[1], Agnes Machnik[5], Dietmar Vestweber[6], Jochen Zwerina[5], Georg Schett[5], Stefan Dübel[3] and Reinhard Voll[5]. [1]Georg-August-University of Göttingen, [2]Johann Wolfgang Goethe University Frankfurt am Main, [3]Technical University of Braunschweig, [4]University of Erlangen-Nürnberg, Erlangen, Germany, [5]University of Erlangen-Nürnberg, [6]University of Münster

Background: Therapeutical strategies that systemically block nuclear transcription factor-kappaB (NF-kappaB)-signalling may cause serious side effects due to the important role of NF-kappaB in a variety of homeostatic regulatory pathways, for instance in the central nervous system, the liver and the immune system. NF-kappaB is a key player in inflammatory disorders such as rheumatoid arthritis. Activation induces the expression of multiple mediators involved in the initiation and perpetuation of inflammatory processes. We developed a novel class of NF-kappaB inhibitors, designated as ligand-sneaking construct (LSC), that interfere with the NF-kappaB signalling

pathway selectively in endothelial cells. We have choosen this cell population, because of its essential role in the extravasation of leukocytes in inflammation.

Methods: The LSC is a multimodular recombinant protein that consists of three domains: 1) an oligopeptide specifically binding the cytokine-activated endothelium 2) the translocation domain of pseudomonas exotoxin A (ETA II) that facilitates the endosomal release of the construct into the cytosol and 3) the NEMO-binding peptide (NF-kappaB inhibiting effector domain) (5). The effectiveness of this E-selectin specific construct (LSC1) on NF-kappaB activation was analysed in vitro by an NF-kappaB-luciferase reporter gene assay and EMSA. In vivo binding of LSC1 to the cytokine-activated endothelium was proven by using the Olympus OV100 whole-mouse imaging system. The therapeutic effect of LSC1 in vivo was investigated in the antigen-induced arthritis and the KBN serum transfer model.

Results: E-selectin mediated internalization of LSC1 inhibited the transcriptional NF-kappaB activity in E-selectin expressing cells (CHO_E cells). Additionally, EMSA indicated a reduced nuclear translocation of NF-kappaB upon cytokine activation in LSC1-pretreated CHO_E cells. In vivo imaging emphasized specific LSC1 binding to the activated endothelium. By whole mount immunofluorescence microscopy of tissue specimens derived from cytokine-activated mouse skin, nuclear form of NF-kappaB p65 was strongly suppressed in mice pretreated with LSC1 but not in control mice that had received the MutNBP2 construct. In the mouse model of antigen-induced arthritis, we observed a reduced joint swelling after LSC1 treatment. Moreover, LSC1 leads to an amelioration of inflammatory joint disease induced by anti-glucose 6 phosphoisomerase (anti-G6PI) mouse serum. Histological studies confirmed the clinical data.

Conclusions: We presented for the first time an endothelium specific NF-kappaB inhibitor that shows therapeutic potential to treat inflammatory joint diseases in different mouse models of arthritis. This proof of concept study can be employed for targeting other cell types and to interfere with distinct signalling pathways.

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Citrullination of Mouse Collagen Breaks Tolerance and Induces an Inflammatory Arthritis in the Absence of Adjuvant. Jordan P. Lacy, Michael J. Duryee, Carlos D. Hunter, James R. O'Dell, Ted R. Mikuls, Geoffrey M. Thiele and Lynell W. Klassen. University of Nebraska Medical Center

Purpose: Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease that primarily affects the synovial joints. Anti-citrullinated protein antibodies (ACPA) are predictive markers of the disease and its severity. Previous studies have demonstrated that ACPA can be induced in mice following injection of citrullinated type II collagen (Cit-Coll) in the presence of Freund's complete adjuvant (FCA). Therefore, it was the purpose of this study to determine whether mouse Cit-Coll in the absence of adjuvant can break tolerance and initiate an inflammatory arthritis in DBA/1 mice.

Methods: Mouse type II collagen was citullinated using peptidyl arginine deiminase (PAD) and injected into DBA/1 mice at a concentration of (100 μg) in the base of the tail weekly for 5 weeks. Control groups were immunized with PBS, collagen, and collagen FCA. Animals were evaluated weekly for inflammation of the joints and serum was collected for the presence of anti-collagen or modified collagen antibodies. At week 6, animals were sacrificed paws removed for histology and spleens collected. The CD3+ T cells were then isolated and proliferated against collagen, albumin, Cit-Coll or Cit-albumin. Supernatants from the proliferation assays were collected and assayed for the presence of cytokines.

Results: Following 6 weeks of immunization, a significant increase in inflammation was observed as assessed by paw thickness and scoring in the Cit-Coll mice compared to controls. An increase in serum antibodies to Cit-Coll and Cit-albumin was present. However, no significant increase in antibodies to collagen was observed. In contrast, the immune response to Cit-Coll was predominantly T cell as shown by the increase in proliferative response to collagen and Cit-Coll. Assessment of cytokines from the proliferation supernatants reveled increases in IL-6 and IL-23 following from Cit-Coll immunized mice. Finally, histological analysis of joints from these animals showed an increase in joint erosion an inflammation in the Cit-Coll immunized mice.

Conclusions: These data support the observation that citrullination of proteins increases the risk of this erosive inflammatory disease. Also, that citrullinated mouse type II collagen immunized in the absence of adjuvant causes an increase in T-cell proliferation with minimal antibody response to native collagen. The T-cell cytokine responses generated an IL-6 and IL-23 profile indicating an autoimmune response. Also, joint erosion and inflammation is evident in the Cit-Coll immunized mice as determined by scoring, paw thickness, and histology. Thus, this report suggests that citrullinated self-proteins may result in the abrogation of tolerance and the induction of an autoimmune response.

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2236

Differentiation and Activation of Regulatory T-Lymphocytes in a TNF-alpha Transgenic Model of Arthritis, and the Impact of Passive or Active Anti-TNF Therapies. Jerome Biton[2], Luca Semerano[3], Laure Delavallée[2], Geraldine Grouard-Vogel[1], Delphine Lemeiter[2], Marie-Christophe Boissier[3] and Natacha Bessis[2]. [1]Neovacs, Paris, France, [2]Paris 13 University, Bobigny, France, [3]Paris 13 University and APHP, Bobigny, France

Background: TNF-alpha is a critical cytokine in rheumatoid arthritis (RA). We recently demonstrated the efficacy of active immunotherapy against TNF-alpha (TNF-K) in a human TNF-alpha transgenic (TTg) mouse model of arthritis. Studies with anti-TNF-alpha treatments in autoimmune diseases suggest that TNF-alpha and TNF-alpha antagonists might act through the involvement of a T cells subset, namely $CD4^+$ $CD25^+$ $FoxP3^+$ regulatory T cells (Tregs).

Objectives: In the present study, we aimed to better characterize the impact on the Treg population of (1) a TNF-alpha driven disease, specifically arthritis in TTg mice, and (2) active or passive anti-TNF-alpha immunotherapy in this same model.

Methods: First, untreated TTg mice were euthanized sequentially at the age of 7 weeks, 12 weeks, 17 weeks and 24 weeks. 7 week-old and 24 week-old C57Bl/6 wild type (WT) mice were used as controls. Subsequently, three groups of mice were used: TTg mice given three doses of TNF-K at 15, 16 and 19 weeks of age, TTg mice treated with infliximab and untreated TTg mice. Then half the mice in each group were euthanized at 24 weeks and the other half at 31 weeks. After each euthanasia, the percentage and number of Tregs and the percentage of Tregs cells expressing CTLA-4, TNFR2 and CD62L from the spleen and lymph nodes (LN) were determined. Finally, the immunosuppressive activity of the Treg cells was studied.

Results: hTNF-alpha overexpression induced an initial decline in Tregs. Then, once chronic inflammation was established, the frequency and the number of Tregs cells slightly increased with time, although it remained lower than in WT mice. We also observed a progressive and dramatic increase in TNFR2 expression (65.8% to 88.6% at weeks 7 and 24, respectively, $P<0,0001$) and MFI on Tregs from LN during the course of arthritis. We also confirmed that TNF-K was as effective as infliximab in treating established arthritis in TTg mice. Compared to untreated mice, hTNF-alpha blockade with either infliximab or TNF-K resulted in an increased Tregs frequency both in 24 and 31 week-old mice. Our study also showed that hTNF-alpha blockade induces an up-regulation of CTLA-4 expression by Treg cells in LN, accompanied by an increased Tregs suppressive activity on $CD4^+$ $CD25^-$ effector T cell proliferation. Finally, in LN of infliximab and TNF-K treated TTg

mice, we observed an expansion of induced Treg cells defined by the $CD4^+$ $CD25^+$ $FoxP3^+$ $CD62L^-$ phenotype.

Conclusion: In this study, in a strictly hTNF-alpha dependent inflammation model, we show for the first time that TNF-alpha can have different effects on Tregs, depending on the duration of exposure and on disease phase. Our work also shows that TNF-alpha blockade either by TNF-K or infliximab could depend not only on TNF-alpha neutralization but also on Treg upregulation.

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2237

The TRAF6 Binding Molecule p62/SQSTM1 Controls Inflammatory Bone Destruction in hTNFtg Mice. Adelheid Korb[7], Marianne Niedermeier[3], Anja Hillmann[7], Susanne Bürgis[1], George Kollias[5], Sven Herrmann[2], Thomas Pap[4], Thomas Weide[7], André Gessner[6] and Herrmann Pavenstädt[7]. [1]Department of Immunology, University Erlangen, Erlangen, Germany, [2]European Institute of Molecular Imaging, University Muenster, Germany, [3]Institute for Experimental Musculoskeletal Medicine, University Hospital Muenster, Muenster, Germany, [4]Institute for Experimental Musuculoskeletal Medicine, University Hospital Muenster, Muenster, Germany, [5]Institute of Immunology, Biomedical Science Research Center, Vari, Greece, [6]Institute of Microbiology - Clinical Microbiology, Immunology and Hygiene, University Hospital Erlangen, Erlangen, Germany, [7]Internal Medicine D, Department of Nephrology and Rheumatology, University Hospital Muenster, Muenster, Germany

Background: Activation of NF-kappaB via RANK is essential in regulating osteoclastogenesis. This process is enhanced by pro-inflammatory cytokines such as TNFalpha. P62/SQSTM1 directly modulates these pathways through complex formation with TRAF6, aPKCs and ubiquitin. However, the function of p62/SQSTM1 in regulating bone turnover under inflammatory conditions and specifically the role of the signal transduction domains of p62/SQSTM1 in this process is not known.

Methods: Mice carrying a mutant of p62 with functional ubiquitin-binding but defective signal transduction domains ($p62^{aa\Delta 69-251)}$ were interbreed with arthritic hTNFtg mice. All resulting genotypes were scored for clinical parameters for 14 weeks. For quantification of inflammation, cartilage degradation and number of osteoclasts, joints of 14 wks old mice were stained with toluidin-blue and TRAP. To identify abnormalities in bone metabolism and bone structure high resolution micro-CT and Fluoride/FDG-PET analyses were performed. In addition, bone marrow derived monocytes (BMDMs) of wt and $p62^{aa\Delta 69-251}$ mice were isolated and osteoclastogenesis was studied using an established osteoclast formation assay. To investigate the underlying signalling pathways, cells were treated with TNFalpha and RANKL at different time points, and the activation of MAPKs was studied by Western Blot analysis.

Results: Histology and in vivo PET/CT studies revealed an increase in bone metabolism and bone mass in the hind paws, knees and vertebrae of $p62^{aa\Delta 69-251}$ mice, but the number and size of osteoclasts of $p62^{aa\Delta 69-251}$ and wt animals showed only minor changes suggesting that under physiological conditions the lack of the signal transduction domains of p62 is compensated by regulatory mechanisms. Compared to wt cells, however, BMDMs of $p62^{aa\Delta 69-251}$ mice showed a significantly increased osteoclastogenesis, especially when stimulated with TNFalpha. Crossing of $p62^{aa\Delta 69-251}$ mice with hTNFtg animals resulted in a dramatic increase in the severity of joint damage in the hTNFtg/$p62^{aa\Delta 69-251/wt}$ mice as determined clinically, by histomorphometry and PET/CT analysis. This was accompanied by an increase in the number and size of osteoclasts in vivo. During osteoclastogenesis, BMDMs from $p62^{aa\Delta 69-251}$ mice showed an enhanced TNFalpha- induced ERK1/2 and p38 MAPK phosphorylation compared to that of wt mice.

Conclusion: In summary, our data suggest that p62 plays a relevant role in regulating TNFalpha mediated joint damage. They indicate that the loss of the TRAF6 and aPKCs binding domains has essential consequences for osteoclastogenesis under inflammatory conditions.

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ACR Concurrent Abstract Sessions
Systemic Lupus Enrythematosus - Clinical Aspects and Treatment
Thursday, November 11, 2010, 9:00 AM–11:00 AM

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Low Blood Concentration of Hydroxychloroquine Is Associated with Failure of Hydroxychloroquine Treatment in Patients with Cutaneous Lupus: Results of a Prospective Study. Camille Francès[1], Anne Cosnes[1], Pierre Duhaut[2], Noël Zahr[3], Boutros Soutou[1], Saskia Oro[1], Didier Bessis[1], Jacqueline Chevrant-Breton[1], Nadege Cordel[1], Dan Lipsker[1] and Nathalie Costedoat-Chalumeau[3]. [1]Department of Dermatology, Hôpital Tenon, Paris, France, [2]Department of Dermatology, Hôpital Tenon, [3]Internal Medicine Department, French National Reference Center for SLE, Pitié-Salpêtrière Hospital (GHPS), Paris, France

Introduction: We have previously demonstrated that low whole-blood concentration of Hydroxychloroquine [HCQ] is a marker for and a predictor of disease exacerbations in SLE patients, and we proposed 1,000 ng/ml as the target [HCQ] (Costedoat-Chalumeau, Arthritis Rheum, 2006). Very low [HCQ] (i.e. [HCQ] < 200 ng/ml) is a marker for poor adherence to HCQ treatment (Costedoat-Chalumeau, Ann Rheum Dis, 2007).

We studied for the first time, the relationship between [HCQ] and efficacy of HCQ in patients with cutaneous lupus.

Methods: Patients treated with HCQ for a cutaneous lupus were prospectively included in this multicentric study. Clinical status was determined by a dermatologist who was blinded for [HCQ]. Complete remission was defined by the disappearance of all cutaneous lesions, partial remission by an improvement > 50% and failure by other cases. At the end of the study, [HCQ] was measured by HPLC.

Results: We included 300 patients: 253 (84%) women and 47 (16%) men, median age 44 years [12–86]. Cutaneous lupus included discoid lupus (n=160), subacute cutaneous lupus (n=86), lupus tumidus (n=52), chilblain lupus (n=26), and panniculitis (n=16), and 41 patients had 2 or more associated forms. Most patients (83%) were treated with 400 mg/d of HCQ. Clinical status was complete remission (n=114), partial remission (n=86) or failure (n=100).

The median [HCQ] was 758 ng/ml [<50–3057]. [HCQ] was significantly higher in patients with complete remission (910 [<50–3057] vs 692 [<50–2843] if partial remission, and 569 [<50–2242] if failure; p=0.007).

[HCQ] was significantly lower in men (557 [<50–1572] vs 801 [<50–3057] in women; p = 0.006) who more frequently reported poor adherence to HCQ treatment (28% vs 11%; p = 0.002). [HCQ] correlated with the number of reported omissions of HCQ (p = 0.01).

Thirty patients (10%) had [HCQ] below 200 ng/ml and were considered as non-adherent. There were 8 patients in complete remission group, 8 in partial remission group, and 14 in failure group. Number of self-reported omissions of HCQ was significantly higher (p = 0.0001) in non-adherent patients.

After exclusion of non-adherent patients, [HCQ] was 850 ng/ml [201–3057] in the remaining 270 patients. [HCQ] remained significantly higher in patients with complete remission (952 [224–3057] vs 755 [212–2843] if partial remission and 692 [201–2242] if failure, p=0.026).

In the whole group, [HCQ] was significantly correlated to BMI (p = 0.02), weight (p = 0.002) and height (p = 0.05). There was no correlation between [HCQ] and cigarette smoking, daily dose of HCQ or number of omissions of HCQ.

In multivariate analysis, factors associated with complete remission were higher [HCQ] (p=0.005), and the absence of discoïd lesions (p=0.037). This remained true when analysis was performed after

exclusion of non-adherent patients (p=0.01 and p=0.016 respectively).

Comment: [HCQ] allowed detection of non-adherence to treatment in 10% of cases. Even after exclusion of non-adherent patients, low [HCQ] was associated with failure of HCQ treatment in patients with cutaneous lupus. Regular drug assaying and individual tailoring of treatment might help to improve the efficacy of HCQ treatment in patients with cutaneous lupus.

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Factors Associated with Low Blood Concentration of Hydroxychloroquine in 523 Patients with Systemic Lupus Erythematosus: Data from the PLUS Study. Nathalie Costedoat-Chalumeau[2], Lionel Galicier[2], Camille Francès[2], Olivier Aumaître[2], Frédéric Lioté[2], Véronique Le Guern[2], Nicolas Limal[2], Amar Smail[2], J. Ninet[2], Laurent Perard[2], Du Le Thi Huong[2], Bouchra Asli[2], Catherine Grandpeix[2], Laurent Sailler[2], F. Ackermann[2], Thomas Papo[2], Benoit Brihaye[2], Olivier Fain[2], Jérome Stirnemann[2], Moez Jallouli[2], Gaelle Leroux[2], Jean-Sébastien Hulot[2], Philippe Lechat[2], Lucile Musset[2], Jean-Charles Piette[2], Zahir Amoura[2] and The Investigators of the PLUS Study[1]. [1]Internal Medicine Department, French National Reference Center for SLE, Pitié-Salpêtrière Hospital, Paris, France, [2]Internal Medicine Department, French National Reference Center for SLE, Pitié-Salpêtrière Hospital

Objectives: We have previously demonstrated that low whole-blood Hydroxychloroquine concentration [HCQ] is a marker for and predictor of systemic lupus erythematosus (SLE) flares [1]. The French multicenter randomized PLUS study (NCT 00413361) is currently assessing the potential benefits of individualized HCQ dosing schedules aimed at maintaining the [HCQ] above 1,000 ng/ml in SLE patients. According to the design of PLUS study, all patients have a measurement of [HCQ]. We studied the relationship between [HCQ] and epidemiological data at baseline.

Methods: Among the 569 included in the PLUS study, 523 patients who were treated with the same dose of HCQ (400 mg/d) were studied. [HCQ] was measured at the time of inclusion, and the patients were divided into 2 groups according to their [HCQ]: group A ([HCQ] $<$ 750 ng/ml), and group B ([HCQ] $\geq$ 750).

Results: The following parameters were similar between group A (179 patients) and group B (344 patients): mean age and duration of SLE, current smoking status, family history of SLE, frequency of associated antiphospholipid syndrome, values of C3, anti-nucleosome antibodies and anti-DNA antibodies, % of patients treated with immunosuppressive drugs, and mean daily dose of prednisone

In group A (low [HCQ]), the % of men (14.6 vs 6.2, p=0.004), weight (69±15 vs 62±12 kg, p<0.0001), BMI (25.4±4.2 kg/m2 vs 23.2±5.3; p<0.001) and estimated creatinine clearance (114±35 vs 99±29 ml/min; p<0.0001) were significantly higher compared to group B. After exclusion of men, the difference remained significant for weight and creatinine clearance.

At inclusion, 106 patients in group A (58%) were treated with steroids vs 238 in group B (69%, p = 0.02). Adherence to the prescription of HCQ assessed by the investigator on a VAS (from 0 to 10) was significantly lower in group A (8.99±1.3) compared to group B (9.3±1.03, p=0.003). Even though patients were excluded if they had a SLEDAI $>$ 12, we found a significantly higher SLE activity in group A (mean SLEDAI: 2.41±2.5 vs 1.88±2.34, p = 0.016). This difference held on even in the subset of patients treated with steroids (2.94 ± 2.62 vs 2.16±2.54, p=0.019). Platelet counts were significantly lower in group A (225,000± 75,000 vs. 268,000±71,000/mm3, p<0.0001).

In multivariate analysis, factors associated with low [HCQ] were low level of platelets (p<0.0001), high clearance of creatinine (p<0.001), absence of treatment with steroids (p=0.003), poor adherence (p=0.003), high BMI (p=0.007) and SLE activity (p=0.024).

Conclusion: This preliminary analysis confirms in a new set of patients our previously reported association of low [HCQ] with a higher SLE activity [1]. This was not expected given that patients included in PLUS study have low SLE activity according to inclusion criteria. Other parameters associated with low [HCQ] included high BMI, poor adherence assessed by the investigator, low platelet count, and high estimated creatinine clearance.

References:

[1] Costedoat-Chalumeau, N, Amoura, Z, Hulot, JS, et al. Arthritis Rheum 2006; 54: 3284–90.

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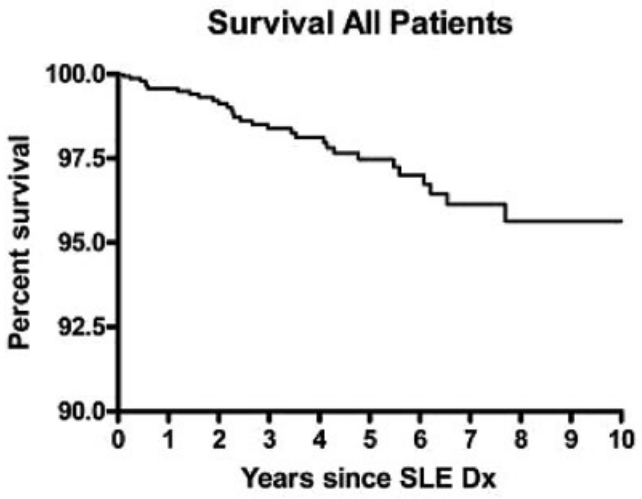
Mortality in a Multinational Inception Cohort of SLE. Murray B. Urowitz[33], Dafna D. Gladman[22], Dominique Ibanez[32], Caroline P. Gordon[29], Sang-Cheol Bae[6], Ann E. Clarke[15], Sasha R. Bernatsky[15], F. Jorge Sanchez-Guerrero[9], John G. Hanly[19], David A. Isenberg[24], Anisur Rahman[25], Paul R. Fortin[33], Daniel J. Wallace[1], Ellen M. Ginzler[20], Joan T. Merrill[18], Graciela S. Alarcón[28], Barri J. Fessler[23], Ian N. Bruce[13], Gunnar K. Sturfelt[27], Ola Nived[27], Kristjan Steinsson[12], Munther A. Khamashta[21], Michelle A. Petri[2], Rosalind Ramsey-Goldman[17], Susan Manzi[34], Mary Anne Dooley[31], Ronald V. Vollenhoven[11], Cynthia B. Aranow[4], Thomas Stoll[10], Manuel Ramos[7], Kenneth C. Kalunian[26], Asad A. Zoma[5], Guillermo Ruiz-Irastorza[8], Peter J. Maddison[16], Diane L. Kamen[14], S. Sam Lim[3] and Christine A. Peschken[30]. [1]West Hollywood, CA, [2]Timonium, MD, [3]Emory University, Atlanta, GA, [4]Feinstein Institute, Manhasset, NY, [5]Hairmyres Hospital, East Kilbride, United Kingdom, [6]Hanyang University Medical Center, Seoul, Korea, Republic of, [7]Hospital Clinico I Provincial, [8]Hospital de Cruces, Universidad del Pais Vasco, [9]Instituto Nacional Nutricion, Mexico City, DF, Mexico, [10]Kantonsspital Schaffhausen, Schaffhausen, Switzerland, [11]Karolinska University Hospital, [12]Landspitalinn University Hospital, [13]Manchester Royal Infirmary, Manchester, United Kingdom, [14]Medical University South Carolina, Charleston, SC, [15]Montreal General Hospital, Montreal, QC, Canada, [16]North West Wales NHS Trust, Colwyn Bay, United Kingdom, [17]Northwestern University, Chicago, IL, [18]Oklahoma Med Research Foundation, Oklahoma City, OK, [19]Queen Elizabeth II Health Services Center, Halifax, NS, Canada, [20]SUNY-Downstate Medical Center, Brooklyn, NY, [21]The Rayne Institute, London, United Kingdom, [22]Toronto Western Hospital, Toronto, ON, Canada, [23]UAB Rheumatology, Birmingham, AL, [24]UCL Div of Medicine, London, United Kingdom, [25]UCL Div of Medicine, [26]UCSD School of Medicine, La Jolla, CA, [27]University Hospital Lund, Lund, Sweden, [28]University of Alabama, Oakland, CA, [29]University of Birmingham, Birmingham, United Kingdom, [30]University of Manitoba, Winnipeg, MB, Canada, [31]University of North Carolina at Chapel Hill, Chapel Hill, NC, [32]University of Toronto Lupus Clinic, Toronto Western Hospital, [33]University of Toronto Lupus Clinic, Toronto Western Hospital, Toronto, ON, Canada, [34]West Penn Allegheny Health System, Pittsburgh, PA

Background: A large multicentre multinational inception cohort was established to study risk factors for atherosclerosis (AS) in SLE. This study describes survival, mortality and causes of death during the first 10 years of observation of the SLICC inception cohort.

Methods: Patients enter the cohort within 15 months of SLE diagnosis (≥4 ACR criteria). Clinical and laboratory features of SLE and comorbidities are gathered in a standardized protocol at yearly intervals. Deaths are recorded as they occur and the cause of death is determined according to the ICD9 code. Demographic and disease related factors present at enrolment were compared in patients who died and in survivors using descriptive statistics, Kaplan-Meier curve as well as life table analysis.

Results: Since 2000, 1593 patients have been entered into the cohort (89.4%F, age at SLE 34.6y, mean followup of 3.7 years). 30 patients have died during the course of follow-up. Survival was 99.6% at 1 year, 98.4% at 3 years and 97.5% at 5 years (figure 1)

Causes of death included coronary artery disease (CAD) in 7, SLE in 9, infection in 9, 1 from other causes and 4 unknown. Patients who died were older at diagnosis, more often had CAD, and had higher SLICC/ACR damage index scores at enrolment and a decreased physical components score (PCS) of the SF-36 at enrolment. Patients who died were also more likely to have used corticosteroids (HR=6.4 p=0.01) and immunosuppressives(HR=2.4 p=0.02) and less likely to have used antimalarials(HR=0.3 p=0.001) at enrolment.



Conclusion: This multinational inception cohort of SLE patients demonstrates the improved survival noted among patients with SLE. Causes of death in the first 10 years of observation of the SLICC inception cohort with an average followup of 3.7 years include CAD, SLE and sepsis. Even early on in the course of SLE, CAD is an important cause of death. Older age, history of CAD, early damage and impaired physical function, use of corticosteroids and immunosuppressives are associated with mortality.

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Mycophenolate Mofetil and Hydroxychloroquine but Not Azathioprine Improve HDL Function in Women with SLE. Maureen McMahon[3], Jennifer M. Grossman[4], Jessica Gomez[3], Lori Sahakian[3], Weiling Chen[3], John Fitzgerald[3], Brian Skaggs[2], Joan T. Merrill[1] and Bevra H. Hahn[5]. [1]Oklahoma Med Research Foundation, Oklahoma City, OK, [2]UCLA, Los Angeles, CA, [3]UCLA School of Medicine, Los Angeles, CA, [4]University of California Los Angeles, Sherman Oaks, CA, [5]University of California Los Angeles School of Medicine, Los Angeles, CA

Objective: Women with SLE have an unexplained increase in CAD compared to controls. Normal HDL protects against plaque by preventing oxidation of LDL and the resulting inflammatory response. Pro-inflammatory HDL (piHDL) are abnormal HDL that cannot protect LDL from oxidation. We previously reported that 45% of SLE women vs. 5% of controls have piHDL In addition, SLE patients with piHDL are 16 times more likely to have plaque on carotid ultrasound than patients with normal functioning HDL. SLE function is stable over time; however, it is unknown how disease modifying agents affect HDL function.

Methods: This prospective observational study included any SLE subject from our cohort who was started on a new immunosuppressive agent. Cryopreserved plasma samples were taken at three time points: baseline (prior to initiation of drug), 6 weeks, and 12 weeks post initiation of therapy. To determine the antioxidant function of HDL, we measured change in fluorescence intensity caused by oxidation of DCFH by OxLDL in the presence or absence of test HDL. Fluorescence in the absence of HDL was normalized to 1.0. Values greater than 1.0 after the addition of HDL indicated piHDL. (In previously published studies, mean HDL function in healthy controls ranges from0.44 to 0.66).

Results: 13 subjects were started on mycophenolate (MMF), 11 subjects on azathioprine (AZA), and 22 subjects on hydroxychloroquine (HCQ). The mean SLEDAI score at baseline was 8.9 $\pm$ 5.4 in the MMF group vs. 9.2 $\pm$ 4.1 in AZA vs. 6.4 $\pm$ 3.2 in HCQ (p=ns among all groups). In MMF treated subjects, HDL function improved from baseline, with a score of 2.18 $\pm$ 1.46 prior to therapy dropping to 1.28 $\pm$ 0.87 after 6 weeks of therapy (p=0.04,paired t-test), and to 0.89 $\pm$ 0.56 after 12 weeks of therapy (p=0.02). In hydroxychloroquine treated subjects, HDL function did not significantly change from baseline at 6 weeks of therapy from 1.66 $\pm$ 1.16 to 1.31 $\pm$ 1.27 (p=0.19); however, it did significantly improve after 12 weeks of therapy, 0.96 $\pm$ 0.71(p=0.027). In those treated with azathioprine, HDL function remained relatively stable (1.07 $\pm$ 0.53) vs. 1.30 $\pm$ 0.77 at 6 weeks (p=ns), and 1.00 $\pm$ 0.99 at 12 weeks (p=ns). In addition, there was a trend towards a correlation between change in HDL function and improvement in SELENA-SLEDAI in all groups, (r=0.367, p=0.09), although this did not reach statistical significance.

Conclusions: In conclusion, HDL function is significantly improved by therapy with mycophenolate mofetil, although not to normal levels. There was also improvement with hydroxychloroquine, but not with azathioprine.

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2242

Screening for Cognitive Impairment in Systemic Lupus Erythematosus. John G. Hanly[2], Li Su[3], Vern Farewell[3], Tina Linehan[1] and John D. Fisk[2]. [1]Capital Health, Halifax, NS, Canada, [2]Capital Health and Dalhousie University, Halifax, NS, Canada, [3]MRC Biostatistics Unit, Institute of Public Health, University Forvie Site, Cambridge, UK

Purpose: Cognitive impairment is frequent in patients with systemic lupus erythematosus (SLE). In order to make an accurate diagnosis of cognitive impairment formal neuropsychological assessment is required which is not universally available. Our objective was to determine the accuracy of a screening questionnaire for the detection of cognitive impairment in patients with SLE.

Methods: Ambulatory patients with SLE and rheumatoid arthritis (RA) were studied at a single academic medical center. Each subject completed a cognitive symptom inventory (CSI), which provides a total score and 4 subscale scores, and the hospital anxiety and depression scales (HADS). The SLEDAI and ACR/SLICC damage index were used to assess global SLE disease activity and severity respectively. In addition the Automated Neuropsychological Assessment Metrics (ANAM) which is a computerized test battery that takes 45 minutes to administer was used to evaluate the cognitive performance of SLE and RA patients. ANAM measures reaction time and accuracy in Simple Reaction Time (SRT), learning and recall using Code Substitution subtests (CDS and CDD), working memory using the Mathematical Processing (MTH) and the Sternberg Memory Scanning (ST6) subtests, sustained attention using a Continuous Performance subtest (CPT), visual-spatial processing using the Matching Grids (MSG) subtest, and short-term visual memory using the Match to Sample subtest (MSP). Efficiency of performance on each subtest was examined by "throughput"(TP) (number of correct responses per minute) and "inverse efficiency" (IE) (response speed/proportion of correct responses). Linear regression was applied to the log-transformed CSI scores to examine their associations with ANAM scores as well as other factors.

Results: Sixty-eight patients with SLE and 33 with RA were studied. Both groups were predominantly female (92.7% and 97.0 %) with a mean $\pm$ SD age of 45.5$\pm$13.4 and 49.8$\pm$10.2 years respectively. SLE patients had significantly higher total CSI scores (33.6$\pm$10.5 vs. 29.4$\pm$6.8; p=0.041) and attention/concentration subscale CSI scores (15.7$\pm$5.3 vs. 13.3$\pm$3.4; p=0.016) compared to RA patients. There was a positive association overall between CSI scores and HADS anxiety ($p<0.0001$) and depression ($p<0.0001$) scores. After adjusting for age and education, there was no significant association ($p>0.05$) between ANAM global and subscale scores and CSI scores in SLE and RA patients. The results were similar using either "throughput", "inverse efficiency" or the number of impaired ANAM subscales after adjusting for simple reaction time.

Conclusion: The use of self-report questionnaires of cognitive symptoms does not reliably screen for cognitive impairment in SLE patients. The results obtained with such instruments are confounded by the presence of anxiety and depression.

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2243

Autoantibodies as Biomarkers for the Prediction of Neuropsychiatric Events in Systemic Lupus Erythematosus. John G. Hanly[2], Murray B. Urowitz[20], Li Su[13], Sang Cheol-Bae[6], Caroline Gordon[26], Jorge Sanchez-Guerrero[7], Ann Clarke[12], Sasha Bernatsky[12], Archana Vasudevan[17], David Isenberg[23], Anisur Rahman[23], Daniel J. Wallace[3], Paul Fortin[20], Dafna Gladman[20], Mary Anne Dooley[28], Ian Bruce[19], Kristjan Steinsson[10], Munther Khamashta[18], Susan Manzi[29], Rosalind Ramsey-Goldman[14], Gunnar Sturfelt[24], Ola Nived[24], Cynthia Aranow[4], Ronald van Vollenhoven[9], Manuel Ramos-Casals[16], Ken Kalunian[21], Graciela Alarcon[25], Barri J. Fessler[25], Guillermo Ruiz-Irastorza[22], Michelle Petri[8], Sam Lim[5], Diane Kamen[11], Christine Peschken[27], Vern Farewell[13], Kara Thompson[2], Chris Theriault[1] and Joan Merrill[15]. [1]Capital Health, Halifax, NS, Canada, [2]Capital Health and Dalhousie University, Halifax, NS, Canada, [3]Cedars-Sinai/David Geffen School of Medicine at UCLA, Los Angeles, CA, [4]Columbia University Medical Center, New York, NY, [5]Emory University, Atlanta, GA, [6]Hanyang University Hospital for Rheumatic DIseases, Seoul, Korea, [7]Instituto Nacional de Ciencias Medicas y Nutricion, Mexico City, Mexico, [8]John Hopkins University School of Medicine, Baltimore, MD, [9]Karolinska Institute, Stockholm, Sweden, [10]Landspitali University Hospital, Reykjavik, Iceland, [11]Medical University of South Carolina, Charleston, SC, [12]Montreal General Hospital, McGill University Health Centre, Montreal, QC, Canada, [13]MRC Biostatistics Unit, Institute of Public Health, University Forvie Site, Cambridge, United Kingdom, [14]Northwestern University and Feinberg School of Medicine, Chicago, IL, [15]Oklahoma Medical Research Foundation, Oklahoma City, OK, [16]Servicio Enfermedades Autoinmunes Hospital Clínico y Provincial, Barcelona, Spain, [17]SUNY Downstate Medical Center, Brooklyn, NY, [18]The Rayne Institute, St. Thomas' Hospital, King's College London School of Medicine, London, United Kingdom, [19]The University of Manchester, Manchester, United Kingdom, [20]Toronto Western Hospital and University of Toronto, ON, Canada, [21]UCSD School of Medicine, La Jolla, CA, [22]Universidad del Pais Vasco, Barcelona, Spain, [23]University College, London, United Kingdom, [24]University Hospital Lund, Lund, Sweden, [25]University of Alabama at Birmingham, Birmingham, AL, [26]University of Birmingham, Birmingham, United Kingdom, [27]University of Manitoba, Winnipeg, Canada, [28]University of North Carolina, Chapel Hill, NC, [29]University of Pittsburgh School of Medicine, Pittsburgh, PA

Purpose: Neuropsychiatric (NP) events are frequent in patients with systemic lupus erythematosus (SLE) and can occur unpredictably at any time over the disease course. The availability of validated biomarkers for NP events would be advantageous. Our objective was to determine if the presence of selected autoantibodies at enrollment predicted the occurrence of NP events in a large disease inception cohort of SLE patients.

Methods: The study was conducted by an international research network of 30 academic centers. Patients were enrolled within 15 months of SLE diagnosis and assessed annually for up to 10 years for the occurrence of NP events using the ACR case definitions for 19 NP syndromes. These were categorized into diffuse/focal and central/peripheral NP events. Decision rules of different stringency (model A and model B) were used to determine the attribution of NP events to SLE and non-SLE causes. Plasma/serum samples were available from 1047 patients for the determination of the following autoantibodies in a central laboratory: lupus anticoagulant, IgG anticardiolipin, anti-β_2 glycoprotein-I, anti-ribosomal P and anti-NR2 glutamate receptor antibodies. The association between the presence of autoantibodies and the risk of the first occurrence of NP events was examined by Cox regression.

Results: Of the 1047 patients 89.1% were female and the mean ($\pm$ SD) age was 35.2 $\pm$ 13.7 years. The mean disease duration at enrollment was 5.4 $\pm$ 4.2 months and the mean length of followup was 3.27 $\pm$ 2.8 years. Over the period of study 495/1047 (47.3%) patients had 1 or more NP events (total of 917 events) encompassing 17 of 19 NP syndromes. The proportion of NP events attributed to SLE varied from 15.4% (model A) to 28.2% (model B). The frequency of autoantibodies at enrollment was 21.9% (lupus anticoagulant), 13.4% (anticardiolipin), 15.1% (anti-β_2-GPI), 9.2% (anti-ribosomal P) and 13.7% (anti-NR2 antibodies). There was no significant positive association between any of the autoantibodies and first occurrence of NP events overall, or events attributed to SLE (model A or model B). Clustering of NP events into diffuse/focal and central/peripheral manifestations did not change the outcome. However, LA at baseline was associated with the occurrence of stroke/sinus thrombosis (total n=22) attributed to SLE (model B) (Hazard ratio (95% CI): 2.54 (1.08–5.94); p=0.03). Furthermore anti-ribosomal P antibodies at enrollment were associated with psychosis (total n=14) attributed to SLE (model B) (Hazard ratio (95% CI): 3.92 (1.23–12.5); p=0.02).

Conclusion: The detection of LA and anti-ribosomal P antibodies near the time of diagnosis of SLE is associated with an increased risk for intra-cranial thrombosis and lupus psychosis respectively.

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ARHP Concurrent Abstract Sessions
What a Pain Rheumatic Diseases Can Be!
Thursday, November 11, 2010, 9:15 AM–10:45 AM

2244

Patellofemoral Osteoarthritis in Middle-Aged Adults: What Are the Best Measures of Physical Performance and Pain for Use in the Clinic and in Research? Lisa T. Hoglund[3], Margery A. Lockard[1], Jinsup Song[2] and Mary F. Barbe[2]. [1]Drexel University, Dresher, PA, [2]Temple University, Philadelphia, PA, [3]University of the Sciences in Philadelphia, Morrisville, PA

Purpose: Osteoarthritis (OA) of the knee is common in Western society. The prevalence of knee OA in adults in the US is estimated to be 23–33%, totaling more than 9 million adults. The patellofemoral (PF) compartment of the knee is frequently involved. Isolated PF OA is present in 24% of persons aged $\geq$ 50 years with knee pain; 40% have combined PF and tibiofemoral OA. The presence of PFOA is associated with pain and disability. Activities that load the PF compartment by strong quadriceps contraction with a flexed knee can be particularly painful. This includes the task of rising from a chair, i.e., sit-to-stand. It is unknown if a physical performance test including sit-to-stand is a more sensitive test of function in persons with PFOA versus a test of ambulation. Clinicians need tests of physical performance, perceived function, and pain to measure the impact of disease in patients. One goal of this study was to examine the impact of PFOA on physical performance, perceived function, stiffness, and pain in persons with bilateral PFOA compared to healthy, painfree subjects without PFOA. A second goal was to determine the best clinical tests to quantify physical performance and pain.

Methods: Thirty-two adults, aged 40– 65 years, underwent radiographic screening for PF and tibiofemoral OA; 15 remained after radiographic exclusions. This cross-sectional study compared 2 groups: subjects with bilateral, symptomatic, radiographic PFOA (PFOA) and age- and gender-matched asymptomatic subjects with no radiographic PFOA (control). There were 8 PFOA subjects and 7 control subjects remaining after radiographic analysis. Both groups completed questionnaires regarding knee pain, stiffness, and function [WOMAC for the past 48 hours and Visual Analog Scale (VAS) for knee pain severity in the past 30 days]. Subjects performed the Timed Up and Go (TUG) and fifty-foot walk (FFW) physical performance tests; subjects rated knee pain severity before and after these tests with a VAS. WOMAC and VAS data were analyzed with Mann-Whitney U-tests, $p < 0.05$; TUG and FFW results were analyzed with t-tests, $p < 0.05$.

Results: The PFOA group reported significantly greater knee pain severity versus the Control group for the past 30 days, post-TUG and post-FFW (VAS). Results of the WOMAC indicated that the PFOA group had greater knee pain and stiffness and significantly less physical function in the past 48 hours. The PFOA group required a significantly longer time to complete the TUG versus controls. No significant difference was found between the groups in time to complete the FFW.

Conclusions: The results of this study demonstrate that middle-aged adults with PFOA have significant functional deficits, greater knee stiffness, and greater knee pain versus painfree adults without PFOA. The TUG is more sensitive than the FFW to detect physical performance deficits in persons with PFOA. The best test of function in this population is the TUG as it is more sensitive than the FFW and has been shown to be reliable and valid in persons with knee OA. The TUG is simple, quick and requires less clinical space than the FFW. Clinicians should use the TUG, accompanied by a VAS rating of pain, to capture the impact of PFOA on an individual's function and pain.

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2245

Differences in Muscle Strength and Pain Thresholds between Postmenopausal Women with and without RA. Ulrika Thoors, Christina H. Opava, Birgitta Glenmark, Eva Kosek, Ingrid E. Lundberg and Cecilia Fridén. Karolinska Institutet, Stockholm, Sweden

Muscle weakness, in particular loss of muscle mass, pain and tenderness are common symptoms in rheumatoid arthritis (RA). This seems to be the case even when inflammation is well controlled and may result in increasing disability with increasing age. Increased pain and increased loss of muscle mass is also found among healthy women at the time of menopause. The aim of our study was to examine differences in muscle strength and pain thresholds between postmenopausal women with and without RA.

Ten postmenopausal women with early (<2 years) RA (median age 57.5, median BMI 24) and ten healthy women (median age 58.5, median BMI 25) were recruited for the study. All women were independent in daily living, had passed menopause and did not use hormone replacement therapy. The median DAS 28 score was 2.7 (range 1.3–4.0) and the median HAQ score was 0.57 (range 0–1) in the RA group.

Measurements of isokinetic muscle strength in knee flexors and extensors, grip strength, timed standing, pressure pain thresholds (PPT), supra threshold pressure pain rated as 4/10 and 7/10 respectively on a Borg CR-10 scale, and segmental and plurisegmental endogenous pain inhibitory mechanism during muscle contraction were assessed in all participants.

No significant difference in knee extensor strength was detected between the women with RA and the healthy ones. Participants with RA were significantly weaker in the knee flexors ($p=0.01$) and in grip strength ($p=0.007$), and they were slower in the timed standing ($p=0.05$). Compared to the healthy women, those with RA had increased sensitivity to threshold pain ($p=0.007$) and to supra threshold pressure pain at both levels measured ($p=0.001$ and $p=0.004$ respectively). PPTs increased at the contracting muscle as well as at a distant resting muscle during standardized static contractions in both groups alike.

Our results indicate that previously noted difference in muscular strength between women with and without RA is present in early disease, in patients with low disease activity and seems to remain even after menopause. Further, the women with RA have generalized allodynia and hyperalgesia, but no dysfunction of segmental and plurisegmental pain inhibitory mechanisms. The normal function of endogenous pain inhibitory mechanisms despite chronic pain in women with RA might contribute to the good effects of physical activity in this group of patients.

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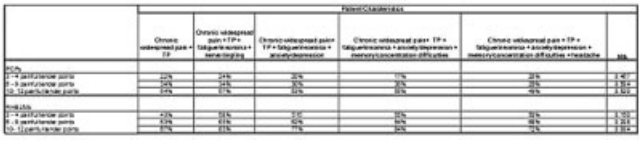
2246

Fibromyalgia Diagnosis Is Significantly Impacted by the Number of Tender Points Presented on Patient Physical Exam. Terence W. Starz[1], Robert J. Sanchez[2], Bruce Duncan[3], Kaite Ka[3], Elizabeth Pinner[2], Shera D. Gruen[2] and Dennis C. Turk[4]. [1]Arthritis & Internal Med Associates, Pittsburgh, PA, [2]Pfizer, [3]Roger Green and Associates, [4]University of Washington, Seattle, WA

Statement of Purpose: To evaluate whether the number of tender points (TP) in simulated case vignettes influenced the likelihood of primary care physicians (PCPs) and rheumatologists (RHEUMs) diagnosing fibromyalgia (FM).

Methods: 200 PCPs and 100 RHEUMs experienced in treating chronic pain were recruited from an online panel to review simulated patient cases. All simulated patient cases included chronic wide spread pain (CWP) + varying degrees of painful TPs (3–4, 6–8, and 10–12) on physical examination and various constellations of other FM related-symptoms (Table 1).



Each physician evaluated 20 cases and was asked to provide a diagnosis. The primary outcomes of interest were the diagnosis of FM, which was based on groups that include descriptions of varying numbers of TP present on physical examination and symptoms, by PCPs and RHEUMs. Bivariate statistics were used to examine the association between TPs and symptoms. Logistic regression models were used to examine predictors of FM diagnoses.

Results: 300 physicians reviewed 6000 simulated patient case vignettes. The overall FM diagnosis rate was 35% for PCPs and 63% for RHEUMs. The rate of FM diagnosis for the PCPs did not change among the different constellation of symptoms; however, as the number of painful TPs increased, the FM diagnosis also increased (Table 1). Among the RHEUMs, there was no significant difference in the dx rate among the different constellations of patient symptoms for those experiencing 3–4 or 6–8 painful TPs. However, among those with 10–12 painful TPs, a significant difference in diagnosis (67%–84%, $p = 0.004$) among the different constellation of patient symptoms were seen. The FM diagnosis rate for RHEUMs also increased as the number of TPs increased (Table 1). After controlling for covariates, the odds of an FM diagnosis among PCP was significant for those experiencing 6–8 painful TPs (odds ratio 1.82, $p < .001$) and 10–12 painful TPs (odds ratio 4.64, $p < .001$). Among the RHEUMs, the odds of an FM diagnosis was significant for those experiencing 6–8 painful TPs (odds ratio 1.57, $p < .001$) and 10–12 painful TPs (odds ratio 3.20, $p < .001$). The presence of 3–4 TPs did not impact the likelihood an FM diagnosis.

Conclusion: Although not all simulated patient cases met the ACR FM diagnosis criteria, the diagnosis of FM by RHEUMs was consistently higher than the diagnosis by PCPs across the different patient TPs and symptom groups. When evaluating simulated patients with FM who are describing widespread pain with or without other FM symptoms and a variable number of tender points on physical examination, the number of tender points is the most significant patient characteristic that leads both primary care physicians and rheumatologists to make the diagnosis of FM. Further analysis is needed to understand reasons behind misdiagnosis.

Disclosure: T. W. Starz: Pfizer Inc, 5; **R. J. Sanchez:** Pfizer Inc, 1, 3; **B. Duncan:** Pfizer Inc, 5; **K. Ka:** Pfizer Inc, 5; **E. Pinner:** Pfizer Inc, 1, 3; **S. D. Gruen:** Pfizer Inc, 1, 3; **D. C. Turk:** Pfizer Inc, 5.

2247

Measuring Pain in Systemic Sclerosis: The Short-Form McGill Pain Questionnaire or a Single Item Measure of Pain? A Confirmatory Factor Analysis. Ghassan El Baalbaki[1], Janie Lober[2], Marie Hudson[4], Murray Baron[1], Brett D. Thombs[3] and Canadian Scleroderma Research Group (CSRG). [1]Jewish General Hospital, Montreal, QC, Canada, [2]McGill University, [3]McGill University, Montreal, QC, Canada, [4]McGill University and Jewish General Hospital

Background: Pain is common in patients with systemic sclerosis (SSc), and severity levels are comparable to other rheumatic diseases. Patients with SSc report a number of painful symptoms. Existing studies of pain in SSc have used a variety of pain assessment tools, including a single-item pain Visual Analog Scale (VAS), a pain numerical rating scale (NRS), and the longer 15-item short-form McGill Pain Questionnaire (MPQ-SF). OMERACT 6 reported that the pain VAS is valid to measure pain related to Raynaud's phenomenon and digital ulcers in SSc, but has not been examined as a general pain measure. VAS and NRS measures have been shown to function similarly in other patient groups. Despite being longer, the MPQ-SF would be a potentially attractive measure if it were to demonstrate more robust validity characteristics than single-item measures or if it were able to differentiate between sensory and affective components of pain, as has been suggested in some patient groups. The objectives of this study were (1) to assess whether the MPQ-SF has stronger validity characteristics among patients with SSc compared to two single-item measures, the pain NRS and the Present Pain Index (PPI), a single Likert item, and (2) to determine whether the MPQ-SF differentiates meaningfully between sensory and affective components of pain in SSc patients.

Methods: Patients with SSc were recruited from the Canadian Scleroderma Research Group Registry. To assess convergent validity compared to the NRS and PPI, Pearson's correlations, with 95% confidence intervals (CIs), were computed between the MPQ-SF, NRS, and PPI with other outcome measures, including the Center for Epidemiologic Studies Depression scale (CES-D), the Health Assessment Questionnaire – Disability Index (HAQ-DI), and the Mental andd Physical Component Summaries(MCS and PCS) scores of the Short-Form 36 Health Survey Questionnaire. To assess the degree that the MPQ-SF differentiated between sensory and affective factors, confirmatory factor analysis (CFA) models were conducted using MPlus, treating items as ordinal data. In addition, Pearson's correlations with 95% CIs of sensory and affective factor scores with CES-D, the HAQ-DI, the MCS and PCS were calculated to test for differences between the sensory and affective correlations.

Results: A total of 1,091 patients were included. The MPQ-SF, NRS and PPI correlated similarly to all other outcome measures with no significant or substantive differences. Model fit for the two-factor model (sensory and affective) was good ($c^2(55) = 198.3$, $P < 0.001$; CFI = 0.97, TLI = 0.99, RMSEA = 0.05), but a single-factor model that did not differentiate sensory and affective pain fit similarly well ($c^2(54) = 234.2$, $P < 0.001$; CFI = 0.96, TLI = 0.99, RMSEA = 0.06). Sensory and affective factor scores correlated similarly with other outcome measures.

Conclusion: The MPQ-SF did not improve on the PNRS or PPI as a measure of pain in SSc. In addition, no evidence was found that the MPQ-SF provides substantively different assessment of sensory and affective pain. The PNRS is a reliable and valid measure of pain in SSc, and is advantageous for use because of its brevity in administration and scoring.

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2248

Daily Electronic Reports of Pain and Activity Difficulties in Children with JIA Versus Children with Other Rheumatic Diseases. Mark Connelly[1], Maggie H. Bromberg[4], Kelly K. Anthony[3], Lindsey Franks[2], Karen M. Gil[4] and Laura E. Schanberg[2]. [1]Children's Mercy Hospital and Clinics, Kansas City, MO, [2]Duke University Medical Center, Durham, NC, [3]Duke Unviversity Medical Center, Durham, NC, [4]University of North Carolina at Chapel Hill

Purpose: To compare children with JIA vs juvenile rheumatic disease (JRD) across daily measures of pain and associated symptoms. The role of pain in predicting activity difficulty also was examined in both disease groups.

Method: Children participated in a larger study to evaluate pain and functional limitations using electronic reports on handheld computers. Children with polyarticular JIA (26) and children with JRD (15), aged 8–18 yrs, were recruited from a pediatric rheumatology clinic. For 7 days, children completed morning, afternoon, and evening reports of pain characteristics (pain locations on a body map, pain duration on a 4-point scale ranging from "just a few minutes" to ">4 hours", pain intensity and unpleasantness on a visual analog scale [VAS]), fatigue (VAS), and difficulty in school, social, and physical activities (4-point scale ranging from "not at all difficult" to "extremely difficult"). A pediatric rheumatologist provided a diagnosis and disease severity score. Independent sample t-tests were used to evaluate differences in patients' average responses across all assessments between patients in both groups. Hierarchical linear modeling was used to evaluate whether activity difficulty increased at times of greater pain intensity, and whether this relationship differed in direction or magnitude as a function of diagnostic group.

Results: Children were predominantly Caucasian (81% JIA, 73% JRD) and female (85% JIA, 67% JRD). Children with JIA on average reported significantly greater pain intensity (m=30.6 vs m=9.1, p <.05), pain unpleasantness (m=31.4 vs m=9.8, SD=20.6, p<.05), and pain duration (m=1.7 vs m=.7, SD=1.05, p<.05) than children with JRD. The JIA group experienced pain in more locations (m=.8 vs m=.3, p<.05), greater stiffness intensity (m=30.7 vs m=7.4, p<.05), and higher levels of fatigue (m=43.6 vs m=17.7, p<.05) across all days. Children with JIA on average reported comparably mild levels of activity difficulty relative to children with JRD (m=0.4 vs m=0.6, ns). However, results of hierarchical linear modeling suggested that activity difficulty increased reliably at moments of greater pain intensity for both groups with the magnitude of this relationship greater for children with JIA ($t(240)=3.2$, $p<.01$).

Conclusions: Although children with JIA experience comparably mild difficulty in daily activity participation relative to children with JRD, pain appears to uniquely influence the extent of difficulty these children have participating in daily activities. Pain management should therefore be a focus of JIA treatment to enable children to participate as fully as possible in normative social, academic, and physical activities.

Disclosure: M. Connelly: None; **M. H. Bromberg:** None; **K. K. Anthony:** None; **L. Franks:** None; **K. M. Gil:** None; **L. E. Schanberg:** None.

2249

How Do Patients Approach Risk-Benefit Trade-Offs: A Qualitative Analysis Using a Think Aloud Protocol. Liana Fraenkel, Paul Falzer and Kristin Mattocks. Yale University, Newtown, CT

Purpose: Eliciting patient preferences and incorporating them into treatment strategies can be beneficial for treatment adherence, patient empowerment, and clinical outcomes. Despite the importance of incorporating patient preferences into treatment strategies, little is known regarding the factors that influence how patients evaluate risk-benefit trade-offs. The purpose of this study was to gain a more complete understanding of how patients approach trade-offs using a think aloud protocol.

Methods: Patients with chronic pain were randomly drawn from primary care and women's clinics at a large medical center. Participants were audiotaped as they performed an Adaptive Conjoint Analysis survey and were instructed to: "Think out loud as you answer the questions on the computer. Just say out loud everything that comes into your head. Remember there is nothing right or wrong to say". Participants were reminded by the research assistant to say their thoughts aloud after silent periods of 15 or more seconds. Audiotapes were transcribed and two analysts independently read and coded the transcripts using the constant comparative method.

Results: Ninety-eight transcripts were analyzed. Four themes emerged regarding how patients approach risk-benefit trade-offs: 1) Selection of a dominant attribute to guide decision-making: Some participants evaluated all risk and benefits against one dominant attribute: "When you are in pain and you want to get rid of it you make that your top priority and worry about the side effects later." 2) Leveraging values and worldviews: Many participants were influenced by personal values: "I am thinking. . .I have a son and I don't want to leave him without me." 3) Influence of personal experience: Personal experience with specific side effects had variable effects on risk aversion: "I have experienced nausea and dizziness and it is not a party. It really knocks you out and I want to avoid that if I can." Vs. "The nausea and the dizziness and trouble thinking clearly that is not that big of a deal. I know what that is like and it is not that big of a deal." 4) Use and manipulation of numerical information: Participants also varied significantly in their use of numbers: "The differences in pain and the improvement percentages were really close together and these were further apart being 3 out of 10 compared to 8 out of 10." Vs. "Well, it is the percentage: 3 in 10 as opposed to 1 in 10 which is a little bit less risky."

Conclusions: Our findings suggest that patients draw on a range of strategies and values to evaluate risk-benefit trade-offs. Understanding of how patients approach trade-offs may enable physicians to better understand how their patients consider competing treatment options in clinical practice.

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ACR Concurrent Abstract Sessions
Antiphospholipid Syndrome
Thursday, November 11, 2010, 11:00 AM–12:30 PM

2250

Evaluation of 'Non-Criteria" Antiphospholipid (aPL) Assays at a Wet Workshop during the 13th International Congress on Antiphospholipid Antibodies. Roger Albesa[1], Victoria Nelson[1], Zakera Shums[1], Gary Norman[1], X.-X. Gu[2], Jacob Rand[2], Walter Binder[1], Bas deLaat[4] and Silvia S. Pierangeli[3]. [1]INOVA Diagnostics, San Diego, CA, [2]Montefiore, Albert Einstein School of Medicine, New York, NY, [3]Univ of TX Med Branch, Galveston, Galveston, TX, [4]Utretch Medical Center, Utrecht, The Netherlands

Background: Recently new assays for the detection of Antiphospholipid antibodies (aPL) have been developed. These include immunoassays that detect antibodies directed to domain I (DI) of β2glycoprotein, that has been shown to be detect "thrombosis-related" anti-β2glycoprotein I (aβ2GPI) antibodies and a new clotting/mechanistic test named the Annexin A5 resistance assay (A5R), that measures the ability of aPL antibodies to reduce the anticoagulant activity of A5 in vitro. Recent studies have shown a good correlation between aPL antibodies that recognize domain I of β2GPI and the reduction of the A5 anticoagulant activity.

Objective: to evaluate the performance of two different ELISAs for the detection of DI (one in-house method and one commercial kit) and the A5R

test in a wet workshop at the 13th International Congress on Antiphospholipid Antibodies in Galveston, TX (April 13th, 2010).

Methods: An in-house method developed by B de Laat and colleagues that utilizes hydrophobic microtiter plates coated with recombinant domain I and a commercial kit (INOVA) were evaluated for the detection of anti-DI antibodies. Samples were also evaluated simultaneously in an IgG aβ2GPI (INOVA) for comparison purposes. Aliquots of 26 APS patients and 21 controls (14 from healthy individuals and 7 from patients with infectious diseases) were distributed to the participants/groups. For the two-step A5R assay, procedure was carried out as published (Blood 2004; 104:2783–2790). Five plasmas from APS patients and five controls were tested prior to the workshop and at the workshop. In addition, normal plasmas were "spiked" with dilutions of various aPL monoclonal antibodies (MoAbs) IgG and IgM: a) HCAL and EY2C9 [Center for Diseases Control (CDC)]; b) AbyD05045 and AbyD03892 (Phadia); c) "Sapporo" (INOVA). The workshop was open to all congress attendees who registered for this event.

Results: 18 out of the 26 APS samples were positive in the IgG aβ2GPI (INOVA) ELISA. Fourteen and 10 out of the 18 APS samples that were positive in the IgG aβ2GPI, were positive in the DI ELISA (INOVA) and in-house respectively. This discrepancy is likely due to the fact that the in-house method is not calibrated for serum samples. All the samples that were positive in the DI ELISA (either in-house or INOVA kit) had evidence of thrombosis associated with aPL antibodes. All the APS plasmas as well as the IgM and IgA MoAbs (Phadia, INOVA and CDC) as well as the IgG INOVA MoAb reduced significantly the A5 anticoagulant activity. All negative plasmas were negative in the A5R.

Conclusions: In this workshop, the A5R showed to be a sensitive and specific new mechanistic assay for aPL antibodies. Samples tested in the DI assays, which were tested single-blinded, appear to correctly identify a subset of "pathogenic" aβ2GPI antibodies. Both assays appear to be promising assays for detecting patients at risk for thrombosis.

Disclosure: R. Albesa: Inova Diagnostics, Inc., 3; **V. Nelson:** Inova Diagnostics, Inc., 3; **Z. Shums:** Inova Diagnostics, Inc., 3; **G. Norman:** Inova Diagnostics, Inc., 3; **X.X. Gu:** None; **J. Rand:** None; **W. Binder:** Inova Diagnostics, Inc., 3; **B. deLaat:** None; **S. S. Pierangeli:** Louisville APL Diagnostics, Inc., 4.

2251

Evaluation of the Performance of Monoclonal and Polyclonal Antibody Standards in Different Assays for the Detection of Antiphospholipid (aPL) Antibodies: Report of a Wet Workshop at the 13th International Congress on Antiphospholipid Antibodies. Ricardo Forastiero[8], Elizabeth Papalardo[6], Michael Watkins[1], Hoang Nguyen[1], Maria Crisostomo[1], Wendy Vandam[1], JOel Hardy[1], Roger Albesa[2], Victoria Nelson[2], Zakera Shums[2], Gary Norman[2], Walter Binder[2], Kerrie Morin[3], Catherine Kirbach[3], Karl Mattias[4], Gabriella Lakos[5] and Sivia S. Pierangeli[7]. [1]Bio-Rad Laboratories, Hercules, CA, [2]INOVA Diagnostics, San Diego, Ca, [3]Instrumentation Laboratories, Bedford, MA, [4]Phadia GMBH, Freiburg, Germany, [5]TherTest, Lombard, IL, [6]Univ of TX Med Branch, Galveston, Galveston, TX, [7]Univ of TX Med Branch, Galveston, TX, [8]Universidad Favaloro, Buenos Aires, Argentina

Background: The standardization of tests used in the diagnosis of Antiphospholipid Syndrome (APS) [anticardiolipin (aCL) and the anti-β2glycoprotein I (aβ2GPI)] is still a matter of debate and concern. One important topic of discussion is whether to use monoclonal (MoAbs) or polyclonal antibody preparations for the calibration and/or quality control of these assays. However, the proper cross-validation and evaluation of the available preparations is lacking.

Objective: to evaluate the performance of various MoAbs and polyclonal antibody calibrators for the detection of aCL and aβ2GPI antibodies (IgG, IgM) at a wet workshop at the 13th International Congress on Antiphospholipid Antibodies.

Methods: Polyclonal standards G2 and M3 for IgG, IgM aCL [Louisville APL Diagnostics, Inc.(LAPL)], MoAbs IgG and IgM: a) HCAL and EY2C9 [Center for Diseases Control (CDC)]; b) AbyD05045 and AbyD03892 (Phadia); c) "Sapporo" (INOVA) were distributed to the groups for evaluation. All serum and calibrator preparations were from the same lot and were tested in the following aCL and aβ2GPI IgG and IgM assays: QUANTA LITE™ (INOVA), TheraTest, Phadia, Bio-Rad (ELISA PhD™ lx and Multiplex BioPlex™ 2200), in the APhL ELISA® [an assay that utilizes a mixture of negatively charged phospholipids and β2GPI (LAPL)] and in a new chemiluminescent assay HemosIL® AcuStar Antiphosphilipid assay panel [Instrumentation Laboratory, IL)]. Calibrators and kits were assayed as per the manufacturers' instructions. The workshop was open to congress participants who registered for the event and the groups evaluated the calibrators at least on two occasions.

Results: All groups reported values of the polyclonal aPL calibrators within the expected range including the new chemiluminescent and the multiplex assays. Excellent correlation and linearity was observed with two monoclonal preparations (AbyD05045 IgG and IgM and Sapporo INOVA IgG and IgM). As expected, AbyD3092 showed negative results in various tests (this antibody has aCL activity only). The "Sapporo" and the "CDC" monoclonal antibodies, although originally derived from the same hybridoma sources showed apparent different concentration, specificity and presentation (liquid affinity purified Ig for the Sapporo and freeze-dried hybridoma supernatant for the CDC). A large variability of the results of the CDC MoAbs was reported by the groups at this workshop when tested at the same final concentration (HCAL: from 8.2 to 75.3 GPL units for IgG aCL and 20.9 to 424.5 Units for IgG aβ2GPI; EY2C9: from 30.4 to 145.3 MPL units for IgM aCL and from 0 to 520.4 Units for IgM aβ2GPI). Participants reported difficulties with the reconstitution of the CDC MoAb freeze-dried material, indicating problems with the stability and variability between vials of the preparations. Those included not only differences among any given assay but also within the same test, run in more than one occasion.

Conclusions: The LAPL polyclonal and the Phadia and INOVA monoclonal preparations are suitable sources for calibration of aCL and aβ2GPI assays. Based on results obtained at this wet workshop, the use of the CDC MoAbs is questionable and not recommended at this time.

Disclosure: R. Forastiero: None; **E. Papalardo:** None; **M. Watkins:** BioRad Laboratories, 3; **H. Nguyen:** BioRad Laboratories, 3; **M. Crisostomo:** BioRad Laboratories, 3; **W. Vandam:** BioRad Laboratories, 3; **J. Hardy:** BioRad Laboratories, 3; **R. Albesa:** Inova Diagnostics, Inc., 3; **V. Nelson:** Inova Diagnostics, Inc., 3; **Z. Shums:** Inova Diagnostics, Inc., 3; **G. Norman:** Inova Diagnostics, Inc., 3; **W. Binder:** Inova Diagnostics, Inc., 4; **K. Morin:** Instrumentation Laboratories, 3; **C. Kirbach:** Instrumentation Laboratories, 3; **K. Mattias:** Phadia, 3; **G. Lakos:** TheraTest Laboratories, 3; **S. S. Pierangeli:** Louisville APL Diagnostics, Inc., 4.

2252

Comparative Evaluation of Different Immunoassays for the Detection of Antiphospholipid Antibodies: Report of a Wet Workshop during the 13th International Congress on Antiphospholipid Antibodies. Ricardo Forastiero[9], Elizabeth Papalardo[8], Kerrie Morin[4], Catherine Quirbach[4], Gabriella Lakos[6], Karl Mattias[5], Roger Albesa[3], Victoria Nelson[3], Zakera Shums[3], Gary Norman[3], Walter Binder[3], Bruno Larida[1], Maria Crisostomo[2], Michael Watkins[2], Hoang Nguyen[2], Wendy Vandam[2], Joel Hardy[2] and Silvia S. Pierangeli[7]. [1]Bio-Rad Laboratories, Hercules, CA, [2]Bio-Rad Laboratories, Her, [3]INOVA Diagnostics, San Diego, CA, [4]Instrumentation Laboratories, Bedford, MA, [5]Phadia GMBH, Freiburg, Germany, [6]TheraTest Laboratories, Lombard, IL, [7]Univ of TX Med Branch, Galveston, Galveston, TX, [8]Univ of TX Med Branch, Galveston, TX, [9]Universidad Favaloro, Buenos Aires Argentina

Background: The performance and standardization of antiphospholipid (aPL) laboratory tests used in the confirmation of diagnosis of Antiphospholipid Syndrome (APS) is still a matter of debate and concern. In addition, recently novel methodologies and platforms for the detection of aPL antibodies have become available, but proper inter-assay simultaneous comparisons have not been carried out. Objective: to evaluate the performance of different ELISAs and other new immunoassays for the detection of aCL and aβ2GPI antibodies (IgG, IgM) in a wet workshop at the 13th International Congress on Antiphospholipid Antibodies.

Methods: Aliquots of 26 un-identified APS serum samples (diagnosis according to Sapporo modified criteria) and 21 controls (14 from healthy individuals and 7 from patients with infectious diseases) were distributed to all participants/groups. All serum samples were evaluated in various aCL and aβ2GPI ELISAs, in the APhL ELISA® (an assay that utilizes a mixture of negatively charged phospholipids instead of cardiolipin, Louisville APL Diagnostics (LAPL)] and in in three fully automated methodologies: HemosIL® AcuStar Antiphospholipid assay panel, a chemiluminescent immunoassay panel on the ACL AcuStar™ [Instrumentation Laboratory (IL)] a fluoro-enzyme immunoassay (Phadia) and in the BioPlex 2200, random access, multiplex testing immunoassay system (Bio-Rad), using either an automated or "manual" platforms (see table). All kits were evaluated as per the manufacturers' instructions and results were expressed in their respective units of measurement. The workshop was open to congress participants who registered for the event. Samples were evaluated in the different assays at least on two separate occasions.

Results: Clinical sensitivities and specificities and positive predictive values were calculated.

Manufacturer	Assay	Method/Instrumentation	Clinical sensitivity (%)	Clinical Specificity (%)	PPV
Bio-Rad	aCLGM	Multiplex/BioPlex2200	100	95	0.95
Bio-Rad	aβ_2GPIGM	Multiplex/BioPlex2200	100	95	0.95
Bio-Rad	aCL GM	ELISA/PhD	100	95	0.95
Bio-Rad	aβ_2GPIGM	ELISA/PhD	100	91	0.92
IL	HemoSIL aCL GM	Chemiluminescent/Acustar	100	95	0.95
IL	HemoSIL aβ_2GPIGM	Chemiluminescent/Acustar	100	100	1.0
INOVA	QUANTA LITE™aCL GM	ELISA/manual	96	91	0.92
INOVA	QUANTA LITE™ aβ_2GPIGM	ELISA/manual	88	100	1.0
LAPL	APhL GM	ELISA/manual	100	100	1.0
Phadia EliA	aCL GM	ELISA/Phadia 250	100	100	1.0
Phadia EliA	aβ_2GPIGM	ELISA/Phadia 250	100	95	0.95
Theratest	aCL GM	ELISA/DSX2	100	100	1.0
Theratest	aβ_2GPIGM	ELISA/DSX2	100	95	0.9

Although not all the assays reported the titers of aCL and aβ2GPI antibodies in the same units, the correlation of positive titers among the assays was excellent. All the healthy control samples were correctly identified by all groups as negative. Some of the aβ2GPI tests reported positive one of the infectious disease sample. All the assays, but in particular the AcuStar chemiluminescent immunoassay panel and the BioPlex2200 assays showed excellent intra-assay variation (<10 % CV).

Conclusions: All aCL and β2GPI tests showed excellent clinical sensitivities, specificities and positive predictive values and good agreement with respect to the levels of the IgG and IgM antibodies, regardless of assay type, or whether tests were done using automated or "manual" systems. New methodologies for the detection of aPL antibodies look promising and comparable to currently approved ELISA tests. This study validates current recommendations of the Sapporo revised criteria to use aCL and aβ2GPI for proper confirmation of diagnosis of APS.

Disclosure: R. Forastiero: None; **E. Papalardo:** None; **K. Morin:** Instrumentation Laboratories, 3; **C. Quirbach:** Instrumentation Laboratories, 3; **G. Lakos:** TheraTest Laboratories, 3; **K. Mattias:** Phadia, 3; **R. Albesa:** Inova Diagnostics, Inc., 3; **V. Nelson:** Inova Diagnostics, Inc., 3; **Z. Shums:** Inova Diagnostics, Inc., 3; **G. Norman:** Inova Diagnostics, Inc., 3; **W. Binder:** Inova Diagnostics, Inc., 3; **B. Larida:** BioRad Laboratories, 3; **M. Crisostomo:** BioRad Laboratories, 3; **M. Watkins:** BioRad Laboratories, 3; **H. Nguyen:** BioRad Laboratories, 3; **W. Vandam:** BioRad Laboratories, 3; **J. Hardy:** BioRad Laboratories, 4; **S. S. Pierangeli:** Louisville APL Diagnostics, Inc., 4.

2253

Elevated Cytokines and Chemokine Levels in Antiphospholipid Antibody (aPL)-Positive Patients. Vijaya L. Murthy, Shraddha Jatwani, Renan A. Aguilar-Valenzuela, Ellis D. Doan, Elizabeth Papalardo, Emilio B. González and Silvia S. Pierangeli. University of Texas Medical Branch, Galveston, TX

Background: Based on *in vitro* and animal studies, certain cytokines and chemokines such as tissue factor (TF), vascular endothelial growth factor (VEGF), soluble (s) E-selectin (sE-sel), and tumor necrosis factor (TNF)-α have been shown to be associated with antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE). Here we examined the levels of cytokines/chemokines in aPL-positive patients with or without SLE, and compared them to controls.

Methods: Baseline sera/plasma of persistently aPL-positive patients [IgG/M Anticardiolipin antibody (aCL) > 40U, IgG/M anti-β_2 glycoprotein-I antibody (aβ_2GPI) > 20U, and/or positive lupus anticoagulant test] were obtained from an ongoing pilot interventional clinical study (clinical trials. gov #: NCT00674297). The biomarker levels of these 22 aPL-positive patients (primary APS: 8, APS with SLE: 8, asymptomatic aPL without SLE: 4 and asymptomatic aPL with SLE: 2) were compared to 22 matched healthy controls with no evidence of autoimmune, infectious, or inflammatory diseases. Interleukin (IL)-1b, IL6, IL8, TNF-α, VEGF, interferon inducible protein (IP)-10 and sCD40L were measured in serum using a Multiplex Assay (Millipore Milliplex™); titers of sE-sel, and sTF were detected by ELISA. The Kruskal-Wallis test was used to compare the levels of biomarkers in aPL-positive subjects as compared to the controls. Spearman test was used to correlate the levels of the biomarkers in the different subgroups of patients.

Results: As compared to controls, we found an increase in the levels of IL-1b, IL6, TNF- α, IP-10, sCD40L and sTF in patients with APS. In a subgroup analysis, patients with aPL/APS and SLE (n=10) had significantly higher levels of TNF-α, IP10 and sCD40L as compared to aPL/APS patients without SLE (n=12) (p= 0.05, 0.029 and 0.05, respectively).

Biomarker	# Of aPL (+) samples elevated above cut-off points/(%)	Means of aPL positive samples	Means of controls	p
IL1b	16/22 (73)	7.65	0.35	<0.0001
IL6	17/22 (77)	42.15	0.71	<0.0001
IL8	9/22 (41)	27.44	40.87	0.1763
TNF-α	22/22 (100)	14.71	0.46	<0.0001
VEGF	12/22 (54)	208.78	113.59	0.9778
IP-10	22/22 (100)	683.43	106.7	<0.0001
sCD40L	21/22 (95)	1070.19	24.67	<0.0001
s TF	16/16 (100)	449.59	13.05	<0.0001
sE-sel	3/16 (19)	20.78	42.04	0.0006

Conclusions: Our results underscore the importance of biomarkers in aPL-positive patients. This may help better understand the pathogenic mechanisms involved, and the development of targeted treatments.

Disclosure: V. L. Murthy: None; **S. Jatwani:** None; **R. A. Aguilar-Valenzuela:** None; **E. D. Doan:** None; **E. Papalardo:** None; **E. B. González:** None; **S. S. Pierangeli:** None.

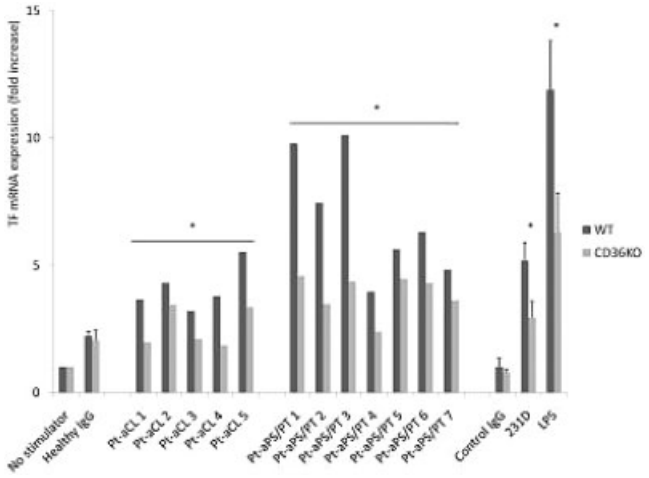
2254

The Involvement of CD36 in the Monocyte Activation by Antiphospholipid Antibodies. Masaru Kato[1], Tatsuya Atsumi[2], Kenji Oku[3], Olga Amengual[3], Yuichiro Fujieda[3], Kotaro Otomo[3], Tetsuya Horita[3], Shinsuke Yasuda[3] and Takao Koike[3]. [1]Department of Medicine II, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan, [2]Department of Medicine II, Hokkaido University Graduate School of Medicine, Sapporo, Japan, [3]Department of Medicine II, Hokkaido University Graduate School of Medicine

Purpose: CD36, known as a scavenger receptor, is a transmembrane glycoprotein expressed on monocytes, macrophages, platelets and capillary endothelial cells. CD36 recognizes multiple ligands, including phosphatidylserine, and is a mediator of both atherogenesis and thrombosis. However, little data are available regarding the correlation between CD36 and thrombotic diseases. The purpose of this study is to investigate the possible involvement of CD36 in the pathophysiology of thrombosis in patients with antiphospholipid syndrome (APS).

Methods: This study comprised two sets of experiments. Firstly, a genomic polymorphism of CD36 was explored. Rs3765187, a single nucleotide polymorphism (SNP) linked to CD36 deficiency, was investigated by TaqMan PCR genotyping method in 795 Japanese, including 108 patients with APS, 265 with systemic lupus erythematosus (SLE) in the absence of APS, and 422 healthy subjects. In the second part of this study, the involvement of CD36 in antiphospholipid antibody (aPL)-induced tissue factor (TF) expression was examined using CD36 deficient mice or anti-CD36 antibody with the CD36 signal blocking property (FA6–152). Purified IgG from APS patients either anticardiolipin antibodies or phosphatidylserine dependent antiprothrombin antibodies positive (Pt-aCL and Pt-aPS/PT, respectively) and monoclonal aPS/PT (231D) were used in the experiments. The aPL-induced TF expression was tested by real-time PCR method on peritoneal macrophages from CD36 deficient mice or human peripheral blood mononuclear cells (PBMC) from healthy donors pretreated with FA6–152.

Results: The minor allele frequency of rs3765187 was less frequent in APS patients (2.8% p = 0.024), but not in SLE patients (7.9% p = 0.32), compared with healthy subjects (10.2%). Pt-aCL, Pt-aPS/PT and 231D-induced TF mRNA expressions were not completely but significantly suppressed in peritoneal macrophage from CD36 deficient mice compared to wild type mice (WT).



FA6–152 dose-dependently inhibited Pt-aCL, Pt-aPS/PT and 231D-induced TF mRNA expressions in human PBMC from healthy donors.

Conclusion: The SNP linked to CD 36 deficiency was less frequent in APS patients, suggesting that CD36 insufficiency is protective for developing APS. The deficient or suppressed CD36 function significantly reduced aPL-induced TF expression in vitro. Taken together, scavenger receptor function may be involved in the thrombotic pathophysiology in APS patients. CD36 is a new potential therapeutic target of the affected patients.

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2255

Potential Protein Targets for the Treatment of the Antiphospholipid Syndrome with Statins and Hydroxychloroquine. Anastasia Lambrianides[2], Silvia S. Pierangeli[1], Katie Bell[3], Wendy Heywood[3], David S. Latchman[3], David A. Isenberg[3], Anisur Rahman[3] and Ian Giles[3]. [1]Univ of TX Medical Branch, Galveston, TX, [2]University College London, London, United Kingdom, [3]University College London, London, UK

Introduction: A major mechanism of hypercoagulability in the antiphospholipid syndrome (APS) is antiphospholipid antibody (aPL)-mediated up-regulation of tissue factor (TF) on monocytes. Recent attention has been focused on other therapeutic tools for the APS to ameliorate the risk of the hemorrhagic compications associated with the use of anticoagulant drugs currently used for treatment. Statins have been shown to modify the function of endothelial cells and platelets by decreasing the expression of adhesion molecules, inhibiting TF expression and down-regulating inflammatory cytokines after treatment with aPL. Similarly, hydroxychloroquine (HCQ) has been shown to reduce the extent of thrombosis in an animal model of injury-induced thrombosis in APS and reversed aPL-induced platelet activation. Using proteomic analysis, our aim was to identify the effects of simvastatin and HCQ in protein expression in monocytes treated with IgG aPL from patients with vascular thrombosis (VT).

Methods: IgG was purified from 7 patients with the APS who had experienced VT but no pregnancy complications and 7 healthy controls. A human monocyte cell line was treated with 100μg/ml IgG for 6 hours. In some experiments, cells were pretreated with simvastatin (5μM) or with HCQ (1μg/ml). The cell extracts were examined by fluorescence 2D difference gel electrophoresis (DIGE).

Results: We have identified that there are 24 proteins showing significant differences in expression in monocytes treated with IgG from patients with VT in the presence of simvastatin – the majority with decreased expression between 2.1 and 5.2 fold. Furthermore, there are five proteins with altered protein expression patterns in monocytes treated with IgG from patients with VT in the presence of HCQ – four proteins with decreased expression between 2.1 and 2.3 fold and one protein with increased expression 2.6 fold.

Conclusion: Our findings demonstrate, for the first time, that statins and HCQ significantly altered the expression/modification of proteins in monocytes. These proteins may be critical targets that might be involved in the pathogenesis of the APS and supports the possibility that statins and HCQ may offer an alternative nonanticoagulant therapeutic approach for treating the APS.

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ACR Concurrent Abstract Sessions
Rheumatoid Arthritis - Clinical Aspects: Radiographic and Other Outcomes in RA
Thursday, November 11, 2010, 11:00 AM–12:30 PM

2256

Irreversible Physical Disability in Rheumatoid Arthritis (RA) Is Determined by Cartilage Damage Rather Than Bone Destruction. Josef S. Smolen[2] and Daniel Aletaha[1]. [1]Medical University of Vienna, Austria, [2]Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Background: RA is characterized by joint damage leading to irreversible disability (assessed by health assessment questionnaire [HAQ]). Joint destruction is comprised of cartilage and bone damage, consequences of distinct pathogenetic mechanisms. They are evaluated by joint space narrowing (JSN) and erosion (ERO) components of the Sharp score. We aimed to determine the contribution of cartilage and bone damage to irreversible disability.

Methods: We evaluated data from randomized controlled clinical trials (ASPIRE, ATTRACT, DE019, ERA, Leflunomide, PREMIER, TEMPO). We extracted patients who were in stringent remission by the simplified disease activity index (SDAI≤3.3) to eliminate the activity-related component of disability. In these patients, we determined the residual HAQ at the time of remission (irreversible disability[1]) and the JSN and ERO scores at baseline. We then compared effects of ERO and JSN on residual HAQ (across tertiles using ANOVA, and in regression models).

Results: Mean residual HAQ in remission increased across tertiles of JSN and ERO (ERO: 0.21, 0.25, 0.35 JSN: 0.19, 0.24, 0.39; $p<0.001$ for both). In patient groups formed according to JSN tertiles, increasing ERO scores did not lead to an increase in irreversible HAQ (for example, mean residual HAQ in the middle JSN tertile: 0.24, 0.24 and 0.23 for 1st, 2nd and 3rd ERO tertile, respectively; p=ns). In contrast, within each ERO tertile, increasing JSN was associated with an increase in residual HAQ (Figure 1). This relationship was maintained when adjustments for residual disease activity, age or disease duration were done (data not shown).

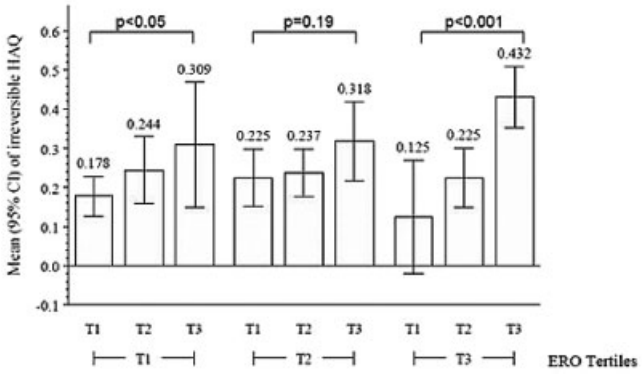

Figure 1. HAQ values in remission ("irreversible HAQ") as attained when grouping patients by ERO or JSN tertiles and within each ERO terile by JSN tertiles and vice versa. Note that increasing JSN conveyed higher irreversible HAQ within each ERO tertile but not vice versa.

Conclusion: Irreversible physical disability is primarily mediated by cartilage and not bony damage, suggesting that therapeutic attention should be given to interference with cartilage destruction.

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[1]Aletaha D, Smolen J, Ward MM. Arthritis Rheum 2006; 54:2784–2792.

Disclosure: J. S. Smolen: Abbott Laboratories, 2, Amgen Inc., 5, Bristol-Myers Squibb, 2, Centocor, Inc., 5, Hoffmann-La Roche, Inc., 2, sanofi-aventis, 5, Schering-Plough, 2, UCB, Inc., 2, UpToDate, 7, Wyeth Pharmaceuticals, 2; **D. Aletaha:** Abbott Laboratories, 5, Bristol-Myers Squibb, 5, Hoffmann-La Roche, Inc., 5, Schering-Plough, 5, UCB, Inc., 5, UpToDate, 7, Wyeth Pharmaceuticals, 5.

2257

The Impact of Body Weight on the Progression of Radiographic Joint Damage in Rheumatoid Arthritis Patients. Axel Finckh[4], Almut Scherer[1], Anne Lubbeke-Wolff[3], Hans Schwarz[1] and Cem Gabay[2]. [1]SCQM Foundation, Switzerland, [2]Univ Hosp of Geneva, Geneva, Switzerland, [3]University of Geneva, Switzerland, [4]University of Geneva, Geneva, Switzerland

Background: Obese individuals experience elevated levels of circulating pro-inflammatory cytokines. While obesity might be associated with an increased risk of developing RA and with impaired quality of life, the role of obesity on the progression of RA disease severity is not well established.

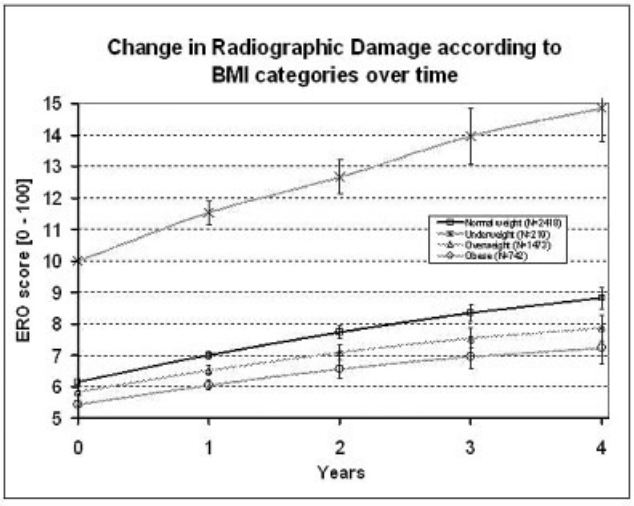
Objective: To examine if obesity is associated with more radiographic joint damage progression.

Methods: This is a prospective cohort study of the Swiss RA cohort (SCQM-RA) including all patients with available Body Mass Index (BMI) and complete sets of radiographs of the hand and feet. Patients were categorized according to the WHO BMI categories as "underweight" (BMI < 18.5), "normal weight" (BMI ≥ 18.5, < 25), "overweight" (BMI ≥ 25, < 30) and "obese" (BMI ≥ 30, < 35). The primary outcome of this analysis is the progression of ERO over time. Joint erosions (ERO) were assessed in 38 joints of hands and feet with a validated scoring method (Ratingen score, expressed in % of the maximum score) by a single experienced reader, blinded to clinical information. The evolution of ERO is analyzed using regression models for longitudinal data, adjusting for potential confounders.

Results: The mean BMI of the 4852 RA patients included was 25. The groups were similar for most disease characteristics, but for baseline radiographic damage, which was significantly higher for underweight patients.

	Underweight BMI<18.5	Normal weight (BMI 18.5–25)	Overweight (BMI 25–30)	Obese (BMI > 30)
N patients (%)	219 (5%)	2418 (50%)	1473 (30%)	742 (15%)
Age [yrs]	52	54	58	58
Disease duration [yrs]	6.1	4.3	3.7	3.4
% Female	94	81	66	73
% RF+	77	77	73	70
DAS28(ESR) [0–10]	4.6	4.5	4.5	4.6
HAQ-DI [0–3]	1.05	0.96	1.01	1.17
ERO score [% of max]	10	6.2	5.8	5.4
Estimated ERO rate at baseline [%/yr]	2.1	1.6	1.5	1.3
% Steroid	31	26	24	29
% Biologics	23	20	20	21

Patients were followed over a median duration of 4 years and assessed radiographically on average 3.3 times. After adjusting for baseline differences in prognostic markers of disease progression, underweight patients developed significantly more erosions over time then the other weight groups (p <0.001).



At 4 years, underweight patients ERO score progressed by 4.9 % (95% CI: 3.8–5.9), compared to 2.7 (CI: 2.3–3.0) in normal weight patients, 2.0 (CI: 1.6–2.4) in overweight patients and 1.8 (CI: 1.3–2.3) in obese patients.

Conclusion: Underweight was associated with more joint damage over time, probably reflecting uncontrolled disease and 'rheumatoid cachexia'. Obesity and overweight was not associated with more rapid progression of radiographic damage in hand and feet joints.

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2258

Clinical Rather Than Serologic Measures of Inflammation Determine Radiographic Progression in Rheumatoid Arthritis (RA). Daniel Aletaha[1] and Josef S. Smolen[2]. [1]Medical University of Vienna, Austria, [2]Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Background: Disease activity in RA can be measured clinically by assessing joint inflammation, typically swollen joint counts (SJC), or systemically by evaluating the acute phase reactants, typically C-reactive protein (CRP). It has been suggested that both SJC and CRP contribute to progression of joint damage[1;2]. However, since these measures are interrelated, it is not sufficiently clear, which of them is of primary relevance in driving radiographic changes. We aimed to determine the contribution of SJC and CRP to joint damage progression.

Methods: We evaluated data from methotrexate (MTX) monotherapy arms of recent randomized controlled clinical trials kindly provided by the respective sponsors (ASPIRE, ERA, Leflunomide, PREMIER, TEMPO). We pooled patients with complete clinical and radiographic data at baseline and 6, 9 and 12 months (n=871). In these patients, we determined the average SJC and average CRP levels from 6–12 months. We then dichotomised both variables into active and not active, where non active was defined as a mean SJC of <1 joint, or a mean CRP of <1mg/dL. Radiographic progression was calculated based on the baseline and 12 months Sharp score readings. We cross-tabulated the mean radiographic progression in 2×2 tables according to activity/non activity of the two variables, SJC and CRP. We assessed the differences using the Wilcoxon two sample test.

Results: As shown in the Table, progression of joint damage in patients with mean CRP≥1 was higher if SJC were also active, and vice versa. If there was no joint activity (SJC<1), radiographic progression was unaffected by CRP status. However, if there was no serologic activity (CRP<1mg/dL), SJC status still determined radiographic progression.

Table. Radiographic progression ± standard deviation (n) in accordance to SJC/CRP activity status.

	CRP active	CRP non active	
SJC active	4.6 ± 16.4 (n = 259)	2.0 ± 5.9 (n = 477)	p < 0.0001
SJC non active	0.9 ± 5.9 (n = 24)	0.7 ± 4.4 (n = 111)	p = 0.146
	p = 0.015	p = 0.005	

Conclusions: Joint swelling rather than CRP contributes to progression of joint damage in RA.

Acknowledgement. We thank Abbott, Amgen, Centocor, Sanofi-Aventis and Pfizer-Wyeth for kindly providing us with data of their clinical trials and Farideh Alasti for expert statistical support.

(1) van Leeuwen MA et al. J Rheumatol 1994; 21:425–429.
(2) Smolen JS et al. Arthritis Rheum 2006; 54:702–710.

Disclosure: D. Aletaha: Abbott Immunology Pharmaceuticals, 5, Roche, 5, Schering-Plough, 5, UCB, Inc., 5, UpToDate, 7, Wyeth Pharmaceuticals, 5; **J. S. Smolen:** Abbott Immunology Pharmaceuticals, 2, Amgen Inc., 5, Bristol-Myers Squibb, 2, Centocor, Inc., 5, Roche, 2, Schering-Plough, 2, UCB, Inc., 2, UpToDate, 7.

2259

Coronary Atherosclerosis in Patients with RA and Acute Coronary Events: No Different Than in the Rest of Us? Marie E. Holmqvist[1], Lennart T. H. Jacobsson[3], Lars Alfredsson[1], Stefan James[4] and Johan Askling[2]. [1]Karolinska Institutet, [2]Karolinska University Hospital, [3]Malmö University Hospital, [4]Uppsala University Hospital

The risk of ischemic heart disease (IHD) and the prevalence of atherosclerosis is increased in patients with rheumatoid arthritis (RA) compared to the general population. Based on individuals with clinical manifestations of IHD, few, and conflicting, studies that compare patients with RA and general population comparators with respect to extent of coronary artery disease (CAD) have been published.

Objective: To investigate whether angiographic patterns differ between patients with RA, known to be at increased risk of CAD, and the general population, at the time of clinical manifestations of acute CAD (unstable angina, ST-elevation myocardial infarction [STEMI], silent infarction and central chest pain).

Methods: RA patients diagnosed 1995–2006 with<18 months symptom duration at diagnosis included in the Swedish RA register were identified, n=6,919. For each patient, 5 sex/age/residential area/calendar time-matched general population comparators were identified, n=34,638. Participants were linked to the national Swedeheart register, which includes information on indication for angiography and number of vessels with>50% stenosis for all subjected, and also presenting symptoms, status at admission and discharge diagnosis for all admitted to coronary care units (CCU). Relative risks (RR) and 95% CI were estimated using proportional hazards models. To compare the odds of different angiography patterns, logistic regression models were fitted with RA (yes/ no) as the independent variable, and extent of atherosclerosis classified according to the number of vessels with significant stenosis as the dependent variable.

Results: 218 (3.2%) patients and 737 (2.1%) controls underwent angiography due to any ischemic heart disease (stable and unstable angina, STEMI, silent infarction or central chest pain) after study entry, RR=1.5 (95% CI 1.2, 1.7). Of those, 168 (77%) patients with RA and 534 (72%) comparators were investigated due to acute CAD. The proportion of patients with RA that underwent angiography due to STEMI was slightly higher, although no statistically significantly so, than in the population comparator (33% of the patients with RA and 26% of the comparators underwent angiography due to STEMI). There was no difference in the extent of atherosclerosis when patients with RA were compared to general population comparators.

Logistic regression modeling the risk of having significant stenosis in the below specified vessels comparing patients with RA who underwent angiography due to unstable angina, STEMI, central chest pain or silent myocardial ischemia to general population comparators who underwent angiography for the same reasons. Odds ratios (OR) and 95% confidence interval (CI) adjusted for age at angiography and sex.

	Patients with RA with outcome, n (% of all with angiography results)	Comparators with outcome, n (% of all with angiography results)	OR (95% CI)
Left main artery*	13 (8.2)	30 (5.9)	1.4 (0.7, 2.8)
-LMA	0 (0)	1 (0.2)	–
-LMA+1 coronary	1 (0.6)	4 (0.8)	0.7 (0.08, 6.8)
-LMA+2 coronary	3 (1.9)	6 (1.2)	1.6 (0.4, 6.4)
-LMA+3 coronaries	9 (5.7)	19 (3.8)	1.5 (0.7, 3.4)
1 coronary	47 (29.8)	162 (32.0)	0.9 (0.6, 1.3)
2 coronaries	37 (23.4)	110 (21.7)	1.1 (0.7, 1.7)
3 coronaries	26 (16.5)	90 (17.8)	0.9 (0.6, 1.4)
Normal coronaries	35 (22.2)	115 (22.7)	1.0 (0.6, 1.6)

* including all with afflicted LMAs regardless of status of other vessels. 10 patients with RA were missing on findings on angiography and 27 comparators.

Conclusion: These results confirm the increased risk of ischemic heart disease in RA, and further suggest that the angiographic pattern is similar among patients with RA and general population controls who develop acute CAD. This indicates that the increased risk of IHD/CAD in RA is not explained by more widespread atherosclerosis in those who develop acute IHD/CAD.

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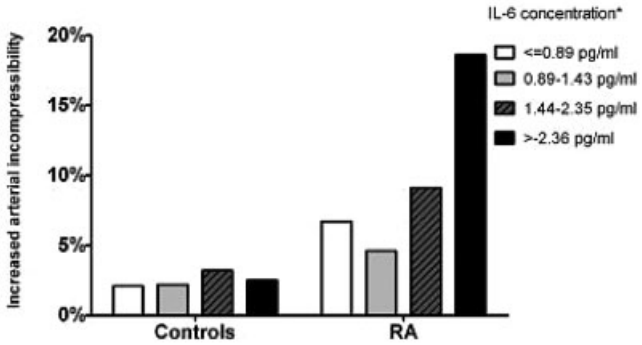
2260

Interleukin-6 Levels Are Associated with Elevated Ankle Brachial Index in Rheumatoid Arthritis. Cecilia P. Chung[4], Jon T. Giles[3], Moyses Szklo[5], Wendy Post[5], Michelle A. Petri[1], Roger Blumenthal[5], Allan C. Gelber[2], Russell Tracy[6] and Joan M. Bathon[4]. [1]Timonium, MD, [2]Baltimore, MD, [3]Johns Hopkins Univ, Baltimore, MD, [4]Johns Hopkins University, Baltimore, MD, [5]Johns Hopkins University, [6]University of Vermont

Purpose: Recent evidence suggests that arterial incompressibility, determined by elevated ankle brachial index (ABI), is associated with poor cardiovascular outcomes and increased mortality. Patients with RA may have an increased risk of arterial incompressibility, partially explained by the use of systemic corticosteroids. However, little is known about the role of inflammation in arterial incompressibility. Thus, we tested the hypothesis that arterial incompressibility is more prevalent in patients with RA than in control subjects and is associated with disease activity and markers of inflammation.

Methods: ABI, a reliable marker of peripheral and generalized subclinical atherosclerosis, was measured in 196 patients with RA enrolled in the Evaluation of Subclinical Cardiovascular Disease and Predictors of Events in Rheumatoid Arthritis (ESCAPE) study and in 1062 control subjects enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA) study. Patients and control subjects were classified into three groups as follows: ABI >0.9 and ≤1.3 (normal), ABI >1.3 (incompressible), ABI ≤ 0.9 (obstructed). Demographic and clinical data were obtained and in patients with RA the disease activity score based on 28 joints (DAS28) calculated. Venous blood was drawn to measure the concentration of interleukin-6 (IL-6), C-reactive protein (CRP), e-selectin, and intercellular adhesion molecule-1 (ICAM-1).

Results: Arterial incompressibility was more prevalent in patients with RA (n= 27, 13.8%) than in control subjects (n=25, 2.4%), p<0.001. This association was independent of age, sex, and race (OR=7.5, p<0.001) and remained significant after adjustment for Framingham risk score, IL-6, fibrinogen and CRP (OR=5.8, p<0.001). RA patients with increased arterial incompressibility were more frequently male (66.7%) than those without (36.7%), p=0.005. Increasing quartiles of IL-6 concentrations were associated with higher prevalences of arterial incompressibility in patients (p for trend=0.04) but not in controls (p for trend=0.59). (Figure) The association between arterial incompressibility and IL-6 in RA patients remained significant after adjustment for HAQ (OR=1.9, p=0.04), but was attenuated after adjustment for DAS28 (OR=1.8, p=0.06). There was a trend towards higher cumulative doses of systemic corticosteroid use in patients with increased arterial incompressibility (median of 3.2 grams) compared to patients with normal ABI (2.8 grams), p=0.09. No statistically significant differences were observed in DAS28 (p=0.89), CRP (p=0.87), e-selectin (p=0.63), or ICAM-1 (p=0.63) between those with normal ABI vs. those with arterial incompressibility.



*IL-6 concentration was categorized according to quartiles based on the whole dataset.

Conclusions: Patients with RA are at an increased risk of arterial incompressibility than control subjects. In patients with RA, higher concentrations of IL-6 are associated with a higher risk of arterial incompressibility.

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2261

Diagnostic Accuracy of the 2010 ACR/EULAR Used at Baseline after a 10 Year Follow Up in a Cohort of Patients with Recent-Onset Arthritis. Divi Cornec[5], Sophie Varache[6], Johanne Morvan[5], Valérie Devauchelle-pensec[5], Jean-Marie Berthelot[7], Sandrine Jousse-joulin[5], Catherine Le Henaff[2], Sylvie Hoang[4], Jean-Baptiste Thorel[1], Antoine Martin[3], Gérard Chalès[8], Pierre Youinou[5] and Alain Saraux[5]. [1]CH Lorient, [2]CH Morlaix, [3]CH St Brieuc, [4]CH Vannes, [5]CHU Brest, [6]CHU Brest, [7]CHU Nantes, [8]CHU Rennes

Objective: We recently (EULAR 2010) evaluated the diagnostic accuracy of the 2010 ACR/EULAR and 1987 ACR criteria (unmodified and modified by Liao et al. Ann Rheum Dis 2008;67:1557–61) for rheumatoid arthritis (RA) in a cohort of patients with recent-onset arthritis after a 2 year follow up. Our goal is now to verify the results after a ten year follow-up.

Methods: 164 patients with recent-onset arthritis of less than 1 year's duration were prospectively included between 1995 and 1997 and followed

for 10 years. The diagnosis of RA was defined at follow-up completion as having a diagnosis of RA made by an office-based rheumatologist. All items of the unmodified and modified 1987 ACR criteria sets [criteria: 1-Morning stiffness≥1 hour, 2-Arthritis of three or more joint areas, 3-Arthritis of hand joints, 4-Symmetric arthritis, 5-Rheumatoid nodules, 6-Rheumatoid factor (positive), 7-Radiographic changes and 8-Anti-CCP antibodies (positive)] and of the ACR/EULAR 2010 criteria set (algorythm and scoring) were evaluated in each patient. Unmodified 1987 ACR criteria set were considered positive ≥4 of the 1–7 criteria, and the modified 1987 ACR criteria set for ≥4/7 of the 1–2-3–4-6–7-8 criteria (Liao 1) or ≥3/6 of the 1–2-3–4-6–8 criteria (Liao 2). We compared the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the criteria sets.

Results: At baseline, 60 of the 164 patients had alternative diagnoses better explaining the arthritis and 13 had erosions typical for RA; of the 91 remaining patients, 33 had more than 6 ACR/EULAR points (indicating definite RA), and 58 had fewer than 6 points. After 10 years, 9/13 patients with erosions and 25/33 with more than 6 points had RA. Sensitivity, specificity PPV, and NPV of ACR/EULAR 2010 were 34/57 (59.6%), 95/107 (88.8%), 34/46 (73.9%), 95/118 (80.5%), respectively, i.e., better than both un modified (34/57, 78/107, 34/63 and 78/111) and modified 1987 ACR criteria (47/57, 58/107, 47/96 and 58/68 for Lioa2 and 37/57, 78/98, 37/66 and 78/98 for Liao1, respectively). After 10 year, of 9 patients who received biologics, 7 were detected by ACR/EULAR criteria. Similar results were observed for prediction of joint replacement.

Conclusion: ACR/EULAR 2010 criteria perform clearly better than the ACR 1987 criteria to predict a diagnosis of RA at 10 years. Much of the improvement was ascribable to the use of exclusion criteria.

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ACR Concurrent Abstract Sessions
Rheumatoid Arthritis Treatment - Small Molecules, Biologics and Gene Therapy: Existing Biologics
Thursday, November 11, 2010, 11:00 AM–12:30 PM

2262

Tocilizumab (TCZ) Plus Methotrexate (MTX) in Rheumatoid Arthritis (RA) Patients (pts) Who Increased TCZ Dose from 4 mg/kg to 8 mg/kg: LITHE Radiographic and Safety Data. Roy M. Fleischmann[4], Ricardo Blanco[2], Geraldo Castelar-Pinheiro[3], Emma Vernon[5], Christopher Mela[5] and Joel M. Kremer[1]. [1]Albany Medical College, Albany, NY, [2]Hospital Marqués de Valdecilla Cantabria, [3]Hospital Universitario Pedro Ernesto, Rio de Janeiro, Brazil, [4]Metroplex Clinical Research Center, Dallas, TX, [5]Roche, Welwyn, United Kingdom

Purpose: Results of the TCZ clinical development program have shown that for most endpoints, the 8 mg/kg dose is more effective than the 4 mg/kg dose. In the US, TCZ 4 mg/kg has been approved as the starting dose with a subsequent escalation to 8 mg/kg based on clinical response. This analysis evaluated the effect of increasing the TCZ dose from 4 to 8 mg/kg on inhibition of radiographic progression and safety in the LITHE study.

Methods: RA pts with inadequate responses to MTX were randomly assigned to TCZ 4 or 8 mg/kg (TCZ4 or TCZ8) or placebo Q4W + MTX. From wk 16, blinded first-step rescue was allowed if pts had <20% improvement in SJC and TJC (eg, pts on placebo went to TCZ4, pts on TCZ4 or TCZ8 went to TCZ8). If <20% improvement persisted after 3 doses of blinded first-step rescue, pts received second-step rescue with TCZ8. At wk 52, pts were treated with open-label (OL) TCZ8 except those with ≥70% improvement in SJC and TJC, who could continue blinded therapy to wk 104. X-rays were performed at baseline and wks 24, 52, 80, and 104. Data were analyzed in pts whose dose increased from TCZ4 to TCZ8. Data from this TCZ dose-escalation analysis must be interpreted with caution because 78 pts who withdrew (44 for safety, 8 for insufficient response, 26 for other reasons) from the study before dose escalation are not included. In addition, criteria for dose escalation and/or dose continuation were based on efficacy results that were predetermined per study protocol. Safety data are provided for all randomly assigned pts who received ≥1 TCZ dose and who had at least 1 post-randomization safety assessment.

Results: Of 1190 pts (393, 399, and 398 randomly assigned to placebo, TCZ4, and TCZ8, plus MTX, respectively), 451 pts increased their dose from TCZ4 to TCZ8. In these 451 pts, annualized rate of progression of Genant-modified Total Sharp Score, erosion, and joint space narrowing slowed after the dose increased from TCZ4 to TCZ8 (Table A). Rates/100 patient-years (PY) of serious adverse events (AEs) and serious infections were lower than previously reported (Kremer et al, EULAR 2010) before dose escalation but increased to rates comparable to those of the TCZ pooled groups (TCZ4, n =597, includes pts who received TCZ4 as initial or rescue therapy; TCZ8, n=983 pts, includes those who received TCZ8 as initial and/or rescue and/or OL therapy) after dose escalation (Table B). The low predose escalation event rates for the TCZ4 group are influenced by a selection bias—ie, pts who withdrew while on TCZ4 do not contribute safety data to the analysis of the switching group but continue to contribute to the rates in the TCZ4 pooled analysis.

Conclusions: For this analysis of pts who increased dose, the annualized rate of progression was reduced after pts increased their TCZ dose from 4 to 8 mg/kg; safety in these pts after dose escalation was comparable to that in the TCZ pooled groups.

Table A. Mean (SD) Annualized Rate of Radiographic Progression by Treatment Increase up to Week 104 (n = 451)

	Predose increase (TCZ4) n = 451	Postdose increase (TCZ8) n = 451
n	336	346
Genant-modified Total Sharp Score	0.31 (1.07)	0.10 (0.52)
Erosion	0.20 (0.83)	0.04 (0.36)
Joint space narrowing	0.11 (0.53)	0.06 (0.36)

Data collected after study withdrawal are excluded

Table B. Safety up to Week 104 Before and After TCZ Dose Increase and by Pooled Treatment Groups

	Dose escalation group n = 451[a]		Pooled treatment group[b]	
	Predose increase (TCZ4)	Postdose increase (TCZ8)	TCZ4 n = 597[c]	TCZ8 n = 983[d]
Exposure, PY	338.6	475.9	521.9	1320.4
Serious AEs/100 PY	5.9	11.3	12.1	11.4
Serious infections/100 PY	0.9	2.7	3.1	3.2

[a] 78 patients who received TCZ4 and withdrew (44 for safety, 8 for insufficient response, 26 for other reasons) from the study before dose escalation are not included.
[b] Patients in pooled treatment groups could be in both pooled groups and also in the dose-escalation group.
[c] All patients who received ≥1 TCZ4 dose, including those initially assigned to placebo who received rescue with TCZ4 and those initially assigned to TCZ4, and whose only TCZ dose was 4 mg/kg; data are up to study withdrawal, when dose increased to TCZ8, or wk 104.
[d] All patients who received ≥1 TCZ8, including patients initially assigned to placebo who received second-step rescue with TCZ8, patients initially assigned to TCZ4 who received rescue with TCZ8, patients initially assigned to TCZ8, patients whose only TCZ dose was 8 mg/kg, and patients on OL TCZ8; data are up to study withdrawal or wk 104.

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2263

Rituximab Treatment Induces the Expression of Genes Involved in Healing Processes in the Rheumatoid Arthritis Synovium. Ilse Gutierrez-Roelens[4], Christine Galant[3], Ivan Theate[3], Rik J. Lories[2], Patrick Durez[4], Adrien Nzeusseu Toukap[4], Benoît Van den Eynde[1], Frédéric A. Houssiau[4] and Bernard R. Lauwerys[4]. [1]de Duve Institute & Ludwig Institute for Cancer Research, Brussels Branch, [2]Department of Musculoskeletal Sciences, Division of Rheumatology, Laboratory for Skeletal Development and Joint Disorders, Katholieke Universiteit Leuven, [3]Department of Pathology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, [4]Department of Rheumatology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain

Objectives: In previous experiments, we performed transcriptomic analyses on synovial biopsies obtained from anti-TNF resistant rheumatoid arthritis (RA) patients prior to (T0) and 12 weeks (T12) after initiation of rituximab therapy. We found that genes down-regulated between T0 and T12 were significantly enriched in immunoglobulin genes, and genes involved in chemotaxis, leucocyte activation and immune responses. By contrast, genes

up-regulated between T0 and T12 were significantly enriched in transcripts involved in cell development and wound healing. We wondered whether up-regulation of the latter genes was a true effect of rituximab therapy, or whether the relative decrease in inflammatory cells and relative increase in resident synovial fibroblasts resulted in a biased appreciation of global gene expression profiles at T12.

Methods: Paired synovial biopsies were obtained from the affected knee of 20 anti-TNF resistant RA patients at T0 and T12. Fresh synovial biopsy tissue samples were fixed overnight in 10% formalin buffer and embedded in paraffin. Immunolabeling experiments were performed using the following antibodies: BMPR1A (Bone Morphogenetic Protein Receptor 1A), MEOX2 (Mesenchyme Homeobox2), LAMA4 (Laminin alpha 4), phospho-SMAD1/5 and phospho-SMAD3. Quantitative analysis of the antibody immunostained sections was performed using ImageJ software, according to the Digital Image Analysis process.

Results: BMPR1A, MEOX2 and LAMA4 are markers of mesenchymal cell differentiation. Immunolabeling experiments and digital quantification of the slides indicated that synovial expression of the three molecules is significantly induced by rituximab therapy in RA synovial tissue.

Up-regulation of these genes triggered us to investigate whether administration of rituximab resulted in synovial activation of TGF-β or BMP signaling. To explore this hypothesis, we performed phospho-SMAD3 (a marker of TGF-β activation) and phospho-SMAD1/5 (a marker of BMP activation) immunohistochemistry studies. No significant difference in phospho-SMAD3 staining was observed between T0 and T12. The phospho-SMAD1/5 signal significantly decreased between T0 and T12. These results indicate that synovial up-regulation of genes involved in healing processes is not associated with an increased TGF-β or BMP activity through its canonical pathways at T12.

Conclusion: Rituximab induces the expression of molecular markers of mesenchymal cell differentiation in the synovium. We did not find evidence of increased TGF-β and BMP signalling in the synovium at T12. Further studies are needed in order to investigate the possibility of increased BMP or TGF-β signaling at earlier time-points or the presence of alternative mechanisms of induction of mesenchymal cell differentiation.

Disclosure: I. Gutierrez-Roelens: None; **C. Galant:** None; **I. Theate:** None; **R. J. Lories:** None; **P. Durez:** None; **A. Nzeusseu Toukap:** None; **B. Van den Eynde:** None; **F. A. Houssiau:** None; **B. R. Lauwerys:** None.

2264

Golimumab and Methotrexate Combination Therapy Significantly Improves Synovitis, Osteitis and Bone Erosion Compared to Methotrexate Alone—A Magnetic Resonance Imaging Study of Methotrexate-Naïve Rheumatoid Arthritis Patients. Mikkel Østergaard[6], Paul Emery[4], Philip G. Conaghan[5], Roy M. Fleischmann[7], Weichun Xu[2], Elizabeth C. Hsia[3], Anna Beutler[1] and Mahboob U. Rahman[3]. [1]Centocor Research and Development, Inc., Collegeville, PA, [2]Centocor Research and Development, Inc., [3]Centocor Research and Development, Inc./Univ. of Pennsylvania School of Medicine, Malvern, PA, [4]Chapel Allerton Hospital, Leeds, United Kingdom, [5]Chapel Allerton Hospital, Leeds, United Kingdom, [6]Copenhagen University Hospital at Glostrup and Hvidovre, Hvidovre, Denmark, [7]University of Texas SW Medical Center, Dallas, TX

Background: In the GO-BEFORE study, golimumab (GLM) improved signs and symptoms of RA, improved physical function, and slowed the progression of structural damage in patients who were methotrexate (MTX) naïve.

Objective: To evaluate the effect of GLM on the inflammation and structural damage detected by magnetic resonance imaging (MRI) in patients with RA who were MTX naïve.

Methods: Patients (n=637) were randomly assigned to receive placebo (PBO) + MTX, GLM 100 mg + PBO, GLM 50 mg + MTX, or GLM 100 mg + MTX. A subset of study sites capable and willing participated in the MRI substudy. All patients from each substudy site were eligible for substudy participation (n=318). GLM and PBO were administered via subcutaneous injection every 4 weeks. The primary comparison was between the PBO + MTX and combined GLM + MTX groups. MRIs of the patient's dominant wrist and metacarpophalangeal joints were obtained at baseline and weeks 12, 24, 52, and 104 using 1.5T MRI with contrast enhancement. Results through week 24 are presented here. Images were scored by two independent expert readers blinded to image time point or sequence, patient identity, or treatment group. Readers scored synovitis (0–21), bone edema (osteitis) (0–69), and bone erosions (0–230), using the Rheumatoid Arthritis MRI Scoring (RAMRIS) system; the average of each RAMRIS score provided by the readers was used in the analysis.

Results: Mean baseline RAMRIS bone edema and RAMRIS bone erosion scores were numerically slightly lower in the PBO than GLM groups. Significant improvements in RAMRIS synovitis, osteitis and bone erosions were observed at weeks 12 and 24 in the combined GLM + MTX groups relative to PBO + MTX (Table). Significant improvements in synovitis and bone edema were observed in both GLM + MTX dose groups at both weeks 12 and 24 versus the PBO + MTX group. Significantly less bone erosion progression was documented at week 12 for the GLM 50 mg + MTX group and at 24 weeks for both GLM + MTX doses. Comparison of radiographic data (using the van der Heijde modification of the Sharp score) within the MRI substudy patients (n=318) showed no significant difference between the PBO + MTX and combined GLM + MTX groups (mean ± SD changes from baseline to week 28 of 0.92 ± 2.96 and 0.49 ± 3.23, respectively; p=0.19), thus demonstrating MRI to be superior to x-rays in terms of sensitivity to changes in erosive progression.

Conclusion: Results of this MRI substudy of the GO-BEFORE trial demonstrated that patients who received GLM + MTX had improvements in inflammation (synovitis and osteitis) and improvements in erosions exceeding those observed with PBO + MTX as early as week 12 and continuing through week 24, confirming the clinical and radiological findings previously reported for the overall study population. MRI assessment was superior to x-ray in terms of sensitivity to change in erosive progression.

RAMRIS scores: values are mean/median (interquartile range)	Placebo+MTX (n = 82)	GLM 100mg+PBO (n = 77)	GLM 50mg+MTX (n = 78)	GLM 100mg+MTX (n = 81)	Combined GLM+MTX (n = 159)
Synovitis*					
Baseline	8.8 8.5 (5.0, 12.0)	9.3 9.0 (4.0, 14.5)	10.3 10.5 (7.0, 14.0)	9.6 9.5 (6.0, 13.5)	9.9 10.0 (6.5, 13.8)
Week 12	0.1 0.0 (−1.0, 1.5)	−1.8 −1.0 (−3.5, −0.5)	−1.7 −1.0 (−2.5, −0.2)	−2.2 −2.0 (−4.0, 0.0)	−1.9 −1.5 (−3.5, 0.0)
p value		<0.001	<0.001	<0.001	<0.001
Week 24	−1.0 −1.0 (−1.6, 0.0)	−1.6 −1.1 (−2.5, 0.0)	−2.2 −1.5 (−3.5, −0.3)	−2.7 −1.5 (−4.5, −0.5)	−2.5 −1.5 (−4.0, −0.5)
p value		0.344	0.011	0.001	<0.001
Bone edema (Osteitis)					
Baseline	8.4 5.0 (2.5, 11.5)	10.6 6.5 (1.5, 17.8)	11.5 9.5 (4.0, 17.0)	9.5 7.0 (2.0, 13.0)	10.5 7.5 (3.0, 15.3)
Week 12	0.6 0.3 (−1.0, 2.0)	−2.0 −0.1 (−3.0, 0.5)	−2.5 −1.0 (−3.5, 0.0)	−1.2 −0.5 (−2.5, 0.0)	−1.8 −1.0 (−2.9, 0.0)
p value		0.001	<0.001	0.003	<0.001
Week 24	−0.3 0.0 (−1.5, 1.0)	−1.9 −0.5 (−2.0, 0.0)	−2.5 −1.0 (−3.0, 0.0)	−2.1 −0.8 (−2.5, 0.5)	−2.3 −0.8 (−3.0, 0.0)
p value		0.043	<0.001	0.015	<0.001
Bone erosion					
Baseline	17.7 13.5 (8.8, 19.0)	21.0 15.8 (10.8, 25.3)	25.0 15.5 (11.2, 27.0)	21.3 13.3 (10.0, 19.5)	23.1 13.9 (11.0, 22.8)
Week 12	0.2 0.0 (0.0, 0.5)	0.5 0.0 (0.0, 0.5)	−0.8 0.0 (−0.5, 0.5)	0.0 0.0 (−0.1, 0.0)	−0.4 0.0 (−0.5, 0.5)
p value		0.660	0.036	0.054	0.016
Week 24	−0.2 0.0 (0.0, 0.5)	0.5 0.0 (0.0, 0.5)	−0.7 0.0 (−0.6, 0.0)	−0.2 0.0 (−0.5, 0.0)	−0.4 0.0 (−0.5, 0.0)
p value		0.973	0.016	0.028	0.010

* Given that several sites did not have the capability to obtain postgadolinium images, synovitis evaluations of the wrist and MCP joints were obtained in 71, 66, 67, and 68 patients in the PBO + MTX, 100 mg + PBO, 50 mg + MTX, and 100 mg + MTX groups, respectively.

Disclosure: M. Østergaard: Centocor Research and Development, Inc., 2, 9; **P. Emery:** Centocor Research and Development, Inc., 2, 9; **P. G. Conaghan:** Centocor Research and Development, Inc., 2, 9; **R. M. Fleischmann:** Centocor Research and Development, Inc., 2, 9; **W. Xu:** Centocor Research and Development, Inc., 3; **E. C. Hsia:** Centocor Research and Development, Inc., 3; **A. Beutler:** Centocor Research and Development, Inc., 3; **M. U. Rahman:** Centocor Research and Development, Inc., 3.

2265

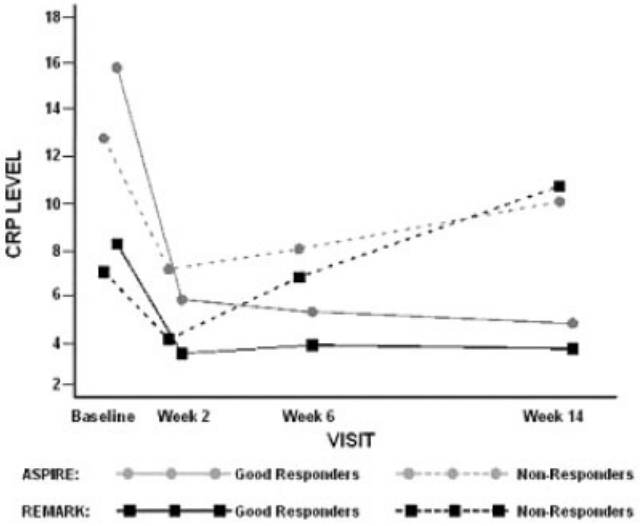
Changes in CRP Levels Are Associated with Clinical Response Patterns during Treatment with Infliximab—A Potential Role for CRP in Guiding Dose Optimization. Cees Meeuwisse[5], Josef S. Smolen[4], Dimitrios Boumpas[7], E. William St Clair[2], Mahboob U. Rahman[1], Nathan Vastesaeger[6], Wilbert van Duijnhoven[5], Robert L. H. Nelissen[5] and Ronald Van Vollenhoven[3]. [1]Centocor, Malvern, PA, [2]Duke University Medical Center, Durham, NC, [3]Karolinska University Hospital, Stockholm, Sweden, [4]Krankenhaus Lainz, Vienna, Austria, [5]MSD, Oss, The Netherlands, [6]MSD, Brussels, Belgium, [7]University Hospital of Heraklion, Crete, Greece

Background: Infliximab (IFX) can be used in RA at a range of doses and frequencies. Biomarkers to guide dose optimization would be of clinical

importance. Our objective was to investigate CRP kinetics during 14 weeks of IFX treatment to determine whether CRP can be used as a biomarker to guide dose optimization in RA patients.

Methods: This was a phase-IV, multicenter, observational study conducted in Europe. Adult patients with RA for whom treatment with IFX 3 mg/kg had been chosen per label were invited to participate. Patients were classified as good-responders (GR), moderate-responders (MR), or non-responders (NR) according to EULAR response at week 14. We built a statistical model to estimate mean (95% CI) CRP levels prior to each infusion by response group, and adjusted it for baseline CRP values and patient characteristics. We then analyzed CRP change among patients and CRP differences between groups. To confirm our results, we performed a similar analysis using data from the 3-mg/kg arm of the blinded randomized controlled ASPIRE study in early RA (St. Clair, 2004).

Results: 481 patients from the study were included in the analysis—79.8 % female; mean age 53 (SD 13) years. Baseline mean DAS28 was 5.2 (SD 1.1). At week 14, 34.5% of patients were GR, 41.2% MR and 24.3% NR. CRP levels steeply declined in all groups from baseline to week 2. In the GR group, CRP remained stable at low levels during weeks 2 to 14. In the NR group, a CRP-rebound started at week 2 and reached near-baseline levels at week 14 (see figure; for clarity only GR and NR profiles are shown, CRP levels for MR were higher but close to those for GR).



Estimated CRP levels adjusted for baseline value and patient characteristics. Values at baseline are geometric means of original data.

This rebound showed significant increases in CRP from weeks 2 to 6 and again from weeks 6 to 14 ($P < 0.0001$). Between-group differences were significant at weeks 6 and 14 for both GR and MR groups compared to the NR group. The confirmatory ASPIRE analysis included 277 patients who received IFX 3 mg/kg. At week 14, 27.4% of patients were GR, 46.9% MR, and 25.6% NR. CRP levels showed a similar pattern, with an initial improvement from baseline to week 2 in all groups and a significant increase in the NR group from weeks 2 to 14. Between-group differences were observed at weeks 6 and 14 for both the GR and MR groups compared to the NR group.

Conclusion: CRP kinetics during the first 14 weeks may help guide IFX treatment. Good response is characterized by stabilization of CRP at low levels, and non-response by a CRP rebound between weeks 2 and 14 during which time the infusion interval is increased. Studies of dose/frequency adjustments in non-responders to optimize therapy are needed.

Reference:

St Clair EW, van der Heijde D, Smolen J, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis. Arthritis Rheum 2004, 50:3432–3443.

Disclosure: C. Meeuwisse: Merck Pharmaceuticals, 3; **J. S. Smolen:** Centocor, Inc., 2, 5, Schering-Plough, 2, 5; **D. Boumpas:** None; **E. W. St Clair:** None; **M. U. Rahman:** Johnson & Johnson, 1, 3; **N. Vastesaeger:** Merck Pharmaceuticals, 1, 3; **W. van Duijnhoven:** Merck Pharmaceuticals, 3; **R. L. H. Nelissen:** Merck Pharmaceuticals, 3, Schering-Plough, 3; **R. Van Vollenhoven:** Abbott Immunology Pharmaceuticals, 2, 5, 9, Merck Pharmaceuticals, 2, 5, 9, Pfizer Inc, 2, 5, 9.

2266

Comparative Effectiveness of Biologic Therapies for Treating Rheumatoid Arthritis (RA) in Patients Who Failed an Anti–Tumor Necrosis Factor Agent: A Meta-Regression Analysis. A. Benedict[2], D. J. Vanness[3], S. Roy[1] and M. A. Cifaldi[1]. [1]Abbott Laboratories, [2]United BioSource Corporation, [3]University of Wisconsin

Background and Purpose: In the absence of clinical studies involving all agents, evaluating comparative efficacy of biologic therapies for patients with RA who failed an anti–tumor necrosis factor (anti-TNF) agent is difficult. Assessing comparative effectiveness of these interventions is challenging. We used meta-regression (MR) methods to estimate probability of clinical response for biologic therapies abatacept, adalimumab, anakinra, etanercept, golimumab, infliximab, rituximab, and tocilizumab, all in combination with methotrexate (MTX), for patients who failed prior anti-TNF therapy.[1,2]

Methods: We updated earlier systematic reviews of biologic therapies in longstanding RA to identify relevant randomized controlled trials (RCTs) that reported American College of Rheumatology (ACR) response criteria. Prospective, open-label studies were included. Dose-finding RCTs and safety studies were excluded. A hierarchical Bayesian mixed effects MR model was estimated (WinBUGS 1.4.3); adjustments for study-arm level heterogeneity included concomitant MTX, age, RA duration, baseline Health Assessment Questionnaire (HAQ) score, follow-up time, % failing prior anti-TNF therapy, and whether assigned treatment was a subsequent biologic. ACR responses in each arm were modeled simultaneously to reflect their nested nature (ie, patients with ACR70 also attain ACR50 and ACR20). Adalimumab, etanercept, golimumab, and infliximab were grouped for this analysis and overall efficacy for anti-TNF agents was compared with non-TNF biologics.

Results: The final dataset included 96 comparator arms from 32 studies. Covariate estimates indicated that prior anti-TNF agent failure was associated with a reduction in the log odds ratio (LOR) of ACR response for all treatments, but subsequent biologic treatment offset much of that reduction. Controlling for other factors, longer duration of disease and greater baseline HAQ score increased the LOR of ACR response for biologic relative to nonbiologic treatment. Likewise, longer follow-up decreased the LOR of ACR response. The table summarizes posterior mean predicted ACR response rates for patients with mean baseline HAQ score of 2.0, disease duration of 11 years, and at 6 months of follow-up.

	Placebo/ None+MTX	anti-TNF+ MTX	Anakinra+ MTX	Abatacept+ MTX	Rituximab+ MTX	Tocilizumab+ MTX
ACR20	27.4%	66.5%	49.9%	54.3%	64.1%	66.6%
ACR50	12.0%	43.1%	27.7%	31.4%	41.5%	43.4%
ACR70	4.8%	22.9%	13.0%	15.2%	22.3%	23.2%

Conclusions: This MR analysis drew on a large body of clinical data and statistically controlled for heterogeneity to reliably estimate the relative treatment effects of a second biologic therapy in patients with RA who failed prior anti-TNF therapy. Patients treated with a second anti-TNF agent achieved comparable or superior clinical response compared with non-TNF agents. As such, for patients failing their first anti-TNF, a second anti-TNF agent should be considered an appropriate treatment option before switching to a non-TNF biologic therapy.

References:

1. Lu G, Ades AE. *Stat Med.* 2004;23:3105–24.
2. Nixon et al. *Stat Med.* 2007;26:1237–54.

Disclosure: A. Benedict: Abbott Laboratories, 2, United BioSource Corporation, 3; **D. J. Vanness:** University of Wisconsin, Madison, 3; **S. Roy:** Abbott Laboratories, 1, 3; **M. A. Cifaldi:** Abbott Laboratories, 1, 3.

2267

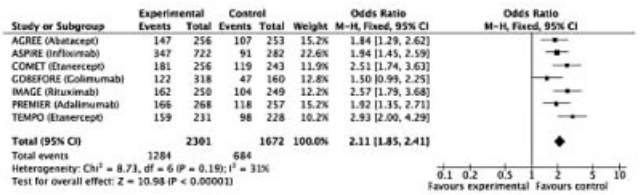
Clinical and Radiological Efficacy of Biologics in Rheumatoid Arthritis Patients Naive or Inadequate Responders to Methotrexate: A Metanalysis. Pierreisnard Audrey, Issa Nahema, Barnetche Thomas, Richez Christophe and Schaeverbeke Thierry. Bordeaux University Hospital, Rheumatology Department, France

Purpose: Recently, an overview of Cochrane reviews comparing efficacy and safety of six biologics in rheumatoid arthritis (RA) was published. However, this study did not include tocilizumab, certolizumab and golimumab, and was not stratified based on previous methotrexate (MTX) use. Our objective was to perform a metanalysis of all biologics available in RA into two situations: MTX naive patients and MTX inadequate responders

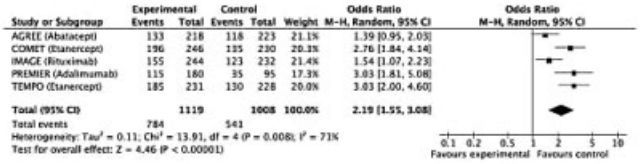
(IR). Furthermore, there are no randomized controlled trials (RCT) comparing biologics head to head. In this study, we performed indirect comparisons of biologics for efficacy.

Methods: A comprehensive literature review was performed by searching Medline for RCTs from 1995 to December 2009 and conference abstracts from ACR Annual Scientific Meetings and EULAR's. We included studies evaluating the five anti-TNF, tocilizumab, rituximab and abatacept, in combination with MTX in MTX naive patients and in IR, using the standard dosing regimens of each product. The primary clinical outcome was ACR50 response. Indirect comparisons of biologics were performed for efficacy using the number needed to treat (NNT) for ACR50 criteria. The primary radiological endpoint was the proportion of patients with no progression of total Sharp score at one year. Statistical analyses were based on odds ratio (OR) for efficacy. Using these combined estimates, we calculated the NNT for each product.

Results: 22 studies were included, 7 in MTX naive patients and 15 in IR. In MTX naive patients, biologics therapy showed significantly increased efficacy compared to MTX with OR for achieving an ACR50 response: OR: 2.11 (95%IC: 1.85, 2.41).



In IR, the same OR was 4.79 (95% IC: 3.49,6.59). The NNT for ACR50 for etanercept were: 5 for MTX naive patients and 3 for IR; for adalimumab were: 7 and 3, respectively; for infliximab were: 7 and 4, respectively; for abatacept were: 7 into the two groups; for rituximab were: 5 into the two groups; for tocilizumab: 4 for IR; for certolizumab were: 4 for IR. NNT were not evaluable for golimumab as the confidence intervals for the risk comprised null or negatives values. The radiographic primary endpoint is shown in figure 2.



Conclusions: Response to biologic therapy in combination with MTX, compared to MTX alone was significant in IR and MTX naive group, but to a lesser extent in the MTX naive group. This difference could be explained by a relative efficacy of MTX in MTX naive patients. Interestingly, patients treated by anti-TNF therapy had significantly less radiograpghic progression than those with cellular therapy, in MTX naive patients.

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ACR Concurrent Abstract Sessions
Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment - Therapy
Thursday, November 11, 2010, 11:00 AM–12:30 PM

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Outcome of an Education and Home Exercise Program for Ankylosing Spondylitis Patients: A Nationwide Randomized Study. Carlos Rodríguez-Lozano[2], Xavier Juanola[2], Juan Cruz-Martínez[1], Andrés Peña-Arrébola[4], Juan Mulero[2] and Eduardo Collantes[3]. [1]for the Spondyloarthropathies Study Group of the Spanish Society of Rheumatology (GRESSER), [2]for the Spondyloarthropathies Study Group of the Spanish Society of Rheumatology (GRESSER), [3]for the Spondyloarthropathies Study Group of the Spanish Society of Rheumatology (GRESSER); Hospital Ramón y Cajal. Madrid, [4]Hospital Ramón y Cajal. Madrid

Purpose: To assess the impact of a structured education and home exercise program on different outcome measures in patients with ankylosing spondylitis attended in daily practice.

Methods: Patients with ankylosing spondylitis (modified New York criteria 1984) aged 18–70 years participated in a 6-month nationwide prospective study, in which they were randomized to an education intervention (education group) or standard care (controls). The intervention included a 2-hour session in which professionals provided information about the disease and its management, and the implementation of a physical activity program at home. Patients received a printed leaflet and a fitness DVD to take home. All patients completed a diary card and received monthly remainder phone calls. Main outcome measures included a 0–10 cm visual analog scale (pain, global disease activity); Bath Ankylosing Spondylitis Disease Activity and Functional Index (BASDAI, BASFI); Patient Acceptable Symptomatic State (PASS); and quality of life (ASQoL). Data at 6 months were compared with baseline.

Results: A total of 622 patients (EG group 308, controls 314) participated (73% males, mean age 45 years, mean duration of disease 17 years). Regular medications included NSAIDs in 52% of patients and anti-TNF agents in 40%. Fifty-four percent of patients used to exercise regularly (mean [SD] 3.2 [3.3] hours/week). At baseline, both groups were well balanced (table). At 6 months, mean improvements in all outcome measures were statistically significant in both study groups except for ASQoL and patients in PASS condition, which were only significant in the education group. Between-group mean differences were statistically significant for ASQol, BASFI, and percentage of patients changing from negative to positive PASS (table). Patients in the education group practiced more regular exercise than controls ($P = 0.002$) and increased their knowledge about the disease significantly

Table. Outcome Measures at Baseline and after 6 Months

Variable	Baseline, mean (SD)		Mean difference at 6 months		Between-group differences mean (95% CI)
	Education group	Control group	Education group	Control group	
VAS global pain (0–10)	3.77 (2.59)	4.01 (2.67)	−0.68*	−0.47*	−0.21 (−0.57 to 0.15)
VAS nocturnal pain (0–10)	3.35 (2.83)	3.61 (2.99)	−0.62*	−0.52*	−0.09 (−0.47 to 0.28)
VAS patient activity (0–10)	3.98 (2.58)	4.17 (2.56)	−0.68*	−0.39*	−0.28 (−0.63 to 0.07)
BASDAI (0–10)	3.34 (2.27)	3.61 (2.26)	−0.62*	−0.52*	−0.24 (−0.51 to −0.03)
BASFI (0–10)	3.51 (2.54)	3.61 (2.62)	−0.51*	−0.21*	−0.30 (0.52 to −0.08)*
ASQoL (0–18)	6.50 (4.87)	6.24 (4.82)	−0.96*	−0.19	−0.76 (−1.23 to −0.30)†
PASS (positive)	58.9%	61.3%	12.7%*	3.2%	17.5% vs 11.8%‡

* $P < 0.001$ versus baseline; † $P < 0.01$; ‡ Patients changing from negative to positive PASS, $P = 0.026$

Conclusions: An education session and a structured exercise home program for patients with ankylosing spondylitis with relatively low disease activity improved physical function, quality of life and patients who were in PASS condition. Besides drug treatment, incorporating education and exercise in daily practice is feasible and reported substantial benefits.

Disclosure: C. Rodríguez-Lozano: None; **X. Juanola:** None; **J. Cruz-Martínez:** None; **A. Peña-Arrébola:** None; **J. Mulero:** None; **E. Collantes:** None.

2269

SAPHO Syndrome Treated by TNF alpha-Blocking Agents. Report of 45 Cases. Gilles Hayem[7], Rim Ben M'Barek[8], Eric Toussirot[4], Christian Compaoré[6], Thao Pham[9], Eric Houvenagel[13], Antoine Martin[3], Nathalie Balandraud[9], Jean-Marie Berthelot[10], Grégoire Cormier[2], Anne Dubois[1], Rose-Marie Javier[11], Sylvain Lanot[12], Marie-José Wattiaux[7], Olivier C. Meyer[8] and Daniel Wendling[5]. [1]CH Brive, France, [2]CH La Roche sur Yon, France, [3]CH Saint-Brieuc, France, [4]CHU Besançon, France, [5]CHU Besançon, for the "Club Rhumatismes et Inflammation", Besancon, France, [6]CHU Bichat, Paris, France, [7]CHU Bichat, Paris, France, [8]CHU Bichat, Paris, Tunisia, [9]CHU Marseille, France, [10]CHU Nantes, France, [11]CHU Strasbourg, France, [12]Private Office, Paris, France, [13]UC Lille, France

Objectives: To evaluate the efficacy and safety of TNF-α-blocking agents in SAPHO syndrome.

Methods: A retrospective study was conducted by the "Club Rhumatismes et Inflammation" (depending from the French Society of Rheumatology) to find and analyse all the case records from patients suffering from SAPHO syndrome, who had been treated with at least one of the three following TNFα-blocking agents: adalimumab (ADA), etanercept (ETN), or infliximab (IFX). Demographic and clinical data were collected, including previous treatments and incident side effects. The efficacy of anti-TNFα

treatment was evaluated at last follow-up visit, based on the decrease of SAPHO syndrome-related symptoms, appreciated by each patient on a visual analogic scale (VAS). A score decrease of more than 80% was considered as a remission. An improvement comprised between 50 and 79% indicated a partial efficacy and a reduction less than 50% was interpreted as a lack of response.

Results: The case records of 45 patients (33F/12M; mean age 45) were available for analysis. The mean age at disease onset was 31 years (range 11–61). In all patients, SAPHO syndrome was previously considered as refractory to at least three of the five following types of treatments: non steroidal anti-inflammatory drugs, corticosteroids, antibiotics (various regimens), synthetic disease modifying anti-rheumatic drugs (methotrexate or sulfasalazin), and bisphosphonates. Forty-four patients also had active cutaneous manifestations when TNF-α-blocking agent was started. Thirty patients received ETN (25 mg biw or 50 mg qw SC; first biologic to be used in 17 patients; follow-up: 3–60 months). Remission was observed in 11 patients, and partial efficacy in 10. Twenty-two patients were treated with ADA (40 mg SC eow; first biologic in 7 patients; follow-up: 2 to 17 months). Remission and partial efficacy were registered in 12 and 2 patients, respectively. IFX was administered to 18 patients (5 mg/kg, infusions at week 0, 2 and 6, then every 8 weeks; first biologic in 12 patients; follow-up: 3–65 months). Remission and partial efficacy were noted in 5 and 5 patients, respectively.

The treatment with TNF-α-blocking agents was stopped 11 times for a side effect, in 9 patients: 3 times with ETN (1 papillomavirus cutaneous and genital infection, 1 psoriasis vulgaris, 1 optic neuritis); 4 times with ADA (2 allergic reactions, 1 pyelonephritis, 1 hidradenitis suppurativa of the breast) and 4 times with IFX (1 psoriasis vulgaris, 1 flare of palmoplantar pustulosis, 1 hidradenitis suppurativa of the breast and 1 peritonitis).

Conclusion: TNF-α-blocking agents seem to represent an interesting therapeutic option in refractory cases of SAPHO syndrome, without unpredicted side effects.

Disclosure: G. Hayem: None; **R. Ben M'Barek:** None; **E. Toussirot:** None; **C. Compaoré:** None; **T. Pham:** None; **E. Houvenagel:** None; **A. Martin:** None; **N. Balandraud:** None; **J.-M. Berthelot:** None; **G. Cormier:** None; **A. Dubois:** None; **R.-M. Javier:** None; **S. Lanot:** None; **M.-J. Wattiaux:** None; **O. C. Meyer:** None; **D. Wendling:** None.

2270

Radiographic Findings after 5 Years of Infliximab Treatment in Patients with Ankylosing Spondylitis. Xenofon Baraliakos[6], Frank Heldmann[6], Desiree M. Van Der Heijde[4], Joachim Listing[3], Joachim Sieper[2], Alessandra Oortwijn[1], Rebecca Bolce[1] and Juergen Braun[5]. [1]Centocor Inc, [2]Charite Campus Benjamin Frankl, Berlin, Germany, [3]German Rheumatism Research Center, [4]Leiden University Medical Center, Meerssen, The Netherlands, [5]Rheumazentrum Ruhrgebiet, Herne, Germany, [6]Rheumazentrum Ruhrgebiet Herne

Background: Anti-TNF therapy with infliximab significantly reduces inflammatory activity (clinical assessments, MRI) in patients with active ankylosing spondylitis (AS) but does not seem to have a major impact on radiographic progression over 2 years. Recent studies have indicated that patients where structural changes have already occurred show higher rates of radiographic progression as compared to those without occurrence of radiographic chagnes. The European Infliximab AS cohort (EASIC) has been started after the end of ASSERT and patients were treated with infliximab in a real-life setting for 5 years.

Objectives: To study the long-term effect of anti-TNF treatment with infliximab on the chronic AS related radiographic changes over 5 years.

Methods: Complete sets of radiographs of the cervical (CS) and the lumbar (LS) spine at baseline (BL) and after 2 (FU1) and 5 years (FU2) were available from 53 patients from EASIC. Images were mixed with images from different studies and scored blinded for time order and treatment by an experienced reader using the mSASSS.

Results: At baseline, the mean age was 42.4±7.9, 45/53 patients (85%) were HLA-B27 positive and 46/53 (86.8%) were male. The mean BASDAI was 6.3±1.3, the mean BASFI was 4.0±1.7 and the mean BASMI was 5.9±1.6. The mean mSASSS score at BL was 20.5±19.9 units and the number of patients with syndesmophytes in the cervical and/or lumbar spine was 31/53 (59%). Radiographic progression was observed in almost all patients, with a mean mSASSS change of 1.0±2.0 and 2.1±2.7 at FU1 and FU2, respectively, in the entire group (both $p<0.05$ as compared to BL). There were no differences between the CS and the LS.

Overall, there was a trend for more severe radiographic progression at BL for the group with syndesmophytes at BL, as compared to the group without. New syndesmophytes were found in 14/31 patients (45.2%) when BL syndesmophytes were present vs. 9/22 patients (40.1%) without. Similarly, the overall mSASSS progression at FU2 differed between patients with (2.4±2.7) and without (1.6±2.8) syndesmophytes at BL.

Conclusion: In constrast to RA, patients with AS show ongoing radiographic progression under anti-TNF treatment. Future studies with head-to-head comparisons with historical cohorts may indicate whether the velocity of this process of new bone formation is changed by this medication.

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2271

Effects of Etanercept vs. Sulfasalazine on Acute Inflammatory Lesions as Detected by Whole Body MRI in Early Axial Spondyloarthritis—A 48 Week Randomized Controlled Trial. In-Ho Song[2], Kay-Geert Hermann[4], Hildrun Haibel[3], Christian Althoff[4], Joachim Listing[7], Gerd-Rüdiger Burmester[5], Andreas Krause[6], Martin Bohl-Bühler[9], Bruce Freundlich[8], Martin Rudwaleit[3] and Joachim Sieper[1]. [1]Charite Benjamin-Franklin, Med. Clinic I, Rheumatology, Berlin, Germany, [2]Charite Campus Benjamin, Med. Clinic I, Rheumatology, Berlin, Germany, [3]Charite Campus Benjamin-Franklin, Med. Clinic I, Rheumatology, Berlin, Germany, [4]Charite Campus Mitte, Radiology, Berlin, Germany, [5]Charite Campus Mitte, Rheumatology, Berlin, Germany, [6]Clinic Buch Rheumatologie, Berlin, Germany, [7]German Rheumatism Research Center, Berlin, Germany, [8]Pfizer-Wyeth, PA, [9]Private Practice, Rheumatology, Potsdam, Germany

Purpose: To evaluate the potential of etanercept (ETA) versus sulfasalazine (SSZ) to reduce active inflammatory lesions on whole-body magnetic resonance imaging (wb-MRI) in active axial spondyloarthritis (SpA) with a symptom duration of short symptom duration.

Method: 76 patients with NSAID-refractory axial SpA were randomized to etanercept (ETA 25 mg given twice weekly subcutaneously; n= 40) or sulfasalazine (SSZ 2–3 g per day orally; n= 36) treatment over 48 weeks. All patients fulfilled the recently published ASAS-classification criteria for axial SpA, showed active inflammatory lesions (bone marrow edema) on whole-body MRI (wb-MRI) in either the sacroiliac joints (SIJ) or the spine and had a symptom duration of less than 5 years. All patients underwent wb-MRI at week 0, 24 and 48. MRIs were scored by two radiologists, blinded for treatment arm and MRI time point, resulting in a score for the SIJ of between 0 and 24 and for the spine between 0 and 69. The primary endpoint was the reduction of active inflammatory lesions on wb-MRI, clinical outcome parameters were secondary endpoints.

Results: Patients' characteristics were similar for the ETA group (mean age 35, 58% male, 85% HLA-B27 positive, mean symptom duration 2.6 years), and the SSZ group (mean age 33 years, 58% male, 78% HLA-B27 positive, mean symptom duration 3.0 years). At baseline, 92% of the patients showed active inflammatory lesions in the SIJ, 41% in the spine, but only 5% in the spine but not in the SIJ. According to the early disease stage, the mean score in the SIJ with 6.6 (standard deviation SD 5.9) out of 24 was relatively higher compared to a mean score of 1.8 (SD 3.3) out of 72 for the spine. In the ETA group, the reduction of the SIJ score from 7.7 at baseline to 2.0 at week 48 was significantly ($p=0.003$) larger compared to the SSZ group from 5.4 at baseline to 3.5 at week 48. A similar reduction of inflammation was found in the spine: 2.2 to 1.0 in the ETA group vs. 1.4 to 1.3 in the SSZ group between baseline and week 48, respectively ($p=0.0024$). Enthesitis improved also significantly ($p= 0.027$) better in the ETA compared to the SSZ group. Inflammation on the posterior segments showed no significant difference between the two treatment groups. 50% of the patients reached ASAS clinical remission and 70% ASAS 40 response in the ETA group vs 19% and 31% in the SSZ group at week 48.

Of the 6 patients who became completely free of inflammation both in SIJ and spine in the ETA group all patients were also in clinical remission. In contrast, none of the 2 patients reaching remission on the SULFA group were free of inflammation as shown by wb-MRI.

Conclusion: In patients with early axial SpA active inflammatory lesions detected by wb-MRI improved significantly more in ETA- versus SSZ-treated patients. This effect correlated with a good clinical response in the ETA group.

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2272

A Prospective Inception Cohort Study of the Clinical Presentation and Response to Treatment of Undifferentiated Spondyloarthritis Versus Ankylosing Spondylitis and Psoriatic Arthritis.

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Background: Ankylosing spondylitis (AS) and psoriatic arthritis (PsA) are the best described and studied subtypes of spondyloarthritis (SpA). A significant proportion of SpA patients, however, does not fulfil the classification criteria for AS and PsA and are at risk to be diagnosed and treated late. The aim of this study was to assess whether patients with undifferentiated SpA (USpA) are different from AS and PsA in terms of patient characteristics, disease activity and response to treatment.

Methods: 175 patients presenting on a dedicated SpA outpatient clinic fulfilling the European Spondyloarthropathy Study Group (ESSG) criteria were recruited in a prospective inception cohort. Global assessment of disease activity visual analogue scale (VAS) patient and physician, Bath Ankylosing Spondylitis Disease Activity (BASDAI), 68 swollen and tender joint count, Schober, ESR and CRP were measured every 3 months. Parametric tests were used for normally distributed data and non-parametric tests for non-normally distributed data.

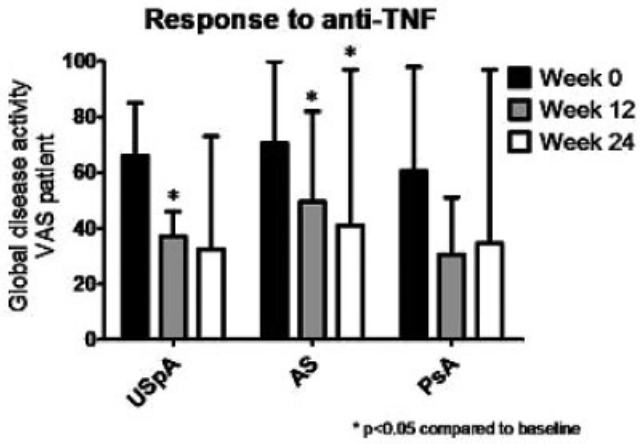
Results: The baseline demographic and clinical data are shown in Table 1.

Baseline demographics and disease activity

	USpA (n = 40)	AS (n = 74)	PsA (n = 45)
Median age of onset (yrs) (range)	31.7 (11.2–62.1)	36.5 (8.1–75.6)	44.2 (20.9–68.2)**
Median disease duration (yrs) (range)	1.3 (0.0–36.1)	4.2 (0.0–46.8)**	4.5 (0.0–29.1)**
Male sex (%)	17 (42.6)	43 (68.1)	30 (66.7)**
Inflammatory back pain (%)	35 (87.6)	72 (97.3)**	22 (48.9)**
Peripheral arthritis (%)	25 (62.5)	26 (35.1)**	37 (82.2)**
HLA-B27 positive (%)	17 (42.6)	49 (68.1)**	11 (36.5)
Sacroiliitis high grade (%)	1 (2.5)	74 (100.0)**	10 (22.2)**
Sacroiliitis low grade (%)	18 (45.0)	0 (0.0)**	5 (11.1)**
Positive family history for SpA (%)	20 (50.0)	23 (31.1)**	16 (35.6)
NSAIDs (%)	31 (77.5)	51 (68.9)	24 (53.3)**
DMARDs (%)	15 (37.5)	8 (10.8)**	26 (57.8)*
Anti-TNF (%)	4 (10.0)	19 (25.7)**	18 (40.0)**
VAS patient (mm) median (range)	62.5 (10–100)	50 (1–98)**	38 (0–98)**
VAS physician (mm) median (range)	51 (4–82)	45 (1–90)	30 (2–84)**
BASDAI median (range)	5.3 (0.9–9.1)	6.0 (0.3–9.2)	3.2 (0.0–7.8)**
BASDAI ≥ 4 (%)	27 (69.2)	45 (63.4)	20 (45.5)**
SJC (68) median (range)	0 (0–8)	0 (0–26)**	0 (0–26)
TJC (68) median (range)	1 (0–34)	0 (0–16)	3 (0–21)
Schober (cm) mean (SD)	4.1 (1.1)	3.6 (1.2)**	4.2 (1.0)
Chest expansion (cm) mean (SD)	4.6 (1.4)	4.3 (1.5)	4.5 (1.2)
ESR (mm/h) median (range)	7 (1–64)	10.6 (2–61)	5 (1–61)
CRP (mg/l) median (range)	2.0 (1.0–53.9)	4.0 (1.0–38.0)	2.2 (1.0–37.0)

Normally distributed: unpaired t-test not-normally distributed: Mann-Whitney; Categorical data: Chi2
* Trend ($0.05<p<0.1$) and ** significant difference ($p<0.05$) versus USpA

The cohort included 40 USpA, 74 AS and 45 PsA patients. The age of onset (median 32 years; range 11–62), disease duration (1.3 years; 0–36), and proportion of male patients (42.5%) were lower in USpA than in AS and PsA. USpA patients had more axial and less peripheral disease than PsA, but less axial and more peripheral disease than AS. The presence of HLA-B27 (43%) and either high or low grade sacroiliitis (47.5%) were less frequent in USpA than in AS. Only 25% of the USpA patients fulfilled the ASAS criteria for pre-radiological AS, although it should be noted that MRI was not systematically performed. Half of the USpA group had a positive family history. Despite the atypical presentation, the baseline disease activity (VAS patient/physician and BASDAI) was higher in USpA than in the other groups. Upon initiation of TNF blockade in patients with high disease activity, we observed a significant and sustained decrease of the disease activity in USpA, which was similar in amplitude to the response in AS and PsA (Figure 1).



Conclusion: USpA displays an intermediate phenotype between AS and PsA, with only part of the patients representing pre-radiological axial SpA. Despite the atypical presentation and shorter disease duration, a large majority of USpA patients have high disease activity. The apparent efficacy of TNF blockers in this observational study, together with the emerging data of RCT in pre-radiological AS pleas for systematic assessment of novel treatments not only in AS and PsA but also in axial and peripheral USpA.

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2273

Do Patients with Psoriatic Arthritis Who Present Early Fare Better Than Those Presenting Later in the Disease?

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Background: Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis often seronegative for rheumatoid factor. Over the past few decades it has become clear that the disease is more common and more severe than previously appreciated. PsA causes deformities and joint damage leading to impaired quality of life and function and is associated with an increased mortality risk. It remains to be determined whether early diagnosis and treatment would alter the course of the disease. The aims of this investigation were 1) to determine whether patients presenting to a PsA clinic early in the course of the disease had less severe disease at presentation, and 2) whether disease duration at presentation predicts progression of joint damage.

Methods: Patients with PsA have been followed prospectively in a specialized clinic for 32 years. Patients were divided into those first seen within 2 years of diagnosis (group 1) and those seen with more than 2 years of disease (group 2). The two groups were compared with regards to demographics and disease characteristics at presentation to clinic. A multivariate analysis using a negative binomial model was conducted to determine whether patients with early disease had less progression of joint damage. The outcome variable was progression of clinical joint damage and the variables entered in the model were age, sex, group, clinical joint damage at first visit, NSAIDS at first visit, DMARDs at first visit, treatment with biologics at first visit, treatment with NSAIDS after the first visit, treatment with DMARDS, and treatment with biologics after the first visit.

Results: 436 patients were identified in group 1 and 641 patients in group 2. Demographic and disease characteristics at first visit are shown in Table 1.

Table 1. Demographic and disease characteristics of study subjects.

Variable	Early PsA ≤ 2y	Late PsA >2y	P values
No. Patients	436	641	
Gender M/F (%)	57.6/42.4	55.2/44.8	0.447
Age at Psoriasis Diagnosis (yrs)	30.3	27.2	0.001
Age at PsA Diagnosis (yrs)	40.3	34.2	<0.0001
Age at 1st Visit (yrs)	41.1	45.2	<0.0001
Duration PsA at 1st Visit (yrs)	0.92	11.0	<0.0001
Mean No. Actively inflamed Joints	10.5	11.7	0.239
Mean No. Damaged Joints	3.5	9.2	<0.0001
Mean PASI score	6.2	5.5	0.254
Sacroiliitis	26.4%	38.4%	<0.0001
Radiographic damage	39.2%	65.9%	<0.0001
Treatment at first visit			
NSAIDs	56.4%	61.6%	0.089
DMARDs	28.0%	56.8%	<0.0001
Biologics	4.1%	6.7%	0.061

Thus patients in group 2 (late PsA) were older, had longer duration of psoriasis and PsA, more joint damage and were less likely to be treated with DMARDs, but had similar degree of psoriasis severity. Results of multivariate regression analysis on predictors for progression of joint damage are shown in Table 2.

Table 2. Results of multivariate analysis on predictors for progression of clinical joint damage in patients with PsA.

Variable	Relative Rate of joint damage progression	95% CI	P-value
Group (PsA>2 yr vs. PsA≤ yrs)	1.62	(1.28, 2.03)	<0.0001
Age	1.02	(1.01, 1.03)	<0.0001
Sex	1.15	(0.93, 1.42)	0.173
Clinical Joint Damage at 1st visit	1.03	(1.01, 1.05)	0.0003
NSAIDS at first visit	1.04	(0.84, 1.30)	0.690
Biologics at first visit	0.89	(0.543, 1.45)	0.630
DMARDS at first visit	1.20	(0.950, 1.51)	0.130
NSAIDS after first visit	1.22	(0.89, 1.68)	0.230
Biologics after first visit	1.15	(0.90, 1.46)	0.250
DMARDS after first visit	1.52	(1.16, 1.99)	0.002

After adjusting for age, sex, clinical joint damage at first visit and treatment, Group 2 has significantly more rate of clinical damage progression compared to Group 1.

Conclusions: Patients who present within 2 years of diagnosis have less severe disease at presentation than those presenting later in their course. Disease progression is more marked in those patients presenting with established disease of > than 2 years duration. These results suggest that patients with PsA should be treated earlier in the course of their disease.

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ACR Concurrent Abstract Sessions
Systemic Lupus Enrythematosus - Human Etiology and Pathogenesis: Etiology and Pathogenesis
Thursday, November 11, 2010, 11:00 AM–12:30 PM

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Identification of cis-Regulatory Element Binding Differences in the C8orf13/BLK Promoter Region Linked with Risk of SLE. Rufei Lu[5], Nicolas Dominguez[6], Susan Macwana[5], Celi Sun[5], Jennifer A. Kelly[5], Kenneth M. Kaufman[5], Carl D. Langefeld[11], Marta Alarcon-Riquielme for BIOLUPUS Network[5], Sang-Cheol Bae[2], Elizabeth E. Brown for PROFILE[9], Gary S. Gilkeson[3], Timothy B. Niewold[10], Betty P. Tsao[8], Nan Shen[7], Kathy L. Moser[4], John B. Harley[1], Slegen, Carol Webb[5], Judith A. James[5], Swapan K. Nath[5], Patrick M. Gaffney[5] and Joel M. Guthridge[5]. [1]Cincinnati Children's Hospital Medical Center, [2]Hanyang University Hospital for Rheumatic Diseases, [3]Medical University of South Carolina, [4]Oklahoma Med Research Foundation, [5]Oklahoma Medical Research Foundation, [6]Oklahoma Medical Reserch Foundation, [7]Shanghai Ren Ji Hospital, [8]UCLA School of Medicine, [9]University of Alabama at Birmingham, [10]University of Chicago, [11]Wake Forest University Health Sciences

Background: SLE is a complex autoimmune disease with immunological abnormalities that target B cell function and development. Previous genome-wide association studies identified C8orf13/BLK as a SLE risk factor, however the molecular mechanism associated with increased SLE risk is unknown.

Methods: Over 300 SNPs from the C8orf13/BLK region were evaluated in 3546 unrelated SLE patients and 3980 controls of European-decent (EA), 1270 unrelated Asian (AS) SLE patients and 1272 controls, and 1734 unrelated African American (AA) patients and 1406 Controls. The quality of the genotype data was determined by the following inclusion criteria: MAF > 1%, SNP call rate > 90%, and HWE (P >.001) among the controls. Case-control associations were analyzed using PLINK. Population-specific haplotype block structures were examined by Haploview using the HapMap phase 2 release 23 dataset. Both the squared correlation statistic (r2) and Lewontin's D' statistic were used as measures of LD strength within the C8orf13/BLK region. We identified a risk haplotype for C8orf13/BLK across all three populations based on SNPs rs13277113 and rs2736345, which we used to identify homozygous risk cases and homozygous non-risk controls for resequencing of the 20kb regulatory region of BLK. Electrophretic mobility shift assays were performed to assess cis-regulatory binding elements at polymorphisms defined by the genotyping. Probes of ~200 bp flanking each associated SNP within the region were end-labeled by T4 polynuleotide kinase and ^{32}P-ATP and incubated with nuclear extracts from seven cell lines representing different stages of B cell development, epithelial cells, and mature T cells.

Results: We successfully analyzed 259 SNPs in EA, 201 in AS, and 329 SNPs in AA populations in the C8orf13/BLK genomic region. Transracial mapping results demonstrated that the strongest association peak was observed in the AA population and was centered in the proximal promoter region of BLK. The peak association in the AA population was at SNP rs2736345 ($p=1.09\times10^{-6}$, OR= 1.296, C.I.=1.17–1.436). The peak association in the EA population was at SNP 13277113 ($p=2.18\times10^{-12}$, OR= 1.32, C.I.=1.216–1.434). SNPs within the peak association region are tightly linked with r^2 values > 0.98. Resequencing of the 20 kb regulatory region failed to identify any new SLE associated variants. EMSA probes flanking SNP rs13277113 demonstrated a loss of transcription factor binding in risk individuals when using nuclear extracts from cell lines that represent immature B cells, mature B cells, and T cells. Probes spanning the SNPs in the proximal promoter region also showed different nuclear factor DNA binding profiles in all cell types tested.

Conclusion: Our results suggest that multiple polymorphisms in the genomic interval upstream of the BLK gene, including the promoter, influence the binding of nuclear factors at cis-regulatroy elements critical for regulating BLK expression in a cell type and developmental stage specific fashion.

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2275

The HRES-1/RAB4 Lupus Susceptibility Gene Promotes Nitric Oxide Production in Human T Cells through Direct Interaction with Endothelial Nitric Oxide Synthase Interacting Protein. Tiffany N. Telarico[1], Edward H. Doherty[1], David R. Fernandez[1], Adam Bartos[1], Stephanie Oess[2], Werner Muller-Esterl[2] and Andras Perl[3]. [1]SUNY, [2]University of Frankfurt, [3]Upstate Medical Univ, Syracuse, NY

Purpose: Polymophic haplotypes of the HRES-1 endogenous retrovirus influence lupus susceptibility. One of its gene products, HRES-1/Rab4 is overexpressed in lupus T cells and contributes to altered T cell activation via regulating endosomal recycling of cell surface CD4 and transferrin receptors as well as the CD3 zeta chain that transmits signals from the immunological synapse (IS). Increased production of nitric oxide (NO) has been linked to abnormal activation of lupus T cells and NO production has been localized to the IS. Here we investigated the role of HRES-1/Rab4 in compartmentalized production of NO.

Methods: Expression of proteins involved in NO production was investigated by RNA microrray and western blot analysis of negatively isolated T cells from 44 Caucasian female lupus patients and 23 age-matched Caucasian female controls. NO production was measured by flow cytometry. The effect of HRES-1/Rab4 on NO production and expression of proteins involved in

NO synthesis was investigated by overexpression of a wild-type HRES-1/Rab4 and its dominant-negative form HRES-1/Rab4S27N. Direct interaction of HRES-1/Rab4 with potential binding partners was assessed by pull-down assays.

Results: NO production was increased in lupus T cells by 32% ($p=0.009$) Expression of endothelial NO synthase (eNOS) interacting protein (NOSIP) was reduced by 61% in lupus T cells ($p=0.010$). Over-expression of HRES-1/Rab4 suppressed NOSIP expression and shifted it to the cytosol, enhanced eNOS expression, and NO production while dominant-negative HRES-1/Rab4S27N had the opposite effects in human T cells. NOSIP was efficiently pulled down by HRES-1/Rab4-GST but not by GST alone in Jurkat cells and human peripheral blood lymphocytes.

Conclusion: The results indicate that over-expression of HRES-1/Rab4 promotes NO production through direct interaction with NOSIP and its targeting to the cytosol which may activate eNOS and modulate IS formation in human T cells.

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2276

Transcriptional Inflammatory Mechanism in Murine Lupus Nephritis: An Insight into Human Disease. Tania C. Gonzalez Rivera[3], Celine C. Berthier[3], Viji Nair[3], Ramalingam Bethunaickan[1], Matthias Kretzler[3], Anne Davidson[2] and ERCB Consortium. [1]Feinstein Institute, Manhasset, NY, [2]Feinstein Institute for Medical Research, Manhasset, NY, [3]University of Michigan, Ann Arbor, MI

Despite advances in immunosuppressive regimens, lupus nephritis (LN) remains a significant cause of morbidity and mortality in lupus patients. Murine LN models have been used to study this heterogeneous disease but the failure of human trials to reproduce the results seen in mice has raised concerns whether these models truly reflect human disease. Using a transcriptional network comparison we aim to define similarities and differences between three LN murine models and human LN.

Affymetrix based expression profiles from prenephritic vs. nephritic kidneys from 3 LN mouse models (NZB/W, NZM2410, and NZW/BXSB, total n=40) and human renal biopsies from 15 living donors (LD) vs. 32 LN patients underwent disease model specific transcriptional network analysis (Bibliosphere).

Transcriptional networks were compared using the *T*ool for *A*pproximate *L*arg*E* graph matching (TALE) to define cross-species conserved functional interactions. The NZM2410 model shared the highest number of nodes with human LN, followed by the NZB/W and the NZW/BXSB models (70, 46 and 37 major transcriptional network nodes, respectively). Pathway analysis of the 17 nodes shared by the human and murine models highlighted macrophage activation pathways ($p<0.001$).

To distinguish the components of the macrophage-specific signature that were due to an alteration in cell phenotype rather than to infiltration with increased numbers of cells per se, gene expression profiles of macrophages isolated from prenephritic and nephritic NZB/W kidneys were generated and compared with corresponding murine and human LN kidney profiles. A total of 406 transcripts were concordantly regulated between NZB/W kidney isolated macrophages and whole kidneys. Of those, 132 transcripts were regulated in the tubulointerstitium of human LN kidneys, consistent with macrophage-derived expression. This signature was used to define the transcriptional state of kidney resident macrophages in murine and human LN. Network analysis defined Stat3, Anxa2 and TIMP1 as major hubs in the network. Application of the MESH filter "macrophage activation" on the network highlighted Lyn, Spp1 and CD44.

The response of tissue resident macrophages to treatment was assessed in NZB/W mice treated with cyclophosphamide/CTLA4Ig/anti-CD154. From the defined renal macrophage signature, Lyn, Anxa2, and CD44 were major hubs of repressed genes in isolated kidney resident macrophages with induction of remission (histologic remission and absence of proteinuria) with triple therapy.

We were able to define key regulators of inflammation shared between human and murine LN using an integrative transcriptional network analysis approach. Given the similarities between mice and humans highlighted by our studies, therapeutic agents that target macrophage activation should represent a focus in the development of therapies for human LN.

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2277

SLE Serum Deposits C4d on Red Blood Cells, Decreases Red Blood Cell Membrane Deformability, and Promotes NO Production. Ionita C. Ghiran[1], Ourania Kampagianni[1], Mark L. Zeidel[1], Sergey S. Shevkoplyas[2], Jennie M. Burns[2], George C. Tsokos[1] and Vasileios C. Kyttaris[1]. [1]Beth Israel Deaconess Medical Center, [2]Tulane University

Background: Systemic lupus erythematosus (SLE) is characterized by intravascular activation of the complement system and deposition of complement fragments (C3 and C4) on plasma membranes of circulating cells, including red blood cells (RBC). We have recently shown that deposition of complement fragments on RBC in vitro is associated with decreased deformability of the RBC membrane (Karnchanaphanurach P. et al, J Clin Invest 2009). We therefore hypothesized that exposure of RBC to immune complexes present in SLE serum leads to decreased RBC deformability via complement fragment deposition.

Methods: Serum and red cells were isolated from patients with SLE, and healthy controls. RBC from healthy 0Rh- individuals were incubated with SLE or control serum. We used flowcytometry to assess complement fragment deposition on RBC. RBC membrane deformability was measured by 2-D microchannel arrays. Protein phosphorylation levels were quantified by western blotting.

Results: Incubation of healthy donor RBC with sera from patients with SLE but not control sera led to deposition of C4 fragments on the RBC. These complement decorated RBC showed a significant decrease in their membrane deformability. Moreover, RBC from patients with SLE showed a significant decrease in their deformability as compared to healthy donor RBC. As deformability depends on the calcium-mediated phosphorylation of skeletal proteins, we evaluated whether RBC skeletal protein phosphorylation is altered after incubation with SLE sera. We found that sera from SLE patients triggered Ca++ influx in RBC that was followed by decreased phosphorylation of the cytoskeletal protein β-spectrin, and increased phosphorylation of Band 3. Furthermore, RBC membrane flickering, which has been shown to be important for the progression of RBC through capillaries, was irreversibly inhibited by SLE serum-induced complement fragment deposition on RBC membrane. Finally, the complement fragment decorated RBC produced significant amounts of nitric oxide (NO), an important mediator of immune function and vascular tone.

Conclusion: Taken together our data suggest that during periods of high disease activity in SLE, complement activation negatively impacts the ability of RBC to flow through capillaries and thus potentially affects the delivery of oxygen to the tissues. Disruption of complement fragment deposition on RBC may improve hemorrheology and alleviate vasculopathic phenomena often associated with SLE.

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What Are the Pathways by Which Interferon-alpha Decreases Vasculogenesis in Lupus? Seth G. Thacker[2], Celine Berthier[2], Deborah Mattinzoli[1], Maria-Pia Rastaldi[1], Matthias Kretzler[2] and Mariana J. Kaplan[3]. [1]Fondazione IRCCS Ospedale Maggiore Policlinico & Fondazione D'Amico per la Ricerca Sulle Malattie Renali, [2]University of Michigan, [3]University of Michigan Medical Center, Ann Arbor, MI

Objectives: SLE is characterized by accelerated vascular risk due to premature atherosclerosis which is not explained by traditional risk factors. Our group previously proposed that type I Interferons (IFNs) play a crucial role in premature vascular damage by altering the balance between endothelial cell apoptosis and vascular repair mediated by endothelial progenitor cells(EPCs) and myeloid circulating angiogenic cells (CACs). We have now characterized the putative pathways by which type I IFNs interfere with proper vascular repair in SLE.

Methods: EPC/CACs from control and SLE patients were treated with IFN-α for 6 hours and corresponding changes in gene expression were analyzed with Affymetrix Human U133 Plus 2.0 Genechips. Expression levels of genes of interest were validated with real time PCR. Effects on EPC/CAC function were tested utilizing functional in vitro assays. Proliferation and apoptosis were determined by XTT assay and caspase3/7, activation, respectively. DC phenotype was assessed by FACS. In vivo angiogenesis and validation of putative markers at the protein level was assessed by immunohistochemistry staining of kidney sections from lupus nephritis biopsies and controls. STAT2 and STAT6 activation was assessed by FACS.

Inhibition of JAK and PI3K tested abrogation of the antiangiogenic signature induced by interferon-alpha.

Results: Microarray data analysis revealed alterations in various molecules associated to IL-1 mediated signaling and of vascular endothelial growth factor-A (VEGF-A). Downregulation of IL-1β, IL-1 receptor-1 (IL-1R1) and VEGF-A and upregulation of IL-1RN (IL-1 receptor antagonist) and IL-1R2 (decoy receptor) were observed. This indicates a global downregulation of IL-1β function induced by type I IFNs. These abnormalities were more marked in the IFN-treated lupus EPCs/CACs than in the IFN-treated control cells, suggesting that lupus cells were more sensitive to IFN-α effects. Results were confirmed at mRNA and protein level. Treating lupus EPCs/CACs with IL-1β resulted in a significant improvement in their capacity to differentiate into a mature endothelium, therefore abrogating the deleterious effects of IFN-α. The beneficial effects from IL-1β are mediated, at least in part, by increases in EPC/CAC proliferation, decreases in apoptosis, and by preventing the skewing of CACs towards non-angiogenic pathways. IFN-α induces STAT2 and 6 phosphorylation in EPCs/CACs and JAK inhibition abrogates the transcriptional antiangiogenic changes induced by IFN-α in these cells. Immunohistochemistry of renal biopsies from patients with lupus nephritis, but not ANCA-positive vasculitis, showed this pathway to be operational *in vivo*, with increased IL-1RN, downregulation of VEGF-A and glomerular and blood vessel decreased capillary density, compared to controls.

Conclusions: Our study introduces a novel putative pathway by which type I IFNs may interfere with vascular repair in SLE through repression of IL-1-dependent pathways. This could promote atherosclerosis and loss of renal function in this disease.

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ARHP Concurrent Abstract Sessions
Rheumatoid Arthritis: From Clinic to Home
Thursday, November 11, 2010, 11:00 AM–12:30 PM

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The Nurse's Role in Treatment and Management of Patients with Rheumatoid Arthritis: A Delphi-Based Recommendation on Patient Unmet Needs. Jane E. D. Cottrell[2], Monique Jonas[1] and Leeanna M. Bulinckx[3]. [1]Charité University Hospital, Berlin, Germany, [2]Mount Sinai Hospital, Toronto, ON, Canada, [3]PerCuro Clinical Research Ltd, Victoria, BC, Canada

Background: Nurses serve many critical roles in the management and treatment of patients with rheumatoid arthritis (RA), including educating and counseling the patient and liaising between the patient and rheumatologist. Examining how these roles differ among practices can help clarify areas in which nurses can optimize patient outcomes. The objective of this Delphi project was to assess the role of rheumatology nurses in addressing the unmet treatment and management needs of the RA patient

Methods: A modified Delphi method with two rounds of questionnaires was followed by an in-person meeting to explore issues on which consensus had not been reached. A steering committee of 3 nurses developed and refined the questionnaires. An international group of 12 nurses with extensive experience (clinical or research) with patients receiving biologic therapy for moderate to severe RA served as panelists and completed the questionnaires. Prior to the meeting, all responses were anonymous and confidential. Focal topic areas included the nurse's roles as caregiver, provider of information, and assessor of disease status and treatment outcomes. Special attention was paid to understanding patient physical and emotional needs.

Results: In most European and Canadian practices/clinics, nurses spend substantially more time with the patient than the physician. In their interactions with patients, nurses initiate discussions about personal well-being and disease impact on quality of life—topics not always addressed by physicians due to time constraints or comfort level with these issues. Patients are more likely to discuss emotional and social issues related to their diagnosis with a nurse than a doctor and tend to expect the nurse to provide disease and treatment education to them and their families. The panelists agreed that it is critical to customize this information for each patient rather than provide written materials with no verbal explanation. The nurse is in a unique position to judge what level of support or education a patient may need at any given time. Although the benefits of support networks and peer-to-peer interactions were recognized, such interactions need not be limited to structured groups. While all panelists agreed that the doctor is more likely to recommend a particular therapy, the nurse has a critical role in educating the patient on efficacy, potential side effects, method and frequency of administration, product storage, and, if applicable, comfort with self-injection, including demonstrating proper device technique. Additionally, the nurse determines the patient's readiness for and understanding of the treatment, monitors safety and progress, and coordinates care within a multi-disciplinary setting.

Conclusion: The nurse's role in the management and treatment of patients with RA is complex and diverse, yet vitally important to optimal care. Although this Delphi initiative included a small group of nurses, it is clear that information shared across clinics and countries is both useful and practical in terms of improving patient care.

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Self-Efficacy and Follow-Up with Nursing, Medical or Shared Care for Outpatients with Rheumatoid Arthritis. Jette Primdahl[3], Lis Wagner[2] and Kim Hørslev-Petersen[1]. [1]King Christian X's Hospital for Rheumatic Diseases in Graasten and University of Southern Denmark, Graasten, Denmark, [2]Research Unit of Nursing, University of Southern Denmark, Odense, Denmark, [3]University of Southern Denmark, Sønderborg, Denmark

Introduction: Traditionally, people with rheumatoid arthritis (RA) are administered by scheduled medical consultations every 3–12 months. Treatment aims to control disease activity, but also to enable the patients to achieve perceived control over the disease and disease related problems. The latter may be reflected in the patient's self-efficacy (SF) - the belief in one's ability to carry out a task with a desired outcome.

Aim: To explore whether RA outpatients' SF develops differently, depending on whether they have follow-up care in the form of nursing consultations, medical consultations or in a shared care setting with no planned rheumatologic consultations.

Material and Methods: Outpatients (n=287) with low active RA (Disease Activity Score, DAS-28 <3.2 and Health Assessment Questionnaire, HAQ < 2.5) from two Danish hospitals were randomized for one of the three types of follow-up care. The participants' SF was measured by the Danish version of the Rheumatoid Arthritis Self-Efficacy questionnaire (RASE) and the Danish version of the Arthritis Self-Efficacy Scale (ASES). Data were collected at randomization, after three months and at one year. The relation between SF beliefs, outpatient setting, socio-demographic and disease related variables were explored in mixed models. A Wilcoxon signed-rank test was used to test the significance of differences.

Results: For both the RASE and the ASES the three outpatient settings varied significantly over time. During a one year follow-up, the RASE scores decreased in the medical group (mean diff. −5.30, SD 1.29, p=0.0002) and the shared care group (mean diff −4.14 (SD 1.26), p=0.0002). Contrary to this, the participants in the nursing group maintained their SF beliefs at the same level (mean diff. -1.08 (SD 1.32), p=0.47). The RASE score at randomization and time were significant predictors for the development of the RASE scores the first year.

SF measured by the ASES was maintained at the same level in the medical group (mean diff. −17.73 (SD 23.54), p=0.48) and the shared care group (mean diff. −54.56 (SD 27.52), p=0.14), whereas a significant increase was seen in the nursing group (mean diff. 74.56 (SD 19.73), p=0.0001). Disease duration, HAQ, DAS-28 and ASES at randomization were significant predictors for the development of the ASES scores the first year. An increase of 1 in HAQ or DAS-28 at randomization predicted a significant decrease in the ASES of 48.28 (p=0.009) and 38.96 (p=0.002) respectively. No significant differences in disease activity or physical disability between the three outpatient settings were detected at any time.

Conclusion: Outpatients with stable RA, attending three nursing consultations during a one year follow-up stabilized or increased their SF beliefs depending on the questionnaire in use. This differed from medical consultations and shared care cohorts, where the patients' SF beliefs decreased or did not change. The use of ASES as a response variable in longitudinal studies can be problematic because of its high correlation to disease activity and physical disability. The RASE, independent of disease activity and physical disability, confirmed the effect of nursing interventions.

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2281

Future Expectations and Worst Case Scenarios of Patients with Rheumatoid Arthritis: A Focus Group Study in Patients. Laurien Buitinga[3], Louise M. A. Braakman-Jansen[1], Erik Taal[2] and Mart A. F. J. Van de Laar[4]. [1]University of Twente, Enschede, The Netherlands, [2]University of Twente, Enschede, The Netherlands, [3]University of Twente, [4]University of Twente; Medical Spectrum Twente, Enschede

Background: Rheumatoid Arthritis (RA) has a great impact on patients' daily lives. Because of the unpredictable progressive nature of the disease, it is imaginable that people worry about the impact of their disease in the future. Many studies have shown the prevalent difficulties patients experience now. Little attention has been paid to future expectations in RA.

Objective: To examine future expectations, and to reveal worst case future scenarios in patients with RA.

Methods: A qualitative focus group approach was used. Three heterogeneous focus groups of RA patients were composed on the basis of age group (18–40, 40–65, 65–80), gender and having a paid job or not. Eventually, 16 people participated. Transcripts were individually coded by three researchers, including the moderator and note-taker. Participants were asked about their future expectations and worst case future scenarios. Afterwards, the codes were discussed until agreement was reached about all codes. For categorization of the coded expressions, a distinction was made between body functions and structures, activity participation, environmental factors and personal factors, in line with the International Classification of Functioning, Disability and Health (ICF).

Results: This qualitative study revealed that people expected the impact of their RA to be the same or to deteriorate slightly in the future, also in relation to the process of aging. Most people expressed hope for the future and positive feelings because of continuously improving medication. However, also feelings of uncertainty and fears were expressed about the future course of the disease. A major concern was about becoming dependent on others. One of the focus groups particularly expressed concerns about becoming dependent on others with regard to self-care (e.g. toileting, bathing). Concerns were also raised about side effects of medication and losing mobility. For many participants, becoming dependent on others would be the worst imaginable RA-related future scenario, for one participant it would be even worse than dead.

Conclusion: In this study, dependency on others was the most prevailing RA-related worst case future scenario. Many participants expressed their concerns in relation to dependency side effects of medication and losing mobility. Although pain was a prevalent symptom in daily life, no future concerns about pain were raised. Most people in these focus groups also held a positive view of the future because of continuously improving medication.

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2282

Mapping Pathways through Care: Accounts of Help-Seeking in Early Rheumatoid Arthritis (RA). Anne Townsend[2], Catherine L. Backman[3], Paul Adam[1], Susan M. Cox[4], Linda C. Li[3] and Erahse Team. [1]Mary Pack Arthritis Centre, [2]Maurice Young Centre for Applied Ethics, University of British Columbia, Vancouver, BC, Canada, [3]University of British Columbia, Vancouver, BC, Canada, [4]University of British Columbia

Timely treatment can control RA, alter the disease course, and limit its impact on daily life. Prompt intervention with DMARDS is linked to improved outcome, yet there is an avoidable time lag between individuals experiencing the onset of RA and receiving DMARDS1. This delay is influenced by a range of individual and system based factors: accessing the GP consultation; the time between the initial family physician (FP) visit and gaining a rheumatologist referral; and the wait between referral time and the rheumatologist visit1. However, little is known about the relative significance of factors associated with delays along the continuum of care. The current study aims to understand the process of help-seeking for early symptoms of RA from the patient perspective.

38 people (37 women, 1 man), who were diagnosed with RA within the past 12 months, were recruited from offices of rheumatologists and family physicians (FP) and from newsletters of patient advocacy groups. In-depth face-to-face interviews were organized around three overlapping topics: 1) onset of symptoms and initial illness actions; 2) seeking help from health professionals leading to diagnosis; and 3) post-diagnosis experiences. Follow-up phone calls were made to check and elaborate on the interview generated data. Analysis was informed by grounded theory and a narrative approach.

Four stages of delay were identified: 1) onset of symptoms to the FP visit; 2) gaining a referral; 3) waiting for the specialist meeting; 4) gaining the diagnosis and treatment plan. Participant accounts featured delays characterized by a complex array of interlocking bio-psychosocial factors in the personal and broader health care setting. E.g. the nature of symptoms, the impact of symptoms on function, and the ability to fulfill social obligations and maintain daily life and identities; the ability to mobilize effective self-management strategies; patient-professional interactions, access to medical care and knowledge about arthritis and treatment options coalesced to impact the course of help-seeking. A key theme was the impact of personal philosophy and attitude (e.g. stoicism) and self-management practices (e.g. adapting to symptoms, use of over-the-counter medications, and use of the Internet to gain symptom related knowledge) on accessing medical help and specialist referrals.

Our findings concur with the literature on the points of delay in RA care1 and are in line with research on chronic illness, which reveals a direct link between self-management and formal help-seeking 2. Patients typically entered the health-care system as self-managers and continued to self-manage as illness developed. Given the central role of self-management of chronic illness in research, policy and practice, together with the importance of early diagnosis and treatment in RA, further research is required to address the nature and role of self-management along the continuum of care.

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2283

Home-Based Exercise Therapy in Patients with Rheumatoid Arthritis: A Systematic Review. Emalie J. Hurkmans[3], Florus J. van der Giesen[2], Thea P. M. Vliet Vlieland[1], Jan W. Schoones[5] and Cornelia H. M. van den Ende[4]. [1]Department of Rheumatology and Orthopaedics, Leiden University Medical Center, Leiden, The Netherlands, [2]Department of Rheumatology, Groene Hart Ziekenhuis, Gouda, The Netherlands, [3]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands, [4]Department of Rheumatology, Sint Maartenskliniek, Nijmegen, The Netherlands, [5]Walaeus Library, LUMC, Leiden, The Netherlands, The Netherlands

Objective: To assess the effectiveness and safety of home-based (HB) exercise therapy in patients with rheumatoid arthritis (RA).

Method: A literature search up to December 2009 within various databases was performed to identify randomized controlled trials (RCTs) fulfilling the criteria: a) exercise program is performed by patients at home; b) instructions are given at least once; c) program is evaluated not more than once in two weeks; d) the program includes aerobic capacity, muscle strength, joint range of motion, and/or stretching exercises. Two blinded reviewers independently selected studies, rated the risk of bias, categorized the RCTs and extracted data regarding outcome measures of effectiveness (functional ability, aerobic capacity, muscle strength) and safety (self-reported pain, disease activity, radiological damage). A qualitative data analysis was performed.

Results: Eleven RCTs were included; 8 had a low risk of bias. Two RCTs compared a HB program including aerobic capacity and/or muscle strength exercises (8 and 12 months, respectively) with no exercises. Qualitative analysis showed that there is low and moderate quality evidence that a HB program is more effective than no intervention with regard to functional ability and muscle strength, respectively, directly after the intervention. Four RCTs compared a HB program including aerobic capacity and/or muscle strength exercises (8, 12, 24 weeks and 24 months, respectively) with a supervised program. Qualitative analysis showed that there is low quality evidence that a HB program is less effective with regard to aerobic capacity and muscle strength than a supervised program directly after the intervention. Five RCTs compared a HB program including muscle strength exercises and/or stretching exercises (12 weeks, 3, 6, 12 and 24 months, respectively.) with another HB program. Qualitative analysis showed that there is low quality evidence that a HB program including strength and stretching exercises is more effective with regard to functional ability compared to a HB stretching program directly after the intervention. With respect to safety, there

is low and moderate evidence that HB exercise programs have no deleterious effects (see Table I).

Table 1.

Study	Functional ability	Aerobic capacity	Muscle strength	Self-reported pain	Disease activity	Radiological damage
Home-based program versus no intervention						
Masiero 2007	++*		−	++*	−	
Brodin 2008	−		+*	−	−	
Home-based programs versus supervised programs						
Van den Eude 1996	=	++**	+**		=	
Hansen 1993	−	−	−	−	−	−
Hsieh 2009	−	+**	−	−	−	
Lemmey 2009	=		+**		=	
Home-based programs versus other home-based programs						
Van den Berg 2006	−				−	
Stenstrom 1994	−				+#	
O'Brien 2005	+#		=		=	
Stenstrom 1996, 1997	−		−		−	
Hakkinen 1998, 2001, 2003, 2004, 2004	+#		=	+#	=	=

Significant ($p < 0.001$) difference: ++
Significant ($p < 0.05$) difference: +
No significant difference: =
* In favor of home-based program
** In favor of supervised program
# In favor of the home-based program including strengthening and stretching exercises versus exercise programs with only stretching exercises

Conclusion: HB exercise therapy is more effective with regard to functional ability and muscle strength than no exercise therapy. HB exercise therapy is less effective than supervised exercise with regard to aerobic capacity and muscle strength, but equally effective with regard to functional ability. When comparing different types of HB exercise programs, a combined program including strengthening exercises is more effective with regard to functional ability compared to a program without strengthening exercises. No detrimental effects were found in any of HB exercise programs. More research is needed with regard to the specific content and duration of HB exercise program.

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2284

An Interactive Website Reduces the Information Need Regarding the Accessibility of Health Care Services in RA Patients. Jorit J. L. Meesters[1], Ingeborg G. de Boer[2], Marta Fiocco[2] and Thea P. M. Vliet Vlieland[1]. [1]Leiden University Medical Center, Leiden, The Netherlands, [2]Leiden University Medical Center

Purpose: Sufficient knowledge about health care services is mandatory for effective self-management in RA patients (1). This study concerns the effects of an information intervention regarding the accessibility of 18 regional health care services on RA patients' self-perceived knowledge and information need.

Methods: The intervention consisted of a weekly updated interactive internet site covering practical aspects of regional health care services for patients with rheumatic diseases, including an email helpline and a telephone helpline. The intervention also comprised an information kiosk with access to the aforementioned website in the outpatient clinic. Moreover, patients were invited to an information meeting in the hospital, and they received a set of information leaflets based on their individual needs.

A random sample of 400 RA patients from the outpatient clinic of our rheumatological department was asked to fill in a questionnaire before the internet site was launched (T1) and 24 months thereafter (T2) (pretest-posttest design).

The questionnaires concerned socio-demographic data, information need (yes / no), and the level of knowledge (insufficient / sufficient) regarding the accessibility of 18 regional health care services.

Results: 251 patients (response rate 63%) and 200 patients (50%) returned the questionnaire before and after the intervention, respectively, with 160 paired observations (112 females (70%), mean age 60.4 (SD9.9)). Table 1 shows the percentages of patients reporting insufficient knowledge or an information need regarding the accessibility of a health care service (T1) and the changes in these percentages (T2-T1) (Mc-Nemar test). Only the results of the top 10 health care services (highest percentages insufficient knowledge at T1) are shown. At T1, the percentages of patients reporting insufficient knowledge were higher than those reporting an information need in all health care services.

Table 1 shows that there is a significant decrease of the patients who reported insufficient knowledge for 2 out of 10 health care services (in total: 2 / 18 services), and for information need 9 out of 10 health care services (in total: 15 / 18 services).

Table 1 Baseline (T1) respondents reporting insufficient knowledge and information need on the accessibility of health care services and changes (T2-T1)

% Insufficient knowledge	*SP*	*HN*	*SW*	*PS*	*OT*	*SM*	*PO*	*IG*	*HT*	*EC*
T1	67	54	60	61	58	64	59	72	63	79
T2-T1	−1	−1	−5	4	3	2	−1	−12*	−5	−11*
% Information need	*SP*	*HN*	*SW*	*PS*	*OT*	*SP*	*PO*	*IG*	*SE*	*HT*
T1	37	18	16	13	19	31	21	35	34	31
T2-T1	−25*	−15*	−10*	−9*	−13*	−19*	−18*	−19*	−16*	−9

(*: significant difference, $p < 0.05$).
SP: Specialized physical therapist, *HN:* Home nurse, *SW:* Social worker, *PS:* Psychologist, *OT:* Occupational Therapist, *SM:* Self-management programs, *PO:* Podiatrist, *IG:* Intensive Group exercise, *EC:* Exercise for chronic diseases, *HT:* Hydrotherapy.

Conclusions: In RA patients an interactive internet site and the tailored provision of written information leaflets appear to decrease self-perceived information need on regional rheumatology health care services. The effects on self-perceived knowledge were limited. These findings suggest that supplying practical information about health care services should play a greater role in the treatment of RA patients. More research into the optimal strategies to inform patients is needed.

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